14 November 2024
EMA/570488/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lazcluze

International non-proprietary name: lazertinib

Procedure No. EMEA/H/C/006074/0000

Note

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

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List of abbreviations

AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
BDL	Below the limit of detection
BQL	Below the limit of quantitation
CEP	Certificate of Suitability of the EP
CM	Continuous manufacturing
CMS	Concerned Member State
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRS	Chemical reference substance
DL	Detection Limit
DMF	Drug Master File = Active Substance Master File
DMF	Dimethylformamide
DP	Diversion Point
DSC	Differential scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
FID	Flame ionisation detection
FPM	Finished product manufacturer
FRCs	Functionality related characteristics
FT-IR	Fourrier transmission infra red (spectroscopy)
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
ICH	International conference on harmonisation
IR	Infra-red
KF	Karl Fischer

LDPE	Low density polyethylene
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of Detection
LoQ	Limit of Quantitation
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MIA	Manufacturing and Import Authorisation
MS	Mass Spectroscopy
NIR	Near Infra-Red
NIRS	Near Infrared Spectroscopy
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
PAR	Proven Acceptable Range
PAT	Process Analytical Technology
PDA	Photo Diode Array
PDE	Permitted Daily Exposure
PPQ	Process performance qualification
PVC	PolyVinyl Chloride
PVdC	Polyvinyl dichloride
Ph.Eur.	European Pharmacopoeia
QL	Quantitation limit
QOS	Quality Overall Summary
QTPP	Quality Target Product Profile
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRt	Relative Retention time
Rt	Retention time
RT	Room Temperature
RTD	Residence Time Distribution
RTRT	Real Time Release Testing

SAL	Sterility Assurance Level
SEM	Scanning Electron Microscopy
SM	Synthesis Method
SmPC	Summary of Product Characteristics
TLC	Thin Layer Chromatography
TGA	Thermo-Gravimetric Analysis
UV	Ultra Violet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen Cilag International submitted on 21 December 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Lazcluze, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Lazcluze in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0127/2020 on the granting of a product-specific waiver.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest nor to be a major therapeutic innovation. This was based on the fact that the topline clinical data from the pivotal study were not considered outstanding to prompt an accelerated review of the dossier.

1.5.2. New active substance status

The applicant requested the active substance Lazertinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 May 2020	EMEA/H/SA/4457/1/2020/II	*Kevin Cunningham*

The scientific advice pertained to the following clinical aspects:

- the adequacy of the design and key elements of the proposed phase 3 study 738419437NSC3003 including choice of osimertinib as comparator, inclusion of a lazertinib monotherapy arm, study population including EGFR testing approach, choice of dose regimen, primary and secondary endpoints, statistical assumptions and analyses, as well as the potential to support registration; the adequacy of the proposed clinical pharmacology plan to support registration

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

Rapporteur: Thalia Marie Estrp Blicher Co-Rapporteur: Alar Irs

The application was received by the EMA on	21 December 2023
The procedure started on	1 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 April 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 May 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	7 May 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 May 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 July 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	28 August 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 October 2024

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 October 2024
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 Lazcluze on	14 November 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	14 November 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking a marketing authorisation for:

Lazcluze in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.

2.1.2. Epidemiology

Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer worldwide (Globocan 2020). Lung cancer is a major global health concern, with approximately 238,340 new diagnoses annually in the US (SEER 2023), 318,327 in the EU (ECIS 2021), and more than 1.3 million in Asia (Globocan 2020) with 127,070 deaths annually. NSCLC accounts for approximately 85% of lung cancers (Schabath 2019), with 5-year survival rates dependent, in part, upon the stage at diagnosis and ranging from 63% for localized cancer to 8% for cancer that has spread to distant locations (SEER 2023).

2.1.3. Biologic features

In recent years, there has been significant advancement in the understanding of the underlying biology of NSCLC, including the identification of multiple 'driver' mutations that can result in constitutive activation of pro-growth signaling pathways, typically occurring in NSCLC of adenocarcinoma histology. Among patients with NSCLC of adenocarcinoma histology, the most prevalent of these driver mutations that are actionable are those that result in the activation of EGFR, which are identified in approximately 15% of Western patients (Pao 2011) and up to 50% of Asian patients (Jänne 2006). The most frequently identified EGFR mutations, exon 19 deletions and exon 21 L858R substitution mutations, are seen in approximately 85% of patients with NSCLC harboring activating EGFR mutations (Gazdar 2009; Harrison 2020). In up to 10% of EGFR-mutated NSCLC, however, EGFR is activated through one of a group of heterogenous, in-frame base pair insertions in EGFR Exon 20, collectively referred to as EGFR Exon 20ins (Vyse 2019).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The clinical presentation of advanced NSCLC is known to be variable, partially depending on where the cancer has metastasized (Xing 2019). Clinical symptoms of advanced NSCLC may include chronic cough, coughing up blood, chest pain, shortness of breath, difficulty breathing, loss of appetite, weight loss, fatigue, hyponatremia, swollen lymph nodes, lymphadenectasis, fever and headaches (Xing 2019; Cardellino 2023). Without timely diagnosis and treatment, the natural disease progression of advanced NSCLC is that cancer cells continue to move throughout the body and form new metastatic tumors (Wang 2012). Historically the prognosis and 5-year survival rate for patients with advanced NSCLC including advanced EGFR-mutated NSCLC has been poor (often well below 20% likelihood of survival at 5-years) (Shimamura 2022; Cataldo 2011; Lin 2016). The poor prognosis of patients with EGFRm NSCLC is more striking given the fact that patients with this disease are generally younger and healthier than other patients with lung cancer (Zhang 2016; O'Leary 2020; Pecci 2022; Nadal 2023).

2.1.5. Management

The current standard of care for the first-line treatment of EGFRm NSCLC is a third-generation EGFR TKI, most commonly osimertinib. Compared with first- and second-generation EGFR TKIs, third-generation EGFR TKIs provide activity against the T790M resistance mutation and may penetrate the blood-brain barrier better (Reungwetwattana 2018). This may delay the incidence of brain metastases, which are reported in up to one-third of patients with EGFRm NSCLC through disease course, a higher rate than reported for patients with EGFR wild-type NSCLC (Li 2017; Gillespie 2023).

The FLAURA study compared the third-generation EGFR TKI osimertinib versus a first-generation EGFR TKI (gefitinib or erlotinib) as first-line therapy for patients with EGFRm NSCLC (Soria 2018). FLAURA demonstrated a statistically significant improvement in PFS and OS for participants randomized to osimertinib versus a first-generation EGFR TKI. Median PFS was 18.9 months versus 10.2 months, respectively, with a HR of 0.46 when assessed by investigator (17.7 months versus 9.7 months [HR of 0.45] when assessed by BICR) and median OS was 38.6 months versus 31.8 months, respectively, with a HR of 0.80 (Ramalingam 2020; Soria 2018).

Despite the improved initial disease control, almost all patients treated with first-line osimertinib will develop resistance, and there are no approved targeted therapies for treatment of these patients once resistance has developed.

While osimertinib represents a significant advance over earlier EGFR TKIs, there is a need to improve first-line treatment prior to the development of resistance in order to improve treatment outcomes beyond what is seen with available therapies. The most common mechanisms of resistance to osimertinib are due to alterations in the EGFR (eg, C797S mutation, EGFR amplification) and MET (eg, MET amplification, MET exon 14 skipping) pathways. Given this, an agent with activity in tumors with activated EGFR and MET pathways may be of particular interest in EGFR-mutated NSCLC; as described above targeting resistance mechanisms proactively may have been central to the improved outcomes seen with osimertinib in FLAURA.

As a novel bispecific antibody targeting EGFR and MET, amivantamab is designed to target the most common mechanisms of resistance to osimertinib. Lazertinib is a 3rd generation EGFR TKI with preclinical and clinical efficacy in EGFR mutated NSCLC. The distinct mechanisms of action of amivantamab and lazertinib, which target the extracellular ligand binding domain and the intracellular active site of EGFR, respectively, have the potential to inhibit the EGFR pathway more potently than either agent alone.

2.2. About the product

Lazertinib (Lazcluze) is an oral, mutant-selective, and irreversible tyrosine kinase inhibitor (TKI) of activating EGFR mutations (exon 19 deletions, L858R substitution), including the secondary T790M mutation, while having less activity against wild-type EGFR.

Lazcluze is currently approved as monotherapy in South Korea, under the tradename Leclaza (Yuhan Corporation), for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutations and for patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy.

The proposed therapeutic indication for this medicinal product in the European Union is:

Lazcluze in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.

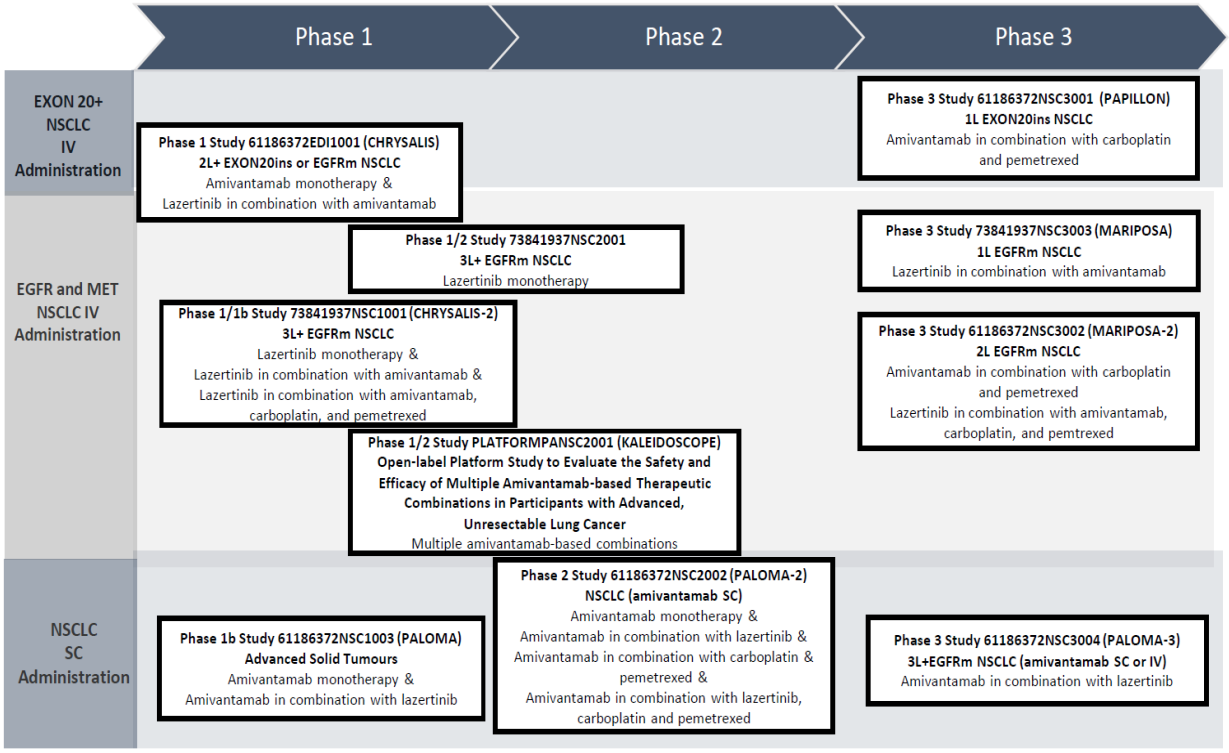
The recommended dose of Lazcluze is 240 mg once daily in combination with amivantamab. It is recommended to administer Lazcluze any time prior to amivantamab when given on the same day. Treatment with Lazcluze should continue until disease progression or unacceptable toxicity.

2.3. Type of application and aspects on development

The clinical development programme for lazertinib consist of 2 compounds (amivantamab and lazertinib) for the treatment of patients with NSCLC. Lazertinib is developed under a license and collaboration agreement between Yuhan Corporation and Janssen (Figure 1).

Key efficacy and safety data to support this submission are derived from the Phase 3 study 73841937NSC3003 (hereby referred to as MARIPOSA). Further supportive data is derived from Phase 1 Study 61186372ED1001 (herereby referred to as CHRYSALIS), Phase 1/1b Study 73841937NSC1001 (hereafter referred to as CHRYSALIS-2), Phase 1/2 Study 73841937NSC2001/YH25448-201 (hereafter referred to as YH25448-201; Parts A to C of the study sponsored by Yuhan Corporation under study identifier YH25448-201 and Part D of the study sponsored by Janssen under study identifier 73841937NSC2001), and Phase 3 Study YH25448-301 (also known as LASER301; hereafter referred to as YH25448-301]).

Figure 2: Janssen Clinical Development Program for Amivantamab and Lazertinib in Patients with Locally Advanced or Metastatic NSCLC



Note: All studies are ongoing
1L=first-line; 2L=second-line; 3L=third-line; EGFRm=epidermal growth factor receptor mutated; exon 20in=exon 20 insertion; IV=intravenous; NSCLC=non-small cell lung cancer; SC=subcutaneous; SC-CF=subcutaneous coformulation with rHuPH20

The applicant received scientific advice from the CHMP on 28 May 2020:
The advice concerned the proposed randomised phase-3 confirmatory study in the first-line setting for lazertinib in combination with amivantamab (see above section 1.6)

Request for accelerated assessment

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest nor to be a major therapeutic innovation. This was based on the fact that the topline clinical data from the pivotal study were not considered outstanding to prompt an accelerated review of the dossier.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as immediate release, film-coated tablets containing 80 or 240 mg of lazertinib as active substance. The finished product is manufactured using lazertinib mesylate monohydrate.

Other ingredients of the tablet core are: hydrophobic colloidal silica, croscarmellose sodium (E468), microcrystalline cellulose (E460 (i)), mannitol (E421) and magnesium stearate (E572). The film coating consists of: macrogols (E1209), polyvinyl alcohol (E1203), glycerol monocaprylocaprate type I (E471), titanium dioxide (E171), talc (E553b), yellow iron oxide (E172) (only 80 mg film coated tablets), red

iron oxide (E172) (only 240 mg film-coated tablets) and black iron oxide (E172) (only 240 mg film coated tablets).

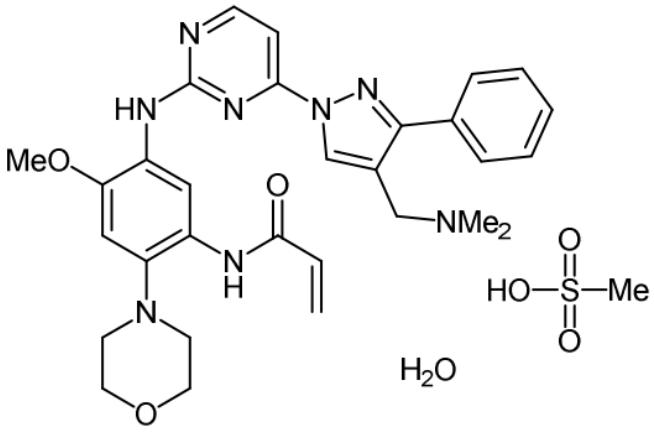
The product is available in white opaque high-density polyethylene (HDPE) bottles with polypropylene child-resistant closures and blister packs with polyvinyl chloride – polychlorotrifluoroethylene film and aluminium push-through foil as described in section 6.5 of the SmPC.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of lazertinib mesylate monohydrate is *N*-[5-[[4-[4-[(dimethylamino)methyl]-3-phenyl-1*H*-pyrazol-1-yl]pyrimidin-2-yl]amino]-4-methoxy-2-(morpholin-4-yl)phenyl]acrylamide methanesulfonate hydrate (1:1:1) corresponding to the molecular formula $C_{30}H_{34}N_8O_3 \cdot CH_4O_3S \cdot H_2O$. It has a molecular weight of 668.77 and the following structure:

Figure 3 : active substance structure



The active substance has a non-chiral molecular structure.

The chemical structure of the active substance was elucidated by a combination of high resolution mass spectrometry (MS), elemental analysis, infrared spectroscopy (IR), ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR) and ultraviolet (UV) spectroscopy. The solid state properties of the active substance were measured by DSC and XRD.

The active substance is is an almost white to slightly yellow-brown non-hygroscopic powder soluble below pH 3.9, practically insoluble at, or above, pH 3.9 in aqueous media, and slightly soluble to freely soluble in organic solvents. It is classified as BCS class 2.

Extensive salt screening was performed to identify a form of the active substance with adequate solubility and to identify the best candidate for further development. The methanesulfonic acid salt of lazertinib wasselected for further development.

An extensive screening study has been performed to identify different polymorphic forms of the active substance. The selected polymorphic form (monohydrate) is the most stable form and is the only one produced by the proposed commercial synthesis process. Manufacture, characterisation and process controls

The active substance is manufactured at the following manufacturing sites. Satisfactory GMP documentation has been provided.

Two alternative synthesis methods are in place for manufacturing lazertinib active substance at industrial scale. Both methods use the same synthesis sequence, including equivalent starting materials and intermediates.

Detailed descriptions of every stage of the two manufacturing processes proposed have been provided. Critical steps and associated controls have been described. In-process controls and process parameters with proven acceptable ranges (PARs) proposed for steps 3-6 are justified and supported by experimental data.

Purge studies conducted with spiked batches support the proposed impurity limits in intermediate specifications. Overall synthesis of the active substance has been adequately described.

Theproposed starting materials for both manufacturing processes are isolated, stable, well-characterised compounds of defined chemical properties and structure and constitute significant structural fragments incorporated into the molecule of active substance. The starting materials have been characterised as needed. The applicant has provided a thorough discussion on fate and carry-over of impurities for each starting material considering actual and potential impurities, residual solvents, elemental impurities and impurities with mutagenic potential. It is demonstrated with spiking studies (at concentrations exceeding proposed impurity limits in starting materials specifications) that steps upstream of the proposed starting materials do not impact the impurity profile of active substance since actual and potential impurities (specified and unspecified) are successfully purged downstream the manufacturing process. Overall, it can be concluded that the proposed starting materials are in line with ICH Q11 and the corresponding Q&A document and hence the proposed starting materials can be considered justified. The starting material specifications have been adequately justified based on the proposed manufacturing process, impurity discussion and batch data presented.
Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. It can be concluded that the minor changes between the 2 processes do no impact the quality of the active substance, and both processes can be considered equivalent.

The active substance is packaged in in double, low-density polyethylene (LDPE) bags (i.e., an inner and outer bag) which comply with Commission Regulation (EU) 10/2011, as amended. Both the inner and the outer bag are appropriately closed and placed in a closed suitable drum or equivalent (secondary non-functional packaging).

The suitability of this container closure system has been demonstrated by the active substance stability data.

2.4.2.2. Specification

The active substance specification shown in Figure 3 includes tests for appearance, identification (including counter ion, IR), assay (HPLC), impurities (HPLC, GC), water content (KF), residual solvents (GC), residue on ignition (Ph. Eur.) and particle size distribution (laser diffraction). The active substance specifications are based on the active substance critical quality attributes (CQA), which

comprise appearance, assay, organic and inorganic impurities, residual solvents, intentionally added elemental impurities and water content.

In the original submission, particle size was not included in the active substance specification. This was not considered acceptable given that the active substance is BCS class 2 and dissolution is significantly affected by changes in active substance particle size. As a result, this parameter was added. The limits were justified by bioavailability and manufacturability studies.

The omission of tests for polymorphism and counter ion assay have been justified in accordance with ICH Q6A given that only one stable polymorphic form exists and that batch analysis data confirm a consistent 1:1 ratio of lazertinib to mesylate. An identity test by IR is considered sufficient.

Overall, the test parameters included in the active specification are considered adequate and cover critical aspects for ensuring the quality of the active substance in line with relevant guidelines.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and specified impurities testing has been presented.

Batch analysis data of the active substance from several batches from development to proposed commercial manufacture are provided. The batch data cover the active substance manufactured by all manufacturers and synthesis methods 1.2 and 2.1. The results are within the specifications and consistent from batch to batch.

2.4.2.3. Stability

Stability data from three pilot scale and three commercial scale batches of active substance manufactured by each of the synthesis methods proposed has been presented. The batches were stored in the intended commercial package for up to 36 months refrigerated (5 ºC), under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. Photostability testing following ICH guideline Q1B was performed on these batches.

The following parameters were tested*: a*ppearance, assay, chromatographic purity, water content and particle size. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications under all conditions. No noticeable changes or trends were observed.

The active substance remained stable when stored unprotected from light according to ICH Q1B.

Forced degradation studies were performed on one batch to test the effects of acid + heat, alkali + heat, oxidants, heat, humidity, and metal ions ($CuCl_2$) on the active substance and to demonstrate that the test method for assay and chromatographic purity of active substance by HPLC is stability indicating. The active substance was found to be prone to minor degradation under all tested conditions except for in hot acid where significant degradation was observed.

The stability data confirms the comparability of active substance from the two proposed synthesis methods.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 48 months with no special storage conditions 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, oval shaped, film-coated tablet for oral administration, containing 96.48 or 289.44 mg of lazertinib mesylate monohydrate, which is equivalent to 80 or 240 mg of lazertinib free base, respectively. The tablet strengths are dose proportional and obtained by compression of different amounts of a common blend.

The tablet strengths are differentiated by colour and debossing. The 80 mg film-coated tablet is yellow with 14 mm length. The tablet is debossed with "LZ" on one side and "80" on the other side.

The 240 mg film-coated tablet is reddish purple with 20 mm length. The tablet is debossed with "LZ" on one side and "240" on the other side.

The composition of the finished product is presented in the tables below.

No overages are used for the manufacture of the finished product.

The physicochemical properties of the active substance that could influence the performance of the finished product and its manufacturability have been identified and discussed (see also active substance section). It has been justified that the active substance synthesis and finished product manufacturing process consistently yield the stable the selected polymorphic form. Supportive data has been presented, confirming that during the stability studies of the finished product no change in the polymorphic form of the active substance occurs.

The pH-solubility profile of the active substance has been determined and discussed. The solubility studies have shown that the active substance solubility is pH dependent and decreases with an increase of pH, the finished product is practically insoluble at pH 6.81.

An evaluation was conducted on the particle size of the active substance to assess its effect on the manufacturing process and the dissolution of the finished product. Given that the active substance is classified as BCS class 2, and that its dissolution is markedly influenced by variations in particle size, the specific particle size of active substance to be used in commercial production has been included in the active substance specification, including suitable acceptance criteria as requested by CHMP (see active substance specification section).

All excipients are well known pharmaceutical ingredients, their quality is compliant with Ph. Eur. standards (with the exception of basic coating premixes) and are commonly used in this type of dosage form. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. An explanation with regards to the function of all constituents in the formulation, with brief justification for their inclusion was provided. However, excipient characterisation and control, crucial aspects to consider in a continuous manufacturing process since material attributes can significantly influence material feeding and process dynamics were not discussed resulting in a major objection (MO1). MO1 was an overarching question, requesting much more detailed information on the product and process development. In response to the above part of MO1, the applicant provided further details and added information on the grade and the specifications of each excipient including relevant functionality related characteristics (FRCs) to the

dossier and explained the impact on the process and associated control strategy. The was deemed sufficient.

The compatibility of the active substance with the excipients was evaluated in a study using binary mixtures. No degradation was observed after 28 days of open dish storage at 60 °C/10% RH and 60 °C/75% RH for all excipients tested, except for microcrystalline cellulose, for which a degradant was detected but at levels below the specified limit. The compatibility of the excipients with the active substance has also been justified by stability results as presented under the finished product stability section.

The finished product was developed on the continuous manufacturing (CM) line at a development site and on a similar CM line at the proposed commercial site in Latina, Italy. Film-coating is performed subsequently in batch mode. The two manufacturing lines have been set up in a comparable configuration and use identical equipment for unit operations (feeders, blenders, tablet press) and process analytical technology (PAT) tools (in-line and at-line) with the same software capabilities. Multiple 80 mg (G004) and 240 mg (G005) core tablet batches were manufactured at both sites to support product and CM process characterisation, including process model (residence time distribution (RTD) and analytical model (PAT) development and validation.

Limited information on the development of the continuous manufacturing process and control strategy was presented in the original dossier. Therefore, the CHMP raised a question as part of MO1 requesting the applicant to provide additional documentation to demonstrate, that the overall control strategy had been developed in accordance with ICH Q13 and ICH Q8–Q10 and ensure that the dossier include sufficient level of detail in line with guidance.

The quality target product profile (QTPP) was an immediate release film-coated tablets for oral administration, containing 80 or 240 mg of lazertinib (as Lazertinib mesylate monohydrate), enabling a daily dose of 240 mg with a possible dose reduction. The finished product must have a sufficiently low level of impurities/degradation products and microbial burden, complying with the ICH requirements, and must meet its specifications over a shelf life of at least 24 months when packaged in bottles or blisters.

The CQAs of the finished product are: appearance, identification, assay, uniformity of dosage units, purity, dissolution and microbial purity. A comprehensive criticality analysis in line with ICH Q9 supplemented with process characterisation studies was conducted to determine an appropriate control strategy for the finished product CQAs.

Originally no critical process parameters (CPP) had been identified in the whole CM train. This was not considered acceptable, and the applicant was requested to justify this as part of MO1. In response, the applicant agreed to define more process parameters as CPPs. This was considered satisfactory.

The applicant clarified, as part of the response to MO1, that set-points or PARs are defined for relevant process parameters and these have been justified by the development data. The proposed control strategy laid down in the dossier therefore consists of material attributes of the input materials, set-points and/or PARs for process parameters, equipment design and system integration, process monitoring and control (including the Residence Time Distribution model), the strategy for diversion and collection of non-conforming material, and the equipment train. With this response, MO1 was considered resolved.

To determine the impact of the compression force on appearance and dissolution, compression studies were performed with different pre- and main compression forces. No tablet defects were observed for any of the compression conditions. However, after film coating, hairline cracks were observed the 240 mg tablets during IPC testing. An investigation was conducted to identify the process parameters that contributed to the hairline crack formation, followed by adjustment of the compression process for

commercial use to prevent the occurrence of hairline cracks on film-coated tablets during commercial production. Results obtained showed that the adjustment had no impact on tablet appearance, weight, friability, disintegration time or dissolution. The batches were put on long term and accelerated stability to complement the primary stability batches for the CQA appearance (see stability section).

The formulation development has been adequately described. The initial clinical formulationwas an immediate release 80 mg film-coated tablet for oral administration. That formulation was optimised by the applicant to the pivotal clinical 80 mg film-coated tablet formulation to improve blend flowability, compactability, and overall manufacturability.

To reduce the pill burden, the pivotal clinical 80 mg film-coated tablet formulation was further optimised to a 240 mg tablet of acceptable size. Subsequently, a dose-proportional 80 mg tablet was developed using this further optimised formulation to allow dose reduction. The optimised film-coated tablet formulations i.e., 80 mg (G004) and 240 mg (G005) are proposed as the commercial formulations. Changes between the pivotal clinical 80 mg film-coated formulation and G0004/5 are minor and have been justified. A bioequivalence study was conducted to demonstrate the bioequivalence of the proposed commercial formulations (80 mg (G004) and 240 mg (G005)) with the 80 mg pivotal clinical formulation. The commercial formulations have been demonstrated to be robust towards minor changes in excipient amounts and coating weight gain. The proposed strengths are considered acceptable considering the dosing regimen.

The proposed commercial 80 mg (G004) and 240 mg (G005) film-coated tablet formulations are manufactured using continuous manufacturing (CM). The primary stability and bioequivalence batches have been produced on the commercial CM line in Latina at the proposed throughput rate according to the proposed commercial process and control strategy.

The development of the dissolution method has been described. The choice of conditions has been adequately justified. To evaluate the discriminatory power of the dissolution method, studies were conducted with variations in the formulation (amount of disintegrant), particle size of active substance, tablet hardness compared to the target formulation composition and process. The discriminatory power of the method has been sufficiently demonstrated.

The primary packaging consists of blisters of polyvinyl chloride-polychlorotrifluoroethylene (PVC-PCTFE) film and aluminium push-through foil, or white opaque HDPE bottles with polypropylene child-resistant closure as described in the SmPC. The materials comply with Ph. Eur. and EC requirements including EC Regulation No. 10/2011 as amended on plastic materials and articles intended to come into contact with food. The choice of the container closure systems 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 Janssen Cilag SpA, Via C. Janssen, Borgo San Michele, Latina 04100, Italy. At the time of marketing authorisation application (MAA) submission the site was only authorized for CM manufacturing operations for investigational medicinal products. An updated MIA covering CM operations as well as for real-time release testing was requested (MO2) and it was satisfactorily provided following a GMP inspection conducted during the procedure.

The applicant has proposed a manufacturing approach in which some unit operations operate in a batch mode while others are integrated and operate in a continuous mode. Briefly, the manufacturing process consists of six main steps: pre-blending the active substance with an excipient in batch mode, followed by continuous feeding of the pre-blend and the remaining excipients using loss-in-weight

feeders, in-line blending (adding the lubricant) and direct compression, followed by film coating in batch mode, and packaging. The process is considered to be a non-standard manufacturing process.

The description of the manufacturing process and schematic diagram were updated with inclusion of more CPPs and justification for classifying some process parameters as non-CPPs, justification of target set-points and PARs, equipment design (e.g. feeders, blender) and system integration as well as further explanation of the gravimetric and volumetric modes of operation part of the response to MO1.

Process Analytical Technology (PAT) is used to monitor the process at 2 points: an in-line NIR probe in the feed frame of the tablet press for real-time determination of the active substance concentration in the blend and an at-line PAT setup at the outlet of the tablet press for analysis of core tablets for physical properties (weight and hardness) and for active substance identification, assay and content uniformity (by NIRS).

The size of a batch produced by CM has been defined as a run time at a defined mass flow rate. The target throughput rate

for the continuous process during commercial production has been defined. The commercial batch size varies as a function of the runtime. The runtime of each batch is documented prior to the start of manufacture. The maximum and minimum run time for both tablets strengths has been defined. . The batch formula has been provided for the largest and smallest batch sizes. The theoretical number of tablets manufactured at minimum and maximum run time has also been specified.

A summary of the start-up, shut down, pause and restart procedures of the continuous manufacturing process has been described including which events would trigger a pause of the process as requested by CHMP as part of MO1. The strategy to monitor and maintain the state of control and to manage disturbances, detect, divert and segregate potential non-conforming material has also been described in the manufacturing process description.

Diversion points (DP) in the CM process have been described and justified. The proposed sampling strategy has been adequately justified.

The proposed bulk holding time for 80 mg and 240 mg film-coated tablets packaged in closed double LDPE bags in a heat-sealed aluminium (Alu) laminated bag placed in a closed container (plastic drum, fibre drum, or equivalent) is justified and acceptable. The stability data comprised one batch of each tablet strength packaged in proposed container stored at 30 °C/75% RH during the requested hold time period. No changes were observed for any of the tested parameters (appearance, assay, chromatographic purity, dissolution or microbial purity). Since both tablet strengths are dose proportional starting from a common blend and the finished product is in general stable (refer to the stability section), the bulk stability data was considered sufficient. The applicant also confirmed compliance with note for guidance on start of shelf-life of the finished dosage form.

No process validation was provided in the initial submission which resulted in a MO (MO4) as the process is considered non-standard. In response, the applicant presented process validation data on three consecutive production scale batches of each product strength manufactured using the proposed commercial process. A robust plan for continued process verification has also been outlined. Detailed evaluation of results and descriptions of deviations has been presented and process validation activities can be considered sufficient. Overall, 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 specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (NIR or HPLC/UV), assay (NIR or HPLC), chromatographic purity (HPLC), uniformity of dosage units (NIR or HPLC), dissolution (in house), water content (Karl Fischer) and microbial quality (Ph. Eur.). The shelf-life specifications are the same as for release except that identification, assay and content uniformity are only measured by HPLC/UV.

Partial real-time-release testing (RTRT) is proposed for the finished product. RTRT is used for identification, assay and uniformity of dosage units tested by NIRS. The remaining specification parameters (appearance, chromatographic purity, dissolution, water content and microbial purity) are tested off-line. In the original submission, the CHMP considered that the strategy for RTRT had not been adequately documented and justified in line with the Guideline on Real Time Release Testing resulting in a MO (MO5). In response, the applicant provided additional documentation including a detailed description of the control strategy for RTRT. The fixed sampling frequency and sample size per sampling point ensures that analytical data is representative of the complete batch is obtained. Furthermore, it has been justified that no lapses in data collection can occur. The use of RTRT and relationship between the end-product testing has been supported by substantial comparative data at commercial scale (parallel testing) and a suitably scoped MIA has been presented, as requested.

In case the at-line NIR-PAT tool for real time release testing is not operational (e.g., model maintenance or technical issues), the core tablet samples are analysed offline in the QC lab by NIR-QC methodology (second option) or HPLC (third option), which is also used as the reference method for the secondary at-line and off-line NIR methods. The methods have been shown to be equivalent.

Stability testing of the finished product is performed on the film-coated tablets.

The use of an alternative test (ATP bioluminescence) for the traditional compendial microbial purity has been described. Sufficient description and validation (including a benefit/risk analysis) according to Ph. Eur. 5.1.6 was presented in the dossier as requested by CHMP.

In the original submission that applicant omitted water content from the finished product specification. This was not considered justified by the CHMP given that a slight increasing trend in water content was observed in batches of 80 mg and 240 mg tablets stored at 25 ºC / 60% RH and 30 °C/75% RH. The applicant agreed with his request and included this parameter defining limits based on the results from primary, in-use and open dish stability studies. This was considered acceptable.

Risk assessment of elemental impurities was carried out as required by ICH Q3D and presented in brief in section 3.2.P.5.5. The excipients and active substance for lazertinib tablets were tested as per ICH Q3D (Guideline for Elemental Impurities) taking into account potential contributions from the active substance, excipients, manufacturing equipment, container closure system (primary packaging), and process water. The control threshold concentrations for all elemental impurities were calculated based on the oral permitted daily exposure (PDEs) and the maximum daily dose. Batch analysis data from multiple batches of each strength were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment for nitrosamine impurities was performed considering all potential all potential 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). Lazertinib mesylate monohydrate contains a secondary aminopyrimidine substructure which is s-amine of category 5 (no hydrogen on α-carbon) according to the current version of EMA/409815/2020. The active substance also contains two tertiary amine substructures (morpholino- and dimethylamino- substituents). The risk assessment considered the finished product components including active substance, excipients and primary container (only HDPE bottle), and the manufacturing process and equipment for the potential presence of any nitrosamine and for risk factors that might induce the formation of nitrosamines. The risk assessment incorporated the principles outlined in ICH Q9 and ICH M7. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product above the respective acceptable intake, considering the indication is within the scope of ICH S9 (advanced cancer). Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The data on development and validation of the at-line and off-line NIRS methods in the originally submitted dossier was not considered acceptable (MO3). The procedure description was not complete, and the scope was not properly defined. The calibration model had not been adequately justified and the lifecycle management plan, including model monitoring and maintenance was not considered acceptable. In response, the applicant provided further documentation and justifications in line with the CHMP guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations (EMEA/CHMP/CVMP/QWP/17760/2009 Rev2). This was considered acceptable.

Satisfactory information regarding the reference standards used for assay and specified impurities testing has been presented.

Batch analysis results are provided for several pilot and production scale batches of both tablet strengths

Batch analysis data has been presented for multiple batches including the initial clinical formulation and pivotal clinical formulation. Batch analysis data has also been presented for several characterisation and stability batches of the commercial formulations 80 mg (G004) and 240 mg (G005), including a total of three characterisation batches of the maximum proposed batch size. End product testing has been performed for all batches for all parameters and the results comply with the specifications. Comparative test results (parallel testing) supporting the relationship between the end-product specification and real-time release testing has been presented. The results confirm 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 commercial scale batches of each tablet strength (80 mg and 240 mg) manufactured at the proposed commercial manufacturing site were presented. Following the start of the stability study, the compression step was further optimised and stability data for one additional 80 mg batch and three additional 240 mg strength batches manufactured post-change were also provided. Batches were stored for up to 24 months under long term conditions (25 ºC/60% RH) and intermediate conditions (30 °C/75% RH), 12 months at 5 °C and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. The batches of Lazcluze are identical to those proposed for marketing and were packed in the two primary packaging formats proposed for marketing (blisters and bottles).

Samples were tested for appearance, assay, water content, chromatographic purity, dissolution, and microbial purity.

All results were within proposed specification limits up to maximum tested time point under all storage conditions. Although hairline cracks were observed for the three primary stability 240 mg batches at release and stability, these were not observed for batches manufactured after the compression step optimisation, thus no question was raised regarding this change in appearance in old batches. An increase in water content was observed after storage at 25 °C/60% RH and 30 °C/75% RH. Variability was observed for assay and a slight increase was observed for the specified impurity, resulting in an accordingly increase in total impurities, but as indicated above all results remained within the proposed limits.

In addition, two commercial scale batches of each tablet strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Although minor degradation was observed, all results were within the proposed specification limits.

Forced degradation studies under extreme stressed conditions were performed to test the effects of hot acid, hot alkali, oxidants, heat, humidity, light, and metal ions on the 80 mg clinical formulation because it is considered worst-case. The results can be considered applicable to the 80 mg (G004) and 240 mg (G005) commercial formulations. The finished product was found to be prone to minor degradation under all tested conditions except for in hot acid where significant degradation was observed. The data confirm the stability indicating nature of the HPLC chromatographic purity method.

An in-use stability study was also conducted under long term and intermediate conditions on one batch of each tablet strength packed in HDPE bottles. The study was designed such that the final in-use testing date coincided with the overall end of shelf-life of 24 months considering the dosage regimen of each tablet strength. The study started after storage under long term conditions for 21 months (80 mg tablets) or 22 months (240 mg tablets) and lasted for 3 or 2 months respectively. No out of specification results were observed and no in-use shelf-life is deemed necessary.

It is confirmed that the first three production batches of the 80 and 240 mg lazertinib film-coated tablets, will be placed on stability under long-term and accelerated storage conditions. The post-approval stability protocol and stability commitment are considered acceptable.[1] Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 2 years for the 80 mg (G004) and 240 mg (G005) film coated tablets packaged in either of the two proposed commercial container closure systems without special temperature storage conditions as stated in the SmPC (section 6.3 and 6.4) is 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 the development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The finished product is manufactured using a hybrid CM mode (i.e. some unit operations operate in a batch mode while others are integrated and operate in a continuous mode). Several MOs were raised during the procedure concerning: MO1 on the limited information on the development of the CM process its control strategy and insufficient details of the manufacturing process description presented in original dossier; MO2 on the need for an updated MIA

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

confirming that the proposed finished product manufacturing site is authorised for commercial CM manufacture of human products; MO3 on deficiencies in the NIR documentation including lack of compliance with the EU NIR guidance and justification of validity and robustness of the procedures; MO4 on the lack of process validation data on the finished product; and MO5 on insufficient documentation and justification for the RTRT control strategy.

Acceptable documentation was provided to address each MO. The proposed control strategy consists of material attributes of the input materials, set-points and/or PARs for process parameters, process monitoring and control (including the Residence Time Distribution model), the strategy for diversion and collection of non-conforming material, the equipment design and system integration. Release testing of the finished product is performed using a combination of testing on the core tablets during manufacturing (RTRT) and on the film-coated tablets. 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.

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. Recommendations for future quality development

n/a

2.5. Non-clinical aspects

2.5.1. Introduction

NSCLC tumor development has been associated with excessive amounts of EGFR which, after binding of EGF in the extracellular domain, leads to tyrosine phosphorylation and ultimately cell proliferation and potential tumor growth. While 1st generation tyrosine kinase inhibitors (TKI) targeted wild-type (wt) EGFR, mutations in the exons coding for the tyrosine kinase domain has developed, rendering the 1st generation TKIs ineffective in mutant-induced resistant EGFRs. Lazertinib has been developed as a 3rd generation TKI (type IV), which binds to the adenosine triphosphate (ATP) binding site of the EGFR. Lazertinib specifically targets EGFR molecules harboring activating mutations in the ATP-binding site such as deletion of exon 19, *L858R* (mutation in exon 21) as well as *T790M* (secondary mutation in exon 20) but it is ineffective against wild-type EGFR tumors.

The non-clinical development program was conducted in line with ICH M3, ICH S9 and ICH S10 and includes investigations of *in vitro* and *in vivo* pharmacology in support of the proposed indication for elucidating the mode of action and proof of concept in relevant non-clinical models of disease, pharmacokinetic properties of the compound as well as the safety profile in rats and dogs, which were determined as the relevant non-clinical species. The non-clinical testing strategy is consistent with the proposed clinical indication, route of exposure (oral) and dosing regimen. In addition to a full non-clinical testing program on lazertinib as monotherapy, additional pharmacological and pharmacokinetic studies were conducted in NSCLC xenograft animal models in support of the combination therapy of lazertinib and amivantamab.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro, in an EGFR family kinase assay, lazertinib was shown to potently inhibit EGFR single mutants (*del19, L858R or T790M*) and double mutants (*L858R/T790M, or del19/T790M*), while binding with less affinity to the wild type EGFR. Results from the kinase assay were confirmed in *in vitro* cell line assays using human NSCLC cell lines with various EGFR mutant status, as lazertinib induced growth inhibition in both PC9 (*Del19*) and H1975 (*L858R/T790M*) cell lines with mutant EGFR and much less potently in wild-type EGFR H2073 cells. The cellular anti-tumor activity against NSCLC cells was correlated with molecular potency as assessed by change in phosphorylation of EGFR mutant protein. It was demonstrated that lazertinib inhibited phosphorylation of mutant EGFR in PC9 and H1975 cells, and only induced negligible inhibition against wild type EGFR in H2073 cells, with a difference in selectivity for mutant EGFR over wild type EGFR of 88- to 118-fold. Thus, a correlation between in vitro kinase potency, anti-tumor activity and molecular potency was demonstrated. Activity of the prominent dog metabolite M7 was also investigated *in vitro* in mutant EGFR-expressing Ba/F3 cells and NSCLC cells. While M7 did demonstrate pharmacological activity, it was weaker than for lazertinib itself. Seen in light of the low levels observed in humans, M7 is not considered to contribute meaningfully to clinical activity. When lazertinib was compared with osimertinib, osimertinib showed a similar profile in the three *in vitro* assays, however, its metabolite AZ5104 showed high affinity for the wild-type EGFR, thus making it a less selective compound. Overall, *in vitro* studies documented the proposed mechanism of action and is considered to support the proposed indication as a potent and selective tyrosine kinase inhibitor, targeting EGFR harboring mutations in the ATP-binding site, specifically *del19* and *L858R/T790M*.

Antitumor activity was assessed in different *in vivo* studies using human NSCLC cell-line derived xenograft models in female BALB/c nude mice representing *Del19* (PC 9 cell line) and *L858R/T790M* (H1975 cell line) EGFR mutation as well as the murine Ba/F3-L858R subcutaneous xenograft model expressing *L858R* EGFR mutation. In all cell lines, lazertinib treatment resulted in significantly reduced tumor growth and tumor regression, confirming the *in vitro* study results of potent inhibition of EGFR mutants. Anti-tumor activity was furthermore correlated to inhibition of EGFR phosphorylation as well as inhibition of downstream signaling of p-AKT and p-ERK1/2 in the H1975 xenograft model. Selectivity was also demonstrated for the mutant EGFR variants as only moderate tumor growth inhibition was demonstrated in a A431 human epidermoid carcinoma xenograft model expressing wild-type EGFR. At the same dose level, lazertinib showed higher anti-tumor activity in the PC-9 xenograft model compared with osimertinib. The efficacy of lazertinib for metastatic lesions in the brain was furthermore investigated in an intracranial cancer cell implantation model using H1975 human NSCLC cells implanted into the brain striatum of female BALB/c nude mice. Treatment with lazertinib resulted in significantly increased brain tumor growth inhibition as well as complete tumor regression, which was observed to a larger extent when compared to equal doses of osimertinib. Overall, *in vivo* primary pharmacology studies, in combination with the *in vitro* pharmacology studies, support the proposed indication for lazertinib and demonstrated significant tumor growth inhibition in EGFR mutant cell line xenograft models, specifically for EGFR cell lines harboring the *Del19* and *L858R/T790M* mutations.

2.5.2.2. Secondary pharmacodynamic studies

The applicant performed an off-target screening assay using 80 targets encompassing transmembrane receptors, soluble receptors, ion channels, and monoamine transporters (Lead profiling screen®, Eurofins Cerep). Only the 5-HT (5-hydroxytryptamine) and 5-HT_{2B} transporters showed potential for off-target activity in the initial screening and follow-up cellular and tissue functional assays were

conducted for both transporters. In a 5-HT uptake test using rat brain synaptosomes, the IC_{50} of lazertinib was 110 nM suggesting the 5-HT transporter is a potential off target for lazertinib. The applicant however states that the unbound C_{max} at the recommended human dose of 240 mg once daily is 9.3 nM thereby resulting in a low likelihood for inhibition of the 5-HT transporter. This is accepted. For 5-HT_{2B}, lazertinib did not significantly affect inositol 1-phosphate (IP-1) levels in 5-HT_{2B} functional agonist or antagonist assays using CHO cells expressing human recombinant receptors up to the highest concentration tested (500 nM). Additionally, lazertinib did not show any agonistic or antagonistic effect on the contraction of isolated rat stomach fundus up to 500 nM. It is therefore accepted that 5-HT_{2B} binding affinity does not seem to indicate any functional consequences.

There are known issues with resistance development for TKIs, as observed for the second generation TKIs, which resulted in development of third generation TKIs such as lazertinib, to counteract these issues. Resistance issues with lazertinib have however already been observed and the mechanisms behind have been described in literature (Shaban et al., 2024). Lazertinib is an irreversible inhibitor of EGFR through covalent binding to the *C797* residue in the ATP binding region. Patients can however develop resistance to treatment with lazertinib due to a specific point mutation in the *C797* residue in the EGFR ATP-binding site as well as deletion of the secondary mutation *T790M*, which is also one of the targets of lazertinib. The applicant has not further addressed issues with resistance development, however, fourth generation TKIs are under development to counteract resistance issues with third generation TKIs, where patients would be unresponsive to treatment with lazertinib.

2.5.2.3. Safety pharmacology programme

Lazertinib was tested in a standard battery of *in vitro* and *in vivo* safety pharmacology assays for effects on cardiovascular, respiratory, or central nervous systems. Lazertinib was tested in a GLP-compliant hERG assay where it inhibited hERG channel current at actual concentrations from 1 µM to 9.3 µM with an IC_{50} of 5.3±2.0 µM. The inhibition was statistically significant. According to the applicant, the IC_{50} value is 570-fold the unbound C_{max} 9.3 nM at the maximum daily recommended human dose of 240 mg (MRHD). The effects of lazertinib was further investigated in an *ex vivo* non-GLP study on the electrocardiographic, electrophysiological, and proarrhythmic potential in the isolated perfused rabbit heart, including QRS duration, QT interval, QT_{peak} interval, T_{peak}-T_{end} duration and the appearance of early after depolarizations. No significant electrocardiographic or electrophysiological changes were observed up to 30 µM lazertinib as well as no changes in proarrhythmic parameters at ≤10 µM with minimal observations up to 30 µM lazertinib. Finally, the potential cardiovascular effects of lazertinib were investigated in conscious, telemetry-instrumented male beagle dogs in a GLP study with single dosing of up to 20 mg/kg on Days 1, 8, 15, and 22 of the dosing phase. Assessment of cardiovascular function included qualitative ECG evaluation and quantitative analyses of ECG as well as hemodynamic parameters. At 20 mg/kg, lazertinib mildly lowered heart rate (-16 BPM; -19%), but the effect was not considered physiologically relevant because of the small magnitude within physiological variability and short duration. No other cardiovascular changes were observed in dogs up to 20 mg/kg, which corresponded to 2.9- and 3.5-fold to Cmax at MRHD in males and females, respectively. Lack of observations in the general toxicity study in beagle dogs up to 8 mg/kg/day by repeated dosing for 13-weeks including 4-weeks recovery (~2-fold to MRHD), supported the low risk of cardiovascular events in animals. However, in a prior 4-weeks oral repeat dose toxicity study in dogs, cardiotoxicity (degeneration/necrosis of the myocardium and vessel, mixed cell inflammation, thrombus, and hemorrhage) was noted at 20 mg/kg/day in 2 of 3 males in the main toxicity group but was not present in main toxicity group females or 20 mg/kg/day recovery group animals. While the mechanism of cardiotoxicity is unknown, the applicant states that higher exposure may have contributed to the observed cardiotoxicity as AUC_{24h} was significantly higher in the two affected males (46000 h·ng/mL) versus the mean of other males (26633 h·ng/mL) and versus the mean of all females (14900 h·ng/mL)

at 20 mg/kg/day. Exposure in the two affected males at 20 mg/kg/day corresponded to 7-fold to AUC at MRHD. Overall, non-clinical data indicates a low cardiovascular risk of lazertinib at clinically relevant dose levels. The class of TKI compounds are however known for their association with cardiovascular risk, and venous thromboembolic (VTE) events have already been identified as important risks in the RMP (Module SVIII) for the combination therapy with lazertinib and amivantamab, though some evidence also indicates this risk to be associated with the monotherapy of lazertinib.

Respiratory function (tidal volume, respiration rate, and minute volume) was investigated in a GLP study following a single dose in two phases up to 79/100 mg/kg in male Sprague-Dawley rats (8/group). No effects on respiratory function was observed up to 50 mg/kg. At 79/100 mg/kg, an up to 13% reduction in minute volume and mean tidal volume was observed, which however did not have a clear biological relevance and no compensatory changes was evident in respiration rate. Exposure at 79/100 mg/kg corresponded to exposure multiples of 2.5- and 2.1-fold to Cmax at the MRHD in males and females, respectively. Histopathological changes (alveolar macrophage infiltrate) were observed in the 13-week repeat dose toxicity studies in rats, but the findings were not dose dependent and were partially or fully reversible. No respiratory changes were observed in the 4-week studies in rats or dogs. Interstitial lung disease (ILD)/pneumonitis are known risks associated with treatment with lazertinib, and have been included in the RMP (Module SVII) as well as in the SmPC for management of the risk.

Potential effects on the central nervous system was investigated in a GLP study in male Sprague-Dawley rats (8/group) administered up to 100 mg/kg using a modified Irwin test. No lazertinib-related effects in home cage, hand-held, open-field, or elicited response observations or body temperature measurements were noted at doses up to 100 mg/kg corresponding to exposure multiples of 2.5- and 2.1-fold to Cmax at the MRHD in males and females, respectively. Further, no clinical neurological changes were observed in the general toxicity studies in rats and beagle dogs following repeated dosing for up to 4- or 13-weeks.

Overall, the non-clinical documentation indicates a low risk for cardiovascular, respiratory and neurotoxic events at clinically relevant dose levels.

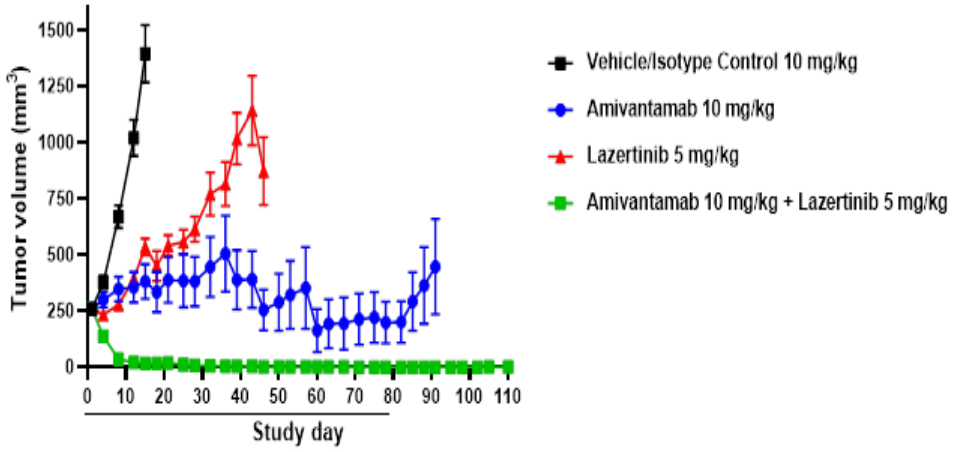
2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted by the applicant. This is acceptable as co-administration with drug substances targeting the same part of the EGFR is not foreseen. Furthermore, co-administration with amivantamab, targeting a different part of the EGFR, was conducted in primary pharmacology studiesto demonstrate superior anti-tumor effect of the combination therapy compared to the single agents.

2.5.2.5. Other pharmacology studies

Combination therapy with ethe EGFR/MET bispecific antibody amivantamab, which binds to the extracellular domains of these receptors, was investigated in terms of enhanced anti-tumor activity in the H1975 xenograft mouse model due to the combined mode of action of the two therapies targeting inhibition of EGFR phosphorylation, immune cell-mediated tumor killing and inhibition of MET signaling.

Figure 4: Effect of Amivantamab and Lazertinib Monotherapies and in Combination on the Growth of H1975-HGF Xenograft Tumors in Mice



HGF = hepatocyte growth factor; SEM = standard error of the mean.
Tumor-bearing mice were assigned to groups and dosing was initiated on Day 1. Isotype control and amivantamab at 10 mg/kg were dosed IP twice a week for 11 weeks. Lazertinib was orally dosed daily for 78 days. The overall dosing period is denoted by the line below the X-axis. Group tumor volumes are graphed as the mean ± SEM (n=10/group) and are graphed while at least 8 mice remained on study.
(DD21087)

Table 1: Tumor Growth Inhibition, p-values, and Partial and Complete Responses for H1975-HGF-Tumor-Bearing Mice

Group	Treatment	% TGI	p-value of TGI	# of PRs	# of CRs
1	Isotype (10 mg/kg) + vehicle control	NA	NA	0	0
2	Amivantamab (10 mg/kg)	89	<0.0001	1	4
3	Lazertinib (5 mg/kg)	76	<0.0001	0	0
4	Amivantamab (10 mg/kg); lazertinib (5 mg/kg)	121	<0.0001	0	10

CR = complete response; NA = not applicable; PR = partial response; TGI = tumor growth inhibition Isotype control and amivantamab at 10 mg/kg were dosed IP twice a week for 11 weeks. Lazertinib was orally dosed daily for 78 days. Percent ΔTGI and p-values were calculated on Day 15. Statistical significance was calculated using the Linear Mixed-Effects analysis. PRs and CRs were determined over the course of the study, which lasted 110 days. (DD21087)

2.5.3. Pharmacokinetics

2.5.3.1. Analytical methods

Lazertinib concentrations in plasma from dogs, rats and rabbits were determined following protein precipitation and analysis of the supernatant using a liquid chromatography tandem mass spectrometry (LC-MS/MS) method. For non-GLP studies in mice, rats and dogs, the validated method described in RDTE15244 was used to analyze plasma samples with the calibration curve range of 1 to 1,000 ng/mL. For other non-GLP studies, a qualified method was used to determine lazertinib plasma concentrations. The methods are considered acceptable to determine plasma concentrations of lazertinib in the non-GLP studies. Fully validated methods were developed for the determination of lazertinib and its metabolite M7 in rat and dog plasma in support of the pivotal GLP studies, as well as for rabbit plasma for lazertinib alone. An assessment of the pivotal studies reveals a program in good control and with both validation and study related bioanalysis in compliance with GLP. Incurred sample

reproducibility was found to comply with guidelines in the assessed pivotal studies. Overall, the methods appear robust and adequate for the purpose of the studies.

2.5.3.2. Absorption

In vitro, lazertinib was of moderate permeability in Caco-2 cells with no active efflux mechanism. Following single oral dosing in mice, rats and dogs, lazertinib was rapidly absorbed with a high oral bioavailability in mice (74.8% to 79.8%), moderate in rats (33.7% to 48.3%) and moderate-to-high in dogs (57.8% to 77.7%). Following IV administration, lazertinib plasma concentrations declined in a biphasic manner with a low plasma elimination half-life (t½: 4.7 and 7.8 hours) across species. At the 24-hour postdose collection of plasma, the apparent half-live of lazertinib in rats and dogs after oral administration ranged from 7.4-10.4 h and 8.3-11 h, respectively. . Meanwhile, the "terminal half-live" of lazertinib in humans following oral absorption was 70.4 h. While there are differences in the reported half-lifes between species, this is accounted for by methodological differences in PK parameter estimation across the studies rather than differences in PK profile between animals and humans. This seems supported by similar concentration-versus-time profiles across the species over the first 24 h of plasma collection as well as a similar accumulation ratio of lazertinib after multiple dosing in animals and human (within 2-fold). Non-specific covalent binding of radioactivity to blood and plasma components was observed in both humans and rats, resulting in incomplete recovery of radioactivity from plasma samples. This was however also observed in in vitro studies and is consistent with binding reported for other covalent TKIs, such as osimertinib and furmonertinib. Overall, the differences in reported half-lifes between species is not considered of concern. Exposure generally increased less than dose-proportionally after both oral and IV administration in rats and dogs. The M7-to-lazertinib exposure ratio was 0.08 based on C_{max}, and 0.14 based on AUC_{last} in mice. There was no apparent effect of food on exposure in rats and dogs and no substantial sex differences were observed. A single dose oral PK study in dogs demonstrated comparable exposure profiles irrespective of the formulation buffers used resulting in either the free base or mesylate salt of lazertinib as well as bioequivalence between reference phase 1 formulation and the pivotal clinical 80 mg phase 2,3 formulation.

Following repeated oral dosing in rats and dogs, no accumulation of lazertinib was observed and exposure was in general dose-proportional on Day 91. Also, no accumulation of metabolite M7 was observed and M7-to-lazertinib exposure ratios based on AUC24h were below 0.062 in rats and 0.6 in dogs on Day 1, generally decreasing by Day 91 while a low M7-to-lazertinib exposure ratio of 0.02 to 0.04 was observed in humans at steady state. No sex differences were noted after repeated dosing in any species. Exposure was also measured in pregnant Sprague-Dawley rats in the GLP EFD study (Study No. 8383617), which in general increased dose-proportionally, however, exposure was lower in pregnant rats than in non-pregnant rats in the 13-week repeat-dose toxicity study (Study No. 8351378). Exposure was also measured in pregnant rabbits in the GLP EFD study (Study No. 8383620) and showed a greater than dose-proportional increase.

2.5.3.3. Distribution

Protein binding of lazertinib and its major metabolite M7 was investigated *in vitro* in mouse, rat, dog, monkey and human plasma. The mean percentage of plasma protein binding of lazertinib was high (>98%) across all species and the free fraction in rat and dog plasma was within 2-fold of the human value. M7 plasma protein binding was similar to lazertinib. Lazertinib bound to both human serum albumin and human α-1-acid glycoprotein with no concentration dependency and showed limited distribution to blood cells. *In vitro*, lazertinib demonstrated high binding in mice and rat brain tissue with no concentration dependency. *In vivo* distribution studies in mice, rats and dogs confirmed

penetration of the blood-brain-barrier and exposure to brain tissue. Furthermore, a high degree of distribution to brain tumor tissue versus plasma and brain tissue was demonstrated in a NSCLC brain tumor mouse model following single dosing with lazertinib. Overall, data supports similar protein binding between species as well as brain barrier penetration and exposure of the brain tumor tissue to lazertinib.

The tissue distribution of ^{14}C-lazertinib-derived radioactivity was determined in male Long Evans rats by quantitative whole-body autoradiography. Melanin-binding was observed in pigmented skin and the uveal tract, with a strong specific affinity for the latter, as radioactivity was accumulated in the uveal tract over time at high amounts. Additionally, a larger proportion of radioactivity was distributed to pigmented skin compared to non-pigmented skin. While high amounts of radioactivity still remained in the uveal tract at the last time point, elimination over time was however observed, specifically at the last two time points, indicating reversibility in melanin-binding tissue. While distribution data indicates strong melatonin binding, lazertinib was however shown to not be of phototoxic potential, as discussed under the Toxicology section. Limited distribution to blood cells was observed in rats, however, lazertinib elimination from whole blood was slower compared to plasma, and higher amounts were observed in whole blood compared to plasma (~6-fold) at the later time points, presumably due to covalent binding in blood. Other target tissues of distribution include adrenal gland, liver, thyroid gland, pituitary gland, spleen, lung, harderian gland and eye. Limited amounts of radioactivity were distributed to male reproductive organs, which was eliminated over time. As the study was only conducted in male rats, no data has been generated to investigate distribution to female reproductive organs. Limited correlation was observed between tissue site of distribution and the identified target organs for toxicities. Rather, data indicates that organ toxicities correlate with pharmacological inhibition of EGFR in tissues expressing this receptor, specifically targeting mucosal tissue and excretory organs such as gastrointestinal tract, liver, eye, skin, lungs and oesophagus, kidneys, reproductive organs and bone marrow. No dedicated tissue distribution studies in pregnant animals were conducted and the extend of placental transfer of lazertinib into fetal tissues is thus unknown. However, developmental toxicity is observed in animals indicating that lazertinib crosses the placenta. Furthermore, excretion in milk in animals has not been investigated.

2.5.3.4. Metabolism

Metabolism of lazertinib was characterised *in vitro* in hepatocytes as well as *in vivo* in plasma, blood and excreta samples from rats, dogs, and humans following oral administration. *In vitro*, GSH conjugation (Phase 2 metabolism via *GSTM1*) with the 2-propene amide moiety of lazertinib was the major metabolic pathway in all three species. *In vivo*, lazertinib was extensively metabolised in all three species before excretion, mainly via feces, with comparable qualitative metabolic profiles between species and no human specific metabolites. The parent compound was the major circulating entity in all species. In human plasma, the most abundant circulating metabolites were GSH adducts and related catabolites, with M12 (+cysteinylglycine on the 2-propene amide moiety; 19.6-23.6%) and M14 (+cysteine on the 2-propene amide moiety; 9.06-12.3%) being present at levels >10%. Another human plasma metabolite was M15 (fused morpholino benzimidazole with net loss of C_3H_2O from parent drug; 6.6-8.0%). GSH-related metabolites also contributed prominently to the metabolite profile in plasma in rats and dogs. The 2-propene amide moiety is the responsible pharmacophore of lazertinib mediating pharmacological activity via binding to EGFR. Phase II GSH conjugation forms adducts at the 2-propene amide moiety, thereby rendering the GSH derived metabolites pharmacologically inactive. Furthermore, phase II GSH conjugation increases clearance of the compound thus acting as a de-toxification mechanism. In spite of the higher levels of GSH-derived metabolites in humans compared to animals, no further characterisation is considered required. In addition, M7 (*N*-demethylation) and derivates thereof were observed as one of the more abundant

circulating entities in dogs in addition to GSH-related metabolites. M7 was however only identified as a minor metabolite in rats and humans. M15 was identified as a circulating metabolite in rats after a single oral dose of 10 mg/kg lazertinib, resulting in a ratio between M15 and unchanged lazertinib of 0.076 (FK13613). This ratio was 0.196 and 0.133 in *GSTM1* non-null and *GSTM1* null patients, respectively, after a single oral dose of 240 mg (FK13695), indicating higher ratios in humans. However, when calculating equivalent M15 exposure levels using the AUC_{Day91} values from the 13-weeks repeat dose study in rats and correcting for the exposure ratio to M15 of 0.076, higher exposure rates seems to be achieved in rats compared to those calculated in patients, i.e. up to 2,288 ng-eq*hr/mL at the 50 mg/kg/day dose level in rats (8351378) compared to mean M15 exposure rates of 980 ng-eq*h/mL (AUC_{0-24h}) after repeated daily dosing (240 mg/day) in patients (FK13698). Thus, human exposure to M15 appears to be covered by the levels estimated in the 13-week repeat dose toxicology study in rats. M15 was also detected in feces at 2.99% in dogs, 5.62% in rats and 4.68%/3.29% in *GSTM1* null/non-null patients, respectively. In addition, M15 is significantly modified structurally relative to lazertinib, with the core EGFR-binding motif (2-propene amide) eliminated, thus making M15 unlikely to be pharmacologically active. No further characterization of M15 is considered warranted. Overall, the rat and dog appear to be relevant non-clinical species based on the metabolism profiles.

2.5.3.5. Excretion

Excretion of lazertinib and metabolites occurred primarily via feces in dogs, rats and humans. In bile-duct cannulated rats, the majority of the recovered radioactivity was in bile followed by feces. Only minor excretion in urine (≤5%) was observed in all three species while significant radioactivity was observed in expired air in rats (16%). Only low amounts of parent compound were found in feces samples from dogs and rats, supporting extensive metabolism before excretion. Overall, the excretion profile in dogs, rats and humans were comparable.

2.5.3.6. Pharmacokinetic drug interactions

In vitro studies showed that direct GSH conjugation of lazertinib was the major metabolic pathway, which is mediated primarily by GST M1-1. Three isoforms of GST M1-1 have been identified and the genotypic effect on systemic exposure to lazertinib and its metabolites in humans is further discussed in the clinical section. Further, in vitro data showed that lazertinib is also metabolized by human CYP isozymes, predominantly CYP3A4 (88.4%) with CYP2C9 (3.46%), CYP1A2 (2.38%), and CYP2A6 (1.72%) contributing to a minor degree. While multiple human UGT isoforms were able to metabolize lazertinib *in vitro*, glucuronidation was not demonstrated to be an important metabolic pathway in *in vitro* or *in vivo* metabolism studies. As discussed in the metabolism section, GSH conjugation forms a major pathway in all species, with metabolites M12 and M14 being present above 10 % in humans. The applicant did however not perform any further DDI characterisation of the GSH-related metabolites. This is considered acceptable as no interactions with GSH-related metabolites are expected based on the increased polarity and excretion of GSH-conjugated compounds and no further DDI studies are warranted for these metabolites. In dogs, metabolite M7 was identified as a major CYP-derived metabolite and therefore, it was further characterised for potential DDI. As discussed above, metabolite M7 is however only a minor metabolite in rats and humans, and it is therefore acceptable that a complete DDI characterisation has not been conducted for M7. *In vitro* studies indicated that lazertinib free base is an inhibitor of CYP3A4 and UGT1A1, while it was shown that M7 is not an inhibitor of human CYP enzymes up to the highest dose tested (IC_{50} >20 µM). Lazertinib is also a substrate of the P-gp transporter, and showed a strong inhibitory effect on BCRP and OCT1. The potential for the induction of CYP1A2, CYP2B6, and CYP3A4 by lazertinib was also evaluated in human

hepatocytes. While no induction was observed for CYP1A2 and CYP2B6, the *in vitro* study indicated some induction of CYP3A4. A clinical DDI study however showed no meaningful induction of CYP3A4 at clinically relevant concentrations (See clinical section).

Due to the differences in types of compounds and mechanism of action between lazertinib (small molecule) and amivantamab (monoclonal antibodies), no interactions are expected when the compounds are co-administered. Further, no DDI effects were seen in the H1975/HGF tumor-bearing mice pharmacology study (DD21087) when the compounds were co-administered, as plasma exposure values of the compounds measured during co-dosing was not affected by either compound. It is therefore accepted that no further DDI studies are conducted.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Lazertinib administered orally in a single dose was tolerated up to 600 mg/kg/day (MTD). Significant mortality occurred at 2000 mg/kg/day (highest administered dose) and was associated with significant body weight loss, which correlated with decreased food consumption.

2.5.4.2. Repeat dose toxicity

The toxicological profile of lazertinib was assessed in pivotal repeat-dose oral 4-week and 13-week toxicity studies in SD rats and Beagle dogs. In rats, the main findings consisted of transient but significant body weight loss in male rats and effects on duodenum, skin, reproductive organs, eye, liver and kidney were observed. Non-adverse clinical observations included clear oral discharge, thinning haircoat over the entire body and rough, discoloured haircoat/skin (nose) in animals administered ≥50 mg/kg/day. Significant decrease was noted of RBC parameters (RBC, HCT, HGB) and increased WBC and neutrophils/monocytes in both sexes. Histopathological adverse changes included liver (Kupffer cell hypertrophy/single cell necrosis accompanying increase of ALT and AST), kidney (papillary necrosis), duodenum (blunting/fusion of villi) and testis (tubular degeneration). In dogs, the main findings were significant body weight loss at highest dose level administered (20 mg/kg/day app. 2.3 x clinical exposure) and effects on eye, lung, kidney, testis, jejunum and oesophagus. Non-adverse clinical observations included excessive salivation and an increased incidence of liquid faeces at dose levels ≥10 mg/kg/day. Macroscopic findings included discoloured lung lobe with histopathological correlates of moderate hyperplasia of alveolar type II cells and slight chronic/active inflammation, and large mediastinal lymph node with histopathological correlates of moderate hyperplasia of lymphocytes and slight acute inflammation. Histopathological adverse findings consisted of inflammation of the renal papillae (2 mg/kg/day), atrophy of the oesophageal epithelium (≥4 mg/kg/day), inflammation/hyperplasia in the lung and other organs and blunting/fusion of villi in the jejunum (8 mg/kg/day). Lung findings persisted in recovery animals.

Target organs for toxicity were similar between species and comprised of skin; lung; kidney; eye; gastrointestinal; reproductive organ; liver; and hematopoietic system in both species. In addition, the heart was considered a target organ in dog alone occurring at clinically relevant exposures. These findings were generally dose-dependent and many were reversible or showed a trend towards reversibility. Persistent effects were indicated especially in rats in skin/subcutis mandibular lymph node liver, testis, epididymis, marrow, eye and rectum, and in lungs in dogs.

Mortality considered related to lazertinib occurred in seven animals in the pivotal repeat dose toxicity studies at exposure levels 2-5.2x exposure at recommended human dose; five female rats at 50 and

100 mg/kg/day and two male dogs at 8 and 20 mg/kg/day. Clinical findings preceding deaths in rats included: body weight loss, squinting of eyes, piloerection, dehydration, discoloured faeces, porphyrin stains around nares, and/or scabs on hind legs (deep red and sensitive to touch), thin and hunched appearance, swollen/discoloured periorbital region, clear oral discharge, discoloured skin (nose), thickened eyelids and rough haircoat. Histopathological findings included: minimal tubular dilatation and papillary necrosis of the kidney; acanthosis, erosion/ulceration, mixed cell inflammation, hair follicle degeneration and exudate of the skin/subcutis, moderate decreased corpora lutea of the ovary, moderate atrophy of the uterus and vagina and moderate vaginal exudate, necrosis of lymphocytes in the thymus, hypercellular femoral and sternal bone marrow, corneal erosion/ulcer of the eye, epidermal hyperplasia and chronic/active inflammation in the eyelids. Findings preceding deaths in dogs comprised hypoactivity, shivering, dehydration, hyperthermia, abdominal splinting; markedly increased cardiac troponin I with microscopical correlates cardiac of necrosis, numerous ventricular premature complexes, thin appearance, hunched posture, lateral recumbency with signs of moderate muscular atrophy of neck/shoulders, fast loss of body weight and difficulty maintaining weight with food supplementation, changes in biochemical parameters consistent with inflammation, macroscopic findings in the form of discoloured lung lobe and large mediastinal lymph node correlated with histopathological observations of moderate hyperplasia of alveolar type II cells and slight chronic/active inflammation and moderate hyperplasia of lymphocytes and slight acute inflammation.

All observations in dead animals were consistent with general deterioration of condition and effects on identified target organs. Especially in the 13- week repeat-dose dog study, marked deterioration of condition in surviving animals administered lazertinib was noted; in addition to a significant negative effect on body weight and food consumption in dogs at 8 mg/kg/day (high dose group), there were 3 events in the control groups (struggling during dosing and thin) vs 14 in lazertinib group (incl. lateral recumbent, hypoactive, muscular atrophy in neck and shoulders and hunched posture) which were indicative of the overall state of condition post administration of lazertinib.

2.5.4.3. Genotoxicity

Lazertinib was shown to be negative in an in vitro bacterial reverse mutation assay and a chromosome aberration assay as well as in an in vivo Rat Bone Marrow Micronucleus Assay according to ICH S2.

Table 2: Overview of genotoxicity studies with lazertinib free acid

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results positive/negative/equivocal**
Gene mutations in bacteria GLP (G115167)	Salmonella typhimurium (histidine auxotrophic strains TA98, TA100, TA1535, TA1537), Escherichia coli (tryptophan auxotrophic strain WP2uvrA)	0, 2.5, 8, 23, 70, 200 µg/plate +/- S9[a]	Negative
Gene mutations in mammalian cells GLP (G115168)	CHL-cells	6h +S9 0, 5, 10, 12.5, 15, 16 µg/mL 6h -S9 0, 0.5, 1, 2, 3, 4 µg/mL 22h -S9 0, 0.25, 0.5, 1, 2, 2.5 µg/mL	Negative
Chromosomal aberrations in-vivo	Rat (Crl:CD(SD)), micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg/day PO for 2 days	Negative

GLP (8333716)	6M/group		

[a] In the bacterial reverse mutation assay, 2 independent experiments were performed, with metabolic activation by Aroclor 1254-induced rat liver S9 in the first experiment and human liver S9 in the second experiment.

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted with lazertinib. As indicated in the ICH S9 guidance, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

2.5.4.5. Reproductive and developmental toxicity

2.5.4.5.1. Fertility and early embryonic development

A dedicated fertility and early embryonic development (FED) study were conducted in Sprague-Dawley rats. Lazertinib showed effects on female fertility parameters, including decreased number of oestrus cycles and corpora lutea as well as increase in post-implantation loss. Although no dose-response relation was observed for changes in corpora lutea, the numbers were significantly decreased compared to concurrent controls at all dose levels. Overall, non-clinical data from the FED study showed treatment-related effects on female fertility at all dose levels occurring at exposure margins of 0.5 compared to the human recommended dose. Furthermore, sperm motility was decreased in males at dose levels corresponding to an exposure margin of <0.6 (extrapolated data; underestimation) to the recommended human dose level. Impaired fertility is a known class effect of EGFR inhibitors and has been included in the RMP as a known effect of lazertinib.

2.5.4.5.2. Embryo-foetal development

The potential impact of lazertinib on embryo-foetal development (EFD) was investigated in Sprague Dawley rats and New Zealand White rabbits. In pregnant rats, lazertinib caused maternal toxicity in the form of decreases in body weight and food consumption. Developmental effects in rat offspring were limited to a decrease in foetal weights with a corresponding reduction in gravid uterine weight. Malformations in the form of fused mandible/zygomatic arch were observed in the rabbit EFD study with a higher incidence in all treated groups as compared to controls and compared to historical controls, though without a clear dose-response relationship. Malformations occured at or below clinically relevant dose levels when compared to the human recommended dose of 240 mg/kg and thus lazertinib treatment may cause developmental toxicity in humans. Prenatal and postnatal development, including maternal function

Prenatal and postnatal development studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer according to ICH S9 guidance, and have not been carried out for lazertinib.

2.5.4.5.3. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Juvenile toxicity studies were not conducted as lazertinib is intended for the treatment of adults.

2.5.4.6. Toxicokinetic data

Lazertinib TK data from the pivotal repeat-dose toxicity studies and DART studies are summarized in Table 3. Exposure to lazertinib generally increased dose-proportionally in the general repeat dose toxicology studies in rat and dog. In the rabbit EFD-study, lazertinib generally increased greater than dose-proportionally. For further evaluation of the TK in the repeat dose toxicity studies see the PK section.

Table 3: Integrative Summary of C_{max} and AUC Parameters for Lazertinib Across Toxicology Studies

Study	Day	Dose (mg/kg/day)	Male		Female	
			Mean C_{max} (ng/mL)	Mean AUC_{0-24h} (h·ng/mL)	Mean C_{max} (ng/mL)	Mean AUC_{0-24h} (h·ng/mL)
Rat 4-week GLP toxicity (8333736): Sprague-Dawley rats (N=6/sex/group and 3/timepoint) received lazertinib free base.	Day 1	25	591	7,070	726	9,330
		50	984	13,700	785	14,800
		100	1,270	23,000	1,080	23,300
	Day 28	25	345	4,500	477	6,670
		50	1,290	20,200	1,290	21,900
		75 [a]	1,410	24,900	1,800	33,200
Dog 4-week GLP toxicity (8333737): Beagle dogs (N=3 to 5/sex/group) received lazertinib free base.	Day 1	5	734 ± 330	5,690 ± 756	1,010 ± 309	8,530 ± 3,780
		10	1,450 ± 255	15,000 ± 2,590	1,390 ± 738	14,700 ± 3,590
		20	1,520 ± 168	22,700 ± 2,230	1,790 ± 284	18,200 ± 1,150
	Day 28	5	716 ± 184	7,940 ± 272	625 ± 78.4	6,400 ± 1,010
		10	1,180 ± 164	11,700 ± 963	829 ± 165	9,690 ± 2,790
		20	2,400 ± 1,280	31,500 ± 11,900	1,280 ± 226	14,900 ± 1,300
Rat 13-week GLP toxicity (8351378): Sprague-Dawley rats (N=6/sex/group and 3/timepoint) received lazertinib mesylate salt.	Day 1	12.5	319	3,910	413	5,220
		25	618	7,800	575	9,150
		50	869	11,800	962	17,000
	Day 91	12.5	449	5,980	730	9,280
		25 [b]	835	11,600	1,210	17,500
		50	1,570	26,400	1,990	33,800
Dog 13-week GLP toxicity (8351379): Beagle dogs (N=3 to 5 /sex/group) received lazertinib mesylate salt.	Day 1	2	540 ± 46.5	2,960 ± 112	376 ± 102	2,180 ± 273
		4	654 ± 460	4,610 ± 2,220	625 ± 96.1	4,310 ± 371
		8	1,350 ± 364	10,300 ± 1,630	805 ± 207	9,330 ± 1,620
	Day 91	2 [c]	280 ± 23.4	3,380 ± 837	219 ± 29.6	2,400 ± 434
		4	520 ± 172	5,780 ± 1,720	520 ± 56.6	5,500 ± 1,020
		8	975 ± 176	14,600 ± 2,080	897 ± 257	11,700 ± 1,180
Rat fertility and early embryonic development GLP toxicity		7.5	Extrapolated from FED rat study (8383617, dams and foetuses) and 13-week repeat dose rat study (8351378, males)			

(8383615): Pregnant Sprague-Dawley rats and male rats (N=22/sex/group) received lazertinib mesylate salt.		15				
		30				
Rat embryo-fetal development GLP toxicity (8383617): Pregnant Sprague-Dawley rats (N=5 to 6/group) received lazertinib mesylate salt from GD 6 to 17.	GD 17	7.5	-	-	230	2,980
		30 [d]	-	-	713	11,100
		60	-	-	1,790	28,000
Rabbit embryo-fetal development GLP toxicity (8383620): Pregnant New Zealand White rabbits (N=23/group) received lazertinib mesylate salt from GD 7 to 19.	GD 19	5	-	-	27.9 ± 9.45 (range:17.1-34.5)	108 ± 41.2 (range: 79.7-156)
		25 [e]	-	-	249 ± 65.0 (180-309)	1,000 ± 168 (815-1140)
		45 [f]	-	-	505 ± 285 (187-736)	3,240 ± 2,210 (1890-5790)

TK analysis was done based on total drug concentrations.
- = not applicable; GD = gestation day; N = animal number; ± value indicated standard deviation
[a] Beginning on Day 21 of the dosing phase, animals were dosed at 75 mg/kg/day.
[b] NOAEL for both males and females.
[c] NOAEL for females only. A NOAEL was not established in males.
[d] NOAEL for both maternal and fetal toxicity.
[e] NOAEL for maternal toxicity.
[f] NOAEL for fetal toxicity.

2.5.4.7. Interspecies comparison and exposure margins to clinical exposure

Exposure multiples for the pivotal repeat-dose toxicity studies, fertility and early embryonic development and embryo-foetal development studies are presented below.

Safety margins based on systemic exposure at NOAEL or LOAEL at recommended human dose of 240 mg/kg/day were low to non-existing. This is expected and accepted due to the sought indication of lazertinib. Major target organs for toxicity were similar between species and were comprised of skin; lung; kidney; eye; gastrointestinal; reproductive organ; liver and hematopoietic system in both species. In addition, the heart was considered a target organ in dog alone. NOAEL was not determined for dog for up to 13 weeks of dosing, indicating that toxicity occurred at all dose levels tested. This was also the case for female rats in the FED study and litter of rabbits in the EFD study. Exposure margins based on LOAEL have been calculated where NOAEL's were not determined.

Clinically relevant exposures-levels were achieved in both species in the pivotal repeat-dose toxicity studies. Systemic exposure was highest in dogs compared to rats (app. 2-4-fold change).

Table 4: Animal-to-human Exposure Margins for Lazertinib

Species	GLP study	Dose (mg/kg/day)	Effect level	AUC24h (h·ng/mL)	Exposure multiple at MHRD of 240 mg
					Based on AUC[a]
Rat	4-week toxicity	25 (M) 25 (F)	NOAEL	4,500 6,670	0.7 1.0
Rat	13-week toxicity	25 (M) 25 (F)	NOAEL	11,600 17,500	1.8 2.7
Dog	4-week toxicity	*5 (M)* *5 (F)*	*LOAEL*	*7940* *6400*	*1.2* *1.0*
Dog	13-week toxicity	*2 (M)* 2 (F)	*LOAEL* NOAEL	*3380* 2400	*0.5* 0.4
Rat	Fertility and early embryonic development	7.5 (M fertility) *7.5 (F fertility)*	NOAEL *LOAEL*	5980[#] *2980[¤]*	<0.9 *0.5*
Rat	Embryo-foetal development	30 (F+foetal)	NOAEL	11100	1.7
Rabbit	Embryo-foetal development	25 (F) *5 (foetal)*	NOAEL *LOAEL*	1000 *108*	0.2 *0.02*

NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; MHRD = maximum human recommended dose; AUC; area under the curve; GLP; good laboratory practice; M = male animals; F = female animals

[a]Animal-to-human exposure margins are based on the human steady-state AUC0-24h value (6,541.96 h.ng/mL) at the recommended Phase 2 dose 240 mg of the Phase 1/2 study (Table 11.1.2.3 in 73841937NSC2001).

[#]AUC0-24 extrapolated from 13-week repeat dose in male rats at lowest dose administration 12.5 mg/kg/day

[¤]AUC0-24 extrapolated from FED study in female rats at dose administration 12.5 mg/kg/day

2.5.4.8. Tolerance

No dedicated local tolerance study was conducted as lazertinib is intended to be administered orally. The applicant did however provide two GLP compliant studies to investigate the potential for sensitization and eye irritation. While no eye irritation was observed in the in vitro assay, lazertinib was classified as a skin sensitizer based on a local lymph node assay with female CBA/J mice.

2.5.4.9. Other toxicity studies

2.5.4.9.1. Antigenicity

Antigenicity studies were not conducted.

2.5.4.9.2. Immunotoxicity

There was no evidence of immunotoxicity in repeat-dose toxicity studies. Further, the mode of action of lazertinib does not raise a concern for potential immunotoxicity, and it is therefore accepted that no further data is provided for the endpoint.

2.5.4.9.3. Dependence

No dedicated studies were conducted to investigate dependence potential of lazertinib. Though lazertinib penetrates the blood brain barrier, data from general toxicity rat and dog studies and a rat central nervous system safety pharmacology study did not indicate a potential for dependence, and no further data is considered warranted for this endpoint.

2.5.4.9.4. Studies on metabolites

As described in the Pharmacokinetics section, no human specific metabolites have been identified. Metabolite M7 was identified as a significant metabolite in dogs and was correspondingly investigated in PD, PK and toxicology studies. As M7 is only a minor metabolite in humans, no further studies are warranted. M15 has however been identified as a more abundant metabolite in humans compared to rats and dogs, and an OC has been raised in the Pharmacokinetics sections for the applicant to discuss the relevance of further non-clinical data to characterise M15.

2.5.4.9.5. Studies on impurities

Two impurities, JNJ-75182640 and JNJ-73858434, were detected in lazertinib and both have been included in the drug substance specification at levels of NMT 0.3% (i.e. above Q3A qualification limits), whereas only JNJ-75182640 is included in the drug product specification at NMT 1.0%.

JNJ-75182640 is the dimer of the drug substance forming a quaternary ammonium bridge in the dimerization reaction. In silico modelling using Lhasa Nexus Derek (6.3.0) and Sarah (3.3.0) reveals no alert for in vitro bacterial mutagenicity for the structure and aligns with the negative result obtained for lazertinib in a battery of GLP compliant genotoxicity testing. The impurity is therefore considered a non-mutagenic impurity. In silico modelling was performed by the assessor to demonstrate if the CH2-N+-CH2 bridge formed via dimerization would give rise to new structural alerts compared to the API. The only two new alerts were for cardiovascular risk as a hERG pharmacophore as well as for irritation due to the quaternary ammonium group. A hERG assay was performed for the parent compound and cardiovascular safety is already sufficiently addressed for the lazertinib. The specified level of JNJ-75182640 is not considered to add significantly to the cardiovascular risk of the API. At the specified amount of the impurity, the alert for irritation is not considered of concern, also as the drug product is intended for oral administration. The dimer impurity of the API is therefore considered covered by the toxicological data for the API. Nonetheless, the applicant performed a stand-alone 4-week repeat dose GLP study in rats including TK measurements to qualify the dimer (Study TOX14158). Lazertinib mesylate monohydrate was administered at a dose level corresponding with the NOAEL in rats either as lazertinib without the impurity or including 1.4% of the lazertinib dimer impurity, corresponding to a dose of 0.35 mg/kg/day. The study demonstrated that lazertinib exposure was not affected, and, as already predicted using in silico tools, no new findings were identified in the in vivo study that could be attributed to the lazertinib dimer impurity. Correlating the rat NOAEL for the dimer to the daily human recommended dose of 289 mg (for the mesylate monohydrate salt) and a body weight of 50 kg, this corresponds to a human dose of 5.8 mg/kg, whereby the impurity is considered toxicologically qualified at level up to 0.35/5.8 = 6.0%. Overall, a specification level for JNJ-75182640 of NMT 1.0% is considered toxicologically qualified.

JNJ-73858434 is a process related impurity and an intermediate in the last step of the synthesis of lazertinib. It is considered API-like, only containing an alkyl halide as a new phamacophore instead of the 2-propene amide moiety. Using in silico modelling, JNJ-73858434 is predicted to be an in vitro bacterial genotoxic compound using both Lhasa Nexus Derek (6.3.0) and Sarah (3.3.0) due to the alkyl halide toxicophore, and the impurity is therefore considered a class 3 mutagenic impurity according to ICH M7. In module 3.2.S.3 Impurities, the applicant arrives at the same conclusion for in silico modelling, however, it is non-mutagenic based on “expert judgement”. No further justification or detailed expert judgement is provided to support this. A reference is given to a negative Ames test (TOX14202), however, the study has not been submitted. According to ICH S9, limits for genotoxic impurities according to ICH M7 are however not appropriate for pharmaceuticals intended to treat patients with advanced cancer. Therefore, the missing data in support of determining the impurity as non-mutagenic is not further pursued. No other new structural alerts were identified and the general

toxicity profile apart from mutagenicity is assumed to be covered by the toxicity profile of the parent compound. JNJ-73858434 was furthermore qualified as part of the 13-week repeat dose study in dogs (study 8351379), as JNJ-73858434 was present up to 0.45% in toxicology batches according to the certificate of analysis. The NOAEL identified in the study was 4 mg/kg/day, and thus the NOAEL for the impurity is 0.018 mg/kg/day. Assuming a daily human recommended dose of 5.8 mg/kg, this corresponds to an impurity level of 0.31%. Based on in silico data and the qualification as part of the impurity profile in the general toxicity test in dogs, the specified level of JNJ-73858434 at NMT 0.30 % can be considered toxicologically qualified.

In addition to the qualification of the two specified impurities, the applicant expressed concern for the potential polymerization of lazertinib and the impact on the safety profile, though the production process has been optimized by the applicant to reduce the level of polymerization, which is why the polymer impurity of lazertinib is not specified. Nonetheless, an additional stand-alone 4-week GLP study in rats was conducted to investigate the impact on toxicity of lazertinib containing 4.2% of the polymer impurity compared to lazertinib without polymer impurity (Study TOX16062). No effect was observed on the exposure concentration of lazertinib or the toxicity profile in the rat study. Based on the NOAEL in rats of 25 mg/kg/day, a level of the polymer impurity JNJ-73841937-ZCY of 18.1% is considered toxicologically qualified. Based on structural considerations, the polymer of lazertinib is not expected to contain any new toxicophores than the dimer impurity, and the in silico assessment of the dimer impurity is therefore considered to cover the expected toxicity of the polymer. Overall, the polymer impurity of lazertinib is considered of low concern based on both in silico and in vivo considerations.

2.5.5. Ecotoxicity/environmental risk assessment

The ERA report was performed according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) and the associated Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev. 1). The ERA comprised a summary of the main study results of Phase I, Phase II Tier A and Tier B, and PBT assessment of lazertinib.

All studies were performed in compliance with GLP and included a QA statement and were based on validated methods. OECD studies 107 + 123, 106, 301B, 308, 201, 210, and 209 were performed at Charles River Laboratories Den Bosch BV in 's-Hetogenbosch, NL. OECD study 211 was performed at Charles River Laboratories, Veszprém, HU. OECD study 305 was performed at ibacon GmbH, Rossdorf, DE.

Several tests might have been influenced by low water solubility and ionic nature of lazertinib - the concentrations in the aqueous phase cannot be measured analytically with sufficient accuracy for substances having low water solubility and being highly charged. However, there is no reason to question the results due to poor analytical performance as further assessment were triggered (e.g. BCF for bioaccumulation) or the results could be hardly influenced (soil adsorption results in OECD 106 test – see further comments for this test).

Summary of main study results

Table 5: Summary of study results

Substance (INN/Invented Name): Lazertinib			
CAS-number (if available): 1903008-80-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107/123	2.1 (pH 5) 3.7 (pH 7) 5.1 (pH 9)	Potential PBT: (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.7 to 5.1	Possible B
	BCF_{SSL} BCF_{KL}	302 L/kg_{ww} 292 L/kg_{ww}	not B
Persistence	ready biodegradability	not readily biodegradable	
	DT_{50} Values are derived from the OECD 308 and have been recalculated to 12°C	$DT_{50water}$ = 5.0 to 13d $DT_{50sediment}$ = 47 to 102d $DT_{50system}$ >>10,000 d	vP
Toxicity	NOEC (Fish, early life stage toxicity, OECD 210) CMR	19 µg/L (> 10 µg/L) Reprotoxicant (R in CMR)	not T T
PBT-statement:	Lazertinib is considered to be not PBT, nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, default	1.2	µg/L	≥ 0.01 threshold: Y
$PEC_{sw,\ refined\text{-}NSCLC+SimpeTreat(v.41)}$	0.0066	µg/L	N
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Soil 1 = Sandy loam Soil 2 = Sandy loam Soil 3 = Loam Sludge 1 = Tilburg Sludge 2 = Aa&Mas	OECD 106	$K_{oc,\ soil\ 1}$ = 265069 L/kg_{oc} $K_{oc,\ soil\ 2}$ = 1028426 L/kg_{oc} $K_{oc,\ soil\ 3}$ = 538548 L/kg_{oc} $K_{oc,\ sludge\ 1}$ = 2621 L/kg_{oc} $K_{oc,\ sludge\ 2}$ = 2770 L/kg_{oc}	 KOC (sludge) < 10000 L/kg Terrestrial risk assessment not considered in Tier II B
Ready Biodegradability Test	OECD 301B	7% biodegradable	Not readily biodegradable
Aerobic Transformation in Aquatic Sediment systems Sediment 1 = Silty clay Sediment 2 = Sand	OECD 308	$DT_{50,\ water}$ = 6/ 3.7 d $DT_{50,\ sediment}$ = 48 / 22 d $DT_{50,\ whole\ system}$ = >10000 / 21 d shifting to sediment = 74/57% CO_2 = <1% NER = 39/54%	DT50s at 20°C 1 / 2at day 1 DAT/3 DAT. As lazertinib was present in the sediment at >10% by day 14, a Chironomid study was conducted at test end at test end

		Transformation products >10% = (Y), TP4 = 11/17 %: TP5 = 15/10 % DT_{50} : TP4: 3250/>10000 d TP5: 354/212 d			
Phase IIa Effect studies					
Study type	**Test protocol**	**Result**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Rahidocelis subcapitata*	OECD 201	NOEC / EC_{10}	111 129	µg/L	Growth rate Growth rate
Daphnia magna, Reproduction Test	OECD 211	NOEC	29	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC / EC_{10}	19 >429	µg/L	Growth, most sensitive endpoint
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC / EC_{10}	32000 189000	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*Cyprinus carpio*	OECD 305	BCF_{SSL} BCF_{KL}	219.9 - 351.6 292	L/kg_{ww} L/kg_{ww}	%lipids: 5% %lipids: 5%
Sediment dwelling organism/*Chironomus riparius*	OECD 218/219	NOEC / EC_{10}	8 29	mg/kg_{dwt}	Developement rate endpoint(s)

The following uncertainties have been identified and will be addressed as post-approval measures:

Report no. 20311209 – Ref 18: Aeropbic transformation in aquatic sediment (OECD 308). The data on the identified transformation products TP-4 and TP-5 in water sediment (OECD 308) will be submitted in an updated ERA report as a post-approval commitment **(Recommendation).**

- Report no. 166781233 – Ref 20: Bioaccumulation in fish (OECD 305) and Report no. 21/330-124DA – Ref 22: Reproduction test on Daphnia (OECD 211). The updated ERA report will also include the recalculated bioconcentration factors (OECD 305) and the determination of no observed effect concentration for *Daphnia* (OECD 211), which both were accepted within the present assessment **(Recommendation).**

Precautionary and safety measures to be taken for administration, disposal and labelling are included in Section 6.6 in the Summary of Product Characteristics (SPC) and Section 5 of the Package Leaflet (PL). Lazertinib is suggested not to be a PBT substance.

2.5.6. Discussion on non-clinical aspects

Pharmacology

In vitro and *in vivo* pharmacology studies with lazertinib sufficiently demonstrated the mechanism of action and proof of concept in relevant models of disease in transgenic mice. Lazertinib demonstrated potent inhibition of EGFR harbouring either single mutations (*del19, L858R or T790M*) and double mutations (*L858R/T790M, or del19/T790M*), while binding with less affinity to the wild type EGFR. Lazertinib treatment resulted in significantly reduced tumor growth and tumor regression *in vivo* in NSCLC and subcutaneous xenograft mouse models expressing EGFR *Del19* and *L858R/T790M* mutations. Furthermore, lazertinib demonstrated significant brain tumor growth inhibition as well as complete tumor regression in an *in vivo* mouse brain tumor model. While it was shown to be more specific with regards to mutant types of EGFR than osimertinib, pharmacologically mediated toxicity

was still observed in the general toxicity studies indicating some interaction with wild type EGFR. The observed toxicities were associated with tissues expressing EGFR rather than tissues of distribution. Metabolite M7 was identified as a significant metabolite in dogs and was therefore pharmacologically characterized *in vitro*. While it did demonstrate pharmacological activity, it was weaker than for lazertinib itself. No clinically relevant off-target binding was observed for lazertinib. A battery of *in vitro* and *in vivo* safety pharmacology assays for effects on cardiovascular, respiratory, or central nervous systems was conducted for lazertinib. In the non-clinical studies, no concerns for cardiovascular, respiratory, or central nervous systems risks were identified. TKIs are however known for cardiovascular and lung-related risks such as venous thromboembolic (VTE) events and interstitial lung disease (ILD)/pneumonitis, and these risks have been adequately described in the relevant section of the RMP and SmPC. A pharmacological study with lazertinib and the EGFR/MET bispecific antibody amivantamab was conducted to investigate the effect of combination therapy on anti-tumor activity in a xenograft mouse model expressing the *L858R/T790M* mutation. The combination therapy shows superior efficacy compared to the treatment with the single agents in terms of tumor growth inhibition and increased survival, and non-clinical data could support a clinical benefit of the combination therapy with amivantamab plus lazertinib.

Pharmacokinetics

The analytical methods in support of the pivotal toxicology studies were GLP-compliant, fully validated and appear robust and adequate for the purpose of the studies. Differences in oral bioavailability was observed, as it was high in mice, moderate in rats and moderate-to-high in dogs. The absolute bioavailability has not been determined in humans, however, as limited excretion of unchanged parent compound was observed in humans, it is assumed that lazertinib is nearly fully absorbed. At the 24-hour postdose collection of plasma, the apparent half-live of lazertinib in rats and dogs after oral administration ranged from 7.4-10.4 h and 8.3-11 h, respectively. Meanwhile, the "terminal half-live" of lazertinib in humans following oral absorption was 70.4 h. While there are differences in the reported half-lifes between species, this is accounted for by methodological differences in PK parameter estimation across the studies rather than differences in PK profile between animals and humans. Overall, the differences in reported half-lifes between species is not considered of concern. Lazertinib demonstrated a similar high protein binding across species. While lazertinib targets pigmented tissue such as the uveal tract and pigmented skin, it was not found to be phototoxic. Distribution to brain tissue was confirmed across species. *In vivo* PD mouse model distribution and exposure of brain tumor tissue was demonstrated correlating with a pharmacologically mediated increased brain tumor growth inhibition. No distribution studies were performed to investigate placental transfer of lazertinib, nor excretion in milk.Only distribution to male reproductive organs was investigated, but not to female reproductive organs. Lazertinib however demonstrated developmental and reproductive toxicities in rats and rabbits, confirming fetal exposure and reproductive organs as target tissues. Qualitatively, the metabolism profile was comparable between species, and no human-specific metabolites were identified. Metabolite M7 was determined as a significant metabolite in dogs and was thus further characterized for PK and safety profile, however, it was found to be a minor metabolite in rats and humans. Conversely, GSH-conjugation was the major pathway in humans leading to pharmacologically inactivated metabolites with increased clearance. Common for all species, lazertinib is mainly excreted via feces, with only minor amounts detected in urine. Low amounts of excreted unchanged parent drug supports an extensive metabolism before excretion. DDI *in vitro* studies demonstrated that lazertinib is an inhibitor of CYP3A4 and UGT1A1 enzymes as well as BCRP and OCT1 transporters, while lazertinib is itself a substrate for the P-gp transporter. Results from *in vivo* DDI adequately address the *in vitro* findings and are included in the SmPC section 4.5. Overall, the PK profile in rats and dogs appears to be well described, and comparisons with human PK data supported the rat and dog as relevant non-clinical species for testing toxicity.

Toxicology

The choice of rats (Sprague-Dawley) and dogs (Beagle) as relevant toxicological species was adequately justified. EGFR TKI's as a class are known to affect many organs and tissues containing epithelial cell lineages, with changes spanning from mild epithelial atrophy to degenerative erosions, inflammation, and necrosis. In both rat and dog oral repeat-dose toxicity studies of lazertinib most observations were consistent with these effects and could be explained with the well-established mode of action and pharmacology of lazertinib with supportive clinical knowledge provided by already marketed EGFR TKI's.

Mortality considered related to lazertinib occurred in seven animals in the pivotal repeat dose toxicity studies at exposure levels 2-5.2x clinical exposure at recommended human dose; five female rats at 50 and 100 mg/kg/day and two male dogs at 8 and 20 mg/kg/day. Clinical and histopathological findings preceding deaths in rats and dogs were related to target toxicities and general well-being of the animals, including body weight loss and organ toxicities of skin, lungs, liver, kidney, GI tract, reproductive organs and hematopoietic system. All of the systemic toxicities observed in animals have also been observed in humans either with lazertinib or other marketed EFGR TKI's. Most of the toxicities are described in the RMP and SmPC and considered manageable in the clinical setting. Effects that were observed in animals following treatment with lazertinib, but have not been identified in clinical trials with lazertinib include effects related to kidney, eye and reproductive organs.

Kidney effects have been described for a few other EGFR TKI's including increase in fluid retention or hypokalaemia. Kidney effects are uncommon with lazertinib, are, if occurring, not expected to be serious and are considered manageable in the clinic. In humans, lazertinib has shown no significant adverse effect in the eye, but other EGFR TKIs have been associated with adverse ocular effects like conjunctivitis, blepharitis, dry eye syndrome, trichomegaly, keratitis, uveitis, and corneal thinning and erosion. In accordance, ocular toxicity with lazertinib is recognised as a risk in humans and is adequately reflected in the SmPC and RMP.

With respect to the observed findings in reproductive organs in dogs and rats upon administration of lazertinib, similar observations have been made with other small molecule EGFR inhibitors, suggesting an effect on reproductive organs due to pharmacology. In support of this, EGF signalling has been implicated in the growth and proliferative effects of oestradiol on the uterine and vaginal epithelium (Levin 2003, Nelson 1991), while G-protein coupled receptor and EGF receptor cross-talk has been implicated in the modulation of steroid production in testis and ovary (Light 2013), and in oocyte maturation and ovulation (Hseih 2011). Adequate wording has, however, been included in the SmPC and RMP on the restriction of use in women of child bearing potential as well as men, to reflect the observed effects on reproductive and developmental effects observed both for lazertinib and other TKIs.

Lazertinib was not mutagenic or clastogenic in a standard battery of in vitro and in vivo tests at oral doses up to 2000 mg/kg/day. Further, carcinogenicity studies have not been conducted with lazertinib due to the sought indication, which is in accordance with relevant guidelines (ICH S9 Q&A document 2018 and ICH S5 (R3) 2020). This has been adequately reflected in section 5.3 of the SmpC. Of note, hyperplasia was observed in the 13-week repeat dose studies, affecting the lungs in dog and the skin in rat. However, these observations remain single occurrences and are not expected to be clinically relevant.

Decreased fertility is a known class effect of VEGFR inhibitors. A dedicated fertility and early embryonic study in Sprague-Dawley rat was conducted and showed, that lazertinib affects female fertility at exposure levels similar to the recommended human dose. Impaired female fertility was reflected by a decrease in the number of oestrous cycles and an increase in post-implantation loss resulting in a lower number of viable foetuses (decreased litter size). With regards to male fertility, one of 10 male

rats had greatly reduced sperm motility, but as a single occurrence could not be firmly linked to treatment with lazertinib. Nonetheless, lazertinib-related histopathology finding in the testis of seminiferous tubule degeneration in both rats and dogs (and the resulting reduction in luminal sperm in dogs) observed in the 4-week general toxicology studies at clinically relevant exposures confirm an infertility risk in males as well.

The potential impact of lazertinib on embryo-foetal development was investigated in Sprague Dawley rats and New Zealand White rabbits. In pregnant rats, lazertinib caused maternal toxicity in the form of decreases in body weight and food consumption. Developmental effects were limited to a decrease in foetal weights with a corresponding reduction in gravid uterine weight. The litter effect was considered a likely consequence of maternal toxicity and occurred at approximating 4x exposure at recommended human dose. The interpretation of the EFD rat study is supported. In pregnant rabbits, lazertinib induced overt maternal toxicity at the highest dose administered, including mortality associated with inappetence and reduced food consumption and body weight loss in the surviving dams. Developmental toxicity was observed as an increased incidence of a foetal skull bone anomaly (zygomatic arch fused to the maxillary process) in rabbit offspring at maternal exposure level well below the human clinical exposure at 240 mg. The findings in the EFD studies with lazertinib are consistent with the known consequences of the pharmacological inhibition of EGFR and are well described in the context of reproduction and embryonic development (Adamson 1990). Inhibition of EGFR signalling during early pregnancy or during organogenesis can lead to embryo lethality. In developmental toxicity studies in rats and rabbits with other marketed small molecule inhibitors of the EGFR pathway, an increase in embryo and foetal loss, decreased foetal weights, and foetal abnormalities has been reported at plasma concentrations similar or slightly above that in humans.

These findings on reproductive toxicology have been included in section 5.3 of the SmPC.

In general, low exposure margins based on systemic exposure at NOAELs or LOAELs were observed in animal studies, and corresponded to clinical exposures at or below the recommended human dose of 240 mg/kg/day. This is expected due to the pharmacological mode of action of lazertinib as a TKI, and the different target toxicities observed in animals correlate with the toxicity profile observed in humans, which is also known from other TKIs. Systemic exposure was highest in dogs compared to rats (app. 2-4-fold change).

In an in vivo distribution study, lazertinib was shown to primarily distribute to pigmented tissue, with long retention in the uveal tract. In vitro and in vivo phototoxicity studies however demonstrated no risk for skin and ocular phototoxicity. No risk for immunotoxicity or dependence was observed based on general toxicity studies. No dedicated local tolerance studies were conducted as lazertinib is intended to be administered orally, however, based on a murine local lymph node assay, lazertinib was classified as a skin sensitizer. Metabolites was considered sufficiently addressed in the PK section, however, an OC on metabolite M15 has been raised for potential further characterisation. Two impurities, JNJ-75182640 and JNJ-73858434, were included in the drug substance specification and the drug product specification up to NMT 1.0% and 0.3% respectively. The specified levels of impurities were adequately qualified using in silico predictions and in vivo testing.

Overall, the ERA report is evaluated as comprehensive and well-performed. All studies were performed in compliance with OECD test protocols and GLP and included a QA statement and were based on validated methods. The step-wise approach and the extend of testing agrees with the guidelines and fully supported. Two transformation products, TP-4 and TP-5, were found and exceeded 10% of applied radioactivity. Corresponding studies on these transformation products are ongoing.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of lazertinib to the environment.

The applicant will perform the following studies as recommendations:

-the data on the identified transformation products TP-4 and TP-5 in water sediment (OECD 308) will be submitted in an updated ERA report.

-the updated ERA report will also include the recalculated bioconcentration factors (OECD 305) and the determination of no observed effect concentration for *Daphnia* (OECD 211), which both were accepted within the present assessment.

Based on the environmental risk assessment studies submitted, it is agreed that Lazertinib is suggested not to be a PBT substance. It is, however, advised that lazertinib should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment. Furthermore, the applicant will submit an updated ERA no later than March 2025 (Recommendation).

2.5.7. Conclusion on the non-clinical aspects

Overall, *in vitro* and *in vivo* pharmacology studies with lazertinib sufficiently demonstrated the proposed mechanism of action and anti-tumour activity in models expressing EGFR *Del19* and *L858R/T790M* mutations. No off-target binding or safety risks were identified in non-clinical models. Non-clinical data support the marketing authorisation of amivantamab plus lazertinib used in combination.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant 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**

Table 6: Overview of Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
73841937 NSC3003 MARIPOSA	Ongoing Total enrolled: 1074 • ARM A: n=429 (efficacy); n=421 (safety) • Arm B: n=429 (efficacy); n=428 (safety) • Arm C: n=216 (efficacy); n=213 (safety)	Phase 3, randomized study of the combination of amivantamab and lazertinib versus osimertinib and versus lazertinib	<u>Phase 3</u> • Arm A: Amivantamab and lazertinib combination: ➢ Amivantamab 1050 mg for body weight <80 kg or 1400 mg for body weight ≥80 kg by IV infusion once weekly for 4 weeks (with a split dose on Cycle 1 Days 1-2) and then once every 2 weeks (subsequent cycles)	Efficacy: • PFS according to RECIST v1.1 by BICR (primary); OS, ORR, DOR, PFS2, TTSP, iPFS (secondary) Safety: • TEAEs, clinical laboratory, vital signs, physical examination, 12-lead ECG, LVEF

			➢ Lazertinib 240 mg administered orally once daily • Arm B: Osimertinib monotherapy ➢ Osimertinib 80 mg administered orally once daily • Arm C: Lazertinib monotherapy Lazertinib 240 mg administered orally once daily	
61186372 EDI1001 CHRYSALIS	Ongoing Total Enrolled: 380 Amivantamab + lazertinib: • Part 1: n=20 at RP2CD (first-line cohort) (efficacy) • Part 1 and 2: n=97 at RP2CD (safety) Amivantamab: • Part 1 and 2: n=380 at RP2D (safety)	Phase 1, first-in-human, open-label, dose escalation, dose expansion, multi-cohort study	<u>Part 1, Phase 1 Combination Dose Escalation</u> • Lazertinib and amivantamab combination: ➢ Lazertinib: 240 mg administered orally once daily ➢ Amivantamab:1050/1400 mg weight-based dosing[a] administered IV infusion once weekly for 4 weeks (with a split dose on Cycle 1 Days 1-2) and then once every 2 weeks (subsequent cycles). Part 2, Phase 1b Combination Dose Expansion Cohort E • Amivantamab and lazertinib combination at the RP2CD[b]	Efficacy: ORR according to RECIST v1.1 by investigator and BICR (primary), CBR, DOR, PFS, change in the sum of diameters of target lesions, OS, TTF (secondary). Safety: TEAEs, clinical laboratory, ECG, vital signs.
73841937 NSC1001 CHRYSALIS-2	Ongoing Total enrolled: 434 • Part 1 Dose Escalation: n=5 at RP2D (Safety) • Part 1 Combination Dose Escalation: n=3 at RP2CD (Safety) • Part 2 Combination Dose Expansion (Cohort A): n=162 (Safety) • Part 2 Combination Dose Expansion (Cohort B): n=69 (Safety) • Part 2 Combination Dose Expansion (Cohort C): n=87 (Safety) • Part 2 Combination Dose Expansion (Cohort D): n=108 (Safety)	Phase 1/1b open-label, dose escalation, dose expansion, multi-cohort safety and PK study	Part 1, Phase 1 Lazertinib Monotherapy Dose Escalation • Lazertinib 240 mg administered orally once daily Part 1, Phase 1b Combination Dose Escalation[c] • Lazertinib and amivantamab combination: ➢ Lazertinib: 240 mg administered orally once daily Amivantamab: 1050 mg for body weight <80 kg or 1400 mg for body weight ≥80 kg by IV infusion once weekly for 4 weeks (with a split dose on Cycle 1 Days 1-2) and then once every 2 weeks	TEAEs, clinical laboratory, physical examinations, vital sign, ECGs, ECOG performance status, ophthalmologic examination, chest x-ray, echocardiography or MUGA scan.

			(subsequent cycles) Part 2, Phase 1b Combination Dose Expansion Cohort A • Lazertinib and amivantamab combination at the RP2CD[b] Part 2, Phase 1b Combination Dose Expansion Cohort B • Lazertinib and amivantamab combination at the RP2CD[b] Part 2, Phase 1b Combination Dose Expansion Cohort C • Lazertinib and amivantamab combination at the RP2CD[b] Part 2, Phase 1b Combination Dose Expansion Cohort D • Lazertinib and amivantamab combination at the RP2CD[b]	
73841937 NSC2001/ YH25448-201	Ongoing Total enrolled: 83 Part A: n=5 at RP2D (safety) Part B: n=19 at RP2D (safety) Part C: n=43 centrally confirmed EGFRm in first-line (efficacy); n=43 for first-line cohort, n=54 for second-line cohort (safety) Part D: n=15 at RP2D (safety)	Phase 1/2, open-label, dose escalation, dose expansion, multi-cohort study	Part A Dose Escalation • Lazertinib monotherapy at 240 mg administered orally once daily Part B Dose Expansion • Lazertinib monotherapy at 240 mg administered orally once daily Part C Dose Extension • Lazertinib monotherapy 240 mg administered orally once daily Part D: Ex-South Korea • Lazertinib monotherapy at 240 mg administered orally once daily	Efficacy: ORR (primary); DOR, DCR, tumor shrinkage, PFS, OS, intracranial efficacy endpoints (for brain metastatic patients only). Safety: TEAEs, physical examination, clinical laboratory, vital signs, ECOG performance status, ECG
YH25448-301	Ongoing Total enrolled: 196 n=196 in lazertinib arm (safety, efficacy)	Phase 3, randomized, double-blind study of lazertinib versus gefitinib	Lazertinib 240 mg orally once daily	Efficacy: PFS according to RECIST v1.1 by investigator (primary); ORR, DOR, DCR, depth of response, TTR, OS (secondary) Safety: TEAEs, clinical laboratory, vital signs, physical examination, ECG, LVEF, WHO performance status, ophthalmologic

				assessments

cMET=hepatocyte growth factor receptor; EGFR=epidermal growth factor receptor; exon 19del=exon 19 deletion; exon 20ins=exon 20 insertion; IV=intravenous; L858R=exon 21 L858R substitution; NSCLC=non-small cell lung cancer; PBC=platinum-based chemotherapy; RP2CD=recommended Phase 2 combination dose; RP2D=recommended Phase 2 dose; TKI=tyrosine kinase inhibitor.

[a] Cohorts A and B were closed to recruitment following protocol amendment 4 and subsequently Cohorts C, D, MET-1, MET-2, wild-type adenocarcinoma, and wild type-squamous were opened to investigate specific subgroups of EGFR-dependent/independent mutations.

[b] RP2CD=lazertinib 240 mg orally once a day and amivantamab (1050 mg [for participants with baseline body weight <80 kg] or 1400 mg [for participants with baseline body weight ≥80 kg]) IV, once weekly for the first 4 weeks (Cycle 1) and then once every 2 weeks (subsequent cycles).

[c] The planned starting combination dose of lazertinib was 240 mg administered orally once daily and the dose of amivantamab was 700 mg administered IV once weekly (first dose was split into 2 doses and given on Cycle 1 Day 1 and Cycle 1 Day 2) for the first 4 weeks and then once every 2 weeks (subsequent cycles). However, the starting dose of lazertinib or amivantamab was permitted to change depending on the emerging data from other studies (73841937NSC2001/YH25448-201 and CHRYSALIS).

Table 7: Detailed overview of phase 1 studies

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
YH25448-101	Open-label, single-dose, 2-group, 2-period, single-sequence crossover study	24 healthy adult male participants	Single oral dose of 240 mg lazertinib in each study period	C_{max} and AUC
73841937NSC1003	Open-label, fixed-sequence, 2 cohort study	32 healthy adult participants Female to Male ratio:- Cohort 1 - 9:7 Cohort 2 - 5:11	Cohort 1: - Study days 1 and 12 single oral dose of 160 mg lazertinib Study days 8 to 16 200 mg itraconazole oral once daily Cohort 2:- Study days 1 and 19 single oral dose of 240 mg lazertinib Study days 8 to 22 600 mg rifampin oral once daily	C_{max} and AUC
73841937NSC1008	Open-label, multiple dose study	20 healthy adult participants Female to Male ratio of 3:17	Study days 1 and 13 Single oral dose of 2 mg midazolam, 10 mg rosuvastatin and 500 mg metformin Study days 5 to 14 160 mg lazertinib oral once daily	C_{max} and AUC
73841937NSC1004	Open-label, single dose study	8 healthy adult male participants	Single oral dose of 14C-lazertinib (240 mg, 0.603 MBq or 16.3 µCi)	$C_{max,}$ AUC, $t_{1/2}$, CL/F of lazertinib in plasma, 14C-lazertinib in plasma, 14C lazertinib in whole blood and fraction of dose excreted in urine and feces.
73841937NSC1007	Open-label, parallel group, multi-center, single-dose study	8 adult participants with moderate hepatic impairment (Child-Pugh B classification) and 8 matched	Single oral dose of 160 mg lazertinib	C_{max} and AUC

		participants with normal hepatic function Female to Male ratio of 4:12		
73841937NSC1002	Randomized, open-label, 2-way crossover study	48 healthy adult participants Female to Male ratio of 2:46	Single oral dose of 240 mg lazertinib in each study period	C_{max} and AUC
73841937NSC1006	Randomized, open-label, 3-way crossover study	18 healthy adult participants Female to Male ratio of 2:16	Single oral dose of 240 mg lazertinib in each study period	C_{max} and AUC
73841937NSC1009	Randomized, open-label, 4-way crossover study	64 healthy adult participants Female to Male ratio of 7:57	Single oral dose of 240 mg lazertinib in each study period	C_{max} and AUC

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalysis

The concentration of lazertinib in plasma was determined using validated LC-MS/MS methods at four different bioanalytical laboratories. The different bioanalytical methods were cross validated. In all bioanalytical methods a stable deuterated internal standard of Lazertinib, Lazertinib-d5, was used for quantification. The bioanalysis of the DDI marker substrates, midazolam and its metabolite 1-OH-midazolam, rosuvastatin and metformin, was conducted with validated LC-MS/MS methods.

PK models

The population PK of lazertinib following oral administration was best described by a 2-compartment model with sequential zero- and first-order absorption. The pooled dataset included 17,235 observations from 1,399 patients. After exclusion of data below the limit of quantification and missing data, a total of 14,936 lazertinib plasma concentrations from 1,389 patients were included in the PPK analysis. The model included the following covariate effects on CL/F: body weight, GSTM1 genotype, sex, Japanese population, and prior treatment (naïve vs. non-naïve); and on the peripheral volume of distribution: body weight and sex. Body weight effects were allometrically scaled and estimated on CL/F (0.586) but fixed to 1 on the central volume of distribution (V2/F). Parameter estimates of the final model are presented below.

Table 8: Parameter Estimates for the Final Population PK Model

Parameter	Estimate[e]	Standard Error	RSE%	IIV, IOV (%)[a,c]	Shrinkage (%)[a]
D_1 (h)	1.51	0.0492	3.3	-	-
K_a (h^{-1})	0.159	0.00448	2.8	-	-
CL/F (L/h) [b]	33.0	0.668	2.0	-	-
V_2/F (L) [b]	81.1	3.92	4.8	-	-
Q/F (L/h) [b]	58.0	1.46	2.5	-	-
V_3/F (L) [b]	2,380	70.7	3.0	-	-
Weight on CL/F [c]	0.586	0.0554	9.4	-	-
Weight on V_2/F [d]	1.0 (fixed)	-	-	-	-
GSTM1 Null on CL/F[c]	-0.157	0.0249	15.9	-	-
GSTM1 Non-null on CL/F [c]	0.504	0.0474	9.41	-	-
JPN on CL/F [c]	-0.215	0.0367	17.1	-	-
Treatment naïve on CL/F [c]	-0.123	0.0207	16.8	-	-
Sex=Male on CL/F [c]	0.149	0.0298	20.0	-	-
Sex=Male on V_2/F [d]	0.527	0.137	26.0	-	-
IIV CL	0.141	0.006	4.3	38.9	9.3
IIV V_2	1.55	0.0976	6.3	193	37.7
IIV Q	0.0801	0.0104	13.0	28.9	59.1
IIV V_3	0.311	0.0187	6.0	60.4	43.9
IOV D_1	1.19	0.057	4.8	151	41.2
IOV K_a	0.119	0.00798	6.7	35.5	51.9
Residual Error	0.134	0.000579	0.4	37.9	13.6

CL=clearance; D_1=input duration of oral administration; F=bioavailability; IIV=interindividual variability; IOV=inter-occasion variability; K_a=first-order absorption rate constant; NONMEM=non-linear mixed effects modeling; PK= pharmacokinetics; Q=inter-compartmental clearance; RSE=relative standard error; V_2=volume of distribution of the central compartment; V_3=volume of distribution of the peripheral compartment; WT=body weight in kilograms.

[a] Estimates in relative percentage scale for IIV, IOV, and residual error, calculated as 100×sqrt(exp(var)-1), where var represents the variance estimate for log-normally distributed random effects and residual error as returned by NONMEM.

[b] CL and CL/F are used interchangeably to represent apparent clearance throughout the report. Same applies to V_2, Q, and V_3.

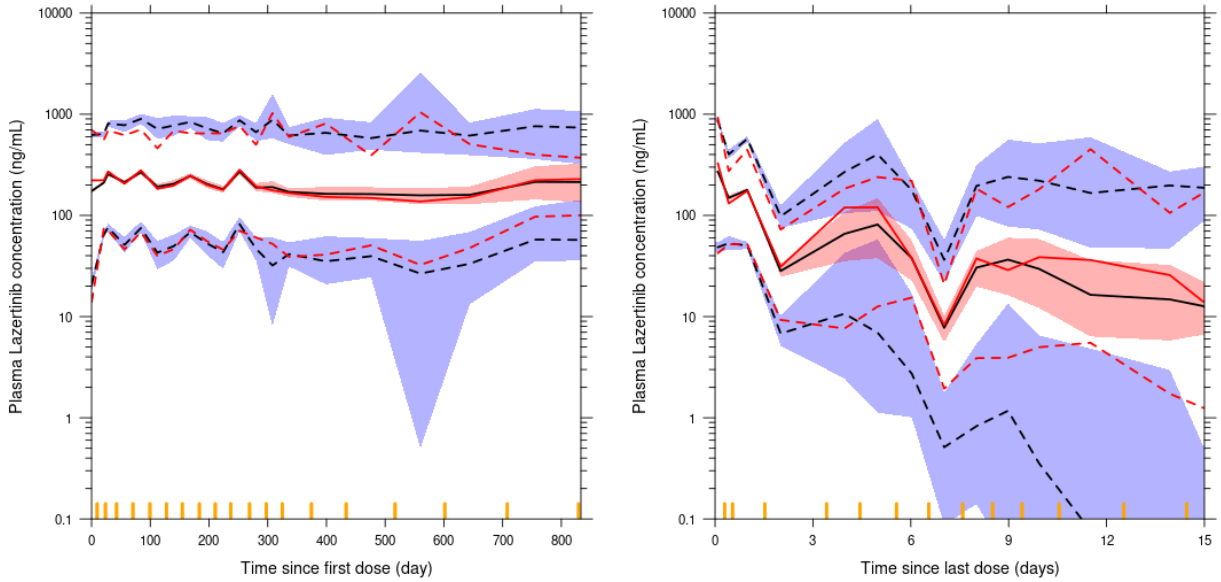
[c] Weight, GSTM1, sex, Japanese, and prior treatment effects on the typical value of CL were modeled as follows: $TVCL=q_{CL} \times (WT/WT_{med})^{q_{wt,CL}} \times (1+q_{sex} \times sex) \times (1+q_{GSTM1\_null} \times GSTM1\_null) \times (1+q_{GSTM1\_non\text{-}null} \times GSTM1\_non\text{-}null) \times (1+q_{JPN} \times JPN) \times (1+q_{PRLN} \times PRLN)$, where TV stands for "typical value," q_{CL} is CL in a typical participant with weight (WT) equal to WT_{med}, $q_{wt,CL}$ is the allometric coefficient for CL. For categorical covariates, $q_{[categorical\ covariates]}$ is the multiplicative term for categorical covariate effects on the corresponding parameter.
sex is an indicator variable for female (*sex*=0; reference category) or male (*sex*=1) participants
GSTM1_null is an indicator variable for GSTM1 null (*GSTM1_null*=1) or GSTM1 undetermined (*GSTM1_null*=0; reference category). *GSTM1_non-null* is an indicator variable for GSTM1 non-null (*GSTM1_non-null*=1) or GSTM1 undetermined (*GSTM1_non-null*=0; reference category).
JPN is an indicator variable for non-Japanese (*JPN*=0; reference category) or Japanese (*JPN*=1) participants.
PRLN is an indicator variable for treatment non-naïve (*PRLN*=0; reference category) or naïve (*PRLN*=1) participants, and q_{PRLN} is the multiplicative term for prior treatment effect on TVCL.

[d] Weight and sex effect on the typical value of V_2 was modeled as follows: $TVV_2=q_{wt,V2} \times (WT/WT_{med})^{q_{wt,V2}} \times (1+q_{sex} \times sex)$, where q_{V2} is V_2 in a typical participant with weight (WT) equal to WT_{med}, $q_{wt,V2}$ is the allometric coefficient for V_2. *sex* is an indicator variable for male (*sex*=1) or female (*sex*=0; reference category) participants.

[e] Estimates for IIV, IOV, and residual error are shown as variance estimates from the model output.

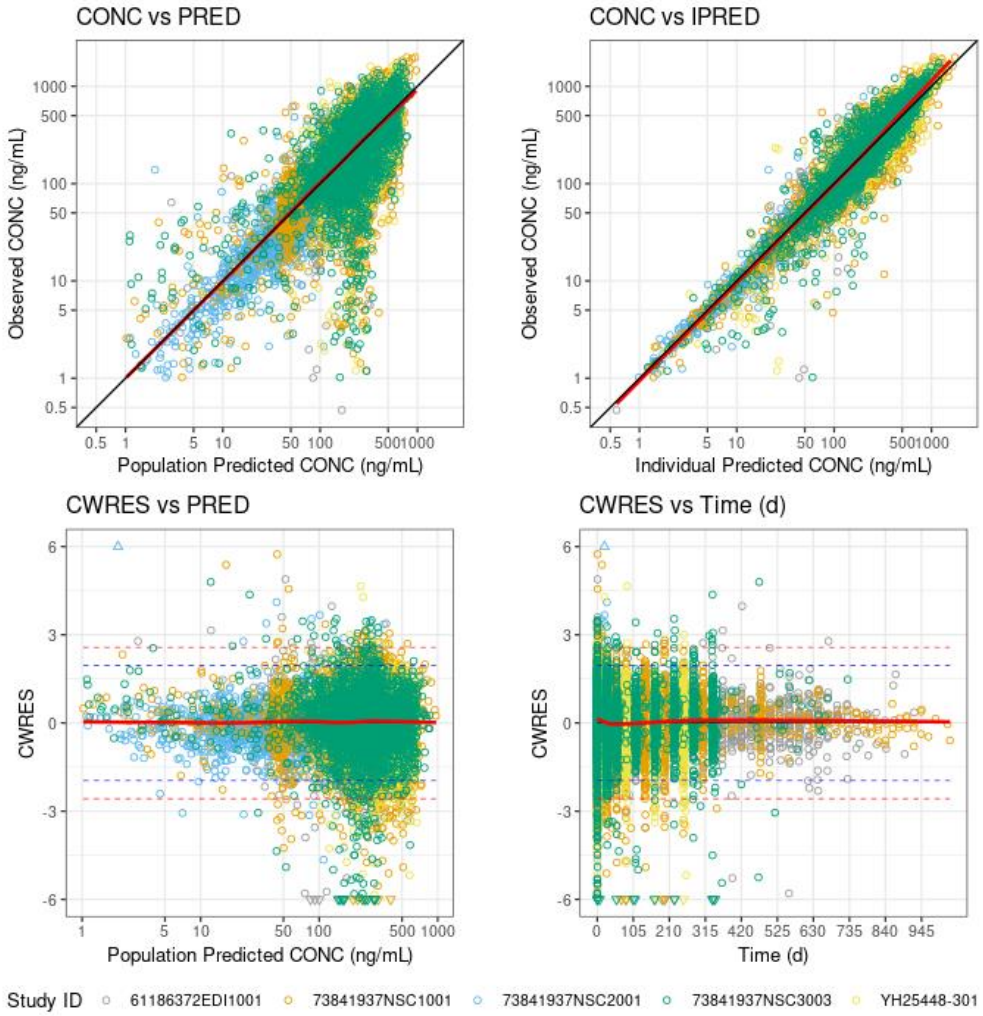
Goodness-of-fit plots and selected pc-VPC's are presented in Figures below. In general, no significant trends or patterns were observed in the majority of the pcVPCs and GOF plots.

Figure 5: pcVPC for Final PPK Model



The left panel shows the plots with time since first dose and right panel shows the plots with time since last dose. Solid red lines are median, dashed red lines are the 2.5th and 97.5th percentiles of the observations. Solid black lines are median, dashed black lines are the 2.5th and 97.5th percentiles predicted by the model. The shaded red area represents the 95% CI of the median and shaded blue areas represent the 95% CI of the 2.5th and 97.5th percentiles predicted by the model.
Source: PPK/Fig4

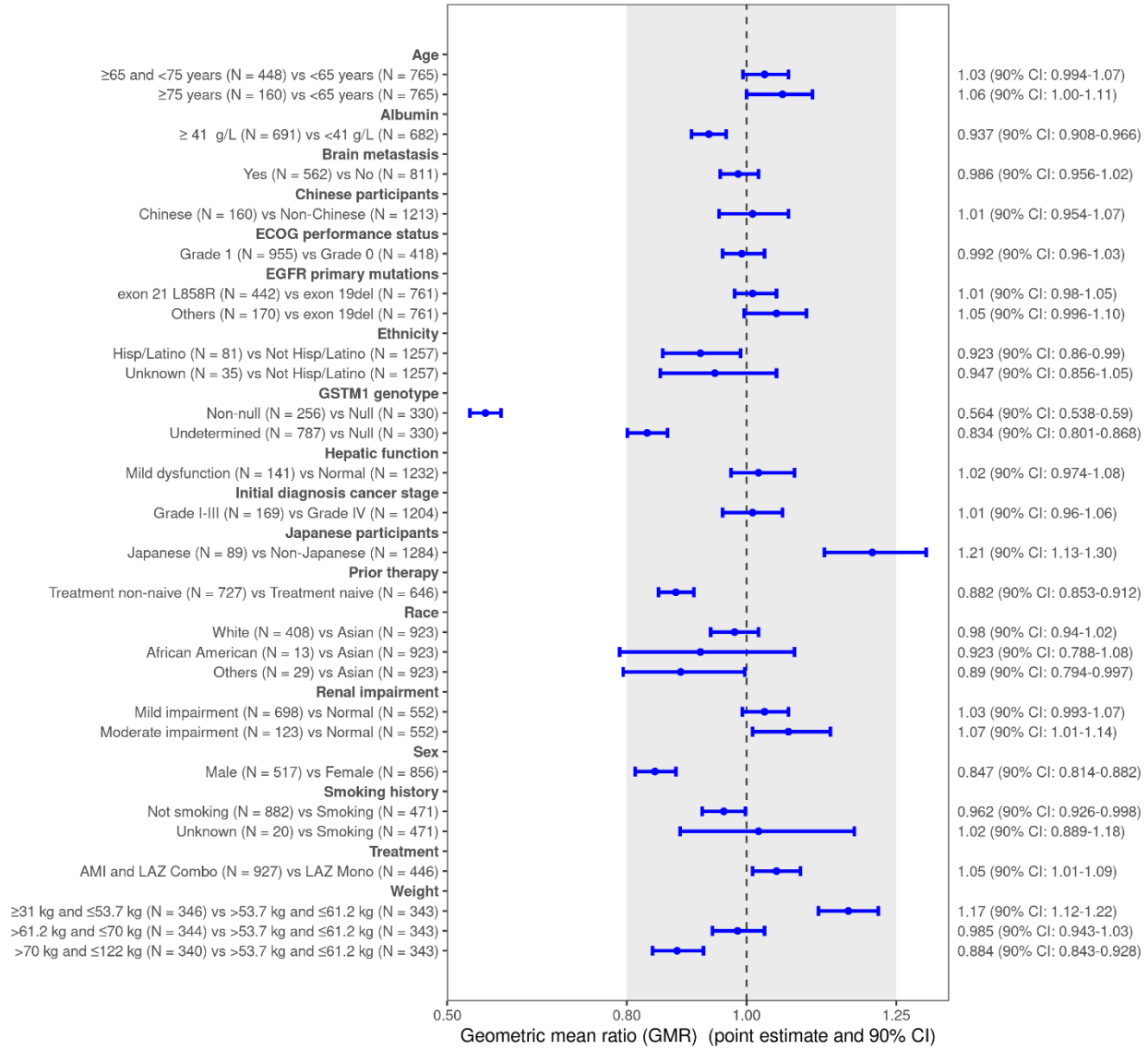
Figure 6: Basic GOF Plots for Final PPK Model (Run48)



The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The circles are the observations. The triangles represent data with |CWRES|>6 (kept in the plot as |CWRES|=6 for traceability and clear visualization of the remaining data).

Using the final population PK model, a comparison of lazertinib exposure in subpopulations was conducted using forest plots showing the GMR (and 95% CI) of $AUC_{0\text{-}24h.ss}$ (presented in Figure 7) and $C_{max.ss}$ with respect to the reference group.

Figure 7: Forest Plot of Subgroup Analyses of the $AUC_{0\text{-}24h.ss}$ at the Recommended Dose Regimen (Final PPK Model)



Note: Solid blue circle represents GMR and horizontal error bar represents 90% CI. Dashed line represents reference value of 1. The associated values are shown on the right column. The gray shaded area refers to 0.8 and 1.25.

The final model (run48) was used to generate the forest plots. The forest plots in assessing the covariate effects were conducted using multivariate regression analysis. Reference subject confidence intervals (CIs) of the GMRs did not include uncertainty in the predictions for the reference participants.

Analyses assumed that all participants included in the PPK analysis dataset received 240 mg lazertinib orally QD for 28 days (assuming steady state on Day 28). Because there was IOV on D1 and K_a (Day 1 vs other days), for participants who received more than 1 dose, Day 2 and beyond PK parameters were used for steady state simulations.

WT categories are based on quartiles of body weight interval.

In Study YH301, WHO performance status was used. For a pooled analysis, ECOG performance status, used in the other 4 studies, was combined with WHO performance status.

Absorption

Lazertinib has a moderate Caco-2 permeability, higher than atenolol and lower than L-propanolol, and shows a pH-dependent solubility i.e. full solubility of the 240 mg dose at low pH (1.2) and very limited solubility at pH 6.8, 0.0001 g/100 mL. Lazertinib was classified as a BCS class 2 compound from these data. Lazertinib was not a substrate of the intestinal efflux transporters BCRP and MRP2; but was a

substrate of MDR1 (P-gp) in the over-expressing MDCK-MDR1 cells. The efflux ratio of lazertinib in Caco-2 cells ranged from 0.354 at 1 µM to 1.09 at 25 µM.

Bioavailability

The absolute bioavailability of lazertinib has not been determined. The relative bioavailability of different lazertinib formulations utilised in the clinical program were investigated in the clinical studies NSC1002 and NSC1006 (see table below). These studies confirmed the comparability of different formulations bioavailability and were confirmatory for the result of the main bioequivalence study NSC1009. In the mass-balance study only limited excretion of unchanged drug was observed (< 5%) indicating that lazertinib is nearly fully absorbed.

Bioequivalence

Lazertinib has been administered in the clinical studies by the oral route as a 240 mg tablet or as multiple of 80 mg tablets, both immediate release tablets. The recommended human dosing regimen is 240 mg, QD. In the clinical program of lazertinib, four different oral tablet formulations (80 mg phase 1 formulation, 80 mg phase 2 formulation 80 mg G004, and 240 mg G005) were utilized. The G004 and G005 tablets will be used for the intended marketed product and the phase 1 formulation tablet was used in the pivotal MARIPOSA study. In the clinical study NSC1009 in healthy subjects, bioequivalence of the 4 lazertinib tablet formulations was evaluated. The intended marketed lazertinib tablets G004 and G005 were bioequivalent, 90% confidence interval (CI) of Cmax and AUC0-72h GMR within the 80-125% acceptance interval, with the tablet formulation used in the pivotal clinical study MARIPOSA. The phase 1 formulation tablet also showed BE with other formulations.

Influence of food

The effect of food on lazertinib's PK was evaluated in healthy subjects in the study YH25448-101. The 90% CIs of both Cmax and AUClast GMR were within the BE criteria of 80% to 125%. The intake of food will therefore not influence the PK of lazertinib in a clinically meaningful way.

Table 9: Statistical Assessment of Effects of Food (Study YH25448-101)

PK parameter	Geometric Mean		GMR (Fed/Fasted)	
	Fed (N=24)	Fasted (N=24)	Point estimate	90% CI
C_{max} (ng/mL)	342.06	366.35	0.9337	0.8266-1.0546
AUC_{last} (h*ng/mL)	3900.08	3416.2	1.1416	1.0666-1.2220

Distribution

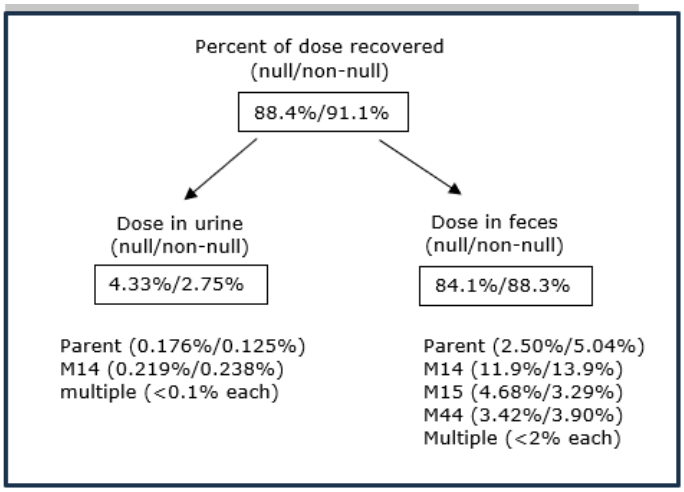
The mean apparent volume of distribution Vd/F of lazertinib was determined in NSCLC patients in the clinical study NSC2001. After a single dose of 240 mg lazertinib a Vd/F of 4264 L (60.9 L/kg for a 70 kg person) was determined. Plasma protein binding was determined at a conc. of 1 and 10 µM lazertinib by equilibrium dialysis. Lazertinib binds to both human serum albumin and human α1-acid glycoprotein with no concentration dependency. Lazertinib was highly bound to plasma proteins, 99.1% at 1 µM and 99.7% at 10 µM. The human blood-to-plasma ratio was determined to 1.15. Plasma protein binding of lazertinib was also determined to 99.2%, as part of the hepatically impairment study NSC1007.

Elimination and excretion

In the clinical study NSC2001 in NSCLC patients, the mean (CV%) apparent plasma clearance and terminal elimination half-life of lazertinib at a 240 mg dose were determined to 44.5 (29.5%) L/h and 64.7 (32.8%) hours, respectively.

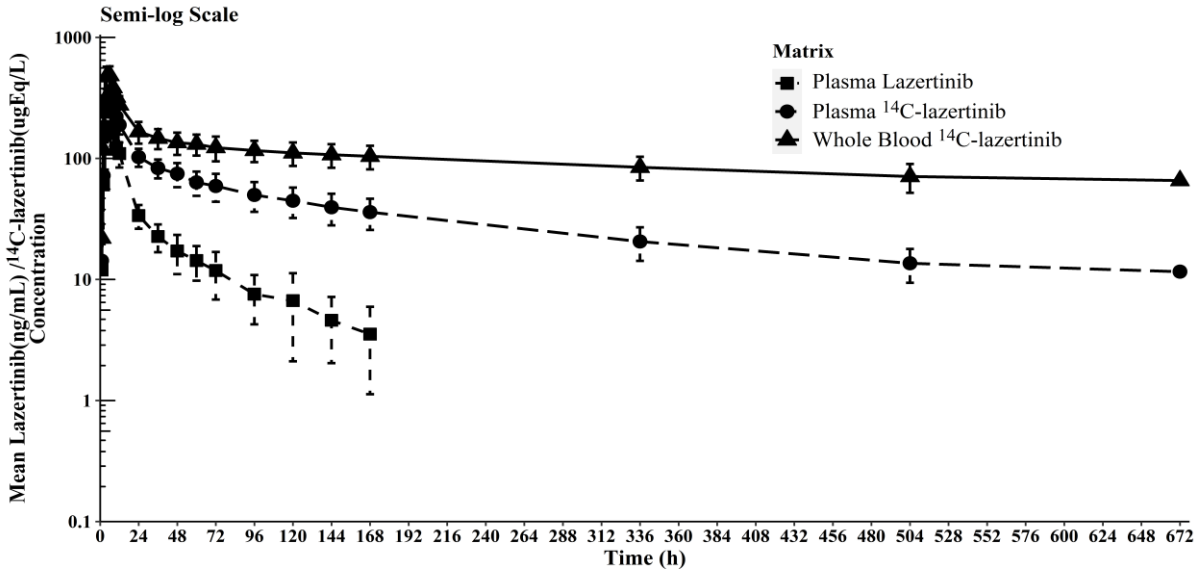
In the mass-balance study NSC1004 study in 8 healthy subjects, 4 GSTM1 null and 4 non-null subjects, a single dose of 240 mg lazertinib containing 14C radiolabeled lazertinib was administered. The radioactive dose was primarily excreted in feces, 86.2% of the administered radioactive dose, ≤5% as unchanged Lazertinib (see figure below). A minor amount was recovered in urine, 3.54% of the administered radioactive dose, <0.2% as unchanged lazertinib. The excretion profile was comparable in GSTM1 null and non-null subjects.

Figure 8: Excretion of 14C-lazertinib in mass balance study (73841937NSC1004)



The longer half-life of total radioactivity, t1/2 = 240 hours, in humans relative to that of unchanged lazertinib, t1/2 = 70.4 hours, is attributed to covalent binding of 14C-lazertinib-related radioactivity to proteins.

Figure 9: Semi-logarithmic Mean (±SD) Concentration-Time Profiles of Plasma Lazertinib, Radioactivity-Time Profiles of Plasma and Whole Blood ^{14}C-lazertinib After Oral Administration of ^{14}C-lazertinib Under Fed Condition (240 mg, 0.603 MBq or 16.3 µCi) in Healthy Adult Participants; Pharmacokinetic Data Analysis Set (Study 73841937NSC1004)



Lazertinib was administered as a single oral dose of ^{14}C-lazertinib under fed condition (240 mg, 0.603 MBq or 16.3 uCi) on Day 1

Table 10: Pharmacokinetic Parameter Results of Plasma Lazertinib, Radioactivity Pharmacokinetic Parameter Results of Plasma and Whole Blood ^{14}C-lazertinib After Oral Administration of ^{14}C-lazertinib Under Fed Condition (240 mg, 0.603 MBq or 16.3 µCi) in Healthy Adult Participants; Pharmacokinetic Data Analysis Set (Study 73841937NSC1004)

Pharmacokinetic Parameters (mean [SD], t_{max}: median [range])	Plasma Lazertinib	Plasma ^{14}C-lazertinib	Whole Blood ^{14}C-lazertinib
n	8	8	8
C_{max} (ng/mL or ugEq/L)[a]	280 (51.9)	353 (52.4)	517 (89.9)
t_{max} (h)	6.00 (3.00-6.00)	6.00 (4.00-6.00)	6.00 (3.00-6.00)
AUC_{last} (h*ng/mL or h*ugEq/L)[b]	4441 (1226)	19962 (4977)	53020 (12605)
AUC_{∞} (h*ng/mL or h*ugEq/L)[b]	4651 (1335)	25796 (6890)[c]	-[d]
λ_z (1/h)	0.011 (0.004)	0.003 (0.000)[c]	-[d]
$t_{1/2}$ (h)	70.4 (28.2)	240 (47.9)[c]	-[d]
$\%AUC_{\infty,ex}$ (%)	4.26 (1.24)	17.4 (2.34)[c]	-[d]
CL/F (L/h)	55.5 (15.9)	10.0 (3.10)[c]	-[d]
V_d/F (L)	5233 (1450)	3385 (834)[c]	-[d]

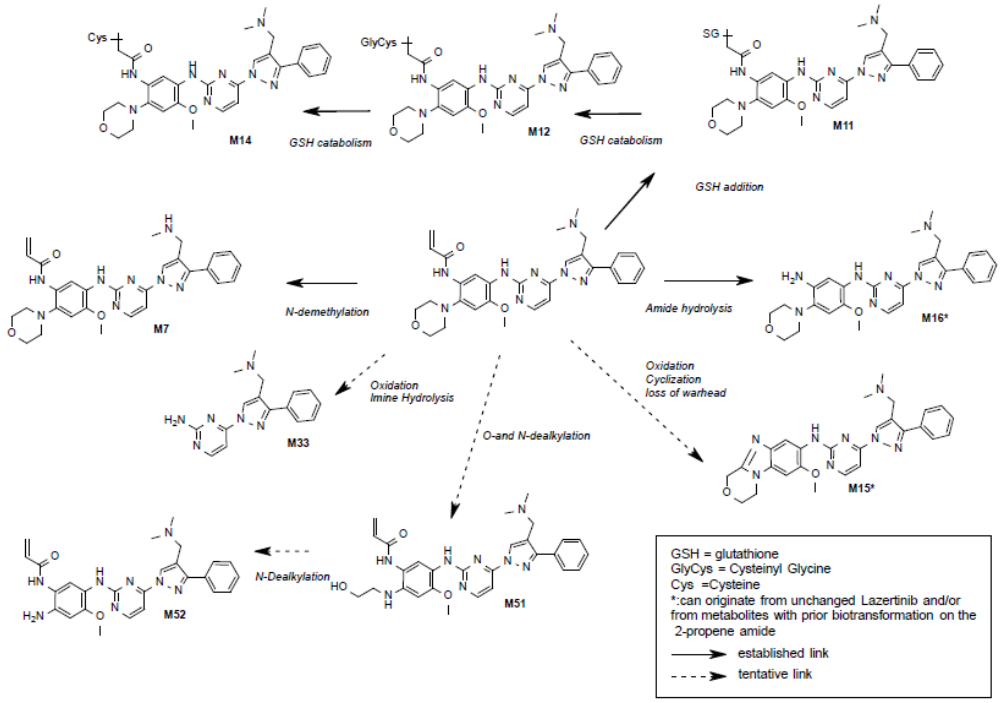
[a] C_{max} for plasma lazertinib reported in ng/mL. C_{max} for plasma and whole blood ^{14}C-lazertinib reported in ugEq/L.
[b] AUC_{last} and AUC_{∞} for plasma lazertinib reported in h*ng/mL. AUC_{last} and AUC_{∞} for plasma and whole blood ^{14}C-lazertinib reported in h*ugEq/L.
[c] n=6
[d] Note: Accurate Determination Not Possible for other PK parameters (AUC_{∞}, $t_{1/2}$, λ_z, CL/F, V_d/F and $\%AUC_{\infty,ex}$) due to $\%AUC_{\infty\_ex}$ > 20.00%, hence not reported.

Metabolism

The metabolism and in vitro clearance of lazertinib was investigated in different in vitro systems, human hepatocyte, human liver microsomes, human plasma, recombinant human CYP and UGT enzymes, human recombinant glutathione S-transferases (GSTs). In human hepatocytes it was demonstrated that CYP3A metabolism was only a minor metabolic pathway, 21% of the total in vitro clearances. In human hepatocytes the main metabolic pathway was GSH adduct formation with the reactive propeneamide moiety of lazertinib to form the metabolite M11, GSH-adduct, and further conversion to M12, Cys-Gly adduct, and further to M14, Cys adduct, see Figure 10. The metabolite M15 was mainly formed by CYP3A. In vitro using recombinant GST enzymes, the clearance of lazertinib was approx. 17 times higher in presence of the GSTM1 isoform compared to the GSTA1 and GSTP1 isoform. Addition of GSH was also observed in the absence of enzyme.

In vivo metabolism of lazertinib was investigated in the mass-balance study NSC1004. In feces M14 was the major metabolite (12-14%) and all other metabolites were below 10%. In plasma, primarily the GSH derived metabolite, M12, was observed in addition to the fused benzimidazole metabolite M15 (minor metabolite).

Figure 10. Proposed metabolic pathways of 14C-JNJ-73841937 as detected in blood and plasma after single oral administration of 240 mg JNJ-73841937 to healthy male adult participants.



Pharmacokinetics of metabolites

During early clinical development, the pharmacokinetics of metabolite M7 was determined, as M7 was pharmacologically active in vitro and abundant in animals. The abundance of M7 in human plasma was low, M7 to parent exposure ratio of 0.02 to 0.04 at steady state in the NSC2001 study. Consequently, M7 is not considered to contribute to clinical pharmacological activity in humans.

The steady-state exposure of main metabolites relative to unchanged drug and the accumulation factors (AF) of the metabolites in plasma was estimated for four patients in the study NSC2001. Unchanged drug was the primarily circulating entity in plasma: 60.5 ± 12.5 % total drug related material (TDRM) after single dosing and 55.9 ± 6.78% TDRM after repeated dosing. An accumulation factor of 2.2 was determined for lazertinib and 2.2 for the major metabolite M12. Only M12 was identified as a major circulating metabolite after repeated dosing: %TDRM: 16.4%, AUC.M12/AUC.Parent: 25.2%. The metabolic profile after a single dose was comparable in GSTM1 null subjects and in non-null subjects.

Consequences of GSTM1 polymorphism

The effect of GSTM1 polymorphism, null and non-null genotype, on the PK of lazertinib was evaluated. The null genotype results in deletion of GSTM1 and therefore a complete lack of GSTM1 enzymatic activity. In the clinical studies of Lazertinib, including a comparable number of null and non-null subjects, an increase in exposure in the GSTM1 null subjects was shown. In the mass-balance study NSC1004 a 1.57 fold decrease in the apparent clearance Cl/F of null subjects was found, in the pivotal MARIPOSA study a 2.06 fold increase in Ctrough of lazertinib in GSTM1 null patients was observed, see Table 11. In the Pop-PK analysis, GSTM1 was a significant covariate accounting for a 44% increase in AUCss for null subjects. The primary endpoint, PFS, in the pivotal study MARIPOSA was not influenced by GSTM1 status.

Table 11: Lazertinib plasma concentration summarized as mean (SD)

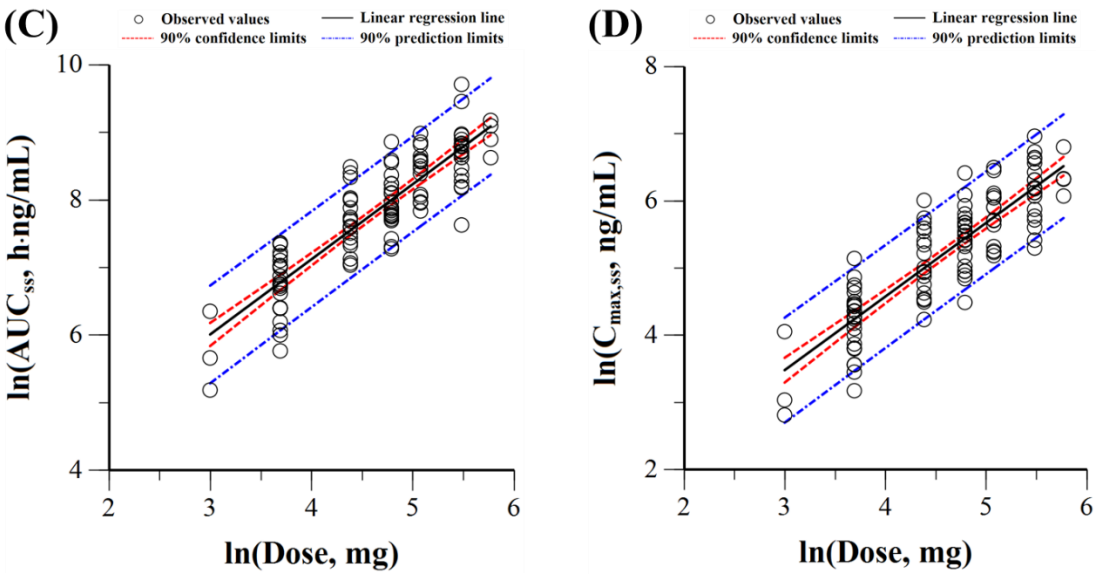
Cycle 2 Day 1	Non-null GSTM1	Null GSTM1
n	103[a]	117[b]
C_{trough}, ng/mL	150 (84.7)	309 (137)
C_{2h}, ng/mL	325 (203)	574 (308)
C_{4h}, ng/mL	395 (189)	616 (285)

[a] n=91 for C_{2h} and n=80 for C_{4h}
[b] n=103 for C_{2h} and n=100 for C_{4h}

Dose proportionality and time dependencies

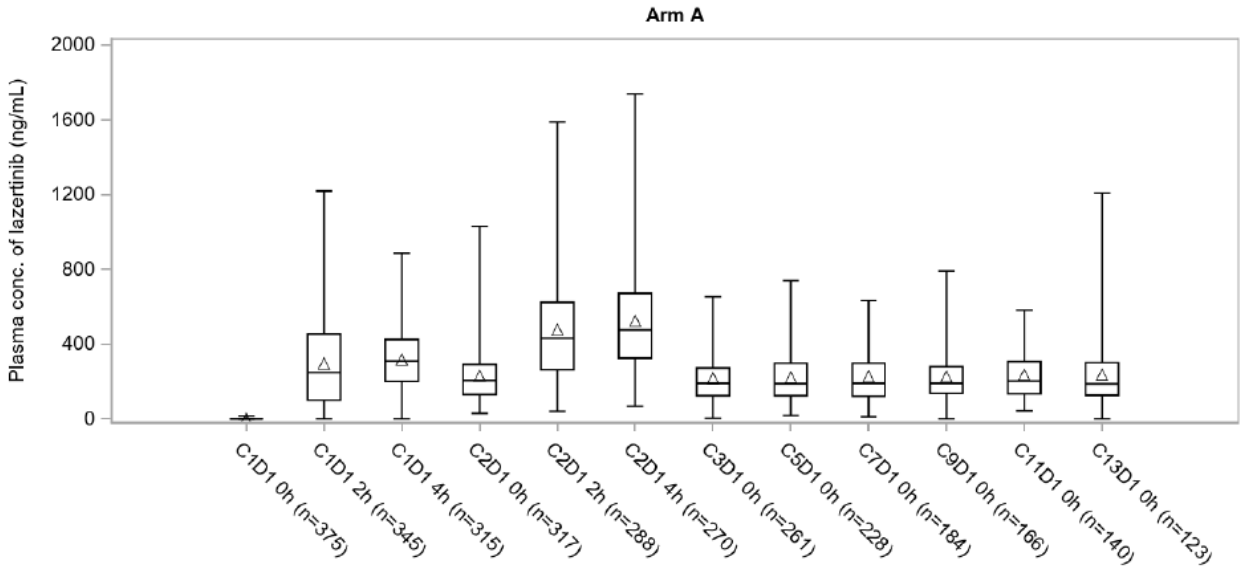
Dose-proportionality of lazertinib was investigated in the study NSC2001, where doses from 20 to 320 mg was administered to NSCLC patients. Using a LN transformed power model it was found that Cmax and Cmax,ss of lazertinib increased in a dose proportional manner and that AUCt and AUCss lazertinib increased in a slightly more than dose-proportional manner over the dose range of 20 to 320 mg, see figure below.

Figure 11: Assessment of Dose Proportionality for Cmax,ss and AUCss: Plot of ln(PK parameter) vs ln(dose) for Lazertinib (PK Analysis Population)



Furthermore in study NSC2001 it was found that steady state was as a minimum reached after 15 days of repeated QD dosing of Lazertinib. This analysis is supported by Ctrough data from the pivotal MARIPOSA study, see figure below. After repeated dosing a 2.3 fold accumulation in exposure AUCss was observed for the intended marketed dose of 240 mg lazertinib.

Figure 12: Box Plot of Plasma Concentrations of Lazertinib vs time in pivotal MARIPOSA study



Source: Attachment FIGPK05
Arm A (amivantamab+lazertinib arm): Open-label treatment with the combination of amivantamab (1050 mg for body weight <80 kg and 1400 mg for body weight >=80 kg by intravenous [IV] infusion, once weekly for the first 4 weeks and then once every 2 weeks) and lazertinib (240 mg orally, once daily)
Legend: The bottom and top edges of the box indicate the interquartile range (the 25th and 75th percentiles). The marker indicates the mean value. The line inside the box indicates the median value. The whiskers indicate the entire range of values.

Intra- and inter-individual variability

After multiple doses of 240 mg lazertinib in participants with NSCLC, the inter-participant variability (geometric CV%) at steady state was 46.7% for Cmax and 47.4% for AUCss. The inter-participant variability in lazertinib PK parameters for participants with NSCLC was comparable when administered alone or in combination with amivantamab.

Pharmacokinetics in the target population

There is no clinically meaningful difference in PK exposure of lazertinib after single-dose administrations between healthy participants and participants with NSCLC, see table below. Co-administration with amivantamab did not impact the pharmacokinetics of lazertinib.

Table 12: Plasma PK Parameters for Lazertinib Following 160 mg or 240 mg Single- and Multiple-Dose of Lazertinib in Healthy Participants and Participants with NSCLC (Biopharmaceutic and Clinical Pharmacology Studies)

Study ID	Formulation	C_{max} (ng/mL)		T_{max} (h)		AUC_{∞} (ng.h/mL)		$t_{1/2}$(h)	
		N	Mean SD)	N	Median (Range)	N	Mean (SD)	N	Mean (SD)
Healthy Participants, Single Dose, Fasting Conditions Unless Otherwise Stated									
YH101	240 mg (80 mg×3 phase 1 formulation tablets) (Caucasian, fasted)	12	325.79 (124.75)	12	2.00 (1.50 to 3.02)	12	2,919.33 (1,139.72)	12	49.71 (17.75)
	240 mg (80 mg×3 phase 1 formulation tablets (Caucasian, fed)	12	319.21 (123.33)	12	3.50 (1.50 to 6.05)	12	3,446.41(1,257.77)	12	49.59 (15.74)
	240 mg (80 mg×3 phase 1 formulation	12	457.54 (124.84)	12	2.00 (1.00 to 3.00)	12	5,190.84 (1,285.34)	12	86.20 (36.14)

Study ID	Formulation	C_{max} (ng/mL)		T_{max} (h)		AUC_{∞} (ng.h/mL)		$t_{1/2}$(h)	
		N	Mean SD)	N	Median (Range)	N	Mean (SD)	N	Mean (SD)
	tablets (Korean, fasted)								
	240 mg (80 mg×3 phase 1 formulation tablets) (Korean, fed)	12	408.86 (121.17)	12	4.00 (3.00 to 6.00)	12	5,688.08 (1,480.32)	12	87.61 (45.79)
NSC1002	Reference Treatment Manufactured at Clinical Scale 240 mg (80 mg×3 phase 2,3 formulation tablets)	47	308 (113)	47	2.05 (1.00 to 6.00)	42	4,096 (1,246)	42	49.3 (14.2)
	Test Treatment Manufactured at Commercial Scale 240 mg (80 mg×3 phase 2,3 formulation tablets)	47	306 (103)	47	3.00 (1.00 to 6.02)	40	4,380 (1,502)	40	49.5 (12.1)
NSC1003	Reference Treatment (160 mg Lazertinib [2×80 mg FC tablets, single dose])	15	238 (75.1)	15	4.00 (3.00 to 4.00)	5	2,781 (824)	5	54.4 (4.74)
	Test Treatment 160 mg Lazertinib [2×80 mg FC tablets, single dose] + 200 mg Itraconazole	15	281 (85.1)	15	4.00 (3.10 to 4.07)	3	3,116 (571)	3	48.8 (2.08)
	Reference Treatment 240 mg Lazertinib [3×80 mg Tablets, single dose]	16	303 (136)	16	3.00 (2.00 to 3.02)	10	3,223 (1,104)	10	47.5 (8.52)
	Test Treatment 240 mg Lazertinib [3×80 mg Tablets, single dose] + 600 mg Rifampin	16	85.5 (35.3)	16	2.00 (1.00 to3.00)	10	612 (236)	10	28.6 (18.4)
NSC1004	Size 00 capsules containing ^{14}C labelled and unlabelled lazertinib under fed condition (240 mg, 0.603 MBq or 16.3 µCi)	8	280 (51.9)	8	6.00 (3.00 to 6.00)	8	4,651 (1,335)	8	70.4 (28.2)
NSC1006	Lazertinib 240 mg (3×80 mg phase 2,3 formulation tablets)	15	413 (170)	15	2.01 (1.99 to 3.00)	13	4,835 (1,825)	13	48.0 (10.6)
	Lazertinib 240 mg (3×80 mg G004 tablets)	16	396 (149)	16	2.00 (1.00 to 4.00)	10	5,005 (1,502)	10	47.1 (13.9)
	Lazertinib 240 mg (1×240 mg G005 tablet)	18	364 (133)	18	2.01 (1.00 to 3.97)	16	4,754 (1,981)	16	53.7 (13.1)

Study ID	Formulation	C_{max} (ng/mL)		T_{max} (h)		AUC_{∞} (ng.h/mL)		$t_{1/2}$(h)	
		N	Mean SD)	N	Median (Range)	N	Mean (SD)	N	Mean (SD)
NSC1007	160 mg (2×80 mg phase 2,3 formulation tablets) lazertinib in participants with moderate hepatic impairment	8	221 (79.3)	8	3.00 (1.00 to 4.00)	8	4,827 (1,500)	8	93.5 (21.4)
	160 mg (2×80 mg FC tablets) lazertinib in participants with normal hepatic function	8	271 (73.4)	8	3.01 (2.00 to 6.00)	7	4,551 (783)	7	80.8 (34.0)
NSC1008	160 mg (2×80 mg FC tablets) Lazertinib	20	201 (86.6)	20	4.00 (1.00 to 6.00)	20	AUC_{0-24} 1,496 (448)	NA	NA
NSC1009	Reference: Lazertinib 240 mg (3×80 mg phase 2,3 formulation)	63	263 (96.7)	63	3.00 (1.00 to 6.00)	58	3,570 (1,860)	60	57.0 (20.8)
	Test: Lazertinib 240 mg (3×80 mg G004)	63	280 (112)	63	3.00 (1.00 to 4.07)	54	3,696 (1,745)	57	62.8 (26.5)
	Test: Lazertinib 240 mg (1×240 mg G005)	62	284 (96.8)	62	3.00 (1.02 to 4.05)	58	3,861 (1,722)	60	59.3 (19.8)
	Test: Lazertinib 240 mg (3×80 mg phase 1 formulation)	62	264 (97.6)	62	3.00 (1.98 to 4.05)	51	3,485 (1,751)	55	66.4 (33.3)
Participants with NSCLC, Single Dose									
NSC2001 (Part A, B and C)	160 mg lazertinib	6	179.49 (60.92)	6	4.09 (2.03 to 10.17)	6	3,984.45 (1,170.30)	6	59.90 (14.79)
	240 mg lazertinib	4	434.05 (125.72)	4	1.99 (1.98 to 4.00)	4	5,783.56 (1,789.60)	4	64.72 (21.24)
NSC2001 (Part D)	240 mg lazertinib	13	441.04 (135.45)	13	2.00 (0.92 to 4.15)	13	6,504.88 (2,542.12)	13	51.28 (14.79)
Participants with NSCLC, Multiple Dose									
NSC2001	240 mg lazertinib	20	517.15 (222.43)	20	2.06 (1.92 to 6.17)	20	6,541.96 (3,227.47)	NA	NA
Participants with NSCLC, Multiple Dose in Combination with Amivantamab									
EDI1001	240 mg lazertinib and amivantamab (1050/1400 mg)	15	573 (186)	15	3.97 (0.93 to 7.90)	NA	NA	NA	NA

Therapeutic window

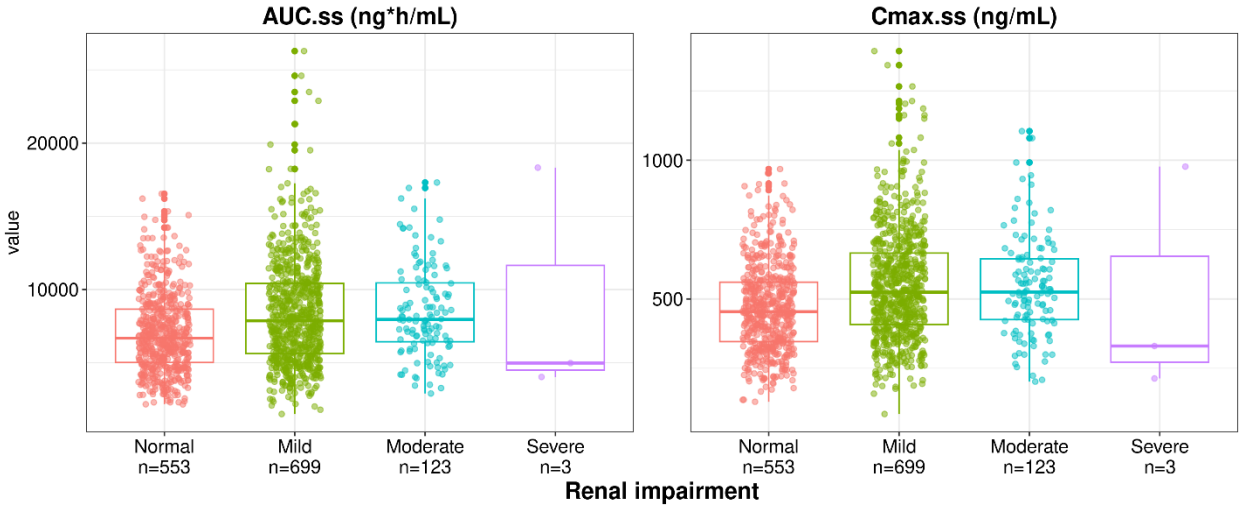
The safety, efficacy, and PK of lazertinib in NSCLC patients have been evaluated clinically over a dose range from 20 mg up to 320 mg QD, in study NSC2001. The maximum tolerated dose of lazertinib was not determined as no dose limiting toxicities were reported in the study. On basis of the E-R analysis from study NSC2001, the minimum target plasma steady state trough concentration to achieve favorable efficacy, measured as PFS, was estimated to be 58.6 ng/mL. This target level can be achieved with a minimum dose of lazertinib 160 mg administered once daily. The higher recommended dose of 240 mg takes GSTM1-mediated differences in PK into account. Dose adjustments of lazertinib based on GSTM1 genotype lazertinib is therefore not necessary.

Special populations

Impaired renal function

The PK of lazertinib was not investigated in a dedicated renal impairment study. The effect of renal impairment on lazertinib's PK was evaluated in the Pop-PK analysis and renal impairment was evaluated on basis of eGFR classification. There was a limited number of subjects in the group of severe renal impairment, 3 subjects (0.2%). Moderate renal impairment was found not to influence the PK of lazertinib in clinically relevant (≤25% difference in exposure), see forest plot Figure 13. Severe renal impairment appears not to impact the exposure of lazertinib.

Figure 13: Comparison of Predicted Exposure in Participants with Normal Renal Function, Mild, Moderate and Severe Renal Impairment



Impaired hepatic function

In the study NSC1007 the impact of moderate hepatically impairment, based on Child-Pugh system, on the PK of lazertinib was investigated. The two cohorts included a comparable number of GSTM1 null and GSTM1 non-null subjects. Moderate hepatically impairment had only limited impact on the exposure Cmax, AUCinf and AUClast, see Table 13. The same conclusion was obtained, when the effect of moderate hepatic impairment was evaluated using unbound concentration.

In the Pop-PK model it was found that mild hepatically impairment, based on the NCI classification system, did not influence the exposure of lazertinib in a clinically relevant manner, see relevant forest plot figure.

Table 13: Statistical Comparison of Total Lazertinib PK Parameters for Moderate Hepatic Impairment Group Vs Normal Hepatic Function Group. Pharmacokinetic Data Analysis Set (Study 73841937NSC1007).

Analyte	PK Parameter	N		Geometric Means			
		Group 2 (Reference)	Group 1 (Test)	Group 2 (Reference)	Group 1 (Test)	Geometric Mean Ratio (%)	90% CI (%)
Lazertinib	C_{max} (ng/mL)	8	8	264	210	79.58	60.79, 104.18

Analyte	PK Parameter	N		Geometric Means			
		Group 2 (Reference)	Group 1 (Test)	Group 2 (Reference)	Group 1 (Test)	Geometric Mean Ratio (%)	90% CI (%)
	AUC_{last} (h*ng/mL)	8	8	4,489	4,250	94.66	75.89, 118.08
	AUC_{∞} (h*ng/mL)	7	8	4,495	4,646	103.35	82.73, 129.10

Influence of gender, race, bodyweight, and age

The effect of gender, race, bodyweight and age on the lazertinib's exposure was evaluated in the population PK analysis. The covariates, gender (518 male, 860 female), ethnicity (White, Asian, African American, others), bodyweight (31 – 122 kg), age (767patients < 65 years, 449 patients 65-75 years, 162 patients >75 years) did not influence the exposure of lazertinib in a clinically relevant manner (≤25% difference in exposure).

Pharmacokinetic interaction studies

In vitro

Victim DDI:

Lazertinib's victim potential was evaluated using different in vitro models. It was found to be a CYP3A substrate and a GSTM1 substrate. The fraction metabolized by CYP3A in hepatocytes was 21%. Furthermore, lazertinib was determined not to be a substrate of the following drug transporters P-gp, ASBT, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, BCRP, BSEP, MRP2, and MRP4 transporters.

Perpetrator DDI:

Lazertinib's perpetrator DDI potential was investigated in appropriate CYP450 inhibition assays (direct and time-dependent inhibition), CYP450 induction assays, UGT inhibition assays and in drug transporter inhibition assays.

Table 14: The In Vitro Inhibitory Effects of Lazertinib on Human CYP Isoforms

CYP Isoform	Test Article	Preincubation	% Inhibition at Max Concentration	IC_{50} (μM)
CYP1A2	JNJ-73841937[1]	–	<10	>30
		+	<10	>30
CYP2B6	JNJ-73841937[1]	–	<10	>30
		+	21.7	>30
CYP2C8	JNJ-73841937[1]	–	47.7	>30
		+	19.9	>30
CYP2C9	JNJ-73841937[1]	–	-	17.3 ± 0.9
		+	-	20.9 ± 1.8
CYP2C19	JNJ-73841937[1]	–	56.0	26.27 ± 1.82
		+	47.0	>30
CYP2D6	JNJ-73841937[1]	–	49.2	>30
		+	42.7	>30
CYP3A4 (Testosterone)	JNJ-73841937[1]	–	-	5.18 ± 0.72
		+	-	1.13 ± 0.09
CYP3A4 (Midazolam)	JNJ-73841937[1]	–	-	8.07 ± 1.07
		+	-	1.37 ± 0.11
CYP3A4 (Testosterone)	JNJ-73841937[2]	–	-	5.90 ± 0.82
		+	-	1.47 ± 0.15
CYP3A4 (Midazolam)	JNJ-73841937[2]	–	-	9.41 ± 0.5
		+	-	1.75 ± 0.17

- not reported/not calculated; + pre-incubated in the presence of lazertinib (TDI assessment); – pre-incubated in the absence of lazertinib (reversible inhibition assessment)
[1] Mesylate salt form
[2] Free base form

Table 15: Summary of in vitro enzyme induction

	Fold induction mRNA								
	CYP1A2			CYP2B6			CYP3A4		
	Lot A	Lot B	Lot C	Lot A	Lot B	Lot C	Lot A	Lot B	Lot C
0.03 μM	1.07	1.46	1.13	1.07	1.09	0.97	0.99	1.32	1.25
0.08 μM	1.25	1.54	1.38	1.24	1.20	0.86	1.44	1.42	2.15
0.3 μM	1.55	2.39	2.22	1.18	1.58	1.26	2.05	1.73	3.89
0.8 μM	1.71	2.62	2.43	1.35	1.78	1.44	2.76	2.16	5.23
3 μM	2.31	3.62	2.70	1.72	2.54	1.58	3.34	2.90	7.63
8 μM	2.73	4.12	2.52	1.79	1.41	0.68	5.43	1.24	4.05
Positive control	83.9	36.3	37.3	11.9	4.35	9.23	237	16.1	305

Table 16: The In Vitro Inhibitory Effects of Lazertinib on Human Uptake and Efflux Transporters

Transporter	Substrate	Method	Maximum Inhibition (% of Control)	IC_{50} (μM)
ASBT	taurocholic acid	Cell monolayer	22	-
BCRP	estrone-3-sulfate	Vesicle	96	0.25
BCRP	prazosin	Cell monolayer	77	-
BSEP	taurocholic acid	Vesicle	99	5.00
MDR1	digoxin	Cell monolayer	38	-
MATE1	metformin	Cell monolayer	66	5.79
MATE2-K	metformin	Cell monolayer	77	3.16
MRP2	estradiol glucuronide	Vesicle	NIO[1]	-
MRP4	DHEAS	Vesicle	64	12.51
OAT1	tenofovir	Cell monolayer	NIO[1]	-
OAT3	methotrexate	Cell monolayer	24	-
OATP1B1	estradiol glucuronide	Cell monolayer	76	8.26
OATP1B1 (+ pre-incubation)	estradiol glucuronide	Cell monolayer	59	8.58
OATP1B3	cholecystokinin	Cell monolayer	56	17.70
OATP1B3 (+ pre-incubation)	cholecystokinin	Cell monolayer	59	7.58
OCT1	metformin	Cell monolayer	97	0.31
OCT2	metformin	Cell monolayer	70	13.41

- not reported/not calculated
[1] Lazertinib stimulated the transport of the prototypical substrate compared to the solvent control.

The potential for the inhibition of the human UGT isoenzymes, UGT1A1, UGT1A6, and UGT2B7 by lazertinib was evaluated in human liver microsomes. Lazertinib inhibited UGT1A1 (IC_{50} = 1.63 μM), but was not an inhibitor of UGT1A6 and UGT2B7 with IC_{50} values of ≥202 μM.

The kinetic constants for CYP3A4 mechanism-based inactivation (MBI) were determined in human liver microsomes: kinact to 0.0243 min-1 and KI to 17.1 μM. Based on basic models of inhibition, in vitro enzyme/transporter inhibition results relative to mean clinical Cmax,ss in the NSC2001 study, 517 ng/mL, and estimates of GI concentrations at the recommended human dose of 240 mg once daily indicates that lazertinib may be a clinical relevant inhibitor of CYP3A4, BCRP, OCT1, and UGT1A1. Furthermore, according to the basic method a clinically relevant CYP3A induction and CYP1A2 induction by lazertinib could not be excluded. In vitro EC_{50} and E_{max} values was determined for the most sensitive hepatocyte donor in the in vitro CYP1A2 induction assay, EC_{50} = 0.18 μM and E_{max} = 2.7.

In vivo

Victim DDI:

The potential CYP3A victim DDI of lazertinib were investigated in the study NSC1003. The study was conducted in healthy subjects including both GSTM1 null and non-null subjects. Co-administration of lazertinib with the strong CYP3A inhibitor itraconazole resulted in an increase in lazertinib's exposure, AUC0-120h, of 46% compared to without inhibitor, see Table 17. Co-administration of lazertinib with the strong CYP3A inducer resulted in a decrease in lazertinib's exposure to 17% of the exposure without inducer. The observed DDI were similar in the two GSTM1 genotype cohorts.

Perpetrator DDI:

Lazertinib's potential perpetrator DDI for CYP3A, BCRP and OCT1 were investigated in the study NSC1008, see table below. The study was conducted in healthy subjects, including both GSTM1 null

and non-null subjects. A lower dose of lazertinib, 160 mg, than the recommended dose was administered in the DDI study.

A clinical DDI was not observed for the OCT1 substrate metformin when co-administered with lazertinib at steady state. The exposure of the BCRP probe substrate Rosuvastatin was increased 2.01-fold by coadministration with lazertinib compared to without and the exposure of the CYP3A probe substrate midazolam was increase with 1.46 fold when co-administered with lazertinib.

Inhibition of UGT1A1 by lazertinib was not evaluated in a dedicated clinical DDI study, as no clinical DDI was expected for the UGT1A1 probe substrate raltegravir by PBPK modelling and from the lack of effect on the bilirubin levels, an endogenous UGT1A1 biomarker.

Table 17 : Summary of clinical DDI studies

Comparison	Substance Ratio, as Percent (90% CI)		Dosing Recommendation
Victim (Study 73841937NSC1003)			
Effect of co-administration with strong CYP3A4 inhibitor Itraconazole	C_{max} 118.70 (108.14, 130.29)	AUC_{0-120h} 145.55 (138.48, 152.98)	No dose adjustment is required when lazertinib is coadministered with CYP3A4 inhibitors.
Effect of co-administration with strong CYP3A4 inducer Rifampin	C_{max} 28.16 (23.16, 34.25)	AUC_{0-120h} 16.52 (14.05, 19.43)	The coadministration of lazertinib with strong CYP3A4 inducers should be avoided.
Perpetrator (Study 73841937NSC1008)			
Effect on CYP3A4 substrate Midazolam	C_{max} 139.04 (122.71, 157.55)	AUC_{0-last} 146.56 (134.39, 159.83)	No dose adjustment is required. For sensitive CYP3A4 substrates with a narrow therapeutic index, monitor for adverse reactions as increased plasma exposure of coadministered CYP3A4 substrates may increase the risk of exposure-related toxicity.
Effect on BCRP substrate Rosuvastatin	C_{max} 224.26 (182.25, 275.96)	$AUC_{0-last.}$ 201.81 (169.54, 240.21)	No dose adjustments is required. For sensitive BCRP substrates with a narrow therapeutic index, monitor for adverse reactions as increased plasma exposure of coadministered BCRP substrates may increase the risk of exposure-related toxicity.
Effect on OCT1 substrate Metformin	C_{max} 80.89 (71.64, 91.33)	AUC_{0-last} 94.34 (83.46, 106.64)	No dose adjustment is required

Evaluation of the effect on the indirect bilirubin level, a UGT1A1 endogenous marker, by administration of lazertinib

Indirect bilirubin levels were monitored during the conduct of study 73841937NSC1008, a Phase 1 study in healthy adult participant. Additional indirect bilirubin data at predose and Cycle 2 Day 1 (each

cycle is 28 days) from NSCLC patients treated with once daily lazertinib 240 mg monotherapy in Study 73841937NSC3003 (MARIPOSA) is presented below. No clinically relevant effect on indirect bilirubin levels was observed due to lazertinib administration, indicating that lazertinib is not a clinically relevant inhibitor of UGT1A1.

Table 18: Summary of Clinical Chemistry Indirect Bilirubin (umol/L); Safety Analysis Set (73841937NSC1008) Overall

Time	N	Mean	SD
Baseline (Prior to 1st dose of 160 mg Lazertinib)	20	9.833	5.051
Study Day 9 (5th once daily dose of 160 mg Lazertinib)	20	10.260	4.225
Study Day 12 (8th once daily dose of 160 mg Lazertinib)	20	10.859	4.307

SD=standard deviation

Table 19: Summary of Clinical Chemistry Indirect Bilirubin (umol/L); Safety Analysis Set (73841937NSC3003/MARIPOSA) Lazertinib Monotherapy Arm

Time	N	Mean	SD
Baseline (Prior to 1st dose of 240 mg Lazertinib)	175	6.849	4.288
Cycle 2 Day 1 (each cycle is 28 days)	163	7.675	4.846

SD=standard deviation

Investigation of the effect of lazertinib's PK by co-administration with gastric acid reducing agents

The effect on lazertinib's PK by co-administration with gastric acid reducing agents, PPIs, was evaluated in a retrospective exploratory analysis using data from patients in the study NSC2001, see Table 20. The ARA group included 9 subjects (5 non-null GSTM1, 1 null-GSTM1 and 3 of unknown GSTM1 status), whereas the reference group included 24 subjects with (11 non-null GSTM1, 10 null GSTM1 and 3 of unknown GSTM1). Patients in the ARA group had co-administration of PPIs with lazertinib for at least 4 days immediately prior to evaluation of PK parameters. The lazertinib's mean exposure (Cmax, AUCss and Ctrough, CD15) was not affected in a clinically meaningful manner by co-administration with a gastric acid-reducing agents, see table below.

Table 20: Comparison of PK Parameters of Lazertinib at 240 mg With and Without Coadministration of Acid-Reducing Agents (ARA) Effect Analysis Population

	Geometric Mean				Geometric Mean Ratio (ARA Group/Non-ARA Group)	
PK parameter	n	ARA	n	Non-ARA	Point Estimate	90% Confidence interval
AUC_{ss} (h·ng/mL)	9	5,621.83	24	6,153.58	0.9136	0.6637, 1.2576
$C_{max,ss}$ (ng/mL)	9	4,34.74	24	482.42	0.9012	0.6703, 1.2116
C_{D15}	10	132.75	115	150.00	0.8850	0.6463, 1.2118

ARA=acid-reducing agent; AUC_{SS}=area under the plasma concentration-time curve from zero to the end of the dosing interval; C_{D15}=trough plasma concentration on Day 15 of Cycle 1; $C_{max,ss}$=maximum plasma concentration at steady state; n=number of participants; PK=pharmacokinetic.

In silico

The PBPK model of lazertinib was evaluated for its ability to predict the clinically observed drug-drug interactions. It was also applied for evaluating in vitro DDI positives. The predicted AUC ratio with the

strong CYP3A4 inducer rifampicin was 0.42 in non-null GSTM1 subjects, whereas an AUC ratio of 0.18 was observed in the clinically study. The moderate CYP3A4 inducer efavirenz, 600 mg once daily, was predicted to result in a reduced decrease in lazertinib plasma exposure in GSTM1 non-null subjects, predicted AUC ratio of 0.56. The perpetrator DDI of lazertinib with CYP3A substrate midazolam was overpredicted in the PBPK model, AUC ratio of 2.36 in non-null subjects and a ratio of 3.58 in null subjects. No clinically relevant change in the exposure of the UGT1A1 substrate raltegravir was predicted when coadministered with lazertinib at steady state, i.e. AUC ratio of 1.08 and 1.12 in GSTM1 non-null and null subjects. Furthermore, no clinically relevant DDI (i.e AUCR < 0.8) was predicted when 240 mg lazertinib was co-administered with the sensitive CYP1A2 substrate caffeine.

2.6.2.2. Pharmacodynamics

Mechanism of action

Lazertinib

Lazertinib is an oral, mutant-selective, irreversible, third generation, EGFR TKI that selectively inhibits both primary activating EGFR mutations (exon 19del, exon 21 L858R substitution) and the EGFR T790M resistance mutation, while having less activity versus wild-type EGFR. The antitumor effect of lazertinib was evaluated in wild-type EGFR, PC9, Ba/F3-L858R, and H1975 EGFR mutant tumor xenograft models and the results demonstrate higher efficacy of lazertinib in xenograft tumor models with mutant EGFR compared to efficacy in a model with wild-type EGFR. Preclinical study results suggest that lazertinib demonstrates activity in a brain metastases model with NSCLC cells carrying the T790M mutation, as well as demonstrating blood-brain barrier penetration profile.

Combination of Amivantamab and Lazertinib

The distinct mechanisms of action of amivantamab and lazertinib, which target the extracellular ligand binding domain and the intracellular active site of EGFR, respectively, inhibit this pathway more potently than either agent alone. Combining amivantamab with lazertinib was hypothesized to broaden the coverage against the development of resistance pathways in tumours harbouring exon 19del or exon 21 L858R EGFR mutations, resulting in prolonged disease control. Combining these agents in the first-line treatment of patients with EGFRm NSCLC may lead to improved treatment outcomes through synergistic anti-EGFR activity, prevention of EGFR- or MET-based resistance to a 3rd generation EGFR TKI, and potential recruitment of Fc-bearing immune cells in the antitumor response.

Primary and Secondary pharmacology

No clinical primary pharmacology studies were performed for lazertinib.
On the basis of a concentration-QTc E-R Analysis from the Phase 1/2 Study YH25448-201 it is concluded that there is no clinically relevant effect of lazertinib on cardiac repolarization following oral administration of 240 mg lazertinib daily.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics:

The pharmacokinetics of lazertinib was evaluated by modelling and simulation studies, in vitro studies and clinical pharmacology studies. The bioanalysis conducted in support of the lazertinib clinical program was found to be in accordance with regulatory requirements. The recommended dose of Lazcluze is 240 mg once daily in combination with amivantamab.

The population PK of lazertinib following oral administration was described by a 2-compartment model with sequential zero- and first-order absorption. Model parameters were well-estimated with RSEs

<30% for all the structural model parameters and bootstrap (n = 78/200) median values of all parameters were similar to the point estimates from the final model with narrow bootstrap 95% CI, indicating adequate and precise estimation of model parameters. Data for the PPK model were based on five studies, namely: NSC3003 (Phase 3, PK sample collection cutoff date 11 April 2023), EDI1001 (Phase 1, PK sample collection cutoff date 15 November 2021), NSC1001 (Phase 1/1b, PK sample collection cutoff date 15 July 2022), YH201 (Phase 1/2, PK sample collection cutoff date 08 January 2021), and YH301 (Phase 3, PK sample collection cutoff date 29 July 2022). The pooled dataset included 17,235 observations from 1,399 patients. After exclusion of data below the limit of quantification and missing data, a total of 14,936 lazertinib plasma concentrations from 1,389 patients were included in the PPK analysis. The IIV (%CV) was low on Q/F, moderate on CL/F and V3/F, and high on V2/F. The large variability on V2/F could be the result of a dose-dependent bioavailability. IOV was included on input duration of oral administration (D1) and absorption rate constant (ka) to account for the large variability in absorption on day 1 and improve individual fitting. ETA shrinkage was low on CL/F but high on all other parameters (37.7%-59.1%); hence, the information for these effects is less informative. Correlations between IIV/IOV and covariates were examined graphically using matrix plots, and some correlations were found. Implementation of off-diagonal elements was attempted but models failed to converge. No major trends were observed in the ETA distributions of CL/F, V2/F, or V3/F versus covariates, which suggests that the large IIVs are caused by large and random distributions not linked to any tested covariates. The model was evaluated by GOF plots and pcVPCs stratified by study/relevant covariates. In general, no significant trends or patterns were observed in the majority of the pcVPCs and GOF plots. Lazertinib steady-state exposure parameters were compared across key subpopulations using forest plots.

A PBPK model was developed for lazertinib using SimCYP v21 in order to (1) predict the DDI potential of a strong CYP3A4 inhibitor, a strong CYP3A4 inducer and a moderate CYP3A4 inducer on a single dose of 240 mg lazertinib in GSTM1 null and GSTM1 non-null NSCLC subject, (2) predict the DDI potential of multiple oral doses of 240 mg lazertinib on CYP3A4 substrate and UGT1A1 substrate in GSTM1 null and GSTM1 non-null NSCLC subjects, and (3) predict the impact of hepatic impairment on the pharmacokinetics of 240 mg lazertinib in moderate hepatically impaired non-cancer subjects. The PBPK model platform is not considered sufficiently qualified under the EMA Guideline on PBPK for predicting moderate or weak inducers of CYP3A4, cannot be used for SmPC recommendations involving UGT1A1 substrate exposure, and should only be considered supportive for moderate hepatic impairment.

Lazertinib was shown to have moderate in vitro permeability and pH-dependent solubility. Lazertinib was classified as a BCS class 2 compound. The suggested BCS classification is supported. It was demonstrated using in vitro methods that Lazertinib is not a substrate of the intestinal efflux transporter BCRP and MRP2. On basis of the limited efflux ratio (<2) in Caco-2 cells the applicant argued that the P-gp contribution is very limited. This analysis is supported and in accordance with the EMA DDI guidance, appendix II. In conclusion, the relevant intestinal drug transporters have been evaluated for lazertinib and the data demonstrates that lazertinib's absorption appears not to be drug transporter dependent.

The absolute bioavailability of lazertinib has not been determined. This is acceptable. In the mass-balance study only limited excretion of parent drug was observed (< 5%) and this indicates according to the applicant that lazertinib is nearly fully absorbed. This analysis is reasonable. The bioequivalence was demonstrated for the different tablet formulations used in the clinical programs and for the intended to be marketed lazertinib tablet formulations G004 and G005.

The effect of food intake on lazertinib pharmacokinetics was adequately evaluated in the study YH25448-101. The absence of a food-effect for lazertinib is reflected in the SmPC. The main PK

parameters of lazertinib, Vd/F, Cl/F and $t_{1/2}$ was satisfactorily determined in NSCLC patients. Lazertinib plasma protein binding was determined appropriately.

The excretion pathway of lazertinib was investigated in the mass-balance study NSC1004. The recovery of radioactive dose in the study was acceptable. The mean exposure of Lazertinib in the mass-balance study, AUCinf was similar to the exposures determined for the to-be-marketed formulation. The bioavailability of the applied 14C labelled lazertinib tablet formulation is therefore comparable to the to-be-marketed formulations G004 and G005. The low amount of unchanged lazertinib excreted in faeces indicates that metabolism is the main elimination pathway of lazertinib and that there is only limited biliary clearance of lazertinib. Only 57-59% of the radioactivity in faeces could be extracted for metabolite identification. It was therefore not possible to fulfil the DDI guideline criteria of preferable being able to identify 80% of the recovered radioactivity. The applicant argues that this is also observed for other irreversible TKI and is due to covalent binding to proteinaceous materials. As support for this interpretation several literature references are cited (Dickinson 2016, Liu 2020, Meng 2022, Scheers 2015). A longer terminal half-life of radioactivity in plasma, 240 hr, was observed than for lazertinib, 70 hr. This is also explained to be a result of covalent binding to proteinaceous materials, in particular plasma proteins. This seems as a reasonable explanation considering the reactivity of lazertinib and as all circulating metabolites are judged to have been identified in the metabolism identification study. Information of the covalent plasma protein binding is included in the SmPC.

The metabolism and in vitro clearance of lazertinib has been investigated sufficiently using different in vitro systems. It was demonstrated that oxidative metabolism by CYP3A was only a minor metabolic pathway and that the main metabolic pathway was GSH adduct formation catalysed by the GSTM1-1 enzyme. The in vivo metabolism of lazertinib was investigated appropriately in the mass-balance study NSC1004. Only one major circulating metabolite was reported by the applicant, the GSH derived adduct M12. It is argued by the applicant that the M12 metabolite is inactive as the reactive propene amide moiety is required for potency as an irreversible inhibitor and that water soluble GSH derived adducts in general has low potency. This analysis is acceptable. The abundance of the metabolites at steady state was determined in 4 subjects from the NSC2001 study. The GSTM1 status of only one out of the 4 subjects was determined. In conclusion, the metabolism of lazertinib has been reasonable elucidated and it is considered as plausible from the provided data.

The effect of GSTM1 polymorphism, null and non-null genotype, on the PK of lazertinib was investigated in accordance to the guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009). GSTM1 is the enzyme primarily involved in the metabolism of lazertinib. The null genotype results in deletion of GSTM1 and therefore a complete lack of GSTM1 enzymatic activity. Approximately 52% Europeans (Caucasian) have the GSTM1 null genotype (Nakanishi et al. 2022). It has been justified that dose adjustment on basis of GSTM1 genotype is not necessary. It was shown that PFS was similar between non-null and null GSTM1 participants. Furthermore, it was demonstrated that the excretion, metabolism and DDI was reasonable comparable in both GSTM1 genotypes.

The dose-proportionality of lazertinib was evaluated using adequate methodology. It was demonstrated that lazertinib shows approximately dose-proportionality over the dose range from 20 to 320 mg. Furthermore, it was shown that steady state was at least reached after 15 days of repeated QD dosing of Lazertinib. This analysis was supported by C_{trough} data from the pivotal MARIPOSA study. After repeated dosing a 2.3 fold accumulation in exposure AUC_{ss} was observed, consistent with the long half-life of Lazertinib and the QD dosing scheme. In conclusion, no time-dependent pharmacokinetics was observed for Lazertinib. The Accumulation is not expected to have any clinical consequences. This analysis is supported.

The Inter- and intraparticipant variability of Cmax and for different AUC-measures in healthy subjects and NSCLC patients has been adequately determined for Lazertinib. It was shown that there is no clinically meaningful difference in PK of lazertinib between healthy subjects and participants with NSCLC.

Sufficient justification regarding the possible limits of the therapeutic window have been provided. The absence of a maximum tolerated dose for lazertinib in the NSCLC patient population is considered acceptable. Upon request, the applicant has further justified the proposed dose reductions to 80 mg lazertinib in the event of adverse reactions. Although this is not the optimal dose in terms of reaching the predefined minimal clinically efficacious exposure, the efficacy findings from 80 mg lazertinib monotherapy, along with its combination with amivantamab, provide sufficient justification for its use in a temporarily modified dosing regimen.

Lazertinib has not been evaluated in a dedicated renal impairment study. The applicant argues that lazertinib' s PK is unaffected by renal impairment, due to the limited renal excretion found in the mass-balance study and that renal impairment status, using eGFR classification, was not a clinically relevant covariate in the Pop-PK analysis. This conclusion is reasonable for mild and moderate renal impairment but in severe renal impairment only limited data are available and the impact of severe renal impairment has therefore not been fully evaluated for lazertinib. The SmPC reflect the limited investigation in patients with severe real impairment. In the study NSC1007 it was demonstrated that moderate hepatically impairment only had limited impact on the exposure and that dose adjustment in these patients is not necessary. In the Pop-PK analysis and additional PK-analysis, it was demonstrated that there was no clinically relevant impact of gender, body weight, and race on lazertinib' s PK. Overall, the pharmacokinetics of lazertinib in special population have been adequately investigated and is appropriately described in the SmPC.

Lazertinib' s victim potential was evaluated using different in vitro models in accordance with the guideline on the investigation of drug interactions. It was demonstrated that lazertinib is a CYP3A substrate and a GSTM1 substrate, additionally it was not shown to be a substrate of the main drug transporters. Lazertinib' s perpetrator DDI potential was investigated in vitro for all the DDI guideline recommended CYP450 enzymes and drug transporters. The potential for clinical DDI was adequately determined using the basic DDI prediction model.

In the two clinical DDI studies, study NSC1003 and study NSC1008, the identified in vitro DDI positives were further investigated. The methodology of the conducted DDI studies are in accordance with the EMA DDI guideline, except that a lower dose of lazertinib, 160 mg, was utilized in the study. The applicant has justified using a lower dose in order to mitigate unanticipated safety risk in the healthy study subjects. This is acceptable. Upon request, the underestimation of the midazolam DDI with lazertinib was estimated to 0.55 fold and it was justified that for the BCRP substrate Rosuvastatin a comparable AUCR is to be expected with a dose of 240 mg lazertinib. Of the DDI in vitro positives, only UGT1A1 inhibtion and CYP1A2 induction of lazertinib have not been evaluated in a dedicated clinical DDI study. The applicant argues on basis of PBPK modelling and the lack of effect on indirect bilirubin levels, an UGT1A1 endogenous biomarker, that no clinically relevant DDI are expected for UGT1A1. This analysis is considered as acceptable. With regards to CYP1A2 induction, the PBPK model, based on the SimCyp platform, is not considered qualified in accordance with the EMA PBPK Guideline to predict DDI scenarios involving CYP1A2 induction. DDI involving CYP1A2 induction by lazertinib can therefore not be fully excluded. This has been reflected in the section 4.5 of the SmPC and therefore caution is advised when co-administering with substrates of CYP1A2 (e.g., tizanidine).

In a retrospective exploratory analysis, it was demonstrated that the plasma exposure of lazertinib was not affected in a clinically meaningful manner by co-aministration with a gastric acid-reducing agents i.e. PPIs, for at least 4 days prior to treatment with lazertinib. PPIs is considered to represent the worst

case with regards to effect on gastric pH and for PPIs the maximum effect of gastric pH elevation should be reached after 4 days of repeated dosing. Furthermore, the lack of a food-effect supports the finding that PK of lazertinib is not impacted by increased gastric pH. It has been justified that the PK of lazertinib is not impacted in a clinically relevant manner by co-administration with ARA's.

The applied PBPK model underpredicted the observed clinical DDI of lazertinib when coadministered with a strong CYP3A inducer. The PBPK prediction of the effect of co-administation of lazertinib with the moderate CYP450 inducers efavirenz could therefore potentially also be underpredicted. In the pivotal MARIPOSA study, 42 participants treated with amivantamab+lazertinib had co-administration with a moderate CYP3A4 inducer, mainly phenobarbital or metamizole/dipyrone. It was justified that the PK effect of a moderate CYP3A inducer could not be reliable evaluated due to considerable variability in dosing of inducer. A retrospective efficacy analysis was conducted to evaluate PFS by BICR of lazertinib co-administered without any CYP3A4 inducers (n=213) and with moderate CYP3A4 inducers (n=42). This analysis should be interpretated with caution due to low sample size receiving concomitant use of moderate CYP3A4 inducers and variability in dosing of inducer. There was no convincing differential trend observed in PFS, indicating that moderate CYP3A4 inducers does not have a major impact on efficacy. Due to the limit of the efficacy analysis and as the predicted effect of a moderate CYP3A inducer on lazertinib is likely underpredicted, it can't be fully excluded that coadministration of lazertinib with a moderate CYP3A inducers can impact efficacy. The following recommendation has been included in the SmPC "the co-administration of Lazcluze with moderate CYP3A4 inducers may also decrease lazertinib plasma concentrations and hence moderate CYP3A4 inducers (e.g. bosentan, efavirenz, modafinil) should be used with caution."

The SmPC also mentions that co-administration of Lazcluze with strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided, while no initial dose adjustment is required when Lazcluze is co-administered with CYP3A4 inhibitors."

Overall, perpetrator and victim DDIs of lazertinib have been acceptable evaluated in accordance with regulatory requirements and adequately reported in the SmPC.

Pharmacodynamics:

The applicant has not defined any PD biomarkers. Accordingly, no PD biomarkers are proposed for monitoring of effect.

No clinically relevant effect of lazertinib on cardiac repolarization following oral administration of 240 mg lazertinib daily has been observed.

No immunogenicity studies have been conducted for lazertinib. All 864 participants treated with the combination of lazertinib and amivantamab were considered negative for treatment emergent antibodies against amivantamab.

Kaplan-Meier plots of PFS showed no apparent relationship with the different combinations of lazertinib and amivantamab exposures (amivantamab High+lazertinib High, amivantamab Low+lazertinib High, etc), suggesting no E-R relationship for either lazertinib or amivantamab.

There was an increased occurrence rate of paresthesia and stomatitis with increased lazertinib exposure. VTE (any Grade) rate in quartile 1 of lazertinib exposure ($C_{avg.1stcycle}$) appeared to be lower. No clear trend was observed in higher exposure quartiles. No clear E-R trend was observed based on $C_{max,max}$. With increasing exposure, no trend of increased occurrence rate was observed for Grade ≥3 VTE.
There were no clear E-R relationships across the following examined safety endpoints: Rash (any Grade and Grade ≥3), pneumonitis/ILD, paronychia, hypoalbuminemia, and diarrhea.

Cox proportional hazard regression analyses of PFS versus lazertinib exposure showed that lazertinib exposure was not associated with PFS.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology of lazertinib, both with regards to pharmacokinetics and pharmacodynamics, using *in vitro* studies, clinical pharmacology studies and by modelling and simulation studies has been appropriately investigated. In conclusion, the clinical pharmacology package supports approval of lazertinib.

2.6.5. Clinical efficacy

Table 21: **Overview of the clinical efficacy studies**

Study Number/Name Status SCE Data Cutoff	**Study Design**	**Treatment Regimen**	**Study Population/Sample Size (Actual)**
MARIPOSA 73841937NSC3003 (Pivotal Study) Ongoing **11 August 2023**	A Phase 3, randomized study of amivantamab+lazertinib combination therapy versus osimertinib, versus lazertinib as first-line treatment in patients with EGFRm NSCLC. The SCE focuses on 3 arms:[a] amivantamab+lazertinib. osimertinib. lazertinib.	**amivantamab+lazertinib arm**: Amivantamab (1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg IV), once weekly for the first 4 weeks (split dose on Cycle 1 Days 1-2) and then once every 2 weeks) and lazertinib (240 mg orally, once daily). **osimertinib arm:** Double-blind treatment with single-agent osimertinib (80 mg orally, once daily). **lazertinib arm**: Double-blind treatment with single-agent lazertinib (240 mg orally, once daily).	**Study Population:** Treatment-naïve participants with EGFRm NSCLC. Randomization was stratified by: mutation type (exon 19del vs exon 21 L858R) race (Asian vs non-Asian) history of brain metastasis (present vs absent) **Sample Size:** amivantamab+lazertinib arm: N=429 osimertinib arm: N=429 lazertinib arm: N=216
CHRYSALIS 61186372EDI1001[b] Ongoing **15 November 2022**	A Phase 1, first-in-human, open-label, dose escalation study in participants with advanced NSCLC. **Part 1 Dose Escalation – First-line Cohort:** Participants with EGFRm NSCLC receiving amivantamab+lazertinib at the RP2CD in a subset of Part 1, as first-line treatment.	**First-line Cohort (subset of Part 1):** Amivantamab: 1050 mg if <80 kg and 1400 mg if >80 kg IV (once weekly for the first 4 weeks [split dose on Cycle 1 Days 1-2] and then once every 2 weeks) and lazertinib (240 mg orally, once daily).	**First-line Cohort (subset of Part 1, n=20):** Treatment-naïve participants with EGFRm NSCLC receiving amivantamab+lazertinib.
YH25448-201 73841937NSC2001 (Part C: Yuhan sponsored) Completed. **8 January 2021**	A Phase 1/2, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of lazertinib given orally to participants with EGFRm NSCLC. **Part C**: lazertinib - Dose extension phase.	**Part C First-line Cohort**: 240 mg lazertinib[c,d]	**Part C: First-line Cohort:** Treatment-naïve participants with EGFRm NSCLC. **Sample Size** Part C First-line lazertinib monotherapy: N=43
YH25448-301 (Yuhan sponsored) Ongoing. **29 July 2022**	A Phase 3, randomized, double-blind, multinational study to assess the efficacy and safety of lazertinib versus gefitinib as first-line treatment in patients with	Lazertinib 240 mg orally once daily[e,f] or Gefitinib 250 mg orally once daily.	Treatment-naïve participants with EGFRm NSCLC. **Sample Size:** Lazertinib: N=196; Gefitinib: N=197

	EGFRm NSCLC.

EGFR=epidermal growth factor receptor; EGFRm NSCLC=EGFR-mutated locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations; exon 19del=exon 19 deletion; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitors.
[a] Further details of the study design are presented in the CSR (73841937NSC3003).
[b] CHRYSALIS study consists of different cohorts in which participants either receive amivantamab+lazertinib combination therapy, or amivantamab and carboplatin/pemetrexed combination therapy. Only information regarding the First-line Cohort with treatment-naïve EGFRm NSCLC is included in this table and SCE. See CSR for details (1LE20/61186372EDI1001-IA-15Nov2022).
[c] YH25448-201 consists of different Parts in which participants received lazertinib monotherapy in a dose escalation, expansion or extension phase, or in Part D where participants outside Korea were evaluated. Only information regarding Part C (participants with EGFRm NSCLC receiving lazertinib as first-line treatment) is included in this table and SCE.
[d] Complete details concerning the design of the YH25448-201 study can be found in the clinical study report (YH25448-301).
[e] YH25448-301 consists of participants who received either lazertinib or gefitinib monotherapy. Only information regarding the lazertinib treatment is included in this table and SCE.
[f] Complete details concerning the design of the YH25448-301 study can be found in the clinical study report (YH25448-301).

2.6.5.1.1. Dose response study(ies)

The tolerability and efficacy of the combination of lazertinib and amivantamab was first evaluated in the CHRYSALIS study and was further evaluated in CHRYSALIS-2 study. The safety and efficacy data from participants with NSCLC treated with combination of amivantamab and lazertinib demonstrated that the combination therapy at the dose of 1050 mg (body weight <80 kg) or 1400 mg (body weight ≥80 kg) of amivantamab and 240 mg once daily lazertinib is tolerable, effective, and generally consistent with the safety profiles of the individual drug when administered as monotherapy. No DLTs were observed with the proposed combination therapy dose and regimen.

Thus, based on totality of PK, safety, and efficacy data the recommended dose for combination of amivantamab and lazertinib therapy, selected for the MARIPOSA study was 1050 mg (body weight <80 kg) or 1400 mg (body weight ≥80 kg) of amivantamab QW for first 4 weeks (Week 1 dose administered as a split dose on Day 1 and Day 2) and then Q2W thereafter with 240 mg lazertinib once daily.

2.6.5.2. Main study(ies)

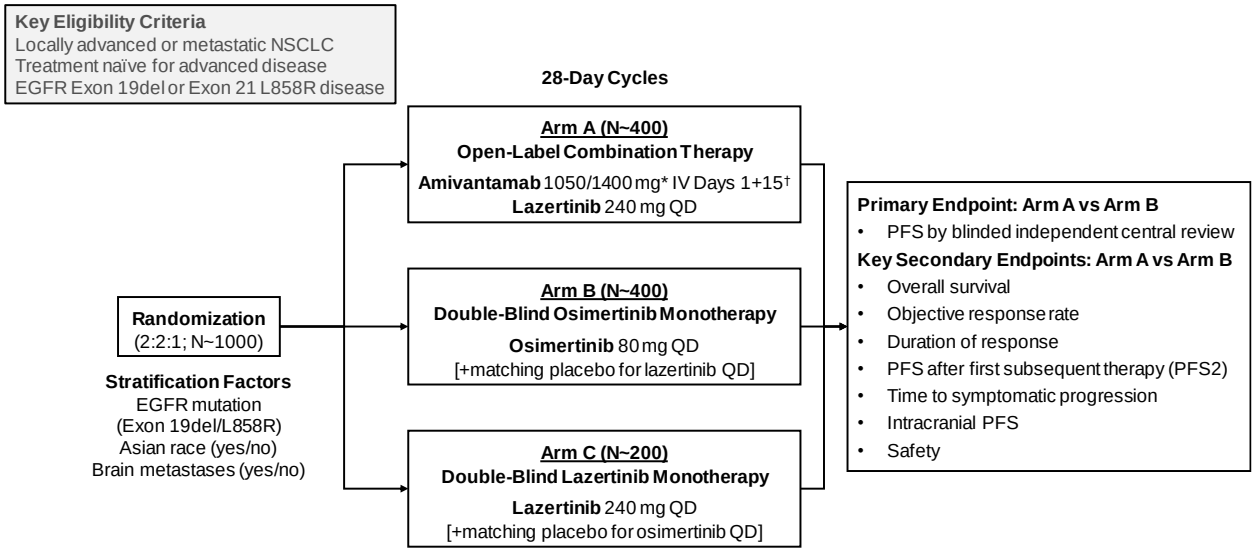
MARIPOSA

Study design

MARIPOSA is an ongoing, randomized, open label, multicenter Phase 3 study to compare the efficacy and safety of the combination of amivantamab and lazertinib versus osimertinib as first-line treatment in participants with EGFRm NSCLC. The contribution of amivantamab to the activity of the combination of amivantamab and lazertinib is also being assessed by comparing the efficacy observed in the amivantamab+lazertinib arm with that in the lazertinib arm.

The study includes a Screening phase, a Treatment phase, and a Follow-up phase.

Figure 14: Study schematic (MARIPOSA)



*Weight-based dosing: <80 kg/≥80 kg. Guidance on dose modification for management of toxicities is provided in the protocol.
†Cycle 1: Days 1-2 (split dose), 8, 15, 22; Cycles 2+: Days 1, 15
EGFR = epidermal growth factor receptor; IV = intravenous(ly); NSCLC = non-small cell lung cancer; PFS = progression-free survival; PFS2 = progression-free survival after the first subsequent therapy; QD = once daily.

The primary objective of MARIPOSA was to assess the efficacy of the combination of amivantamab and lazertinib (Arm A), compared with osimertinib (Arm B), as measured by PFS assessed by BICR in adult participants with EGFRm NSCLC.

The primary efficacy data (CCO date of 11 August 2023) is provided from MARIPOSA, conducted at 262 centres in 27 countries/territories globally.

Upon request from the CHMP an ad hoc OS data update with a CCO of 13 May 2024 was provided.

Study participants

Enrollment in the study was completed on 20 April 2022. A total of 1,074 participants were randomly assigned to treatment in a 2:2:1 ratio as indicated in the schema above.

Main criteria for inclusion and exclusion

Key inclusion criteria in MARIPOSA were as follows:

- Participant must be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).
- Participant must have newly diagnosed, histologically or cytologically confirmed, locally advanced or metastatic NSCLC that is treatment naïve and not amenable to curative therapy including surgical resection or chemoradiation.
- The tumor harbors EGFR exon 19del or exon 21 L858R substitution, as detected by an FDA-approved or other validated test in a CLIA certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US) in accordance with site standard of care. (Note: A copy of the test report documenting the EGFR mutation must be included in the participant records and must also be submitted to the sponsor.)
- Participant must have at least 1 measurable lesion, according to RECIST v1.1 that has not been previously irradiated. Measurable lesions should not have been biopsied during screening,

but if only 1 non-irradiated measurable lesion exists, it may undergo a diagnostic biopsy and be acceptable as a target lesion, provided the baseline tumor assessment scans are performed at least 14 days after the biopsy.

- Participant must have adequate organ and bone marrow function.
- Participant must have ECOG status of 0 or 1.

Key exclusion criteria were as follows:

- Participant has received any prior systemic treatment at any time for locally advanced Stage III or metastatic Stage IV disease (adjuvant or neoadjuvant therapy for Stage I or II disease is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease).
- Participant has symptomatic brain metastases. A participant with asymptomatic or previously treated and stable brain metastases may participate in this study. Participants who have received definitive radiation or surgical treatment for symptomatic or unstable brain metastases and have been clinically stable and asymptomatic for at least weeks before randomization are eligible, provided they have been either off corticosteroid treatment or are receiving low-dose corticosteroid treatment (≤10 mg/day prednisone or equivalent) for at least 2 weeks prior to randomization.
- Participant had a history of deep vein thrombosis or pulmonary embolism within 1 month prior to randomization or any of the following within 6 months prior to randomization: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, any acute coronary syndrome, congestive heart failure or had received any prior treatment with an EGFR TKI

Treatments

Initial dosages for study treatment, by treatment arm, are shown in Table below.

Table 22: Initial Dosages for Study Treatment, by Treatment Arm

	Arm A (Open label)	**Arm B (Double-Blind)**	**Arm C (Double-Blind)**
Amivantamab (350 mg/vial)	1050 mg (1400 mg if ≥80 kg) IV infusion in 28-day cycles Cycle 1: Days 1/2[a], 8, 15, and 22 Cycles 2+: Day 1 and Day 15	-	-
Osimertinib (80 mg capsule)	-	1 osimertinib capsule[b] once daily	1 placebo capsule once daily
Lazertinib (80 mg tablet[c])	3 lazertinib tablets once daily	3 placebo capsules once daily	3 lazertinib tablets once daily

[a]The first dose of amivantamab was split over 2 days as follows: Cycle 1 Day 1, 350 mg (regardless of body weight); Cycle 1 Day 2, 700 mg (1050 mg if ≥80 kg).
[b]Osimertinib was provided as 80-mg tablet (initial dose) and 40-mg tablet (as needed for dose reduction) and over-encapsulated to maintain the blind.
[c]Lazertinib was provided as 80-mg tablets (initial dose is 3 tablets [240 mg]).

Posology: The recommended dose of Lazcluze is 240 mg once daily in combination with amivantamab. It is recommended to administer Lazcluze any time prior to amivantamab when given on the same day.

Duration of treatment: Treatment with Lazcluze + amivantamab, osimertinib + placebo, and Lazcluze + placebo was continued until disease progression or unacceptable toxicity.

Objectives

The primary objective of MARIPOSA was to assess the efficacy of the combination of amivantamab and lazertinib (Arm A), compared with osimertinib (Arm B), as measured by PFS assessed by BICR in adult participants with EGFRm NSCLC.

The primary hypothesis for the study was that the amivantamab and lazertinib combination will prolong PFS compared with single agent osimertinib.

Outcomes/endpoints

Table 23: Objectives and endpoints (MARIPOSA)

Objectives	Endpoints
Primary	
To assess the efficacy of the amivantamab and lazertinib combination, compared with osimertinib, in participants with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC	• PFS according to RECIST v1.1 by blinded independent central review
Secondary	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Overall survival • Objective response rate • Duration of response • PFS after first subsequent therapy • Time to symptomatic progression • Intracranial PFS
To evaluate the safety and tolerability of the amivantamab and lazertinib combination compared with osimertinib	• Incidence of severity of adverse events and clinical laboratory abnormalities, assessment of vital signs, and physical examination abnormalities
To evaluate pharmacokinetics or immunogenicity for amivantamab and pharmacokinetics for lazertinib and assess their relationship to selected endpoints (including but not limited to efficacy, safety, and/or patient-reported outcomes)	• Serum amivantamab and plasma lazertinib concentrations, and serum anti-amivantamab antibodies
To assess health-related quality of life and disease-related symptoms in participants treated with the amivantamab and lazertinib combination compared with osimertinib	• NSCLC-SAQ • EORTC-QLQ-C30
To assess the efficacy of the amivantamab and lazertinib combination, compared with lazertinib monotherapy, in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• PFS • Overall survival
Exploratory	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Disease control rate • Time to treatment discontinuation • Time to subsequent therapy
To assess the intracranial activity of the amivantamab and lazertinib combination compared with osimertinib.	• Intracranial objective response rate • Intracranial duration of response • Time to intracranial disease progression
To further assess health-related quality of life in participants treated with the amivantamab and lazertinib combination compared with osimertinib	• EQ-5D-5L
To explore genetic biomarkers predictive of improved outcome in participants treated with amivantamab in combination with lazertinib, compared with lazertinib and osimertinib monotherapies.	• Characterization of tumor genetics by NGS of ctDNA and genetic analysis of tumor biopsy material at baseline, and at progression • Characterization of circulating EGFR mutation levels by ddPCR of ctDNA at baseline, on therapy, and at progression

To explore mechanisms of resistance to amivantamab and lazertinib and amivantamab/lazertinib combination therapy	• Characterization of tumor protein markers by immunohistochemistry (eg, EGFR, MET) at baseline and at progression • Characterization of changes in tumor genetics, relative to baseline, by NGS of ctDNA and genetic analysis of tumor biopsy material at progression
ctDNA=circulating tumor deoxyribonucleic acid; ddPCR=digital droplet polymerase chain reaction; EGFR=epidermal growth factor receptor; EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L=EuroQol five dimensional descriptive system (5-level version); MET=mesenchymal-epithelial transition; NGS=next-generation sequencing; NSCLC=non-small cell lung cancer; NSCLC-SAQ=Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.	

Sample size

The sample size calculation was based on the assumption that the combination therapy will result in a 27% reduction in the risk of either disease progression or death over the single agent osimertinib therapy (an HR of 0.73, prolongs the median PFS from 19 months to 26 months (Soria 2018)). A total of 450 PFS events in Arm A and Arm B combined would provide approximately 90% power to detect a statistically significant difference between the 2 treatment arms with the stratified log-rank test (2-sided alpha=0.05).

When approximately 390 deaths (Arms A and B combined) have been observed from long-term survival follow-up, final analysis of OS would occur. This would provide approximately 80% power to detect a 25% reduction in the risk of death (an HR of 0.75, prolongs the median OS from 39months to 52 months (Ramalingam 2020) with a log-rank test at a 2-sided alpha of 0.05.

The comparison of the combination of amivantamab and Lazertinib versus Lazertinib was aimed only to demonstrate the contribution of amivantamab to the activity of combination and was not hypothesis tested.

Randomisation and blinding (masking)

A 2:2:1 randomization ratio across three treatment arms was employed, using randomly permuted blocks and stratified by mutation type, race, and history of brain metastases.

Blinded treatment was given in the control arms (Arms B and C) to reduce potential bias during data collection and evaluation of clinical endpoints. Open-label treatment was used in Arm A due to infusion.

Statistical methods

Planned analyses

Table 24: Analysis sets

Population	Description
Full Analysis Set	All randomized participants, classified according to their assigned treatment arm regardless of the actual treatment received.
Safety	Randomized participants who receive at least 1 dose of study treatment.
Pharmacokinetics	Randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline concentration measurement.[a]
Biomarkers	Randomized participants who receive at least 1 dose of study treatment and have at least 1 biomarker measurement.

a. Participants may be removed from the estimation of certain pharmacokinetic parameters on an individual basis due to, for example, missing pharmacokinetic samples such that the pharmacokinetic parameters cannot be appropriately derived. These participants will be identified at the time of the analyses along with their reason for removal.

The primary analysis population for the efficacy analysis was the FAS, which included all randomized participants. The safety population comprised of randomized participants who received at least 1 dose of study drug.

Primary endpoint PFS

The treatment effect of the combination of amivantamab and lazertinib, compared with osimertinib, on PFS was analyzed using a log-rank test stratified by mutation type (exon 19del versus exon 21 L858R), race (Asian versus non-Asian), and history of brain metastasis (present versus absent). The HR for PFS was calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test.

The following sensitivity analyses were conducted to evaluate the robustness of the primary analysis of PFS:

- Unstratified log-rank test
- Proportional hazards assumption was validated
- The stratified analysis of investigator-assessed PFS

The following supplementary analyses were conducted:

-Censored for Death/PD after Start of Subsequent Anti-cancer Therapy

-Not censored for missing two or more consecutive disease evaluations

The analysis of PFS in the study was conducted using both stratified and unstratified methods, with sensitivity analyses to assess the robustness of the primary PFS analysis. Supplementary analyses were also performed, including censoring for death or disease progression after the start of subsequent anti-cancer therapy and handling missing disease evaluations.

The multiplicity strategy utilized a hierarchical testing approach to maintain the overall Type I error rate at the 0.05 level. Testing for the key secondary endpoint of OS was contingent upon the primary endpoint of PFS achieving statistical significance.

Interim analysis

A futility analysis (non-binding) was conducted when approximately 120 PFS events by BICR had occurred in the amivantamab+lazertinib and osimertinib arms combined. A nominal 2-sided alpha of 0.00001 was allocated for futility analysis. The IDMC recommended the study continue without change after the futility analysis.

An interim analysis was planned for PFS when approximately 280 PFS events by BICR from the amivantamab+lazertinib and osimertinib arms combined had occurred. At the time of the 15 January 2023 CCO, there were 321 PFS events observed. After reviewing the data, the IDMC notified the Sponsor Committee that the efficacy stopping criteria had been met for PFS (HR=0.75 [95% CI: 0.60, 0.93], p=0.0097 [less than the 2-sided significance level criterion of 0.0159 based on the O'Brien-Fleming stopping boundary]), in favor of the combination of amivantamab and lazertinib. At the time of the CCO for the interim analysis, the median duration of follow-up was still rather short at 15.1 months, and to better inform the benefit-risk profile, the Sponsor Committee decided to continue the study and maintain the blinding until the next protocol-specified PFS analysis (ie, the final PFS analysis which targeted approximately 450 PFS events from the amivantamab+lazertinib and osimertinib arms combined). This decision was endorsed by the IDMC.

Given that the study continued to the final analysis after the efficacy boundary was crossed at an earlier interim analysis, the statistical significance for the primary endpoint (PFS) can be established if

the final p-value is smaller than the nominal level (2-sided 0.05) without any alpha penalty for the interim look (Hampson 2013).

Key secondary endpoint OS

The key secondary endpoint of OS was analysed using the same methodology and model as for the PFS analysis. A hierarchical testing approach for the primary endpoint and key secondary endpoint was used: the comparison between the combination of amivantamab and lazertinib versus osimertinib for OS was to be conducted only if the comparison for PFS showed statistical significance.

Unstratified analysis of OS was conducted as sensitivity analysis.
The CCO for the final PFS analysis was 11 August 2023. A planned interim analysis of OS was conducted at the time of the final PFS analysis with statistical significance level determined by O'Brien-Fleming alpha spending approach. If the statistical significance for OS was not achieved, the final analysis of OS would be conducted when approximately 390 deaths from amivantamab+lazertinib and osimertinib arms combined have occurred.

Other secondary endpoints

ORR

The ORR was defined as the proportion of participants who achieved either a complete response or PR, as defined by BICR using RECIST v1.1. ORR was analyzed using a logistic regression stratified by mutation type (Exon 19del vs Exon 21 L858R) and race (Asian vs non-Asian), and history of brain metastasis (present vs absent). The results of the analysis were presented in terms of an odds ratio together with its associated 95% confidence intervals.

DOR

The DOR was defined as the time from the date of the first documented response (CR or PR) until the date of documented progression or death, whichever came first. The end of response should have coincided with the date of progression or death from any cause used for the PFS endpoint. If a participant did not progress following a response, then his/her duration of response would use the PFS censoring time. A Kaplan-Meier plot and median duration of response with 95% confidence interval (calculated from the Kaplan-Meier estimate) were presented by treatment group.

PFS2

The PFS2 was defined as the time from randomization until the date of the second objective disease progression, after the initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever came first. Participants who were alive and for whom a second disease progression had not been observed were censored at the last time known to be alive and without a second disease progression. PFS2 was analyzed using the same method as PFS.

TTSP

Time to symptomatic progression (TTSP) was defined as the time from randomization to the documentation in the eCRF of any of the following (whichever occurred earlier): the onset of new symptoms or symptom worsening that was considered by the investigator to be related to lung cancer and required either a change in anticancer treatment and/or clinical intervention to manage symptoms or death. The symptomatic progression could be reported before, after, or at the time radiographic disease progression was identified and should have continued to be assessed after subsequent therapy had been initiated. The TTSP for a participant who did not experience any of these events was censored on the date on which the participant was last known to be event-free. The TTSP was analyzed using similar methods as the analysis of PFS.

Intracranial PFS

Intracranial PFS was defined as the time from randomization until the date of objective intracranial disease progression or death, whichever came first, based on BICR using RECIST v1.1 in participants who had a history of brain metastasis at screening in the full analysis set. Participants who had not progressed intracranially or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. It was analyzed using a similar method as the analysis of PFS.

Interim analyses

Planned

Two interim analyses for PFS were planned for this study. An Independent Data Monitoring Committee (IDMC) was commissioned for the study.

The first interim analysis with the main purpose of futility assessment was to be conducted when approximately 120 PFS events from Arms A and B combined have occurred (27% of the planned events). A nominal 2-sided alpha of 0.00001 was allocated. If the hazard ratio from a stratified Cox proportional-hazard model for the combination therapy versus osimertinib was ≥1.0, the study could be stopped for futility.

The second interim analysis of PFS was to be performed to assess the superiority of the combination therapy versus osimertinib, when approximately 280 PFS events from Arms A and B combined (approximately 350 PFS events overall, i.e., in all treatments arms combined) have occurred. The significance level for superiority was determined based on the observed number of PFS events at the interim analysis, using the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method. Assuming 280 PFS events observed at the interim, the 2-sided alpha to be spent at the interim and final PFS analyses were 0.0090, and 0.0472, respectively.

One interim analysis for OS was planned at the time of the final analysis for PFS, when approximately 270 deaths from Arms A and B combined were anticipated (69% of the 390 events planned). The superiority for OS was to be tested with a total 2-sided alpha of 0.05 only if statistical significance for PFS is achieved. Assuming 270 deaths observed at the interim from Arms A and B combined, based on the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method, the 2-sided alpha to be spent at the interim and final OS analyses were 0.0140 and 0.0457, respectively.

Performed

One futility (non-binding) analysis was performed. The IDMC had recommended that the study continue without change after the futility analysis.

At the time of the interim PFS analysis (CCO of 15 January 2023), there were 321 PFS events by BICR observed from the amivantamab + lazertinib and osimertinib arms combined. After reviewing the data on 31 March 2023, the IDMC notified the Sponsor Committee that the efficacy stopping criteria had been met for PFS (HR=0.75 [95% CI: 0.60, 0.93], p=0.0097 [less than the 2-sided significance level criterion of 0.0159 based on the O'Brien-Fleming stopping boundary]), in favor of the combination of amivantamab and lazertinib. Given that the study continued to the final analysis after the efficacy boundary was crossed at an earlier interim analysis, the statistical significance for the primary endpoint (PFS) can be established if the final p-value is smaller than the nominal level (2-sided 0.05) without any alpha penalty for the interim look (Hampson 2013).

Multiplicity

To strongly control Type I error rate at 0.05 for the study, a hierarchical testing approach for the primary endpoint (PFS) and key secondary endpoint (OS) was used. The comparison between the

amivantamab and lazertinib combination versus osimertinib for OS was to be conducted only if the comparison for PFS showed statistical significance.

The significance level for superiority at the interim and final analysis of PFS and OS, respectively, was to be determined based on the observed number of events using the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method.

Only comparison between the amivantamab and lazertinib combination versus osimertinib was controlled for multiplicity. The comparison of the combination of amivantamab and lazertinib versus lazertinib was not included in the hierarchical testing procedure.

Changes in the SAP

The statistical analysis plan (SAP) was dated February 11th 2021. The primary PFS analysis was reported in 2023. The SAP has two addenda from 2023 that clarified definition of TTSP and the analysis set of intracranial PFS. Also, additional details on PRO analyses were provided.

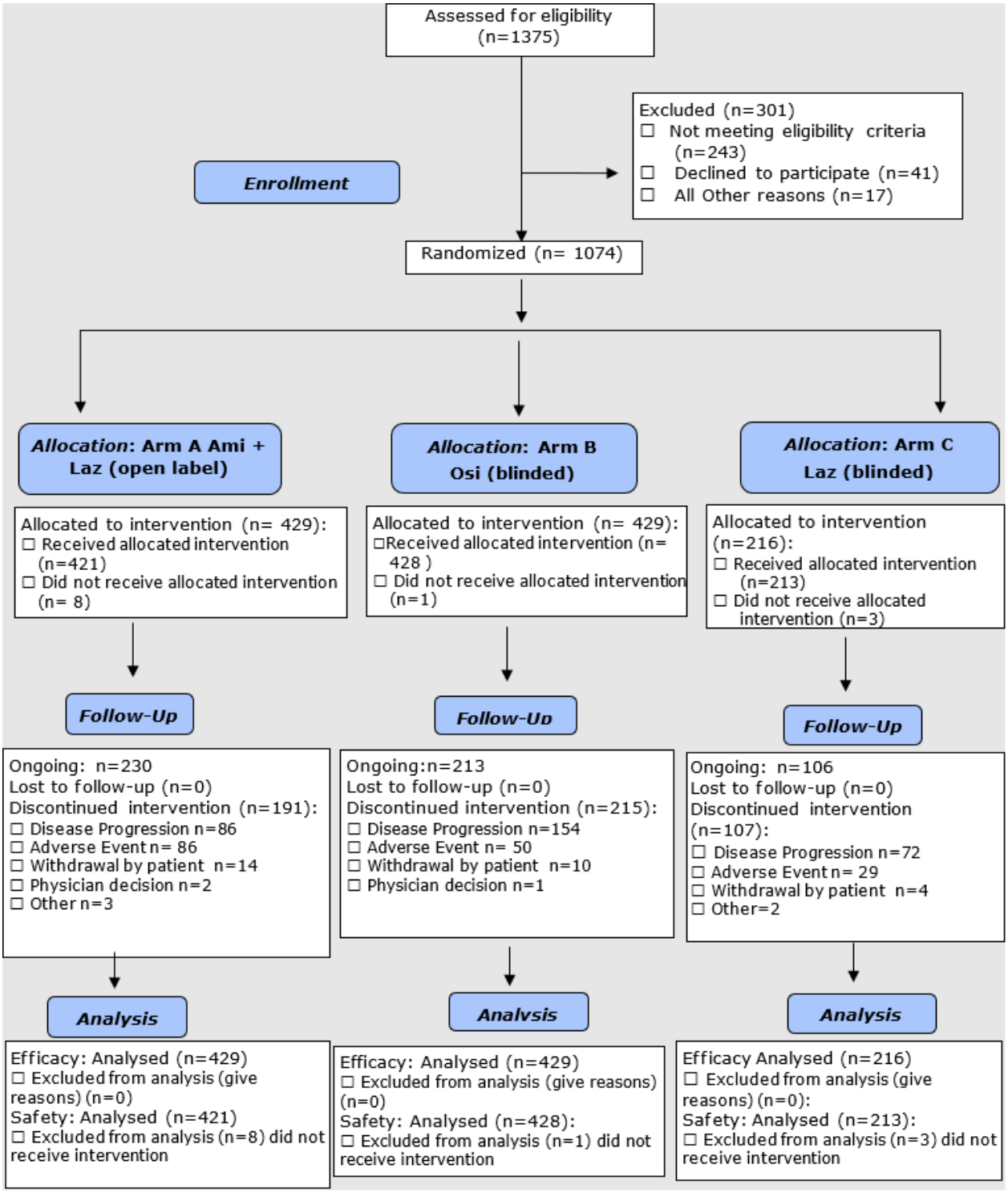
Planned subgroup analyses

Efficacy and safety analyses were performed for pre-specified subgroups of age, sex, race, body weight, history of brain metastasis, mutation type, ECOG performance status score, and history of smoking:

- Age Group: <65 years, ≥65 years; <75 years, ≥75 years
- Sex: Male, Female
- Race: Asian, Non-Asian
- Weight: <80 kg, ≥80 kg
- Mutation type: Exon 19del, Exon 21 L858R
- History of brain metastasis: Yes, No
- ECOG performance status score; 0, 1
- History of smoking: Yes, No

Results

- **Participant flow**



Recruitment

The MARIPOSA study was conducted at 262 centres in 27 countries/territories globally.

The study was initiated (first patient screened) on 16-OCT-2020.

Enrollment in the study was completed on 20 April 2022.

Study status: Ongoing

Study centres: This study was conducted at 262 centers, of which 219 centers enrolled participants in Argentina, Australia, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, Poland, Portugal, Russian Federation, South Korea, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, and the United States (including Puerto Rico)

Disposition of Participants
Of the 1074 participants who entered the study, 429 were randomized to the amivantamab + lazertinib arm, 429 to the osimertinib arm, and 216 to the lazertinib arm. A total of 12 participants (1.1%) who were randomized did not receive any dose of study treatment (8 participants [1.9%] in the amivantamab + lazertinib arm, 1 participant [0.2%] in the osimertinib arm, and 3 participants [1.4%] in the lazertinib arm). 1062 participants (98.9%) (421 [98.1%] in the amivantamab + lazertinib arm, 428 [99.8%] in the osimertinib arm, and 213 [98.6%] in the lazertinib arm) received at least 1 dose of study treatment.
A summary of study disposition is provided below:

Table 25: Study Disposition; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Subjects randomized but not treated	8 (1.9%)	1 (0.2%)	3 (1.4%)	12 (1.1%)
Subjects treated	421 (98.1%)	428 (99.8%)	213 (98.6%)	1062 (98.9%)
Subjects still on the study	313 (73.0%)	297 (69.2%)	149 (69.0%)	759 (70.7%)
Completed study participation [a]	94 (21.9%)	113 (26.3%)	54 (25.0%)	261 (24.3%)
Subjects discontinued the study	22 (5.1%)	19 (4.4%)	13 (6.0%)	54 (5.0%)
Reason for termination				
Withdrawal by subject	19 (4.4%)	18 (4.2%)	13 (6.0%)	50 (4.7%)
Lost to follow-up	3 (0.7%)	1 (0.2%)	0	4 (0.4%)

[a] Completed: if a subject had died before the end of study

At the time of the CCO, 513 participants (48.3%) had discontinued all study treatment:

Table 26: Treatment Disposition; Safety Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Safety	421	428	213	1062
Subjects ongoing any study agent	230 (54.6%)	213 (49.8%)	106 (49.8%)	549 (51.7%)
Discontinued all study agents	191 (45.4%)	215 (50.2%)	107 (50.2%)	513 (48.3%)
Reason for discontinuation of last study agent				
Progressive disease	86 (20.4%)	154 (36.0%)	72 (33.8%)	312 (29.4%)
Adverse event	86 (20.4%)	50 (11.7%)	29 (13.6%)	165 (15.5%)
Adverse event – COVID-19 related	2 (0.5%)	3 (0.7%)	0	5 (0.5%)
Subject refused further study treatment	14 (3.3%)	10 (2.3%)	4 (1.9%)	28 (2.6%)
Physician decision	2 (0.5%)	1 (0.2%)	0	3 (0.3%)
Non-compliance with study drug	1 (0.2%)	0	1 (0.5%)	2 (0.2%)
Lost to follow-up	1 (0.2%)	0	0	1 (0.1%)
Other	1 (0.2%)	0	1 (0.5%)	2 (0.2%)

Note: Adverse events that are considered COVID-19 related (associated) are based on events that code to a COVID-19 MedDRA term and events that are identified via the COVID-19 Case of AEs form

Conduct of the study

Prior to the CCO of 11 August 2023, there were 3 global amendments to the original protocol dated 05 June 2020, as well as several country/territory-specific amendments to address health authority requests.

Table 27: Key Changes Implemented with Global Protocol Amendments

Amendment Number (Date)	Key Changes
Amendment 1 (22 Apr 2021)	• The pregnancy testing requirements were clarified to ensure pregnant women would not receive study treatment. • Clarifications were made to the timing of study procedures to ensure compliance. • Inclusion and exclusion criteria were clarified to ensure only the intended target population was enrolled. • Guidance for the use of concomitant medications that induce, inhibit, or are substrates of CYP3A4/5 was revised based on emerging data regarding the interaction between study treatment and potential concomitant medications. • Several clarifications were made to facilitate study conduct including but not limited to guidance on retreatment at a reduced dose and treatment discontinuation, and clarification of the requirements for collection of tissue samples. • The sponsor's commitment to provide participants with continued access to investigational drug after study closure was added. • The standalone COVID-19 appendix was updated to specify that participants will not be excluded from the study for having received non-live vaccines that are either approved or authorized for emergency use (eg, COVID-19) by local health authorities.
Amendment 2 (23 Sep 2021)	• Clarifications were made to tumor imaging and brain imaging assessments. • Additional information was provided on the amivantamab infusion and on IRRs to provide guidance in case of infusion interruption. • Information for paresthesia and pneumonitis management was added based on emerging data. • Information was added on CT and MRI assessment requirements.
Amendment 3 (22 August 2022)	• Information regarding the AESI of VTE events, as well as associated measures for monitoring and prophylaxis of these events, were added. • Clarifications were made in the schedule of assessments and visits and timing of PK sampling. • Clarifications were made to the reporting of symptomatic progression during the follow up period.

AESI=adverse event of special interest; CT=computed tomography; IRR=infusion-related reaction; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); VTE=venous thromboembolic (events)
Source: 73841937NSC3003 CSR/Tab1

In the MARIPOSA study, 1074 participants were randomized in total. The original MARIPOSA protocol was approved internally on 05 June 2020, with the first participant randomized in November 2020. Globally, there were approximately 689 participants randomized before implementation of Amendment 1 (approved internally on 22 April 2021), 279 participants randomized before implementation of Amendment 2 (approved internally on 23 September 2021), and 106 participants randomized before implementation of Amendment 3 (approved internally on 22 August 2022).

Major protocol deviations:

At the time of CCO, major protocol deviations were identified in 63 participants (5.9%) overall (23 participants [5.4%] in the amivantamab + lazertinib arm, 26 participants [6.1%] in the osimertinib arm, and 14 participants [6.5%] in the lazertinib arm). A listing of individual participants with major protocol deviations is provided below.

Table 28: Summary of subjects with major Protocol deviations; full analysis set

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Subjects with major protocol deviations	23 (5.4%)	26 (6.1%)	14 (6.5%)	63 (5.9%)
Developed withdrawal criteria but not withdrawn	2 (0.5%)	0	1 (0.5%)	3 (0.3%)
Entered but did not satisfy criteria	9 (2.1%)	15 (3.5%)	12 (5.6%)	36 (3.4%)
Received a disallowed concomitant treatment	3 (0.7%)	2 (0.5%)	1 (0.5%)	6 (0.6%)
Received wrong treatment or incorrect dose	6 (1.4%)	1 (0.2%)	0	7 (0.7%)
Other	8 (1.9%)	9 (2.1%)	0	17 (1.6%)
Other - Regional crisis	0	0	0	0
Other - COVID-19	1 (0.2%)	2 (0.5%)	0	3 (0.3%)

Note: Subjects may appear in more than one category.

Baseline data

Table 29: Summary of Demographics and Baseline Characteristics; FAS (MARIPOSA)

		Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full		429	429	216	1074
Age, years	N	429	429	216	1074
	Mean (SD)	62.7 (10.63)	61.9 (11.52)	61.3 (10.69)	62.1 (11.01)
	Median	64.0	63.0	63.0	63.0
	Range	(25; 88)	(28; 88)	(31; 87)	(25; 88)
Age Group 1, years	N	429	429	216	1074
	<65	235 (54.8%)	237 (55.2%)	119 (55.1%)	591 (55.0%)
	>=65	194 (45.2%)	192 (44.8%)	97 (44.9%)	483 (45.0%)
Age Group 2, years	N	429	429	216	1074
	<75	378 (88.1%)	376 (87.6%)	198 (91.7%)	952 (88.6%)
	>=75	51 (11.9%)	53 (12.4%)	18 (8.3%)	122 (11.4%)
Sex	N	429	429	216	1074
	Female	275 (64.1%)	251 (58.5%)	136 (63.0%)	662 (61.6%)
	Male	154 (35.9%)	178 (41.5%)	80 (37.0%)	412 (38.4%)
Race [a]	N	429	429	216	1074
	American Indian or Alaska Native	7 (1.6%)	7 (1.6%)	4 (1.9%)	18 (1.7%)
	Asian	250 (58.3%)	251 (58.5%)	128 (59.3%)	629 (58.6%)
	Black or African American	4 (0.9%)	3 (0.7%)	4 (1.9%)	11 (1.0%)
	Native Hawaiian or other Pacific Islander	1 (0.2%)	1 (0.2%)	0	2 (0.2%)
	White	164 (38.2%)	165 (38.5%)	79 (36.6%)	408 (38.0%)
	Multiple	1 (0.2%)	1 (0.2%)	0	2 (0.2%)
	Unknown	2 (0.5%)	1 (0.2%)	1 (0.5%)	4 (0.4%)
Ethnicity	N	429	429	216	1074
	Hispanic or Latino	56 (13.1%)	45 (10.5%)	24 (11.1%)	125 (11.6%)
	Not Hispanic or Latino	371 (86.5%)	382 (89.0%)	190 (88.0%)	943 (87.8%)
	Unknown	0	1 (0.2%)	1 (0.5%)	2 (0.2%)
	Not Reported	2 (0.5%)	1 (0.2%)	1 (0.5%)	4 (0.4%)

Weight, kg	N	429	429	216	1074
	Mean (SD)	64.4 (13.43)	63.8 (13.44)	63.1 (13.22)	63.9 (13.39)
	Median	62.5	62.4	60.5	62.1
	Range	(32; 118)	(35; 109)	(41; 118)	(32; 118)
	<80 kg	376 (87.6%)	368 (85.8%)	197 (91.2%)	941 (87.6%)
	>=80 kg	53 (12.4%)	61 (14.2%)	19 (8.8%)	133 (12.4%)
Body mass index, kg/m^2	N	429	429	216	1074
	Mean (SD)	24.65 (4.265)	24.15 (4.047)	23.67 (3.982)	24.26 (4.135)
	Median	24.09	23.66	23.03	23.69
	Range	(14.2; 39.6)	(15.6; 42.9)	(16.2; 36.4)	(14.2; 42.9)
Baseline ECOG performance score	N	429	429	216	1074
	0	141 (32.9%)	149 (34.7%)	76 (35.2%)	366 (34.1%)
	1	288 (67.1%)	280 (65.3%)	140 (64.8%)	708 (65.9%)
History of smoking	N	429	429	216	1074
	Yes	130 (30.3%)	134 (31.2%)	73 (33.8%)	337 (31.4%)
	No	299 (69.7%)	295 (68.8%)	143 (66.2%)	737 (68.6%)

ECOG = Eastern Cooperative Oncology Group; SD = standard deviation
[a] Based on investigator reported data recorded on eCRF page.
Note: N's for each parameter reflect non-missing values.

Table 30: Summary of Baseline disease Characteristics; FAS (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
History of brain metastasis [a]				
N	429	429	216	1074
Present	178 (41.5%)	172 (40.1%)	86 (39.8%)	436 (40.6%)
Absent	251 (58.5%)	257 (59.9%)	130 (60.2%)	638 (59.4%)
Mutation Type [a]				
N	429	429	216	1074
Exon 19del	258 (60.1%)	257 (59.9%)	131 (60.6%)	646 (60.1%)
Exon 21 L858R	172 (40.1%)	172 (40.1%)	85 (39.4%)	429 (39.9%)
Initial diagnosis NSCLC subtype				
N	429	429	216	1074
Adenocarcinoma	417 (97.2%)	415 (96.7%)	212 (98.1%)	1044 (97.2%)
Large cell carcinoma	3 (0.7%)	0	0	3 (0.3%)
Squamous cell carcinoma	6 (1.4%)	5 (1.2%)	2 (0.9%)	13 (1.2%)
Other	2 (0.5%)	9 (2.1%)	2 (0.9%)	13 (1.2%)
Not Reported	1 (0.2%)	0	0	1 (0.1%)
Histology grade at initial diagnosis				
N	429	429	216	1074
Poorly differentiated	61 (14.2%)	61 (14.2%)	32 (14.8%)	154 (14.3%)
Moderately differentiated	90 (21.0%)	108 (25.2%)	42 (19.4%)	240 (22.3%)
Well differentiated	46 (10.7%)	50 (11.7%)	19 (8.8%)	115 (10.7%)
Other	14 (3.3%)	11 (2.6%)	11 (5.1%)	36 (3.4%)
Not Reported	218 (50.8%)	199 (46.4%)	112 (51.9%)	529 (49.3%)
Cancer stage at initial diagnosis				
N	429	429	216	1074
IA	10 (2.3%)	9 (2.1%)	5 (2.3%)	24 (2.2%)
IB	12 (2.8%)	8 (1.9%)	2 (0.9%)	22 (2.0%)
IIA	2 (0.5%)	2 (0.5%)	2 (0.9%)	6 (0.6%)
IIB	5 (1.2%)	3 (0.7%)	0	8 (0.7%)
IIIA	3 (0.7%)	6 (1.4%)	0	9 (0.8%)
IIIB	14 (3.3%)	10 (2.3%)	3 (1.4%)	27 (2.5%)
IIIC	4 (0.9%)	5 (1.2%)	2 (0.9%)	11 (1.0%)
IVA	146 (34.0%)	150 (35.0%)	81 (37.5%)	377 (35.1%)
IVB	233 (54.3%)	236 (55.0%)	121 (56.0%)	590 (54.9%)
Location of metastasis at screening [b]				
N	421	424	216	1061
Bone	206 (48.9%)	180 (42.5%)	90 (41.7%)	476 (44.9%)
Liver	64 (15.2%)	72 (17.0%)	32 (14.8%)	168 (15.8%)
Brain	178 (42.3%)	172 (40.6%)	86 (39.8%)	436 (41.1%)
Lymph Node	282 (67.0%)	289 (68.2%)	144 (66.7%)	715 (67.4%)
Adrenal Gland	41 (9.7%)	45 (10.6%)	19 (8.8%)	105 (9.9%)
Lung	257 (61.0%)	280 (66.0%)	135 (62.5%)	672 (63.3%)
Other	14 (3.3%)	16 (3.8%)	8 (3.7%)	38 (3.6%)
Histology grade at screening				
N	429	429	216	1074
Poorly differentiated	59 (13.8%)	66 (15.4%)	36 (16.7%)	161 (15.0%)
Moderately differentiated	86 (20.0%)	111 (25.9%)	40 (18.5%)	237 (22.1%)
Well differentiated	46 (10.7%)	49 (11.4%)	19 (8.8%)	114 (10.6%)
Other	18 (4.2%)	11 (2.6%)	13 (6.0%)	42 (3.9%)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Not Reported	220 (51.3%)	192 (44.8%)	108 (50.0%)	520 (48.4%)
Cancer stage at screening				
N	429	429	216	1074
IIIA	1 (0.2%)	3 (0.7%)	0	4 (0.4%)
IIIB	11 (2.6%)	5 (1.2%)	2 (0.9%)	18 (1.7%)
IIIC	3 (0.7%)	3 (0.7%)	2 (0.9%)	8 (0.7%)
IVA	131 (30.5%)	119 (27.7%)	66 (30.6%)	316 (29.4%)
IVB	283 (66.0%)	299 (69.7%)	146 (67.6%)	728 (67.8%)
Time since initial lung cancer diagnosis (months) [c]				
N	429	429	216	1074
Mean (SD)	4.785 (14.8980)	4.614 (15.2386)	5.024 (22.1585)	4.765 (16.7202)
Median	1.511	1.413	1.347	1.413
Range	(0.16; 207.87)	(0.26; 162.79)	(0.23; 197.26)	(0.16; 207.87)
Time since metastatic disease diagnosis (months) [c]				
N	421	424	216	1061
Mean (SD)	1.669 (1.8189)	1.491 (1.1084)	1.443 (1.1156)	1.552 (1.4363)
Median	1.314	1.248	1.166	1.248
Range	(0.16; 24.08)	(0.13; 11.66)	(0.20; 9.17)	(0.13; 24.08)

Key: NSCLC = non-small cell lung cancer
[a] Based on investigator reported data recorded on eCRF page.
[b] Subjects can be counted in more than one category.
[c] Relative to the date of randomization.

Numbers analysed

All 1074 participants randomized in the study were included in the Full Analysis Set, which was used for the demographics, baseline disease characteristics, and efficacy analyses. A total of 1062 participants received at least 1 dose of study treatment and were therefore included in the Safety Analyses Set. For the amivantamab + lazertinib arm, the PK Analysis Set included 420 participants and the Immunogenicity Analysis Set included 398 participants.

The number of participants included in each analysis set is provided in the table below.

Table 31: Number of Subjects in Each Analysis Set in MARIPOSA Study

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Safety analysis set	421 (98.1%)	428 (99.8%)	213 (98.6%)	1062 (98.9%)
Pharmacokinetics (PK)	420 (97.9%)	-	-	-
Immunogenicity	398 (92.8%)	-	-	-
Measurable disease at baseline by BICR	421 (98.1%)	414 (96.5%)	214 (99.1%)	1049 (97.7%)
Patient-reported outcome	429 (100%)	429 (100%)	216 (100%)	1074 (100%)

At the time of CCO (11 August 2023), the median follow-up in the study was 22.01 months (amivantamab + lazertinib arm: 22.21 months; osimertinib arm: 21.98 months; lazertinib arm: 21.88 months).

The median duration of treatment in the amivantamab + lazertinib arm was 18.50 months ([range: 0.2 to 31.4].

The median duration of treatment in the osimertinib arm was 18 months (range: 0.2 to 32.7), and 17.05 months (range: 0.4 to 32.1) in the lazertinib arm.

Prior therapies

A summary of prior therapies for lung cancer is presented below. The most common prior systemic therapies, all administered in the adjuvant/neo-adjuvant setting, were platinum doublets cisplatin + vinorelbine (8 participants [0.7%]), carboplatin + paclitaxel (3 participants [0.3%]), and cisplatin + pemetrexed (3 participants [0.3%]).

Table 32: Prior Therapies for Lung Cancer; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Total number of subjects with any prior therapies for lung cancer	112 (26.1%)	104 (24.2%)	41 (19.0%)	257 (23.9%)
Prior systemic therapy	8 (1.9%)	10 (2.3%)	3 (1.4%)	21 (2.0%)
Prior radiotherapy	73 (17.0%)	65 (15.2%)	30 (13.9%)	168 (15.6%)
Prior cancer-related surgery	53 (12.4%)	49 (11.4%)	16 (7.4%)	118 (11.0%)
Number of prior lines of systemic therapy				
0	421 (98.1%)	419 (97.7%)	213 (98.6%)	1053 (98.0%)
1	8 (1.9%)	10 (2.3%)	3 (1.4%)	21 (2.0%)

Biomarker analyses

According to the inclusion criterion, the selected patients must have NSCLC tumors that harbors EGFR exon 19del or exon 21 L858R substitution, as detected by an FDA-approved or other validated test in a CLIA certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US) in accordance with site standard of care.

Table 33: List of Local CE-marked Tests Used in the MARIPOSA Study

	Test Name
	AmoyDX® Pan Lung Cancer PCR Panel
	Biocartis Idaylla™
	Roche cobas® EGFR Mutation Test V2
	Diatech EasyPGX
	Qiagen *therascreen* EGFR RGQ PCR KIT
	EntroGene® EGFR Mutation Analysis Kit
	FoundationOne® CDx
	Guardant360® CDx
	Illumina TruSight™ Comprehensive (EU)
	ThermoFisher Ion Torrent Oncomine Dx Target Test
	OncoDEEP
	Roche Real-time PCR Instrument LC480

Concordance between local laboratory and central testing of EGFR exon 19 deletions or exon 21 L858R substitution mutations and central testing:

Of the 871 participants enrolled to MARIPOSA at sites outside of China, 849 participants had a valid central test result (676 via tissue testing and 173 via plasma testing in place of a missing tissue result). Central cobas tissue testing (using the cobas® EGFR Mutation Test v2) was concordant with local testing in 96.3% of the samples with a valid cobas tissue test result. Central testing was concordant with local testing in 74.0% of the samples with a valid central Guardant plasma test (using Guardant 360® CDx) when no valid central tissue test was available.

Exposure

The median duration of treatment in the amivantamab + lazertinib arm was 18.50 months (15.24 months [range: 0.0 to 31.3] for amivantamab and 18.50 months [range: 0.2 to 31.4] for lazertinib). The median duration of treatment was 18.00 months (range: 0.2 to 32.7) in the osimertinib arm and 17.05 months (range: 0.4 to 32.1) in the lazertinib arm. Participants in the amivantamab + lazertinib arm received a median of 16.0 cycles of amivantamab, with 2 participants receiving 35 cycles (the largest number of cycles administered at the time of CCO).

The median relative dose intensity, which is a ratio of actual versus prescribed doses (prescribed dose includes planned interruptions), in the amivantamab + lazertinib arm was 100.00% (range: 2.0 to 100.0) for amivantamab and 96.0% (range: 32.7 to 100.8) for lazertinib. In the osimertinib arm, median relative dose intensity was 99.87% (range: 66.7 to 100.3) and in the lazertinib arm was 99.79% (range: 74.5 to 100.8).

Consistent with prior studies in this study population, treatment beyond disease progression was common, indicating that there is a benefit to targeted therapy beyond RECIST PD (Le 2018; Mu 2019). The median duration of study treatment greater than 28 days beyond disease progression as assessed by investigator was 3.94 months (range: 1.0 to 19.9) in the amivantamab + lazertinib arm (78 participants of 147 with PD [53.1%]), 3.09 months (range: 1.0 to 24.7) in the osimertinib arm (103 participants of 203 with PD [50.7%]), and 3.94 months (range: 1.0 to 19.2) in the lazertinib arm (51 participants of 104 with PD [49.0%]).

Outcomes and estimation

Primary endpoint – PFS by BICR

Table 34: Progression-free Survival – Primary Analysis - Stratified Analysis - BICR; FAS (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	192 (44.8%)	252 (58.7%)	121 (56.0%)
Censored	237 (55.2%)	177 (41.3%)	95 (44.0%)
Time to event (months)			
25th percentile (95% CI)	11.07 (9.36, 12.91)	9.23 (7.49, 10.94)	9.23 (7.43, 11.10)
Median (95% CI)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)	18.46 (14.75, 20.11)
75th percentile (95% CI)	NE (NE, NE)	NE (27.50, NE)	NE (24.05, NE)
Range	(0.0+, 32.3+)	(0.0+, 32.0+)	(0.0+, 30.3+)
6-month event-free rate (95% CI)	0.87 (0.83, 0.90)	0.85 (0.81, 0.88)	0.85 (0.79, 0.89)
12-month event-free rate (95% CI)	0.73 (0.69, 0.77)	0.65 (0.60, 0.69)	0.67 (0.60, 0.73)
18-month event-free rate (95% CI)	0.60 (0.55, 0.64)	0.48 (0.43, 0.53)	0.52 (0.44, 0.58)

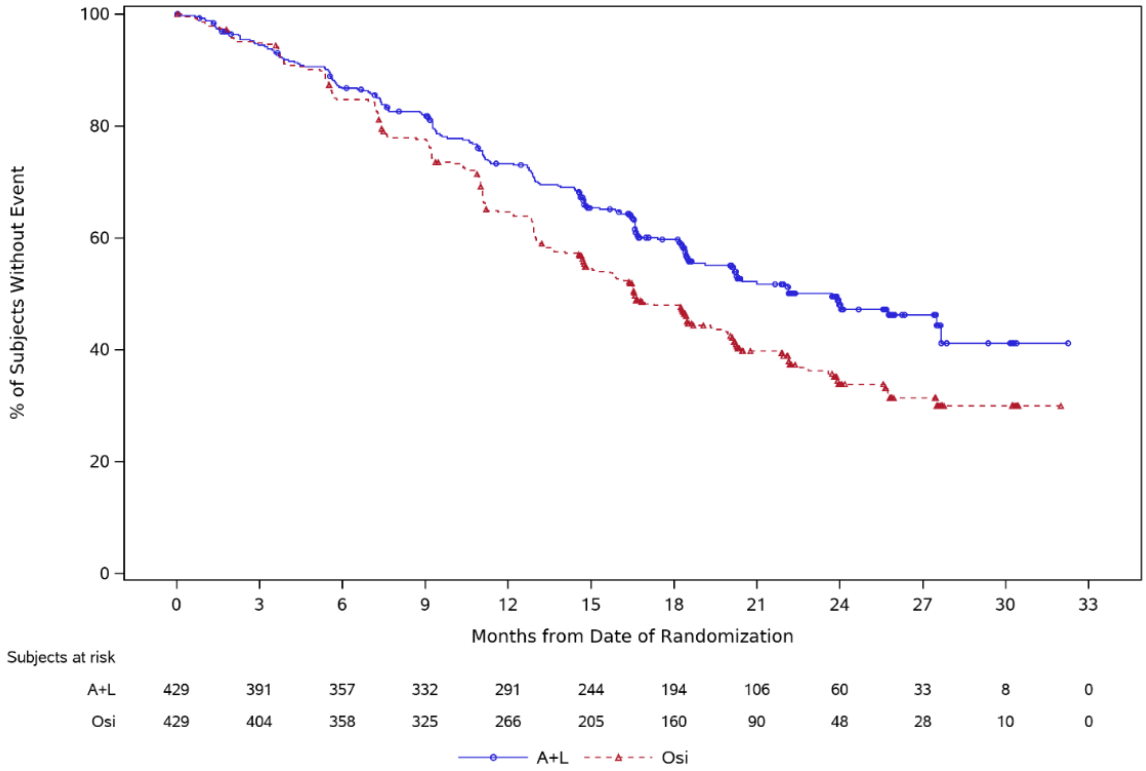
	Amivantamab + Lazertinib	Osimertinib	Lazertinib
24-month event-free rate (95% CI)	0.48 (0.42, 0.54)	0.34 (0.28, 0.39)	0.35 (0.27, 0.42)
Amivantamab + Lazertinib vs Osimertinib Hazard ratio (95% CI)[a,b]; p-value[a]	0.70 (0.58, 0.85); 0.0002		
Amivantamab + Lazertinib vs Lazertinib Hazard ratio (95% CI)[a,b]; p-value[a]	0.72 (0.57, 0.90); 0.0046		

+ = censored observation; CI = confidence interval; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type, race, and history of brain metastasis.
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.
Source: SCE, Sec2.1.4

Table 35: Summary of PFS events and reasons for censoring by BICR

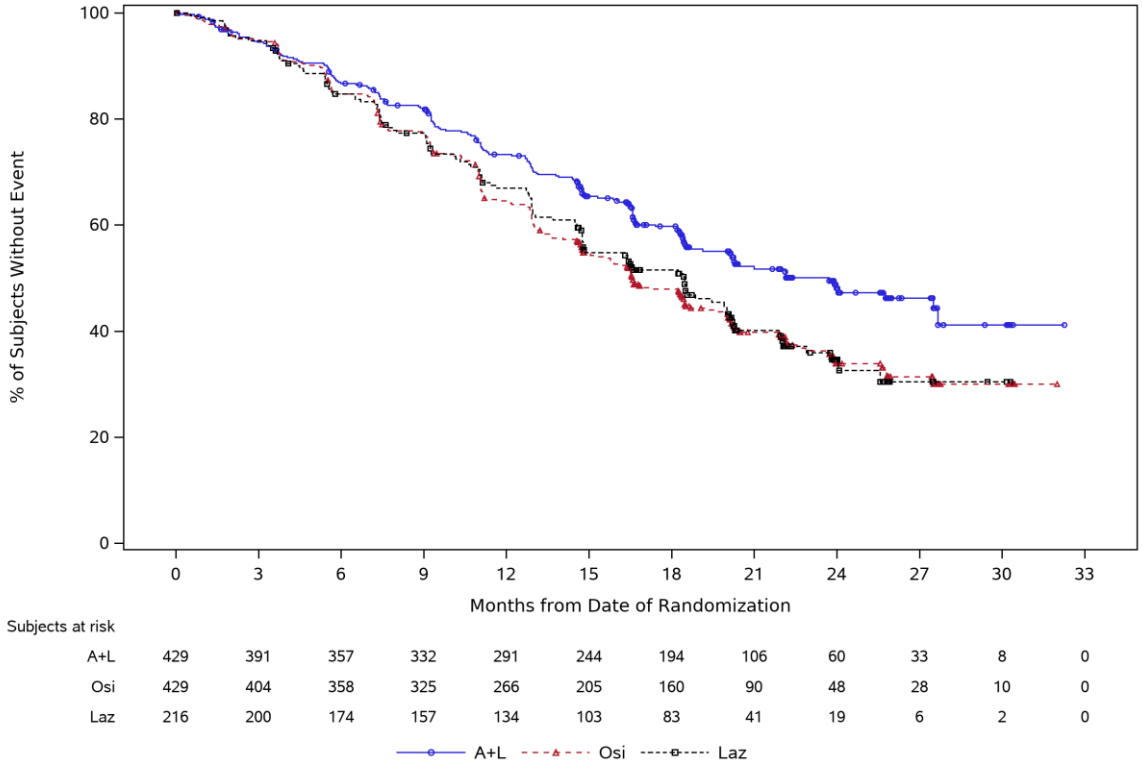
	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Subjects with event	192 (44.8%)	252 (58.7%)	121 (56.0%)
Progressive disease	148 (34.5%)	228 (53.1%)	111 (51.4%)
Death without progressive disease	44 (10.3%)	24 (5.6%)	10 (4.6%)
Subjects censored	237 (55.2%)	177 (41.3%)	95 (44.0%)
Reason for censoring			
Study cut-off	210 (49.0%)	161 (37.5%)	81 (37.5%)
Withdrawal of consent to study participation	15 (3.5%)	8 (1.9%)	8 (3.7%)
No PD or death prior to >= 2 consecutively missing or unevaluable assessments	11 (2.6%)	8 (1.9%)	6 (2.8%)
Lost to follow-up	1 (0.2%)	0	0

Figure 15: Kaplan-Meier Plot of Progression-free Survival for Amivantamab + Lazertinib vs Osimertinib - BICR; FAS (MARIPOSA)



A + L = Amivantamab + Lazertinib; Osi = Osimertinib

Figure 16: Kaplan-Meier Plot of Progression-free Survival for Amivantamab + Lazertinib vs Osimertinib vs Lazertinib - BICR; FAS (MARIPOSA)



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; Laz = Lazertinib

Secondary endpoint – OS at the time of primary analysis (CCO: 11 August 2023)

Table 36: Summary of Overall Survival – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	97 (22.6%)	117 (27.3%)	56 (25.9%)
Censored	332 (77.4%)	312 (72.7%)	160 (74.1%)
Time to event (months)			
25th percentile (95% CI)	23.62 (21.03, NE)	20.30 (18.00, 23.59)	20.30 (14.92, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 32.3+)	(0.3, 32.7+)	(0.0+, 32.1+)
6-month event-free rate (95% CI)	0.93 (0.90, 0.95)	0.96 (0.93, 0.97)	0.95 (0.91, 0.97)
12-month event-free rate (95% CI)	0.90 (0.86, 0.92)	0.88 (0.85, 0.91)	0.86 (0.81, 0.90)
18-month event-free rate (95% CI)	0.82 (0.78, 0.85)	0.79 (0.75, 0.83)	0.78 (0.71, 0.83)
24-month event-free rate (95% CI)	0.74 (0.69, 0.78)	0.69 (0.64, 0.74)	0.71 (0.64, 0.78)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.1099		
Hazard ratio (95% CI)[a,b]	0.80 (0.61, 1.05)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2343		
Hazard ratio (95% CI)[a,b]	0.82 (0.59, 1.14)		

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

Secondary endpoint – OS data update (CCO: 13 May 2024, with median follow-up of 31.3 months)

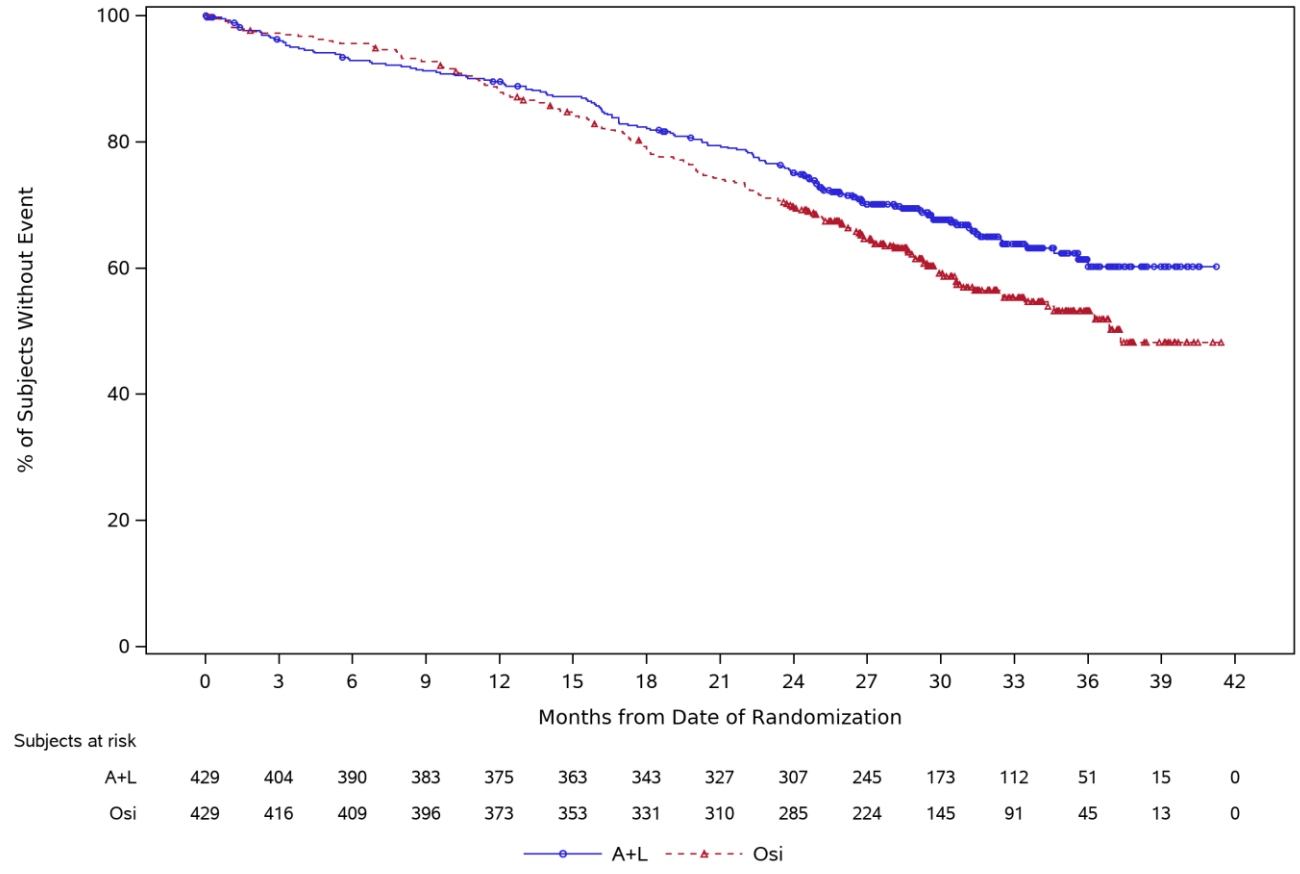
Table 37: Summary of Overall Survival – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	142 (33.1%)	177 (41.3%)	80 (37.0%)
Censored	287 (66.9%)	252 (58.7%)	136 (63.0%)
Time to event (months)			
25th percentile (95% CI)	24.05 (21.03, 26.78)	20.21 (18.00, 23.36)	19.45 (14.85, 26.35)
Median (95% CI)	NE (NE, NE)	37.32 (32.53, NE)	NE (32.99, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 41.2+)	(0.3, 41.4+)	(0.0+, 41.1+)
6-month event-free rate (95% CI)	0.93 (0.90, 0.95)	0.96 (0.93, 0.97)	0.94 (0.90, 0.97)
12-month event-free rate (95% CI)	0.90 (0.86, 0.92)	0.88 (0.84, 0.91)	0.85 (0.80, 0.89)
18-month event-free rate (95% CI)	0.82 (0.78, 0.86)	0.79 (0.75, 0.83)	0.77 (0.71, 0.82)
24-month event-free rate (95% CI)	0.75 (0.71, 0.79)	0.70 (0.65, 0.74)	0.71 (0.65, 0.77)
30-month event-free rate (95% CI)	0.68 (0.63, 0.72)	0.59 (0.54, 0.64)	0.61 (0.54, 0.68)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
36-month event-free rate (95% CI)	0.61 (0.56, 0.67)	0.53 (0.47, 0.59)	0.57 (0.49, 0.64)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.0185		
Hazard ratio (95% CI)[a,b]	0.77 (0.61, 0.96)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2048		
Hazard ratio (95% CI)[a,b]	0.84 (0.64, 1.10)		

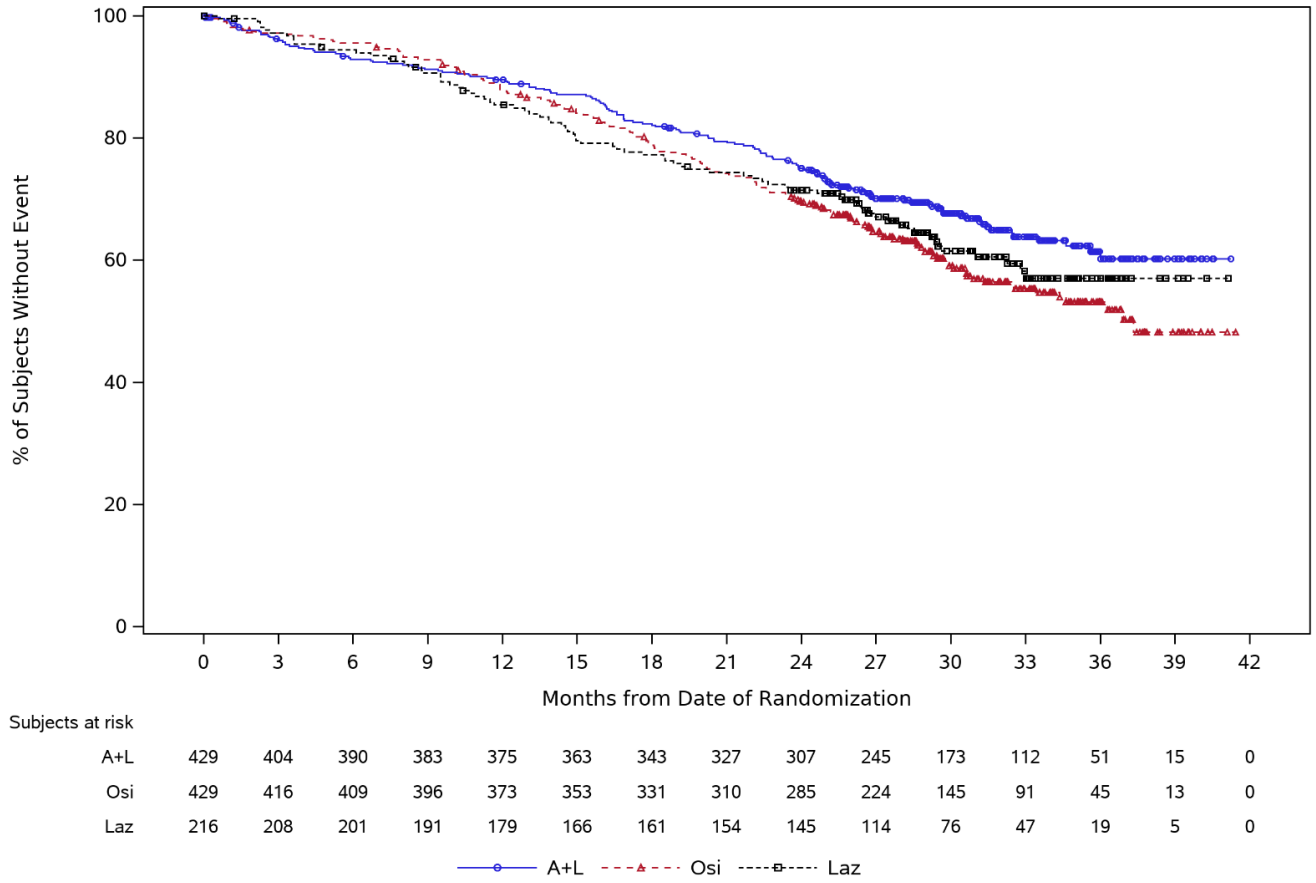
Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

Figure 17: Kaplan-Meier Plot of Overall Survival for Amivantamab + Lazertinib vs Osimertinib; Full Analysis Set (Study 73841937NSC3003), OS data update (CCO: 13 May 2024)



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib

Figure 18: Kaplan-Meier Plot of Overall Survival for OS Update (CCO: 13 May 2024); Full Analysis Set



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; Laz = Lazertinib

Secondary endpoint– Confirmed ORR by BICR (DCO: 13 May 2024, with median follow-up of 31.3 months)

Table 38: Summary of Objective Response Rate (Confirmed) Based on RECIST v1.1 Criteria in Subjects With Measurable Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with measurable disease at baseline	420	414	214
Objective response rate (Confirmed CR + Confirmed PR)	337 (80.2%)	317 (76.6%)	163 (76.2%)
95% CI	(76.1%, 83.9%)	(72.2%, 80.6%)	(69.9%, 81.7%)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.1875		
Odds ratio (95% CI)[a,b]	1.25 (0.90, 1.74)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2356		
Odds ratio (95% CI)[a,b]	1.27 (0.85, 1.89)		
Best Overall Response			
Confirmed Complete Response (CR)	28 (6.7%)	21 (5.1%)	12 (5.6%)
Confirmed Partial Response (PR)	309 (73.6%)	296 (71.5%)	151 (70.6%)
Stable Disease (SD)	54 (12.9%)	74 (17.9%)	37 (17.3%)
Progressive Disease (PD)	8 (1.9%)	11 (2.7%)	9 (4.2%)
Not Evaluable (NE)	21 (5.0%)	12 (2.9%)	5 (2.3%)

Key: CI = confidence interval
[a] p-value and odds ratio are from logistic regression model stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or non-Asian), and history of brain metastasis (present or absent).
[b] Odds ratio >1 favors Amivantamab + Lazertinib.
Note: Percentages are based on the number of subjects with measurable disease at baseline.

Secondary endpoint – DOR by BICR

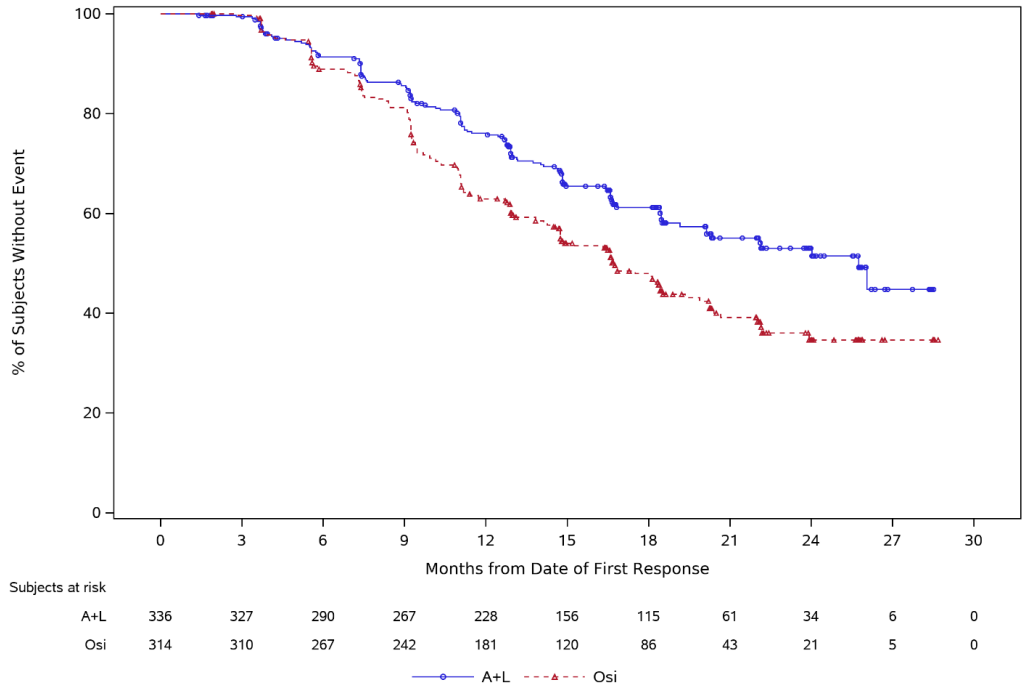
Table 39: Summary of Duration of Response in Confirmed Responders With Measurable Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003) (CCO:11 August 2023)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with measurable disease at baseline	421	414	214
Confirmed Responders (Confirmed CR + Confirmed PR)	336	314	160
Event	127 (37.8%)	163 (51.9%)	83 (51.9%)
Censored	209 (62.2%)	151 (48.1%)	77 (48.1%)
Time to event (months)[a]			
25th percentile (95% CI)	12.68 (11.04, 13.73)	9.26 (9.13, 10.25)	9.23 (7.39, 11.10)
Median (95% CI)	25.76 (20.14, NE)	16.76 (14.75, 18.53)	16.56 (14.75, 20.21)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (21.95, NE)
Range	(1.4, 28.5+)	(1.9+, 28.7+)	(1.9+, 28.6+)
Duration of response >=6 months	290 (86.3%)	267 (85.0%)	132 (82.5%)
Duration of response >=12 months	228 (67.9%)	181 (57.6%)	94 (58.8%)
Duration of response >=18 months	115 (34.2%)	86 (27.4%)	40 (25.0%)
Duration of response >=24 months	34 (10.1%)	21 (6.7%)	5 (3.1%)

Key: CI = confidence interval; + = censored observation; NE = not estimable
[a] Quartiles and 95% CIs are estimated with Kaplan-Meier method.
Note: Percentages are based on the number of subjects who achieved Confirmed CR or Confirmed PR.

Updated outputs for ORR and DoR in confirmed responders with measurable disease at baseline based on the CCO of 13 May 2024 were provided during the procedure with a median follow-up of 31.3 months. The ORR % (95% CI) was 80% (76%, 84%) in the A+L arm and 77% (72%, 81%) in the O arm, respectively. The median Duration of response (DOR) (95% CI) in responders was 25.8 (20.3, 33.9) months and 18.1 (14.8, 20.1) months, respectively.

Figure 19: Kaplan-Meier Plot of Duration of Response in Confirmed Responders With Measurable Disease at Baseline for Amivantamab + Lazertinib vs Osimertinib – BICR; Full Analysis Set (Study 73841937NSC3003)



Secondary endpoint – Progression free survival after first subsequent therapy (PFS2)

Table 40: Summary of Progression-free Survival 2 – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	101 (23.5%)	130 (30.3%)	58 (26.9%)
Censored	328 (76.5%)	299 (69.7%)	158 (73.1%)
Time to event (months)			
25th percentile (95% CI)	22.60 (18.00, 29.14)	18.40 (15.93, 20.50)	19.58 (14.62, 24.80)
Median (95% CI)	30.42 (30.42, NE)	NE (29.31, NE)	28.94 (28.94, NE)
75th percentile (95% CI)	NE (30.42, NE)	NE (NE, NE)	NE (28.94, NE)
Range	(0.0+, 32.3+)	(0.0+, 32.0+)	(0.0+, 30.3+)
6-month event-free rate (95% CI)	0.93 (0.90, 0.95)	0.95 (0.93, 0.97)	0.95 (0.91, 0.97)
12-month event-free rate (95% CI)	0.88 (0.85, 0.91)	0.87 (0.83, 0.90)	0.85 (0.79, 0.89)
18-month event-free rate (95% CI)	0.79 (0.75, 0.83)	0.76 (0.71, 0.80)	0.77 (0.71, 0.82)
24-month event-free rate (95% CI)	0.72 (0.67, 0.77)	0.64 (0.58, 0.69)	0.68 (0.59, 0.75)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.0314		
Hazard ratio (95% CI)[a,b]	0.75 (0.58, 0.98)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2025		
Hazard ratio (95% CI)[a,b]	0.81 (0.59, 1.12)		

	Amivantamab + Lazertinib	Osimertinib	Lazertinib

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

With longer follow-up (CCO: 13 May 2024), these results confirmed the degree of improvement for the combination of amivantamab and lazertinib with a 27% reduction in the risk of progression or death after the first subsequent therapy, ie, PFS2 (HR= 0.73, nominal p= 0.0044) and a 29% reduction in the risk of symptomatic progression or death, ie, TTSP (HR=0.71, nominal p=0.0011.

Secondary endpoint – Time to symptomatic progression (TTSP)

Table 41: Summary of Time to Symptomatic Progression – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	125 (29.1%)	167 (38.9%)	70 (32.4%)
Symptomatic PD	69 (16.1%)	118 (27.5%)	46 (21.3%)
Death without Symptomatic PD	56 (13.1%)	49 (11.4%)	24 (11.1%)
Censored	304 (70.9%)	262 (61.1%)	146 (67.6%)
Time to event (months)			
25th percentile (95% CI)	17.58 (14.23, 22.34)	14.06 (11.60, 15.90)	13.83 (10.41, 18.86)
Median (95% CI)	NE (NE, NE)	29.31 (25.33, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 32.3+)	(0.2, 32.7+)	(0.0+, 32.1+)
6-month event-free rate (95% CI)	0.88 (0.85, 0.91)	0.90 (0.87, 0.93)	0.90 (0.85, 0.93)
12-month event-free rate (95% CI)	0.82 (0.77, 0.85)	0.79 (0.74, 0.82)	0.79 (0.72, 0.84)
18-month event-free rate (95% CI)	0.74 (0.70, 0.78)	0.67 (0.63, 0.72)	0.71 (0.64, 0.76)
24-month event-free rate (95% CI)	0.67 (0.62, 0.72)	0.59 (0.53, 0.64)	0.65 (0.58, 0.72)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.0049		
Hazard ratio (95% CI)[a,b]	0.72 (0.57, 0.91)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.3083		
Hazard ratio (95% CI)[a,b]	0.86 (0.64, 1.15)		

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

Secondary endpoint – intracranial progression free survival

Table 42: Summary of Intracranial Progression-free Survival in Subjects with History of Brain Metastasis – Stratified Analysis - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with history of brain metastasis	178	172	86
Event	75 (42.1%)	75 (43.6%)	37 (43.0%)
Censored	103 (57.9%)	97 (56.4%)	49 (57.0%)
Time to event (months)			
25th percentile (95% CI)	9.46 (8.44, 13.08)	12.75 (9.30, 14.09)	11.04 (9.10, 16.39)
Median (95% CI)	NE (18.43, NE)	21.09 (18.40, NE)	20.30 (16.59, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (22.67, NE)
Range	(0.0+, 30.3+)	(0.0+, 30.3+)	(0.0+, 28.6+)
6-month event-free rate (95% CI)	0.87 (0.81, 0.91)	0.88 (0.82, 0.92)	0.89 (0.81, 0.94)
12-month event-free rate (95% CI)	0.71 (0.64, 0.77)	0.75 (0.68, 0.81)	0.72 (0.61, 0.80)
18-month event-free rate (95% CI)	0.59 (0.51, 0.66)	0.58 (0.50, 0.66)	0.60 (0.48, 0.70)
24-month event-free rate (95% CI)	0.51 (0.42, 0.59)	0.46 (0.36, 0.55)	0.40 (0.24, 0.55)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.8168		
Hazard ratio (95% CI)[a,b]	0.96 (0.70, 1.33)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.7615		
Hazard ratio (95% CI)[a,b]	0.94 (0.63, 1.40)		

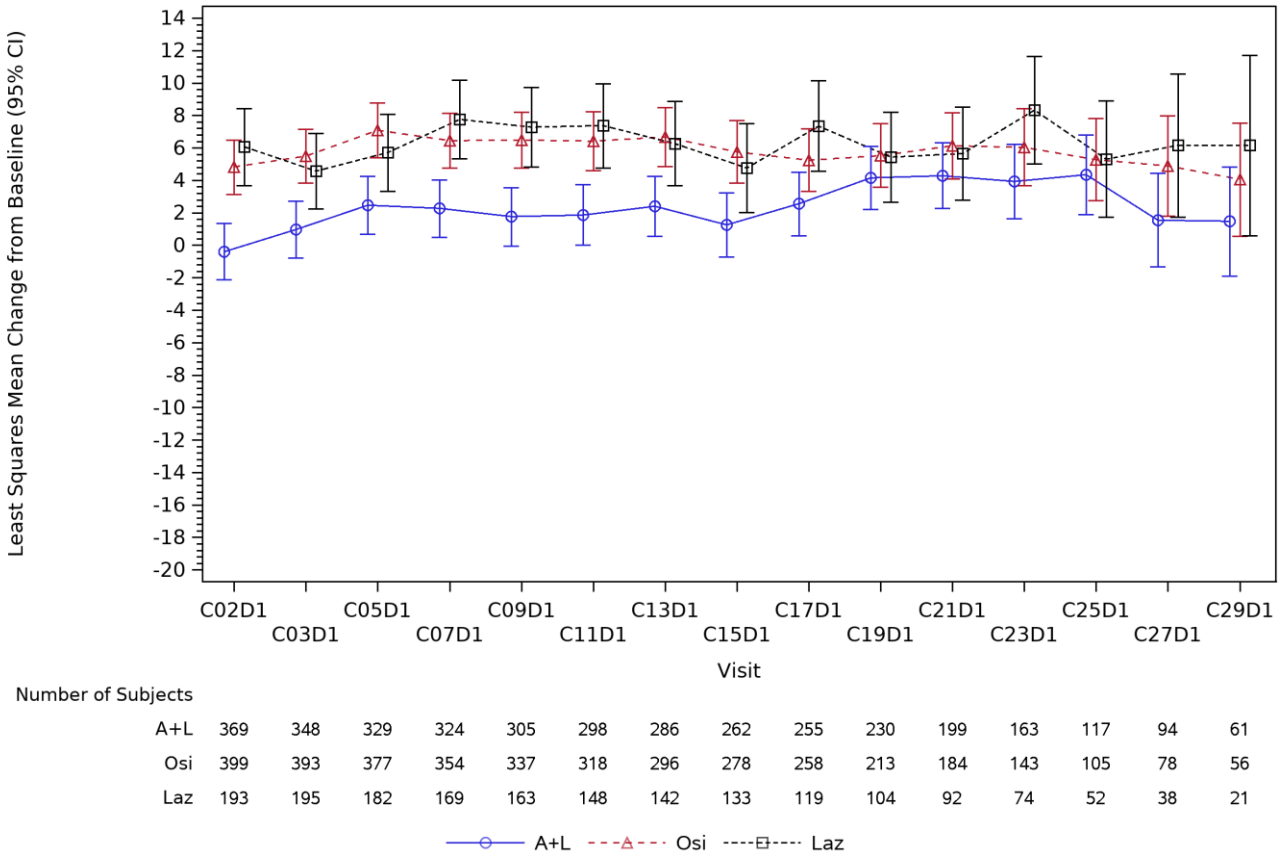
Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R) and race (Asian or Non-Asian).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.
Note: History of brain metastasis is based on investigator reported data recorded on eCRF page.

At the updated analysis based on the CCO of 13 May 2024, with a median follow-up of 31.11 months, the improvement of the iPFS was supported with 24.90 months observed in the amivantamab + lazertinib arm versus 22.18 months in the osimertinib arm.

Secondary endpoint - patient related outcomes

PRO compliance throughout treatment: >96% at baseline and ≥85% through Cycle 31 in each treatment arm for the NSCLC-SAQ and EORTC-QLQ-C30.

Figure 20: Least Squares Mean (95% CI) Change from Baseline for EORTC QLQ-C30: Global Health Status / Quality of Life Score Over Time; Full Analysis Set (Study 73841937NSC3003)



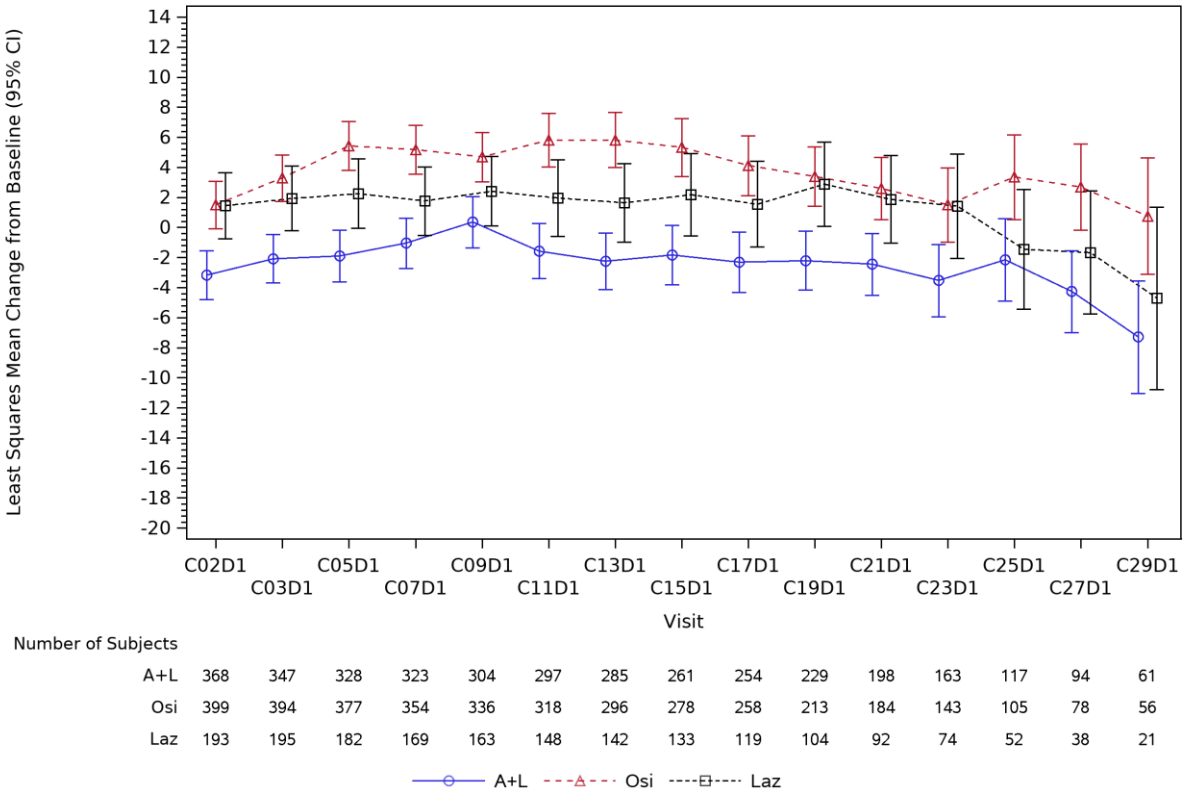
Number of Subjects

A+L	369	348	329	324	305	298	286	262	255	230	199	163	117	94	61
Osi	399	393	377	354	337	318	296	278	258	213	184	143	105	78	56
Laz	193	195	182	169	163	148	142	133	119	104	92	74	52	38	21

Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; Laz = Lazertinib

Note: N is the number of subjects with a non-missing change from baseline value for the specified patient reported outcome at the specified time point.

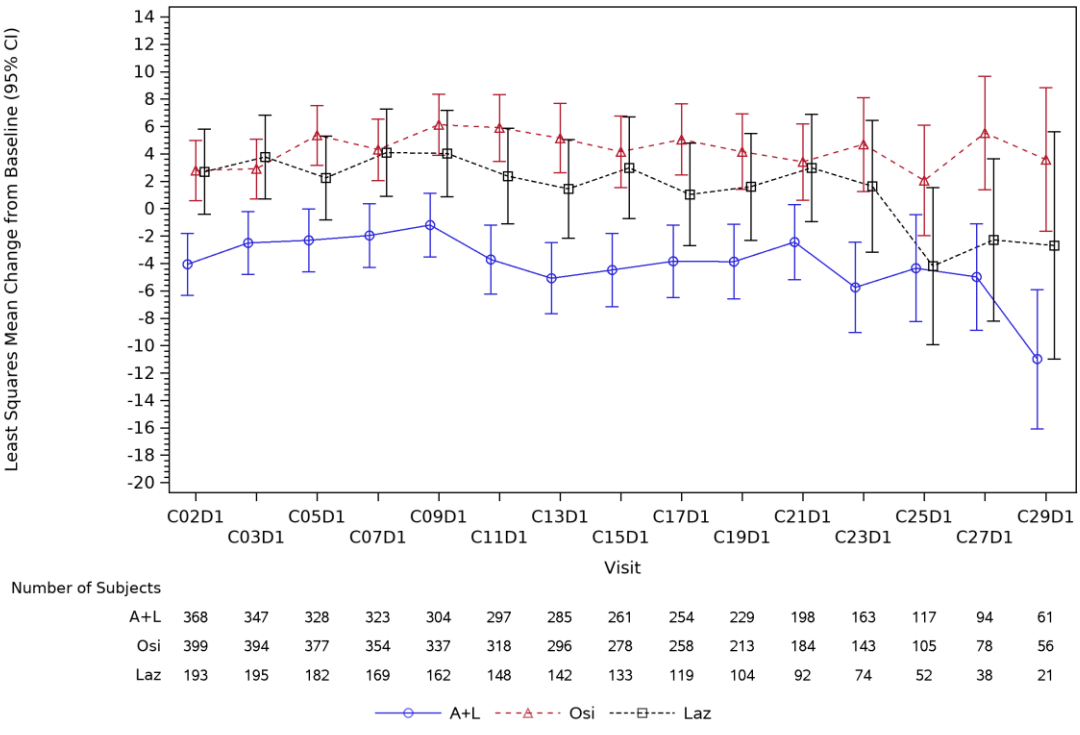
Figure 21: Least Squares Mean (95% CI) Change from Baseline for EORTC QLQ-C30: Physical Functioning Score Over Time; Full Analysis Set (Study 73841937NSC3003)



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; Laz = Lazertinib

Note: N is the number of subjects with a non-missing change from baseline value for the specified patient reported outcome at the specified time point.

Figure 22: Least Squares Mean (95% CI) Change from Baseline for EORTC QLQ-C30: Role Functioning - Score Over Time; Full Analysis Set (Study 73841937NSC3003)



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; Laz = Lazertinib

Note: N is the number of subjects with a non-missing change from baseline value for the specified patient reported outcome at the specified time point.

Key exploratory efficacy analyses

Intracranial objective response rate

There were 180 participants in the amivantamab + lazertinib arm, 187 participants in the osimertinib arm, and 93 participants in the lazertinib arm that had intracranial disease at baseline as assessed by BICR and were included in the analysis of intracranial ORR.

Table 43: Summary of Intracranial Objective Response Response Rate Based on RECIST v1.1 Criteria in Subjects With Intracranial Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with intracranial disease at baseline	180	187	93
Objective response rate (CR+PR)	138 (76.7%)	143 (76.5%)	69 (74.2%)
95% CI	(69.8%, 82.6%)	(69.7%, 82.4%)	(64.1%, 82.7%)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.9964		
Odds ratio (95% CI)[a,b]	1.00 (0.61, 1.63)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.6591		
Odds ratio (95% CI)[a,b]	1.14 (0.64, 2.05)		
Best Overall Response			
Complete Response (CR)	112 (62.2%)	108 (57.8%)	51 (54.8%)
Partial Response (PR)	26 (14.4%)	35 (18.7%)	18 (19.4%)
Stable Disease (SD)[c]	35 (19.4%)	39 (20.9%)	17 (18.3%)
Progressive Disease (PD)	3 (1.7%)	2 (1.1%)	4 (4.3%)
Not Evaluable (NE)	4 (2.2%)	3 (1.6%)	3 (3.2%)

Key: CI = confidence interval

[a] p-value and odds ratio are from logistic regression model stratified by mutation type (Exon 19del or Exon 21 L858R) and race (Asian or non-Asian).

[b] Odds ratio >1 favors Amivantamab + Lazertinib.

[c] Includes non-CR/non-PD in subjects with only non-target lesions at baseline.

Note: CR and PR do not have to be confirmed.

Intracranial duration of response

Among the 138 participants in the amivantamab + lazertinib arm with an intracranial response by BICR, 46 participants (33.3%) had intracranial disease progression or died by the time of the CCO. In comparison, among 143 participants in the osimertinib arm with an intracranial response by BICR, 38 participants (26.6%) had intracranial disease progression or died by the time of the CCO. The median intracranial DOR was not reached for either arm.

Table 44: Summary of Intracranial Duration of Response in Responders With Intracranial Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with intracranial disease at baseline	180	187	93
Responders (CR + PR)	138	143	69
Event	46 (33.3%)	38 (26.6%)	20 (29.0%)
Censored	92 (66.7%)	105 (73.4%)	49 (71.0%)
Time to event (months)[a]			
25th percentile (95% CI)	11.10 (7.52, 14.75)	12.91 (9.30, 18.07)	12.88 (7.46, 19.25)
Median (95% CI)	NE (20.24, NE)	NE (NE, NE)	20.27 (17.81, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 28.5+)	(0.0+, 25.9+)	(0.0+, 26.8+)
Duration of response >=6 months	107 (77.5%)	111 (77.6%)	55 (79.7%)
Duration of response >=12 months	80 (58.0%)	77 (53.8%)	36 (52.2%)
Duration of response >=18 months	43 (31.2%)	30 (21.0%)	13 (18.8%)
Duration of response >=24 months	14 (10.1%)	6 (4.2%)	2 (2.9%)

Key: CI = confidence interval; + = censored observation; NE = not estimable
[a] Quartiles and 95% CIs are estimated with Kaplan-Meier method.
Note: Percentages are based on the number of subjects who achieved CR or PR.

Updated outputs for the intracranial response point estimates based on the CCO of 13 May 2024 were provided under the procedure.

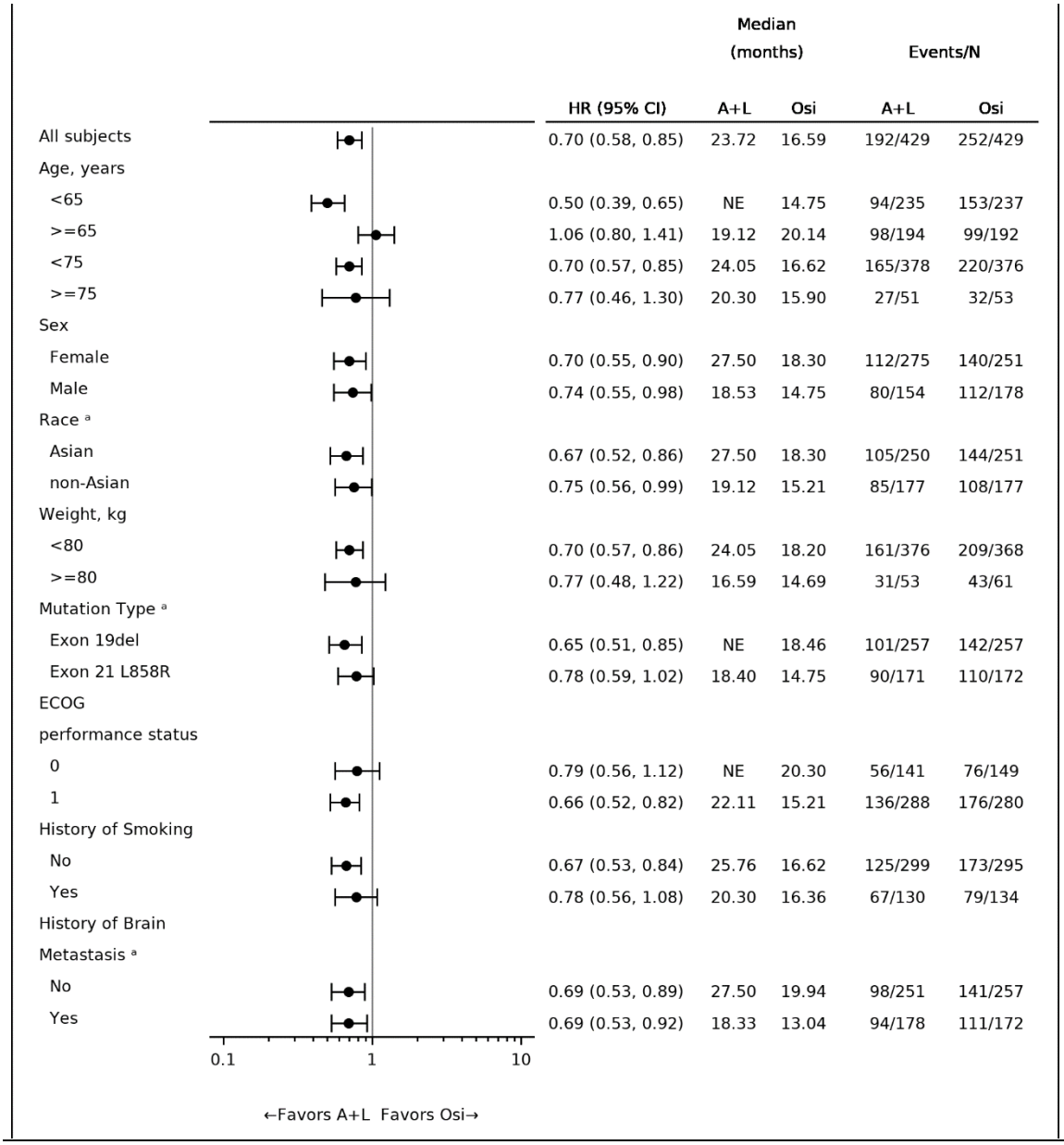
The intracranial ORR (CR+PR), % (95% CI) was 77% (70%, 83%) in the amivantamab + lazertinib arm and 77% (71%, 83%) in the osimertinib arm and the Complete response (CR) was 63% and 59%, respectively.

The median intracranial DOR was NE in the amivantamab + lazertinib arm and 24.41 months in the osimertinib arm at the updated analysis. The 18 and 24-month intracranial DOR improved with further follow-up, with an intracranial DOR of at least 18 months in 50.4% versus 38.9% for the combination of amivantamab and lazertinib versus osimertinib, respectively, and an intracranial DOR of at least 24 months in 30.9% versus 17.4%, respectively.

Ancillary analyses

Subgroup Analyses of Progression-free Survival by BICR

Figure 23: Forest Plot of Progression-free Survival for Amivantamab + Lazertinib vs Osimertinib - BICR; Full Analysis Set (Study 73841937NSC3003)



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; ECOG = Eastern Cooperative Oncology Group; NE = not estimable

[a] Based on investigator reported data recorded on eCRF page.

Note: Hazard ratio for the analysis of all subjects is from a proportional hazards model stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).

Note: Hazard ratio for the analysis of subgroups is from an unstratified proportional hazards model.

Sensitivity analyses for PFS

Supplementary analyses of progression-free survival by BICR

Censored for death/pd after start of subsequent anti-cancer therapy

The results from the analysis of PFS by BICR censored for death/PD after start of subsequent anti-cancer therapy showed a treatment benefit for the amivantamab + lazertinib arm versus the osimertinib arm (HR=0.70 [95% CI: 0.57, 0.84], nominal p=0.0002) and for the amivantamab + lazertinib arm versus the lazertinib arm (HR=0.70 [95% CI: 0.55, 0.88], nominal p=0.0025) similar to that observed in the primary analysis.

Not censored for missing more than one disease evaluation

The results from the analysis of PFS by BICR not censored for missing 2 or more consecutive disease evaluations showed a treatment benefit for the amivantamab + lazertinib arm versus the osimertinib arm (HR=0.72 [95% CI: 0.60, 0.86], nominal p=0.0004) and for the amivantamab + lazertinib arm versus the lazertinib arm (HR=0.72 [95% CI: 0.58, 0.90], nominal p=0.0042) similar to that observed in the primary analysis.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 45: Summary of efficacy for trial MARIPOSA

Title: MARIPOSA			
Study identifier	146319 EudraCT NUMBER 2020-000743-31		
Design	A Phase 3, Randomized Study, of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer		
	Screening phase Treatment phase Follow-up phase		Within 28 days prior to randomization Cycle 1 Day 1 and continued as 28-day cycles until the End of Treatment visit For participants who discontinued study treatment for any reason
Hypothesis	Superiority		
Treatments groups	Arm A: Amivantamab + Lazertinib		N=429
	Arm B: Osimertinib		N=429
	Arm C. Lazertinib		N=216
Endpoints and definitions	Primary endpoint	PFS	
	Secondary endpoint	OS	
	Secondary endpoint	ORR	
Database lock	11 August 2023		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population. Final PFS analysis, Interim OS analysis		
Descriptive statistics and estimate variability	Treatment group	Amivantamab + Lazertinib	Osimertinib (control)
	Number of subjects	429	429
	Primary endpoint Median PFS (months)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)
	HR PFS (95% CI); p-value	0.70 (0.58, 0.85); p=0.0002	
	Secondary endpoint hypothesis tested: OS (events) Median OS (months)	 22.6% NE	 27.3% NE
	HR OS (95% CI); p-value Updated OS (events) Median OS (months) HR OS(95% CI) p-value	HR=0.80 [95% CI: 0.61, 1.05]; p=0.1099. 33.1% NE 0.77 (0.61, 0.96) p=0.0185	 41.3% 37.3
	Secondary endpoints: Updated ORR (%) Updated confirmed Median DoR (95%CI) months	 80% 25.8 (20.3, 33.9)	 77% 18.1 (14.8, 20.1)

2.6.5.3. Clinical studies in special populations

Table 46: Clinical studies in special populations

	Controlled Trials MARIPOSA Amivantamab + Lazertinib (N=421)	Non-controlled trials CHRYSALIS+CHRYSALIS-2 Amivantamab + Lazertinib (N=526)
Renal function at baseline		
Normal (eGFR: >= 90 mL/min/1.73m²)	237 (56.3%)	263 (50%)
Mild (eGFR: 60 to < 90 mL/min/1.73 m²)	163 (38.7%)	216 (41.1%)
Moderate (eGFR: 30 to < 60 mL/min/1.73 m²)	20 (4.8%)	47 (8.9%)
Severe (eGFR: < 30 mL/min/1.73 m²)	1 (0.2%)	0
Hepatic function at baseline		
Normal (Total bilirubin <= ULN and AST <= ULN)	381 (90.5%)	457 (86.9%)
Mild ((Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN))	40 (9.5%)	68 (12.9%)
Moderate (1.5 x ULN < Total bilirubin <= 3 x ULN)	0	1 (0.2%)
Severe (Total bilirubin > 3 x ULN)	0	0
Age		
Paediatric patients <18 years	0	0
18-64 years	233 (55.3%)	297 (56.5%)
65-74 years	139 (33.0%)	178 (33.8%)
75-84 years	44 (10.5%)	49 (9.3%)
85+ years	5 (1.2%)	2 (0.4%)

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Among patients with NSCLC, the most prevalent driver mutations are those that result in the activation of EGFR, which are identified in more than 15% of patients with adenocarcinoma and up to 50% of the corresponding Asian population. Approximately 90% of activating EGFR mutations are exon 19 deletions (exon 19del) or exon 21 L858R substitutions (L858R). There are several authorized assays on the market to detect these common EGFR mutations to support the use of targeted therapy.

Participants enrolled in the MARIPOSA study were enrolled based on a documented local EGFR result using validated PCR or NGS-based assays (a copy of the test report documenting the mutation must have been included in the participant's medical records at the time of randomization). The applicant received scientific advice (EMA/SA/0000052936) that the use of validated local assays for the detection of EGFR mutations was an acceptable approach.

Table 47: concordance study summary results – Tissue and plasma

tagexinv03-ct: Concordance Study Summary Results - Tissue; cAS+ (Study 73841937NSC3003)				
	Local Lab Test Type			
	PCR (excluding cobas tissue)	NGS	PCR (cobas tissue)	Total
Central cobas Aggregate Call for EGFR L858R or Exon 19 Deletion				
Detected	327	171	153	651
Not Detected	11	9	5	25
Total	338	180	158	676
Concordance (2-sided 95% exact CI)	96.7% (94.3% - 98.4%)	95.0% (90.7% - 97.7%)	96.8% (92.8% - 99.0%)	96.3% (94.6% - 97.6%)

tagexinv04-ct: Concordance Study Summary Results - Plasma; cAS- and cAS-NT (Study 73841937NSC3003)				
	Local Lab Test Type			
	PCR (excluding cobas tissue)	NGS	PCR (cobas tissue)	Total
Central Guardant Aggregate Call for EGFR L858R or Exon 19 Deletion				
Detected	52	50	26	128
Not Detected	19	11	15	45
Total	71	61	41	173
Concordance (2-sided 95% exact CI)	73.2% (61.4% - 83.1%)	82.0% (70.0% - 90.6%)	63.4% (46.9% - 77.9%)	74.0% (66.8% - 80.4%)

Central tissue testing concordance overall is 96.3% with 651/676 cobas testing results in agreement with the LLTs. Central testing was concordant with local testing in 74.0% of the samples with a valid central Guardant plasma test (using Guardant 360® CDx) when no valid central tissue test was available.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

CHRYSALIS First-line Cohort: Supportive Efficacy Study (Combination of Amivantamab and Lazertinib)

Efficacy information was summarized for the First-line Cohort from Part 1 (N=20) treated with amivantamab + lazertinib based on a CCO of 15 November 2022.

Primary Efficacy Endpoint

Overall Response Rate

Confirmed responses (PR [no CRs were observed]) per RECIST v.1.1 were observed for all 20 participants in the Part 1 First-line Cohort, resulting in an overall response rate of 100.0% (95% CI: 83.2%, 100%).

Secondary efficacy endpoint

Duration of response

The median DOR was not estimable (NE) (95% CI: 20.30, NE), and the longest response was ongoing at 35.6 months as of the CCO. The median duration of treatment was 33.46 months.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

MARIPOSA, the pivotal trial, is an ongoing, randomized 2:2:1, open label, multicenter Phase 3 study to compare the efficacy and safety of the combination of amivantamab and lazertinib (Arm A) versus osimertinib (Arm B) and lazertinib monotherapy (Arm C) as first-line treatment in participants with EGFRm NSCLC. The contribution of amivantamab to the activity of the combination is being assessed by comparing the efficacy observed in the amivantamab + lazertinib Arm A with that in the lazertinib monotherapy Arm C. However, no formal statistical testing of these comparisons is foreseen.

The comparator in the MARIPOSA study was osimertinib monotherapy which is considered the standard of care in first-line treatment of EGFR mutated (exon 19 deletion or exon 21 L858R) NSCLC. (Hendriks LE et al., ESMO guideline oncogene-addicted mNSCLC, 2023). Thus, the comparator is considered acceptable.

The applicant sought scientific advice in May 2020 (EMA/SA/0000056554) regarding the MARIPOSA study. The main elements of the study are in line with the advice given, including the addition of a lazertinib monotherapy arm to facilitate assessment of contribution of components. The Lazertinib arm was included in the study design before the study initiation with the first patient enrolling 16 October 2020.

Study participants: The inclusion and exclusion criteria are supported and are reflective of the population targeted by the proposed indication.

Treatments: Arm A received open-label combination therapy with amivantamab and lazertinib, Arm B received double-blind osimertinib monotherapy (osimertinib and matching placebo for lazertinib), and Arm C received double-blind lazertinib monotherapy (lazertinib and matching placebo for osimertinib). Study treatments were given until progression (unless continuation of study treatment was deriving clinical benefit per investigator discretion) or unmanageable toxicities. The justification for partial blinding (open-label Arm A and double-blind Arms B and C) of the trial is followed.

Objectives/endpoints: The primary objective of the study was to evaluate the efficacy of the combination of amivantamab and lazertinib in patients with EGFR-mutated NSCLC, compared to osimertinib alone, a valid comparator in this setting. PFS was established as the primary endpoint, defined as the time from randomization to objective disease progression or death, according to BICR and RECIST v1.1 criteria. The fact that PFS and response-related endpoints were evaluated through a blinded radiologist is endorsed, given the open-label nature of arm A. The key secondary efficacy endpoint was OS, defined as the time from the date of randomization until the date of death due to any cause. The remaining secondary endpoints were type-1-error protected. The definition, instruments and datasets in which the other secondary endpoints (ORR, DOR, PROs) were evaluated is acceptable. Planned subgroup analyses are acceptable.

Statistical methods: Sample size calculations appear appropriate and considered relevant factors (enrolment period, dropout rates, expected HR for OS and PFS). Randomisation using randomly permuted blocks was stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-

Asian), and history of brain metastases (present vs absent). The primary endpoint and key secondary endpoint were evaluated in the ITT population. The censoring strategies for OS and PFS are overall agreed. The multiplicity strategy utilized a hierarchical testing approach to maintain the overall Type I error rate at the 0.05 level. Testing for the key secondary endpoint of OS was contingent upon the primary endpoint of PFS achieving statistical significance. An interim analysis for futility was planned. Additionally, this interim analysis for futility had predefined stopping criteria for PFS. The interim analysis approach for the key secondary endpoint of OS employs a hierarchical testing strategy alongside an O'Brien-Fleming alpha spending method. The progression to testing the OS is contingent upon the primary endpoint PFS reaching statistical significance. The application of the O'Brien-Fleming method for type I error control is deemed suitable. Final analysis of OS is to be conducted around 60 months after the first participant was enrolled, when approximately 490 deaths in all treatment arms combined were anticipated (approximately 390 deaths from the amivantamab + lazertinib arm and osimertinib arm combined).

Subject disposition: A total of 1,074 participants were randomly assigned to treatment in a 2:2:1 ratio to receive open label amivantamab + lazertinib (n=429), double blind osimertinib monotherapy (n=429) or double blind lazertinib monotherapy (n=216). At the time of CCO (11 August 2023) for the primary analysis, the median duration of follow-up in the study was 22.01 months. The overall participant flow is as expected. Discontinuation rates are comparable between study arms.

Study conduct: An interim analysis for futility was completed without any recommendation for study changes. Additionally, this interim analysis for efficacy met the predefined stopping criteria for PFS, suggesting a benefit of the combination treatment over the control. Despite this, the decision was made to continue the study to the next planned analysis to better understand the benefit-risk profile (and ensure longer safety follow-up), maintaining study blinding. The interim analysis was only meant to assess futility in this trial and not to stop the study for efficacy, then, the final analysis was conducted at the nominal alpha level without an alpha adjustment is acceptable. Key protocol amendments have been adequately justified. Major protocol violations were balanced among arms and have been appropriately detailed.

The Mariposa protocol amendment 3 added the recommendation that participants receiving the combination of amivantamab and lazertinib should receive prophylactic anticoagulation for the first 4 months of treatment due to markedly increased incidence of VTE events in arm A. Enrolment had already ended by that time. Despite the study being conducted during the main waves of the COVID pandemic, this seemingly only led to few missing assessments and it is not believed that the COVID pandemic had a major impact on study conduct.

Demographics and baseline characteristics: Demographics and baseline disease characteristics were generally balanced among study arms. As expected in the clinical presentation of this disease in an advanced setting, almost half of the patients had previous history of brain metastases. Across all three treatment arms, most participants were female (61.6%) and Asian (58.6%); and 38% were White. The overall median age was 63.0 years (range: 25 to 88 years) with 45% of patients ≥ 65 years and 11% ≥ 75 years. Baseline ECOG performance status was 0 for 34.1% of participants and 1 for 65.9% of participants. A total of 68.6% of participants did not have a history of smoking. 97.2% of study participants were diagnosed with adenocarcinoma; 90% had Stage IV cancer at initial diagnosis; 29.4% had Stage IVA disease and 67.8% had Stage IVB disease at screening.

Biomarkers: Per protocol, the patient samples were required to have one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing. Tumour tissue (94%) and/or plasma (6%) samples for all patients were tested locally to determine EGFR exon 19 deletion and/or exon 21 L858R substitution mutation status using polymerase chain reaction (PCR) in 65% and next generation sequencing (NGS) in 35% of patients. Various CE-marked

tests were used for local testing (LLT). Central testing was performed with either Roche cobas® EGFR Mutation Test v2 (cobas) for tissue samples or Guardant 360® CDx (G360) for plasma samples. The overall concordance between the three LLTs and central cobas tissue test was 96.3% for the samples with a valid cobas central tissue test result (N=676) and consistent across the used LLTs."

Efficacy data and additional analyses

At data cut-off on 11-AUG-2023, the minimum of PFS events in the ITT (192 (44.8%) in arm A and 252 (58.7%) in arm B) that would trigger the final PFS analysis (approximately 450 PFS events from the amivantamab + lazertinib and osimertinib arms combined) had been met. The Mariposa study met its primary endpoint at the time of the final analysis for **BICR-PFS**, demonstrating superiority of amivantamab + lazertinib over the comparator osimertinib with a statistically significant treatment effect (**HR=0.70 [95% CI: 0.58, 0.85]**, p=0.0002). The median PFS in the amivantamab + lazertinib arm was 23.72m compared with a median PFS of 16.59m in the osimertinib.

The key secondary endpoint **OS** difference was not statistically significant at the time of the primary analysis and the OS curves first crossed after 12 months in favour of the amivantamab + lazertinib arm and nearly converged again at the 16-month time mark, whereafter a separation can be observed. A numerical trend towards improved survival in AL arm was observed with an **HR for OS of 0.80 (0.61, 1.05)** with a p-value of 0.1099. As of the CCO date of the primary analysis, 97 participants (22.6%) in the amivantamab + lazertinib arm and 117 participants (27.3%) in the osimertinib arm had died. An ad hoc updated OS analysis with a nominal 2-sided alpha of 0.00001 spent for the analysis has been provided. As of the updated CCO of 13 May 2024, a total of 399 deaths (information fraction of 81%; 37% OS data maturity) were reported across the amivantamab+lazertinib arm, osimertinib arm, and lazertinib arm, including 142 in the amivantamab+lazertinib arm, 177 in the osimertinib arm, and 80 in the lazertinib arm. The updated ad hoc OS analysis shows a survival improvement for the combination of amivantamab and lazertinib over osimertinib, with a HR=0.77 (95% CI: 0.61, 0.96; p=0.0185). Formally, the result is not statistically significant at the specified 2-sided significance level of 0.00001. However, this OS data update is reassuring and the development of the OS data appear to be trending in a favourable direction of ami+lazer over osimertinib monotherapy. The final OS analysis planned per protocol when 490 deaths overall (all treatment arms combined) and 390 deaths from the AL and O arms combined, anticipated in November 2025, is recommended to be submitted (REC).

The secondary endpoints **DOR, PFS2 and TTSP** were consistent with the primary endpoint and are in support of amivantamab + lazertinib over osimertinib. There was no difference between study arms with regard to **ORR and intracranial PFS**. None of these five secondary endpoints were type 1 error controlled.

Regarding **PROs**, there were no clinically meaningful differences between arms in the NSCLC-SAQ and EORTC-QLQ-C30 (global quality of life) or NSCLC-SAQ (lung cancer symptom) scores. In the light of methodological limitation in the comparison of the PRO data between arms (i.e. no prespecified handling of missing data, no prespecified type 1 error control, open label study) it is considered that the PRO claims are not warranted for inclusion in section 5.1 of the SmPC.

Intracranial response endpoints

A similar intracranial ORR across the three arms, suggest similar intracranial activity for all three regimen, AL, O and L respectively (76.7%, 76.5% and 74.2% respectively). Among participants with an intracranial response by BICR, the median intracranial DOR was not estimable in the AL and O arm and 20.27 (17.81, NE) in L arm.

Although not type-1 error adjusted analyses, inclusion of intracranial ORR +DoR in section 5.1 of the SmPC is agreed, in line with recent CHMP decisions.

The outcomes of the subgroup analyses with regard to age, sex, race, weight, mutation types, ECOG performance status, history of smoking, and history of brain metastasis were consistent with the primary analysis and can be considered supportive. Predefined sensitivity analyses of PFS, including investigator assessed PFS, were consistent with the primary analysis.

Contribution of components: Amivantamab + lazertinib (arm A) seems superior to *lazertinib monotherapy* (arm C) with regard to PFS (HR of 0.72 (95% CI: 0.57, 0.90)) but not with regard to OS (HR of 0.82 (95% CI: 0.59, 1.14)) keeping in mind that no analyses of arm A vs. arm C were type 1 error controlled. However, these results allow to preliminarily conclude that the contribution of components in the proposed regimen is justified.

The proposed indication is:

LAZCLUZE in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon21 L858R substitution mutations.

The term "advanced" in therapeutic indications for oncogene-addicted NSCLC is understood to encompass patients with metastatic (stage IV) disease and locally advanced unresectable disease (i.e., stage IIIA/B/C) that for diverse reasons cannot receive concurrent chemoradiotherapy (1L approach) or have already received it and present locoregional –i.e., non-metastatic– progression (such as in 2L+ setting), and would then be approached with systemic therapy as if metastatic. The proposed indication is acceptable.

Healthcare and patient engagement:

A methodology of engaging with patient organisations at the start of evaluation of new MAAs has been agreed by CHMP (for more details see the dedicated process and FAQs document: https://www.ema.europa.eu/en/documents/other/chmp-early-contact-patient-and-healthcare-professional-organisations-process-and-faqs_en.pdf). In this context one healthcare professional society (EORTC) and one patient organisation (Lung cancer Europe (LuCE)) shared their perspectives regarding the assessment of lazertinib for the applied indications on behalf of their members. The responses confirmed the view that there is a need for more treatment options, in particular to meaningfully improve duration of response, survival and the period of treatment and quality of life in patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon21 L858R substitution mutations.

2.6.7. Conclusions on the clinical efficacy

A statistically significant PFS gain, along with a statistical trend towards increased OS, is shown with the combination of lazertinib with amivantamab, compared to osimertinib, in first line in patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. Efficacy has been established. The final OS results remain to be submitted as Recommendation (November 2025).

2.6.8. Clinical safety

The safety data to support the combination of amivantamab and lazertinib for the first-line treatment of patients with EGFRm NSCLC is presented below.

Table 48: Safety data to support MARIPOSA

Study	Study Design	Population	Treatment	Median Total Treatment Duration (months)
MARIPOSA Pivotal	Ongoing, Phase 3, randomized study; open-label for combination therapy; double-blind for osimertinib and lazertinib monotherapies	First-line EGFRm NSCLC	Ami+Laz n=421	18.50
			Osi n=428	18.00
			Laz n=213	17.05
CHRYSALIS Supportive	Ongoing, Phase 1, FIH, dose escalation, dose expansion, multi-cohort, open-label study	**Ami+Laz** Includes pooled data from multiple cohorts of patients with EGFRm NSCLC across different lines of therapy*	Ami+Laz n=97	11.01
		Amivantamab Monotherapy Includes pooled data from multiple cohorts of patients with locally advanced or metastatic NSCLC across different lines of therapy*	Ami n=380	4.14
CHRYSALIS-2 Supportive	Ongoing, Phase 1/1b, dose escalation, dose expansion, multi-cohort, open-label study	**Ami+Laz** Includes pooled data from multiple cohorts of patients with locally advanced or metastatic NSCLC*	Ami+Laz n=429	4.93
		Lazertinib Monotherapy EGFRm NSCLC	Laz n=5	8.11
YH25448-201 Supportive	Ongoing, Phase 1/2, dose escalation, dose expansion, multi-cohort, open-label study	Includes pooled data from multiple cohorts of patients with EGFRm NSCLC across different lines of therapy*	Laz n=136	12.12
YH25448-301 Supportive	Ongoing, Phase 3, randomized, double-blind study	First-line EGFRm NSCLC	Laz n=196	15.06

The pivotal safety data for the amivantamab+lazertinib arm (1st column) comes from MARIPOSA (n=421). The following safety pool are also presented in the results below:
-The all-treated amivantamab+lazertinib group (called "Total" in the tables displays), which includes study participants from MARIPOSA as well as from 2 supportive studies (CHRYSALIS and CHRYSALIS-2) (n=947);
-the data from study participants in the osimertinib monotherapy arm from MARIPOSA (n=428)
-data from the lazertinib monotherapy group which includes study participants from MARIPOSA as well as from 3 supportive studies (YH25448-201, YH25448-301, and CHRYSALIS-2).
-The amivantamab monotherapy group which includes study participants from multiple cohorts from CHRYSALIS. Although the scope of the lazertinib application does not include amivantamab monotherapy data, they are included in all tabular displays in this SCS to support global submissions.

This data was integrated to provide an overview of the safety of the intended registrational regimen of the combination of amivantamab and lazertinib, as well as its components and comparators, in a broader NSCLC patient population.

2.6.8.1.1. Patient exposure

A summary of treatment duration and treatment cycles is provided in the following table.

Table 49: Summary of Treatment Duration and Treatment Cycles; Safety Analysis Set (Study Integrated Summary of Safety)

	Amivantamab + Lazertinib						Osimertinib	Lazertinib	Amivantamab
	MARIPOSA			Total					
	Total	Amivantamab	Lazertinib	Total	Amivantamab	Lazertinib			
Analysis set: Safety	421			947			428	550	380
Duration of treatment (months)									
N	421	421	421	947	947	947	428	550	380
Mean (SD)	16.97 (8.413)	14.13 (8.979)	16.97 (8.413)	12.04 (9.211)	10.50 (8.839)	12.04 (9.211)	16.92 (7.872)	15.20 (8.593)	6.21 (6.239)
Median	18.50	15.24	18.50	10.22	8.48	10.22	18.00	15.23	4.14
Range	(0.2; 31.4)	(0.0; 31.3)	(0.2; 31.4)	(0.0; 38.6)	(0.0; 36.8)	(0.0; 38.6)	(0.2; 32.7)	(0.0; 37.4)	(0.0; 39.7)
Number of Amivantamab dose infusions									
N		421			947				380
Mean (SD)		30.1 (18.14)			23.8 (17.71)				15.7 (13.17)
Median		32.0			20.0				11.0
Range		(1; 69)			(1; 82)				(1; 86)
Dose intensity (mg/cycle)[a]									
N`		421	421		947	947			
Mean (SD)		1725.51 (750.126)	5552.39 (1135.188)		2054.34 (850.810)	5821.48 (7913.044)			
Median		1704.35	5727.27		2100.00	5880.00			
Range		(7.0; 5250.0)	(1360.0; 9120.0)		(5.5; 7000.0)	(240.0; 245040.0)			

[a] Dose intensity (mg/cycle) is calculated as the sum of total doses (mg) received divided by the number of treatment cycles. Cycle is derived based on relative dose day assuming 28 days within a cycle.

Table 50: Summary of Relative Dose Intensity; Safety Analysis Set(Study Integrated Safety Summary)

	Amivantamab + Lazertinib						
	MARIPOSA		Total		Osimertinib	Lazertinib	Amivantamab
	Amivantamab	Lazertinib	Amivantamab	Lazertinib			
Analysis Set: Safety	421	421	947	947	428	550	380
Relative dose intensity (%)							
N	421	421	947	947	428	550	380
Mean (SD)	96.72 (15.145)	93.32 (8.651)	97.19 (13.376)	93.95 (10.170)	98.02 (4.154)	95.99 (9.233)	98.25 (8.979)
Median	100.00	96.00	100.00	98.29	99.87	99.79	100.00

	Amivantamab + Lazertinib				Osimertinib	Lazertinib	Amivantamab
	MARIPOSA		Total				
	Amivantamab	Lazertinib	Amivantamab	Lazertinib			
Range	(2.0; 100.0)	(32.7; 100.8)	(1.6; 133.9)	(13.2; 100.8)	(66.7; 100.3)	(47.8; 150.0)	(10.8; 100.0)

Amivantamab and lazertinib total group includes subjects from studies 61186372EDI1001(CHRYSALIS), 73841937NSC3003(MARIPOSA) and 73841937NSC1001(CHRYSALIS-2).
Osimertinib group includes subjects from study 73841937NSC3003(MARIPOSA).
Lazertinib group includes subjects from studies 73841937NSC1001(CHRYSALIS-2), YH25448-201/73841937NSC2001, YH25448-301 and 73841937NSC3003(MARIPOSA).
Amivantamab group includes subjects from study 61186372EDI1001(CHRYSALIS).

2.6.8.1.2. Adverse events

Table 51: Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Analysis set: Safety	421	947	428	550	380
Subjects with 1 or more:					
AEs	421 (100.0%)	947 (100.0%)	425 (99.3%)	541 (98.4%)	378 (99.5%)
Related AEs [a]	414 (98.3%)	937 (98.9%)	378 (88.3%)	503 (91.5%)	365 (96.1%)
Related to Amivantamab[a]	413 (98.1%)	932 (98.4%)	-	-	365 (96.1%)
Related to Lazertinib[a]	408 (96.9%)	908 (95.9%)	-	503 (91.5%)	-
Related to Osimertinib[a]	-	-	378 (88.3%)	-	-
Grade 3 or higher AEs	316 (75.1%)	655 (69.2%)	183 (42.8%)	233 (42.4%)	158 (41.6%)
Related Grade 3 or higher AEs[a]	252 (59.9%)	472 (49.8%)	59 (13.8%)	101 (18.4%)	67 (17.6%)
Related to Amivantamab[a]	245 (58.2%)	455 (48.0%)	-	-	67 (17.6%)
Related to Lazertinib[a]	216 (51.3%)	396 (41.8%)	-	101 (18.4%)	-
Related to Osimertinib[a]	-	-	59 (13.8%)	-	-
Maximum toxicity grade					
Grade 1	2 (0.5%)	15 (1.6%)	50 (11.7%)	60 (10.9%)	20 (5.3%)
Grade 2	103 (24.5%)	277 (29.3%)	192 (44.9%)	248 (45.1%)	200 (52.6%)
Grade 3	259 (61.5%)	517 (54.6%)	136 (31.8%)	187 (34.0%)	129 (33.9%)
Grade 4	23 (5.5%)	49 (5.2%)	16 (3.7%)	19 (3.5%)	9 (2.4%)
Grade 5	34 (8.1%)	89 (9.4%)	31 (7.2%)	27 (4.9%)	20 (5.3%)
Serious AEs	205 (48.7%)	446 (47.1%)	143 (33.4%)	167 (30.4%)	111 (29.2%)
Related serious AEs[a]	97 (23.0%)	182 (19.2%)	24 (5.6%)	38 (6.9%)	18 (4.7%)
Related to Amivantamab[a]	91 (21.6%)	171 (18.1%)	-	-	18 (4.7%)
Related to Lazertinib[a]	73 (17.3%)	141 (14.9%)	-	38 (6.9%)	-
Related to Osimertinib[a]	-	-	24 (5.6%)	-	-
AEs leading to discontinuation of any study agent	147 (34.9%)	263 (27.8%)	58 (13.6%)	62 (11.3%)	26 (6.8%)
AEs leading to discontinuation of Amivantamab	145 (34.4%)	247 (26.1%)	-	-	26 (6.8%)
Related to Amivantamab[a]	100 (23.8%)	147 (15.5%)	-	-	12 (3.2%)
AEs leading to discontinuation of Lazertinib	85 (20.2%)	176 (18.6%)	-	62 (11.3%)	-
Related to Lazertinib[a]	38 (9.0%)	78 (8.2%)	-	27 (4.9%)	-
AEs leading to discontinuation of Osimertinib	-	-	58 (13.6%)	-	-

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Related to Osimertinib[a]	-	-	14 (3.3%)	-	-
AEs leading to drug interruption of any study agent[c]	350 (83.1%)	705 (74.4%)	165 (38.6%)	193 (35.1%)	287 (75.5%)
AEs leading to interruption of Amivantamab[c]	328 (77.9%)	651 (68.7%)	-	-	287 (75.5%)
Related to Amivantamab[a,c]	282 (67.0%)	527 (55.6%)	-	-	262 (68.9%)
AEs leading to interruption of Lazertinib[c]	299 (71.0%)	575 (60.7%)	-	193 (35.1%)	-
Related to Lazertinib[a,c]	241 (57.2%)	439 (46.4%)	-	116 (21.1%)	-
AEs leading to interruption of Osimertinib[c]	-	-	165 (38.6%)	-	-
Related to Osimertinib[a,c]	-	-	81 (18.9%)	-	-
AEs leading to dose reduction of any study agent	249 (59.1%)	422 (44.6%)	23 (5.4%)	91 (16.5%)	39 (10.3%)
AEs leading to reduction of Amivantamab	193 (45.8%)	289 (30.5%)	-	-	39 (10.3%)
Related to Amivantamab[a]	184 (43.7%)	275 (29.0%)	-	-	39 (10.3%)
AEs leading to reduction of Lazertinib	176 (41.8%)	313 (33.1%)	-	91 (16.5%)	-
Related to Lazertinib[a]	165 (39.2%)	292 (30.8%)	-	86 (15.6%)	-
AEs leading to reduction of Osimertinib	-	-	23 (5.4%)	-	-
Related to Osimertinib[a]	-	-	16 (3.7%)	-	-
AEs leading to death [b]	34 (8.1%)	89 (9.4%)	31 (7.2%)	27 (4.9%)	20 (5.3%)
Related AEs leading to death[a,b]	4 (1.0%)	8 (0.8%)	2 (0.5%)	2 (0.4%)	0
Related to Amivantamab[a,b]	4 (1.0%)	8 (0.8%)	-	-	0
Related to Lazertinib[a,b]	4 (1.0%)	7 (0.7%)	-	2 (0.4%)	-
Related to Osimertinib[a,b]	-	-	2 (0.5%)	-	-
COVID-19 associated AEs[d]	136 (32.3%)	185 (19.5%)	117 (27.3%)	67 (12.2%)	4 (1.1%)
COVID-19 associated serious AEs[d]	13 (3.1%)	18 (1.9%)	11 (2.6%)	4 (0.7%)	0
COVID-19 associated non-serious AEs[d]	128 (30.4%)	176 (18.6%)	110 (25.7%)	63 (11.5%)	4 (1.1%)
COVID-19 associated grade 3 or higher AEs[d]	13 (3.1%)	17 (1.8%)	10 (2.3%)	3 (0.5%)	0
COVID-19 associated AEs[d] leading to death	2 (0.5%)	3 (0.3%)	3 (0.7%)	0	0

Key: AE = adverse event
Amivantamab and lazertinib total group includes subjects from studies 61186372EDI1001(CHRYSALIS), 73841937NSC3003(MARIPOSA) and 73841937NSC1001(CHRYSALIS-2).
Osimertinib group includes subjects from study 73841937NSC3003(MARIPOSA).
Lazertinib group includes subjects from studies 73841937NSC1001(CHRYSALIS-2), YH25448-201/73841937NSC2001, YH25448-301 and 73841937NSC3003(MARIPOSA).
Amivantamab group includes subjects from study 61186372EDI1001(CHRYSALIS).
a AE is assessed by the investigator as related to study agent.
b AEs leading to death are based on AE outcome of Fatal.
c Excludes infusion related reactions.
d COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term and events that are identified via the COVID-19 Case of AEs form.
Note: The data cut for 61186372EDI1001(CHRYSALIS) was March 20th 2021, 60% subjects discontinued study treatment prior to March 2020

Table 52: Number of subjects with treatment emergent adverse events with frequency of at least 20% in any treatment group by system organ class and preferred term (safety analysis set)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Analysis set: Safety	421	947	428	550	380
Subjects with 1 or more AEs	421 (100.0%)	947 (100.0%)	425 (99.3%)	541 (98.4%)	378 (99.5%)
System organ class Preferred term					
Skin and subcutaneous tissue disorders	383 (91.0%)	848 (89.5%)	273 (63.8%)	403 (73.3%)	313 (82.4%)
Rash	260 (61.8%)	517 (54.6%)	131 (30.6%)	224 (40.7%)	143 (37.6%)
Dermatitis acneiform	122 (29.0%)	283 (29.9%)	55 (12.9%)	80 (14.5%)	133 (35.0%)
Pruritus	99 (23.5%)	210 (22.2%)	73 (17.1%)	137 (24.9%)	78 (20.5%)
Infections and infestations	366 (86.9%)	749 (79.1%)	279 (65.2%)	287 (52.2%)	235 (61.8%)
Paronychia	288 (68.4%)	572 (60.4%)	121 (28.3%)	125 (22.7%)	164 (43.2%)
COVID-19	111 (26.4%)	159 (16.8%)	103 (24.1%)	58 (10.5%)	4 (1.1%)
Gastrointestinal disorders	326 (77.4%)	736 (77.7%)	298 (69.6%)	351 (63.8%)	285 (75.0%)
Constipation	123 (29.2%)	250 (26.4%)	55 (12.9%)	93 (16.9%)	86 (22.6%)
Diarrhoea	123 (29.2%)	235 (24.8%)	190 (44.4%)	169 (30.7%)	44 (11.6%)
Stomatitis	122 (29.0%)	289 (30.5%)	90 (21.0%)	87 (15.8%)	77 (20.3%)
Nausea	90 (21.4%)	251 (26.5%)	58 (13.6%)	95 (17.3%)	132 (34.7%)
Vomiting	52 (12.4%)	156 (16.5%)	23 (5.4%)	49 (8.9%)	76 (20.0%)
General disorders and administration site conditions	307 (72.9%)	662 (69.9%)	185 (43.2%)	207 (37.6%)	274 (72.1%)
Oedema peripheral	150 (35.6%)	311 (32.8%)	24 (5.6%)	40 (7.3%)	80 (21.1%)
Chills	5 (1.2%)	38 (4.0%)	1 (0.2%)	3 (0.5%)	102 (26.8%)
Metabolism and nutrition disorders	303 (72.0%)	666 (70.3%)	176 (41.1%)	200 (36.4%)	209 (55.0%)
Hypoalbuminaemia	204 (48.5%)	455 (48.0%)	26 (6.1%)	25 (4.5%)	115 (30.3%)
Decreased appetite	103 (24.5%)	222 (23.4%)	76 (17.8%)	100 (18.2%)	59 (15.5%)
Hypocalcaemia	88 (20.9%)	195 (20.6%)	35 (8.2%)	24 (4.4%)	38 (10.0%)
Injury, poisoning and procedural complications	297 (70.5%)	673 (71.1%)	39 (9.1%)	54 (9.8%)	269 (70.8%)
Infusion related reaction	265 (62.9%)	619 (65.4%)	0	0	256 (67.4%)
Investigations	256 (60.8%)	527 (55.6%)	183 (42.8%)	253 (46.0%)	154 (40.5%)
Alanine aminotransferase increased	152 (36.1%)	326 (34.4%)	57 (13.3%)	106 (19.3%)	56 (14.7%)
Aspartate aminotransferase increased	121 (28.7%)	256 (27.0%)	58 (13.6%)	93 (16.9%)	49 (12.9%)
Respiratory, thoracic and mediastinal disorders	239 (56.8%)	525 (55.4%)	215 (50.2%)	224 (40.7%)	263 (69.2%)
Cough	65 (15.4%)	134 (14.1%)	88 (20.6%)	79 (14.4%)	80 (21.1%)
Dyspnoea	51 (12.1%)	159 (16.8%)	68 (15.9%)	53 (9.6%)	141 (37.1%)
Nervous system disorders	230 (54.6%)	505 (53.3%)	146 (34.1%)	339 (61.6%)	145 (38.2%)
Paraesthesia	58 (13.8%)	126 (13.3%)	25 (5.8%)	153 (27.8%)	18 (4.7%)
Blood and lymphatic system disorders	164 (39.0%)	363 (38.3%)	181 (42.3%)	135 (24.5%)	80 (21.1%)
Anaemia	96 (22.8%)	194 (20.5%)	91 (21.3%)	93 (16.9%)	44 (11.6%)

Key: AE = Adverse Event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
Amivantamab and lazertinib total group includes subjects from studies 61186372EDI1001(CHRYSALIS), 73841937NSC3003(MARIPOSA) and 73841937NSC1001(CHRYSALIS-2).
Osimertinib group includes subjects from study 73841937NSC3003(MARIPOSA).
Lazertinib group includes subjects from studies 73841937NSC1001(CHRYSALIS-2), YH25448-201/73841937NSC2001, YH25448-301 and 73841937NSC3003(MARIPOSA).
Amivantamab group includes subjects from study 61186372EDI1001(CHRYSALIS).
[tsfae02p20.rtf] [xcp_oncology/z61186372_73841937/dbr_dwh_mariposa/re_iss_mariposa/tsfae02p20.sas] 30NOV2023, 13:33

Table 53: Most Commonly Reported Grade 3 or Higher TEAEs

Adverse Event	**Amivantamab + Lazertinib**		**Osimertinib** (n=428)	**Lazertinib** (n=550)	**Amivantamab** (n=380)
	MARIPOSA (n=421)	**Total** (n=947)			
At Least 1 AE					
Grade 3+ Incidence	316 (75.1%)	655 (69.2%)	183 (42.8%)	233 (42.4%)	158 (41.6%)
Grade 3	259 (61.5%)	517 (54.6%)	136 (31.8%)	187 (34.0%)	129 (33.9%)
Grade 4	23 (5.5%)	49 (5.2%)	16 (3.7%)	19 (3.5%)	9 (2.4%)
Grade 5	34 (8.1%)	89 (9.4%)	31 (7.2%)	27 (4.9%)	20 (5.3%)
Rash					

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	65 (15.4%) 65 (15.4%) 0 0	94 (9.9%) 94 (9.9%) 0 0	3 (0.7%) 3 (0.7%) 0 0	7 (1.3%) 7 (1.3%) 0 0	5 (1.3%) 5 (1.3%) 0 0
Paronychia					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	46 (10.9%) 46 (10.9%) 0 0	65 (6.9%) 65 (6.9%) 0 0	2 (0.5%) 2 (0.5%) 0 0	4 (0.7%) 4 (0.7%) 0 0	7 (1.8%) 7 (1.8%) 0 0
Dermatitis acneiform					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	35 (8.3%) 35 (8.3%) 0 0	54 (5.7%) 54 (5.7%) 0 0	0 0 0 0	2 (0.4%) 2 (0.4%) 0 0	3 (0.8%) 3 (0.8%) 0 0
Pulmonary embolism					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	35 (8.3%) 32 (7.6%) 1 (0.2%) 2 (0.5%)	60 (6.3%) 57 (6.0%) 1 (0.1%) 2 (0.2%)	10 (2.3%) 7 (1.6%) 1 (0.2%) 2 (0.5%)	20 (3.6%) 16 (2.9%) 1 (0.2%) 3 (0.5%)	14 (3.7%) 13 (3.4%) 1 (0.3%) 0
IRR					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	27 (6.4%) 23 (5.5%) 4 (1.0%) 0	56 (5.9%) 50 (5.3%) 6 (0.6%) 0	0 0 0 0	0 0 0 0	8 (2.1%) 7 (1.8%) 1 (0.3%) 0
Pneumonia					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	16 (3.8%) 10 (2.4%) 1 (0.2%) 5 (1.2%)	54 (5.7%) 33 (3.5%) 5 (0.5%) 16 (1.7%)	20 (4.7%) 14 (3.3%) 2 (0.5%) 4 (0.9%)	19 (3.5%) 16 (2.9%) 0 3 (0.5%)	16 (4.2%) 9 (2.4%) 2 (0.5%) 5 (1.3%)
Hypoalbuminemia					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	22 (5.2%) 22 (5.2%) 0 0	59 (6.2%) 59 (6.2%) 0 0	0 0 0 0	0 0 0 0	8 (2.1%) 8 (2.1%) 0 0
ALT increased					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	21 (5.0%) 19 (4.5%) 2 (0.5%) 0	44 (4.6%) 41 (4.3%) 3 (0.3%) 0	8 (1.9%) 7 (1.6%) 1 (0.2%) 0	10 (1.8%) 8 (1.5%) 2 (0.4%) 0	7 (1.8%) 5 (1.3%) 2 (0.5%) 0
Dyspnea					
Grade 3+ Incidence Grade 3 Grade 4 Grade 5	6 (1.4%) 5 (1.2%) 1 (0.2%) 0	34 (3.6%) 20 (2.1%) 3 (0.3%) 11 (1.2%)	17 (4.0%) 14 (3.3%) 0 3 (0.7%)	7 (1.3%) 6 (1.1%) 0 1 (0.2%)	19 (5.0%) 16 (4.2%) 1 (0.3%) 2 (0.5%)

2.6.8.2. Serious adverse event/deaths/other significant events

Adverse Events of Special Interest

Rash

Rash is an existing ADR for EGFR inhibitors.

Table 54: Summary of Rash (Grouped Term) (SAF; Pooled Analysis)

Adverse Event	Amivantamab + Lazertinib MARIPOSA (n=421)	Amivantamab + Lazertinib Total (n=947)	Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
Incidence (all grades)	373 (88.6%)	813 (85.9%)	210 (49.1%)	334 (60.7%)	291 (76.6%)
Grade ≥3	114 (27.1%)	182 (19.2%)	4 (0.9%)	15 (2.7%)	11 (2.9%)
Serious	13 (3.1%)	24 (2.5%)	0	0	3 (0.8%)
Treatment Discontinuation	24 (5.7%)	32 (3.4%)	0	2 (0.4%)	3 (0.8%)
Drug Interruption	179 (42.5%)	274 (28.9%)	8 (1.9%)	25 (4.5%)	38 (10.0%)
Dose Reduction	140 (33.3%)	219 (23.1%)	2 (0.5%)	22 (4.0%)	21 (5.5%)

Infusion Related Reaction

IRRs are an existing ADR for amivantamab monotherapy.

Table 55: Summary of IRR (SAF; Pooled Analysis)

Adverse Event	Amivantamab + Lazertinib MARIPOSA (n=421)	Amivantamab + Lazertinib Total (n=947)	Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
Incidence (all grades)	265 (62.9%)	619 (65.4%)	0	0	256 (67.4%)
Grade ≥3	27 (6.4%)	56 (5.9%)	0	0	8 (2.1%)
Serious	9 (2.1%)	23 (2.4%)	0	0	4 (1.1%)
Treatment Discontinuation	19 (4.5%)	32 (3.4%)	0	0	4 (1.1%)
Drug Interruption	229 (54.4%)	529 (55.9%)	0	0	239 (62.9%)
Dose Reduction	3 (0.7%)	3 (0.3%)	0	0	0

Pneumonitis/ILD

Pneumonitis/ILD is an existing ADR for EGFR inhibitors.

Table 56: Summary of Pneumonitis/ILD (Grouped Term) (SAF; Pooled Analysis)

Adverse Event	Amivantamab + Lazertinib MARIPOSA (n=421)	Amivantamab + Lazertinib Total (n=947)	Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
Incidence (all grades)	13 (3.1%)	36 (3.8%)	13 (3.0%)	13 (2.4%)	10 (2.6%)
Grade ≥3	6 (1.4%)	16 (1.7%)	6 (1.4%)	7 (1.3%)	2 (0.5%)
Serious	12 (2.9%)	26 (2.7%)	13 (3.0%)	10 (1.8%)	5 (1.3%)
Treatment Discontinuation	12 (2.9%)	25 (2.6%)	11 (2.6%)	9 (1.6%)	2 (0.5%)
Drug Interruption	1 (0.2%)	9 (1.0%)	3 (0.7%)	1 (0.2%)	7 (1.8%)
Dose Reduction	0	0	0	0	2 (0.5%)

VTE Events

Table 57: Characteristics of the AESI of VTE Events (grouped term)

Adverse Event	Amivantamab + Lazertinib MARIPOSA (n=421)	Amivantamab + Lazertinib Total (n=947)	Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
Incidence (all grades)	157 (37.3%)	278 (29.4%)	39 (9.1%)	69 (12.5%)	38 (10.0%)
Exposure-Adjusted (all grades)per 100 subject-years	157 (35.2)	278 (36.2)	39 (6.6)	69 (10.1)	38 (18.5)
Maximum Toxicity Grade					
Grade 1	5 (1.2%)	17 (1.8%)	0	4 (0.7%)	8 (2.1%)
Grade 2	105 (24.9%)	178 (18.8%)	24 (5.6%)	37 (6.7%)	11 (2.9%)
Grade 3	43 (10.2%)	79 (8.3%)	12 (2.8%)	23 (4.2%)	17 (4.5%)
Grade 4	2 (0.5%)	2 (0.2%)	1 (0.2%)	2 (0.4%)	2 (0.5%)
Grade 5	2 (0.5%)	2 (0.2%)	2 (0.5%)	3 (0.5%)	0

Incidence (Grade 3 +)	47 (11.2%)	83 (8.8%)	15 (3.5%)	28 (5.1%)	19 (5.0%)
Exposure-Adjusted (Grade 3+)per 100 subject-years	47 (8.3)	83 (8.8)	15 (2.4)	28 (3.9)	19 (8.8)
Serious	46 (10.9%)	72 (7.6%)	15 (3.5%)	25 (4.5%)	11 (2.9%)
Treatment Discontinuation	12 (2.9%)	14 (1.5%)	2 (0.5%)	6 (1.1%)	1 (0.3%)
Amivantamab	12 (2.9%)	14 (1.5%)	NA	NA	1 (0.3%)
Lazertinib	7 (1.7%)	9 (1.0%)	NA	6 (1.1%)	NA
Osimertinib	NA	NA	2 (0.5%)	NA	NA
Drug Interruption	47 (11.2%)	67 (7.1%)	10 (2.3%)	12 (2.2%)	6 (1.6%)
Amivantamab	39 (9.3%)	56 (5.9%)	NA	NA	6 (1.6%)
Lazertinib	31 (7.4%)	47 (5.0%)	NA	12 (2.2%)	NA
Osimertinib	NA	NA	10 (2.3%)	NA	NA
Dose Reduction	5 (1.2%)	8 (0.8%)	0	2 (0.4%)	0
Amivantamab	4 (1.0%)	4 (0.4%)	NA	NA	0
Lazertinib	2 (0.5%)	5 (0.5%)	NA	2 (0.4%)	NA
Osimertinib	NA	NA	0	NA	NA

VTE in PALOMA-3 primary analysis

Study JNJ-61186372NSC3004 (hereafter referred to as PALOMA-3) is an open-label, randomised, phase III, non-inferiority study of lazertinib with subcutaneous (SC) amivantamab compared with intravenous (IV) amivantamab in patients with EGFR-mutated advanced or metastatic NSCLC after progression on osimertinib and chemotherapy.

Due to the increased VTE risk identified in the MARIPOSA study, all patients randomised to AL combination treatment were recommended prophylactic anticoagulants as per local guidelines for the first four months of treatment. At that time-point, no patients had been randomised in the PALOMA-3 study. Hence, all PALOMA-3 patients were recommended prophylactic anticoagulant therapy.

The primary analysis report from PALOMA-3, with CCO of 04 January 2024, was provided as support for the recommendation of prophylactic anticoagulant therapy.

At the time of CCO of the primary analysis, 418 patients were enrolled in the PALOMA-3 study, of which 416 received at least one dose of study treatment and constituted the safety analysis set (SAS). Of these 416 patients, 206 were randomised to receive lazertinib + amivantamab SC and 210 to receive lazertinib + amivantamab IV. The median duration of study treatment was 4.65 and 4.12 months in the SC and IV arms, respectively. The study is still ongoing. The median duration of follow-up was 7.0 months (both arms).

Of the patients in the SAS, 335 (80.5%) received any prophylactic anticoagulant therapy for a median duration of treatment of 5.11 months (range 0.1, 131.1). Of these, 220/335 received continuous prophylactic therapy for at least four months and 115/335 received prophylactic therapy with an interruption. The remaining 81 (19.5%) of the patients in the SAS did not receive any prophylactic anticoagulation therapy. Of all patients receiving prophylactic anticoagulants, 137/335 (40.9%) discontinued anticoagulant therapy after four months.

Prophylactic anticoagulants were recommended for four months in the PALOMA-3 study, but not mandated. The treatment duration as well as administration route of prophylactic anticoagulants was decided by the responsible investigator according to local guidelines. Most of the patients (n=275, 66.1% of the SAS, 82.1% of the patients who received any anticoagulants) on prophylactic anticoagulants received DOACs (direct Factor Xa inhibitors). The remaining patients received other agents, including low molecular weight heparin derivatives and vitamin K antagonists.

Table 58: Overall summary of TEAE VTEs by anticoagulant use, safety analysis set (PALOMA-3)

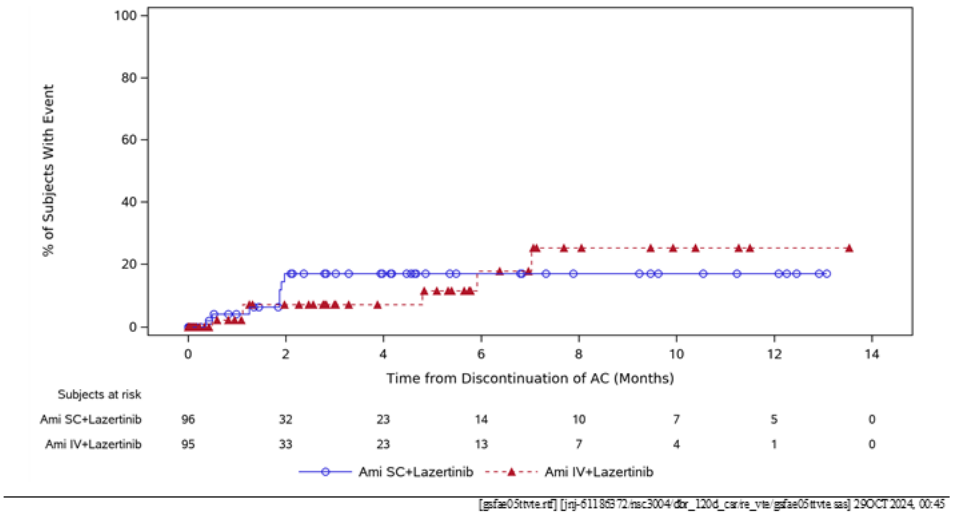
	Total	With Prophylactic Anticoagulation	No Prophylactic Anticoagulation
Analysis set: Safety	416	335	81
% of VTE* events, all grades	49 (11.8%)	32 (9.6%)	17 (21.0%)
Gr3+	9 (2.2%)	4 (1.2%)	5 (6.2%)
Gr5	0	0	0
% of VTE SAE	11 (2.6%)	5 (1.5%)	6 (7.4%)
% of VTE TEAEs leading to discontinuation	2 (0.5%)	0	2 (2.5%)

Key: VTE=Venous Thromboembolic Event; TEAE= Treatment Emergent Adverse Event; SAE=Serious Adverse Event;
Note: *VTEs include all Embolic and thrombotic events, venous (SMQ), Thrombosis and Embolism events.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.

[tsfac01avtca.rtf] [jnj-61186372/nsc3004/dbr_csr/rc_vtc/tsfac01avtca.sas] 18MAR2024, 10:33

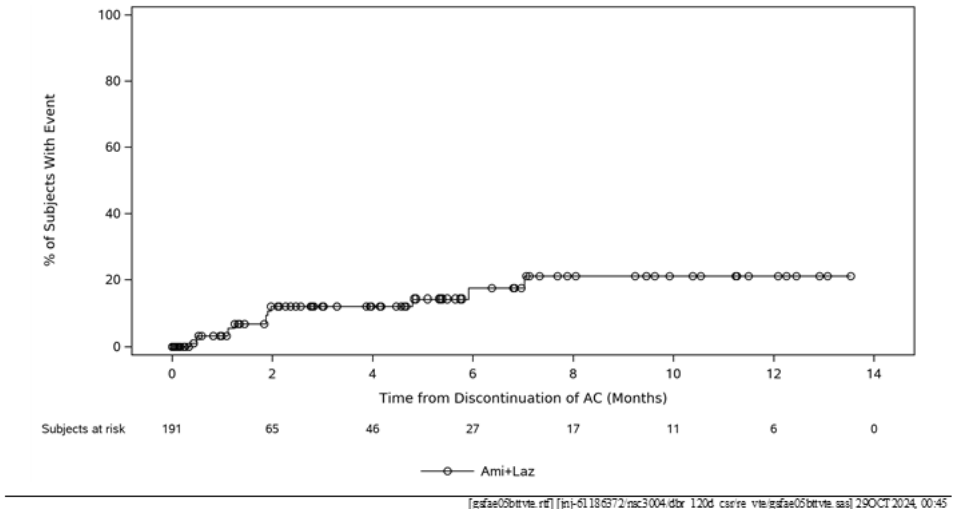
Of all VTE events, 23/49 (46.9%) were symptomatic, and 10 required hospitalisation (seven due to initiation of anticoagulants, as per local routine).The following two K-M curves, depicting time to VTE from time of discontinuing anticoagulation in patients remaining on AL treatment (i.e., censoring patients at the discontinuation of any or both study drugs), were used as support for the notion that four months of prophylactic anticoagulation, as initially recommended, was sufficient.

Figure 24: Kaplan-Meier plot for the time to onset of VTE from discontinuation of anticoagulants by treatment group, safety analysis set (PALOMA-3)



[gsfae05ttvte.rtf] [jnj-61186372/nsc3004/dbr_120d_csrire_vte/gsfae05ttvte.sas] 29OCT2024, 00:45

Figure 25: Kaplan-Meier plot for the time of VTE from discontinuation of anticoagulants, safety analysis set (PALOMA-3)



The incidence and severity of bleeding reported for those participants who received anticoagulation is comparable to the incidence of major bleeding events in patients with lung cancer on anticoagulation (Chen 2020). Most of the bleeding events only occurred in one participant each and there was no consistent signal of a specific type of bleeding.

Table 59:Overall summary of TEAEs of bleeding, safety analysis set (PALOMA-3)

	Total	With Prophylactic Anticoagulation	No Prophylactic Anticoagulation
Analysis set: Safety	416	335	81
% of Bleeding** events, all grades	102 (24.5%)	92 (27.5%)	10 (12.3%)
Gr3+	5 (1.2%)	4 (1.2%)	1 (1.2%)
Gr5	0	0	0
% of Bleeding SAE	4 (1.0%)	4 (1.2%)	0
% of Bleeding TEAEs leading to discontinuation	1 (0.2%)	1 (0.3%)	0

Key: TEAE= Treatment Emergent Adverse Event; SAE=Serious Adverse Event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.
**based on Bleeding terms (excl laboratory terms) (SMQ)
4 subjects from with prophylactic group had bleeding event prior to the start of prophylactic anticoagulant.
[tsfac01ahcm.rtf] [jnj-61186372/nsc3004/dbr_csr/rc_vtc/tsfac01ahcm.sas] 13MAR2024, 16:47

Amivantamab IV + lazertinib VTE subgroup analysis in PALOMA-3

As the MARIPOSA study only studied use of amivantamab IV, the applicant also submitted a subgroup analysis of participants treated with amivantamab IV + lazertinib in the PALOMA-3 study.

Table 60: Overall summary of TEAE VTE by anticoagulants use and treatment groups, safety analysis set (PALOMA-3)

	Amivantamab IV + Lazertinib		
	Total	With Prophylactic Anticoagulants	No Prophylactic Anticoagulants
Analysis set: Safety	210	171	39
% of VTE* events, all grades	30 (14.3%)	20 (11.7%)	10 (25.6%)
Gr3+	7 (3.3%)	2 (1.2%)	5 (12.8%)
Gr5	0	0	0
% of VTE SAE	7 (3.3%)	3 (1.8%)	4 (10.3%)
% of VTE TEAEs leading to discontinuation	2 (1.0%)	0	2 (5.1%)

Key: VTE=Venous Thromboembolic Event; IV=Intravenous; SC=Subcutaneous; TEAE= Treatment Emergent Adverse Event; SAE=Serious Adverse Event.
Note: *VTEs include all Embolic and thrombotic events, venous (SMQ), Thrombosis and Embolism events.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.

Of all VTE events in the amivantamab IV subgroup, 19/30 events occurred during the first four cycles of study treatment.

Of the 210 participants in the amivantamab IV + lazertinib subgroup, 112 participants received continuous anticoagulation per protocol for the first four months of treatment and 59 participants received prophylactic anticoagulation with an interruption.

Among the 171 participants who received one or more anticoagulants in the amivantamab IV + lazertinib group, 143 (83.6%) received DOACs (direct Factor Xa inhibitors) and 28 (16.4%) received other anticoagulants including low molecular weight heparin derivatives, other antithrombotic agents, direct thrombin inhibitors, and vitamin K antagonists.

The incidence of bleeding events was 28.1% (n=48) among the 171 participants in the amivantamab IV + lazertinib group who received prophylactic anticoagulants versus and 12.8% (n=5) among the 39 participants who received no prophylactic anticoagulants. Of note, 3 of the 171 participants in the prophylactic anticoagulation group had a bleeding event and experienced the event prior to initiating anticoagulation therapy. The majority of bleeding events were grade 1-2 and non-serious regardless of prophylactic anticoagulation use.

Hepatotoxicity

Table 61: Overall Summary of Treatment-emergent Adverse Events of Hepatotoxicity; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Analysis set: Safety	421	947	428	550	380
Subjects with 1 or more:					
AEs	199 (47.3%)	423 (44.7%)	105 (24.5%)	155 (28.2%)	107 (28.2%)
Grade 3 or higher AEs	38 (9.0%)	70 (7.4%)	19 (4.4%)	14 (2.5%)	16 (4.2%)
Maximum toxicity grade					
Grade 1	110 (26.1%)	254 (26.8%)	76 (17.8%)	111 (20.2%)	73 (19.2%)
Grade 2	51 (12.1%)	99 (10.5%)	10 (2.3%)	30 (5.5%)	18 (4.7%)
Grade 3	36 (8.6%)	66 (7.0%)	18 (4.2%)	11 (2.0%)	14 (3.7%)
Grade 4	2 (0.5%)	4 (0.4%)	1 (0.2%)	3 (0.5%)	2 (0.5%)
Grade 5	0	0	0	0	0
Serious AEs	10 (2.4%)	12 (1.3%)	9 (2.1%)	5 (0.9%)	2 (0.5%)
AEs leading to discontinuation of any study agent	4 (1.0%)	8 (0.8%)	0	0	0
AEs leading to discontinuation of Amivantamab	4 (1.0%)	6 (0.6%)	-	-	0
AEs leading to discontinuation of Lazertinib	1 (0.2%)	5 (0.5%)	-	0	-
AEs leading to discontinuation of Osimertinib	-	-	0	-	-
AEs leading to drug interruption of any study agent	38 (9.0%)	67 (7.1%)	16 (3.7%)	14 (2.5%)	10 (2.6%)
AEs leading to interruption of Amivantamab	30 (7.1%)	55 (5.8%)	-	-	10 (2.6%)
AEs leading to interruption of Lazertinib	34 (8.1%)	61 (6.4%)	-	14 (2.5%)	-
AEs leading to interruption of Osimertinib	-	-	16 (3.7%)	-	-
AEs leading to dose reduction of any study agent	10 (2.4%)	22 (2.3%)	0	3 (0.5%)	1 (0.3%)
AEs leading to reduction of Amivantamab	7 (1.7%)	12 (1.3%)	-	-	1 (0.3%)
AEs leading to reduction of Lazertinib	6 (1.4%)	16 (1.7%)	-	3 (0.5%)	-
AEs leading to reduction of Osimertinib	-	-	0	-	-

Key: AE = Adverse Event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

Table 62: Number of Subjects With Selected Treatment-emergent Adverse Events of Hepatotoxicity by Preferred Term; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Analysis set: Safety	421	947	428	550	380
Subjects with 1 or more AEs of Hepatotoxicity	199 (47.3%)	423 (44.7%)	105 (24.5%)	155 (28.2%)	107 (28.2%)
Preferred term					
Alanine aminotransferase increased	152 (36.1%)	326 (34.4%)	57 (13.3%)	106 (19.3%)	56 (14.7%)
Aspartate aminotransferase increased	121 (28.7%)	256 (27.0%)	58 (13.6%)	93 (16.9%)	49 (12.9%)
Gamma-glutamyltransferase increased	61 (14.5%)	114 (12.0%)	31 (7.2%)	28 (5.1%)	31 (8.2%)
Blood alkaline phosphatase increased	52 (12.4%)	101 (10.7%)	22 (5.1%)	33 (6.0%)	44 (11.6%)
Hyperbilirubinaemia	28 (6.7%)	48 (5.1%)	14 (3.3%)	21 (3.8%)	8 (2.1%)
Hepatic steatosis	5 (1.2%)	5 (0.5%)	0	0	1 (0.3%)
Hepatic function abnormal	4 (1.0%)	4 (0.4%)	5 (1.2%)	3 (0.5%)	0
Cholestasis	3 (0.7%)	5 (0.5%)	0	0	1 (0.3%)
Hepatitis	3 (0.7%)	4 (0.4%)	0	0	0
Ascites	2 (0.5%)	6 (0.6%)	1 (0.2%)	0	2 (0.5%)
Hepatic cytolysis	2 (0.5%)	2 (0.2%)	1 (0.2%)	0	0
Hepatotoxicity	2 (0.5%)	2 (0.2%)	2 (0.5%)	0	0
Hypertransaminasaemia	2 (0.5%)	3 (0.3%)	2 (0.5%)	0	0
Blood bilirubin increased	1 (0.2%)	1 (0.1%)	1 (0.2%)	10 (1.8%)	0
Blood cholinesterase decreased	1 (0.2%)	1 (0.1%)	0	0	0
Hepatic enzyme increased	1 (0.2%)	1 (0.1%)	0	1 (0.2%)	0
Hepatomegaly	1 (0.2%)	1 (0.1%)	0	0	0
Liver injury	1 (0.2%)	1 (0.1%)	0	0	0
Bilirubin conjugated increased	0	0	1 (0.2%)	8 (1.5%)	0
Bilirubin urine present	0	1 (0.1%)	0	0	0
Drug-induced liver injury	0	1 (0.1%)	0	0	0
Hepatic enzyme abnormal	0	0	1 (0.2%)	0	0
Hepatic failure	0	0	0	1 (0.2%)	0
Hepatic mass	0	0	1 (0.2%)	0	0
Hepatitis toxic	0	1 (0.1%)	0	0	0
Hepatobiliary disease	0	1 (0.1%)	0	0	0
Liver disorder	0	15 (1.6%)	0	0	0
Liver function test abnormal	0	0	1 (0.2%)	0	0
Portal hypertension	0	1 (0.1%)	0	0	0
Total bile acids increased	0	5 (0.5%)	0	0	2 (0.5%)
Urobilinogen urine increased	0	1 (0.1%)	0	0	0
Varicose veins of abdominal wall	0	0	0	0	1 (0.3%)

Key: AE = Adverse Event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

Table 63: Characteristics of EGFR-Associated Commonly Reported TEAEs (Paronychia, Rash, Dermatitis Acneiform, Stomatitis, and Diarrhea)

Adverse Event	**Amivantamab + Lazertinib**		**Osimertinib** (n=428)	**Lazertinib** (n=550)	**Amivantamab** (n=380)
	MARIPOSA (n=421)	**Total** (n=947)			
Paronychia					
Incidence (all grades)	288 (68.4%)	572 (60.4%)	121 (28.3%)	125 (22.7%)	164 (43.2%)
Grade 3+	46 (10.9%)	65 (6.9%)	2 (0.5%)	4 (0.7%)	7 (1.8%)
Serious	0	3 (0.3%)	0	0	0
Treatment Discontinuation	14 (3.3%)	18 (1.9%)	0	1 (0.2%)	2 (0.5%)
Amivantamab	14 (3.3%)	18 (1.9%)	NA	NA	2 (0.5%)
Lazertinib	2 (0.5%)	3 (0.3%)	NA	1 (0.2%)	NA
Osimertinib	NA	NA	0	NA	NA

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Drug Interruption	91 (21.6%)	141 (14.9%)	4 (0.9%)	6 (1.1%)	11 (2.9%)
Amivantamab	84 (20.0%)	121 (12.8%)	NA	NA	11 (2.9%)
Lazertinib	65 (15.4%)	107 (11.3%)	NA	6 (1.1%)	NA
Osimertinib	NA	NA	4 (0.9%)	NA	NA
Dose Reduction	80 (19.0%)	120 (12.7%)	1 (0.2%)	1 (0.2%)	10 (2.6%)
Amivantamab	59 (14.0%)	78 (8.2%)	NA	NA	10 (2.6%)
Lazertinib	48 (11.4%)	75 (7.9%)	NA	1 (0.2%)	NA
Osimertinib	NA	NA	1 (0.2%)	NA	NA
Rash					
Incidence (all grades)	260 (61.8%)	517 (54.6%)	131 (30.6%)	224 (40.7%)	143 (37.6%)
Grade 3+	65 (15.4%)	94 (9.9%)	3 (0.7%)	7 (1.3%)	5 (1.3%)
Serious	7 (1.7%)	11 (1.2%)	0	0	2 (0.5%)
Treatment Discontinuation	11 (2.6%)	13 (1.4%)	0	0	0
Amivantamab	10 (2.4%)	11 (1.2%)	NA	NA	0
Lazertinib	3 (0.7%)	4 (0.4%)	NA	0	NA
Osimertinib	NA	NA	0	NA	NA
Drug Interruption	104 (24.7%)	155 (16.4%)	4 (0.9%)	14 (2.5%)	14 (3.7%)
Amivantamab	95 (22.6%)	135 (14.3%)	NA	NA	14 (3.7%)
Lazertinib	76 (18.1%)	115 (12.1%)	NA	14 (2.5%)	NA
Osimertinib	NA	NA	4 (0.9%)	NA	NA
Dose Reduction	84 (20.0%)	120 (12.7%)	2 (0.5%)	12 (2.2%)	2 (0.5%)
Amivantamab	62 (14.7%)	81 (8.6%)	NA	NA	2 (0.5%)
Lazertinib	42 (10.0%)	71 (7.5%)	NA	12 (2.2%)	NA
Osimertinib	NA	NA	2 (0.5%)	NA	NA
Diarrhea					
Incidence (all grades)	123 (29.2%)	235 (24.8%)	190 (44.4%)	169 (30.7%)	44 (11.6%)
Grade 3+	9 (2.1%)	12 (1.3%)	3 (0.7%)	13 (2.4%)	6 (1.6%)
Serious	4 (1.0%)	5 (0.5%)	2 (0.5%)	5 (0.9%)	2 (0.5%)
Treatment Discontinuation	1 (0.2%)	3 (0.3%)	1 (0.2%)	0	0
Amivantamab	1 (0.2%)	2 (0.2%)	NA	NA	0
Lazertinib	0	1 (0.1%)	NA	0	NA
Osimertinib	NA	NA	1 (0.2%)	NA	NA
Drug Interruption	19 (4.5%)	31 (3.3%)	6 (1.4%)	10 (1.8%)	7 (1.8%)
Amivantamab	15 (3.6%)	23 (2.4%)	NA	NA	7 (1.8%)
Lazertinib	15 (3.6%)	24 (2.5%)	NA	10 (1.8%)	NA
Osimertinib	NA	NA	6 (1.4%)	NA	NA
Dose Reduction	3 (0.7%)	5 (0.5%)	2 (0.5%)	7 (1.3%)	0
Amivantamab	3 (0.7%)	3 (0.3%)	NA	NA	0
Lazertinib	0	2 (0.2%)	NA	7 (1.3%)	NA
Osimertinib	NA	NA	2 (0.5%)	NA	NA
Stomatitis					
Incidence (all grades)	122 (29.0%)	289 (30.5%)	90 (21.0%)	87 (15.8%)	77 (20.3%)
Grade 3+	5 (1.2%)	11 (1.2%)	1 (0.2%)	1 (0.2%)	2 (0.5%)
Serious	0	2 (0.2%)	0	0	0
Treatment Discontinuation	1 (0.2%)	3 (0.3%)	0	0	1 (0.3%)
Amivantamab	1 (0.2%)	3 (0.3%)	NA	NA	1 (0.3%)
Lazertinib	1 (0.2%)	3 (0.3%)	NA	0	NA
Osimertinib	NA	NA	0	NA	NA
Drug Interruption	13 (3.1%)	32 (3.4%)	4 (0.9%)	4 (0.7%)	7 (1.8%)
Amivantamab	10 (2.4%)	26 (2.7%)	NA	NA	7 (1.8%)
Lazertinib	10 (2.4%)	21 (2.2%)	NA	4 (0.7%)	NA
Osimertinib	NA	NA	4 (0.9%)	NA	NA
Dose Reduction	5 (1.2%)	19 (2.0%)	0	2 (0.4%)	3 (0.8%)
Amivantamab	3 (0.7%)	12 (1.3%)	NA	NA	3 (0.8%)
Lazertinib	3 (0.7%)	13 (1.4%)	NA	2 (0.4%)	NA
Osimertinib	NA	NA	0	NA	NA
Dermatitis Acneiform					
Incidence (all grades)	122 (29.0%)	283 (29.9%)	55 (12.9%)	80 (14.5%)	133 (35.0%)
Grade 3+	35 (8.3%)	54 (5.7%)	0	2 (0.4%)	3 (0.8%)
Serious	1 (0.2%)	5 (0.5%)	0	0	1 (0.3%)
Treatment Discontinuation	6 (1.4%)	9 (1.0%)	0	0	1 (0.3%)
Amivantamab	6 (1.4%)	7 (0.7%)	NA	NA	1 (0.3%)
Lazertinib	1 (0.2%)	4 (0.4%)	NA	0	NA
Osimertinib	NA	NA	0	NA	NA
Drug Interruption	50 (11.9%)	72 (7.6%)	1 (0.2%)	5 (0.9%)	11 (2.9%)
Amivantamab	49 (11.6%)	66 (7.0%)	NA	NA	11 (2.9%)
Lazertinib	37 (8.8%)	55 (5.8%)	NA	5 (0.9%)	NA

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Osimertinib	NA	NA	1 (0.2%)	NA	NA
Dose Reduction	38 (9.0%)	64 (6.8%)	0	2 (0.4%)	13 (3.4%)
Amivantamab	26 (6.2%)	42 (4.4%)	NA	NA	13 (3.4%)
Lazertinib	27 (6.4%)	46 (4.9%)	NA	2 (0.4%)	NA
Osimertinib	NA	NA	0	NA	NA

Table 64: Characteristics of Paresthesia and Associated Symptoms (grouped term)

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Incidence (all grades)	145 (34.4%)	283 (29.9%)	41 (9.6%)	248 (45.1%)	37 (9.7%)
Grade 3+	7 (1.7%)	11 (1.2%)	1 (0.2%)	13 (2.4%)	0
Serious	0	1 (0.1%)	0	1 (0.2%)	2 (0.5%)
Treatment Discontinuation	5 (1.2%)	6 (0.6%)	0	7 (1.3%)	0
Amivantamab	5 (1.2%)	5 (0.5%)	-	-	0
Lazertinib	3 (0.7%)	4 (0.4%)	-	7 (1.3%)	-
Osimertinib	-	-	0	-	-
Drug Interruption	17 (4.0%)	30 (3.2%)	1 (0.2%)	16 (2.9%)	3 (0.8%)
Amivantamab	16 (3.8%)	25 (2.6%)	-	-	3 (0.8%)
Lazertinib	10 (2.4%)	22 (2.3%)	-	16 (2.9%)	-
Osimertinib	-	-	1 (0.2%)	-	-
Dose Reduction	21 (5.0%)	40 (4.2%)	0	33 (6.0%)	0
Amivantamab	6 (1.4%)	16 (1.7%)	-	-	0
Lazertinib	19 (4.5%)	29 (3.1%)	-	33 (6.0%)	-
Osimertinib	-	-	0	-	-

Table 65: Characteristics of MET-Associated Commonly Reported TEAEs (Hypoalbuminemia and Peripheral Edema)

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Hypoalbuminemia					
Incidence (all grades)	204 (48.5%)	455 (48.0%)	26 (6.1%)	25 (4.5%)	115 (30.3%)
Grade 3+	22 (5.2%)	59 (6.2%)	0	0	8 (2.1%)
Serious	5 (1.2%)	6 (0.6%)	0	0	0
Treatment Discontinuation	6 (1.4%)	8 (0.8%)	0	0	1 (0.3%)
Amivantamab	6 (1.4%)	8 (0.8%)	NA	NA	1 (0.3%)
Lazertinib	2 (0.5%)	3 (0.3%)	NA	0	NA
Osimertinib	NA	NA	0	NA	NA
Drug Interruption	25 (5.9%)	48 (5.1%)	0	1 (0.2%)	0
Amivantamab	23 (5.5%)	43 (4.5%)	NA	NA	0
Lazertinib	15 (3.6%)	29 (3.1%)	NA	1 (0.2%)	NA
Osimertinib	NA	NA	0	NA	NA
Dose Reduction	11 (2.6%)	16 (1.7%)	0	1 (0.2%)	0
Amivantamab	11 (2.6%)	14 (1.5%)	NA	NA	0
Lazertinib	1 (0.2%)	3 (0.3%)	NA	1 (0.2%)	NA
Osimertinib	NA	NA	0	NA	NA
Peripheral edema					
Incidence (all grades)	150 (35.6%)	311 (32.8%)	24 (5.6%)	40 (7.3%)	80 (21.1%)
Grade 3+	8 (1.9%)	16 (1.7%)	0	3 (0.5%)	3 (0.8%)
Serious	2 (0.5%)	7 (0.7%)	0	2 (0.4%)	0
Treatment Discontinuation	5 (1.2%)	5 (0.5%)	0	0	0
Amivantamab	5 (1.2%)	5 (0.5%)	NA	NA	0
Lazertinib	1 (0.2%)	1 (0.1%)	NA	0	NA
Osimertinib	NA	NA	0	NA	NA
Drug Interruption	20 (4.8%)	41 (4.3%)	0	1 (0.2%)	2 (0.5%)
Amivantamab	18 (4.3%)	37 (3.9%)	NA	NA	2 (0.5%)
Lazertinib	10 (2.4%)	24 (2.5%)	NA	1 (0.2%)	NA
Osimertinib	NA	NA	0	NA	NA
Dose Reduction	7 (1.7%)	20 (2.1%)	0	1 (0.2%)	2 (0.5%)
Amivantamab	5 (1.2%)	14 (1.5%)	NA	NA	2 (0.5%)

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Lazertinib	3 (0.7%)	8 (0.8%)	NA	1 (0.2%)	NA
Osimertinib	NA	NA	0	NA	NA

Table 66: Frequency of Hypoalbuminemia and Oedema ADRs

Adverse reaction	Frequency category	Any Grade n (%)	Grade 3-4 n (%)
Hypoalbuminaemia*	Very common	204 (48.46%)	22 (5.23%)
Oedema*	Very common	197 (46.79%)	12 (2.85%)

* Grouped terms

Serious adverse events

Table 67: Summary of Most Commonly Reported (≥2%) Serious Adverse Events (SAF; Pooled Analysis)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Analysis set: Safety	421	947	428	550	380
Any SAE	205 (48.7%)	446 (47.1%)	143 (33.4%)	167 (30.4%)	111 (29.2%)
Pulmonary embolism	26 (6.2%)	40 (4.2%)	10 (2.3%)	21 (3.8%)	9 (2.4%)
Pleural effusion	9 (2.1%)	19 (2.0%)	17 (4.0%)	5 (0.9%)	5 (1.3%)
Dyspnoea	4 (1.0%)	26 (2.7%)	11 (2.6%)	7 (1.3%)	13 (3.4%)
Pneumonia	17 (4.0%)	54 (5.7%)	21 (4.9%)	22 (4.0%)	19 (5.0%)
COVID-19	10 (2.4%)	14 (1.5%)	10 (2.3%)	4 (0.7%)	0
Infusion related reaction	9 (2.1%)	23 (2.4%)	0	0	4 (1.1%)
Deep vein thrombosis	12 (2.9%)	16 (1.7%)	2 (0.5%)	2 (0.4%)	1 (0.3%)

Deaths

Table 68: Summary of Death and Cause of Death (SAF; Pooled Analysis)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Analysis set: Safety	421	947	428	550	380
Deaths during study	96 (22.8%)	295 (31.2%)	116 (27.1%)	138 (25.1%)	127 (33.4%)
Progressive disease	49 (11.6%)	209 (22.1%)	81 (18.9%)	87 (15.8%)	96 (25.3%)
Adverse event	39 (9.3%)	66 (7.0%)	29 (6.8%)	20 (3.6%)	18 (4.7%)
Other	8 (1.9%)	20 (2.1%)	6 (1.4%)	14 (2.5%)	13 (3.4%)
Disease progression from NSCLC	0	0	0	1 (0.2%)	0
Lung cancer	0	0	0	1 (0.2%)	0
Cause unknown	0	0	0	8 (1.5%)	0
Pneumonia	0	0	0	1 (0.2%)	0
Progress disease, atypical pneumonia	0	0	0	1 (0.2%)	0
Pulmonary thromboembolism	0	0	0	1 (0.2%)	0
Stage IV EGFR-mutant stage IV lung adenocarcinoma with progressive metastases (CNS mets)	0	0	0	1 (0.2%)	0
Cause unknown (patient died in another hospital)	0	0	0	2 (0.4%)	0
Worsening dyspnea	0	0	0	1 (0.2%)	0
Deaths within 30 days of first dose	4 (1.0%)	16 (1.7%)	8 (1.9%)	7 (1.3%)	4 (1.1%)
Adverse event	4 (1.0%)	10 (1.1%)	6 (1.4%)	4 (0.7%)	4 (1.1%)
Pneumonia	0	0	0	1 (0.2%)	0
Progressive disease	0	6 (0.6%)	2 (0.5%)	2 (0.4%)	0

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Deaths within 30 days of last dose	40 (9.5%)	100 (10.6%)	45 (10.5%)	45 (8.2%)	23 (6.1%)
Adverse event	33 (7.8%)	55 (5.8%)	27 (6.3%)	19 (3.5%)	15 (3.9%)
Progressive disease	6 (1.4%)	43 (4.5%)	18 (4.2%)	16 (2.9%)	8 (2.1%)
Other	1 (0.2%)	2 (0.2%)	0	2 (0.4%)	0
Pneumonia	0	0	0	1 (0.2%)	0
Progress disease, atypical pneumonia	0	0	0	1 (0.2%)	0
Pulmonary thromboembolism	0	0	0	1 (0.2%)	0
Cause unknown	0	0	0	4 (0.7%)	0
Worsening dyspnea	0	0	0	1 (0.2%)	0

Table 69: Number of Subjects With Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Analysis set: Safety	421	947	428	550	380
Subjects with 1 or more AEs leading to death	34 (8.1%)	89 (9.4%)	31 (7.2%)	27 (4.9%)	20 (5.3%)
System organ class Preferred term					
Infections and infestations	11 (2.6%)	23 (2.4%)	11 (2.6%)	8 (1.5%)	10 (2.6%)
Pneumonia	5 (1.2%)	16 (1.7%)	4 (0.9%)	3 (0.5%)	5 (1.3%)
Septic shock	2 (0.5%)	2 (0.2%)	1 (0.2%)	1 (0.2%)	0
Acinetobacter sepsis	1 (0.2%)	1 (0.1%)	0	0	0
COVID-19	1 (0.2%)	2 (0.2%)	3 (0.7%)	0	0
COVID-19 pneumonia	1 (0.2%)	1 (0.1%)	0	0	0
Urosepsis	1 (0.2%)	1 (0.1%)	0	0	0
Adenovirus infection	0	0	0	0	1 (0.3%)
Atypical pneumonia	0	0	0	1 (0.2%)	1 (0.3%)
Lower respiratory tract infection	0	0	1 (0.2%)	0	0
Pneumonia aspiration	0	0	1 (0.2%)	1 (0.2%)	1 (0.3%)
Pulmonary sepsis	0	0	0	0	1 (0.3%)
Respiratory tract infection	0	0	1 (0.2%)	1 (0.2%)	0
Sepsis	0	0	1 (0.2%)	1 (0.2%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	8 (1.9%)	34 (3.6%)	11 (2.6%)	7 (1.3%)	8 (2.1%)
Respiratory failure	4 (1.0%)	9 (1.0%)	2 (0.5%)	2 (0.4%)	4 (1.1%)
Pulmonary embolism	2 (0.5%)	2 (0.2%)	2 (0.5%)	3 (0.5%)	0
Acute respiratory distress syndrome	1 (0.2%)	2 (0.2%)	0	0	0
Pneumonitis	1 (0.2%)	3 (0.3%)	0	0	0
Acute respiratory failure	0	2 (0.2%)	0	0	1 (0.3%)
Aspiration	0	0	0	0	1 (0.3%)
Chronic respiratory failure	0	0	0	0	1 (0.3%)
Dyspnoea	0	11 (1.2%)	3 (0.7%)	1 (0.2%)	2 (0.5%)
Haemoptysis	0	1 (0.1%)	1 (0.2%)	0	0
Hypoxia	0	2 (0.2%)	0	0	0
Interstitial lung disease	0	0	2 (0.5%)	1 (0.2%)	0
Pleural effusion	0	0	1 (0.2%)	0	0
Respiratory distress	0	2 (0.2%)	0	0	0
General disorders and administration site conditions	7 (1.7%)	12 (1.3%)	3 (0.7%)	6 (1.1%)	1 (0.3%)
Sudden death	4 (1.0%)	4 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.3%)
Death	3 (0.7%)	3 (0.3%)	2 (0.5%)	5 (0.9%)	0
Disease progression	0	1 (0.1%)	0	0	0
General physical health deterioration	0	3 (0.3%)	0	0	0
Multiple organ dysfunction syndrome	0	1 (0.1%)	0	0	0
Cardiac disorders	6 (1.4%)	8 (0.8%)	2 (0.5%)	2 (0.4%)	1 (0.3%)
Myocardial infarction	3 (0.7%)	3 (0.3%)	0	0	0
Arteriosclerosis coronary artery	1 (0.2%)	1 (0.1%)	0	0	0
Cardiopulmonary failure	1 (0.2%)	1 (0.1%)	0	0	0
Coronary artery disease	1 (0.2%)	1 (0.1%)	0	0	0
Myocardial rupture	1 (0.2%)	1 (0.1%)	0	0	0
Pericardial effusion	1 (0.2%)	1 (0.1%)	1 (0.2%)	0	0
Cardiac arrest	0	1 (0.1%)	0	2 (0.4%)	0
Cardiac failure	0	0	1 (0.2%)	0	0
Cardio-respiratory arrest	0	1 (0.1%)	0	0	0
Cardio-respiratory distress	0	0	0	0	1 (0.3%)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA	Total			
Nervous system disorders	2 (0.5%)	3 (0.3%)	2 (0.5%)	2 (0.4%)	0
Cerebral infarction	1 (0.2%)	1 (0.1%)	0	0	0
Ischaemic cerebral infarction	1 (0.2%)	1 (0.1%)	0	0	0
Cerebral haemorrhage	0	0	1 (0.2%)	0	0
Cerebrovascular accident	0	0	1 (0.2%)	1 (0.2%)	0
Neurological symptom	0	1 (0.1%)	0	0	0
Seizure	0	0	0	1 (0.2%)	0
Vascular disorders	1 (0.2%)	2 (0.2%)	0	0	0
Circulatory collapse	1 (0.2%)	1 (0.1%)	0	0	0
Hypotension	0	1 (0.1%)	0	0	0
Gastrointestinal disorders	0	2 (0.2%)	0	0	0
Large intestinal obstruction	0	1 (0.1%)	0	0	0
Pancreatitis	0	1 (0.1%)	0	0	0
Investigations	0	1 (0.1%)	0	0	0
Lipase increased	0	1 (0.1%)	0	0	0
Metabolism and nutrition disorders	0	0	2 (0.5%)	0	0
Ketoacidosis	0	0	1 (0.2%)	0	0
Metabolic acidosis	0	0	1 (0.2%)	0	0
Musculoskeletal and connective tissue disorders	0	1 (0.1%)	0	0	0
Back pain	0	1 (0.1%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (0.4%)	0	1 (0.2%)	0
Cancer pain	0	2 (0.2%)	0	0	0
Lung neoplasm malignant	0	1 (0.1%)	0	0	0
Malignant neoplasm of unknown primary site	0	0	0	1 (0.2%)	0
Non-small cell lung cancer	0	1 (0.1%)	0	0	0
Psychiatric disorders	0	0	0	1 (0.2%)	0
Completed suicide	0	0	0	1 (0.2%)	0

Key: AE = Adverse Event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 25.0.
Note: AEs leading to death are based on AE outcome of Fatal.

2.6.8.3. Adverse drug reactions

The data source used for determination of ADR terms for lazertinib was MARIPOSA. In MARIPOSA, to characterize the safety profile of lazertinib, data from lazertinib monotherapy was used to identify PTs for ADR determination. TEAE data from the 3 treatment arms of MARIPOSA (amivantamab+lazertinib arm [n=421]; osimertinib arm [n=428]; lazertinib arm [n=213]) were assessed using the approach described below.

Threshold for all adverse events

Any TEAEs with an absolute incidence of (1) ≥10% in the lazertinib arm and (2) a difference of ≥5% (or similar incidence) in lazertinib arm as compared to the osimertinib arm were selected for further analysis to determine if they should be classified as ADRs. Additionally, all TEAEs (regardless of frequency) were reviewed for potential plausible biological or pharmacological association with lazertinib. Where possible, similar PTs were grouped together to assess specific medical concepts.

Serious adverse events and adverse events of grade 3 or higher

All SAEs and TEAEs that were ≥Grade 3 were thoroughly reviewed. Where possible, similar PTs were grouped together to assess specific medical concepts. All events were reviewed for potential plausible biological or pharmacological association with lazertinib. For further details, please see the ADR table in section 4.10.

Frequency of occurrence of lazertinib ADR terms

As the current application is not intended for a lazertinib monotherapy indication, the ADR frequency for lazertinib was calculated based on the exposure for the combination of amivantamab and lazertinib. For each ADR term, the frequency of occurrence was calculated for the following population:

- n=421 participants from the amivantamab+lazertinib arm from MARIPOSA

Table 70: Adverse reactions in patients receiving lazertinib in combination with amivantamab

System organ class Adverse reaction		**Any grade (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders			
Hypoalbuminaemia[a, b]		48	5
Decreased appetite		24	1.0
Hypocalcaemia		21	2.1
Hypokalaemia		14	3.1
Hypomagnesaemia		5	0
Nervous system disorders			
Paraesthesia[a]		34	1.7
Dizziness[a]		13	0
Eye disorders			
Other eye disorders[a]		21	0.5
Visual impairment[a]		4.5	0
Keratitis		2.6	0.5
Growth of eyelashes[a]		1.9	0
Vascular disorders			
Venous thromboembolism[a]		37	11
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease/pneumonitis[a]		3.1	1.2
Gastrointestinal disorders			
Stomatitis[a]		43	2.4
Diarrhoea		29	2.1
Constipation		29	0
Nausea		21	1.2
Vomiting		12	0.5
Abdominal pain[a]		11	0
Haemorrhoids		10	0.2
Hepatobiliary disorders			
Hepatotoxicity[a]		47	9
Skin and subcutaneous tissue disorders			
Rash[a]		89	27
Nail toxicity[a]		71	11
Dry skin[a]		26	1.0
Pruritus		24	0.5
Palmar-plantar erythrodysaesthesia syndrome		6	0.2
Urticaria		1.2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms		17	0.5
Myalgia		13	0.7
General disorders and administration site conditions			
Oedema[a, b]		47	2.9

Fatigue[a]		32	3.8
Pyrexia		12	0
Injury, poisoning and procedural complications			
Infusion-related reaction[b]		63	6

[a] grouped terms
[b] applicable only to amivantamab.

2.6.8.4. Laboratory findings

Table 71: Most Common Grade 3 or 4 Chemistry Abnormalities (SAF; Pooled Analysis)

Laboratory Test		Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
		MARIPOSA (n=421)	Total (n=947)	(n=428)	(n=550)	(n=380)
Hypoalbuminemia	Grade 3	33 (7.9%)	81 (8.6%)	1 (0.2%)	2 (0.4%)	18 (4.8%)
	Grade 4	0	0	0	0	0
Hyponatremia	Grade 3	30 (7.2%)	73 (7.8%)	25 (6.0%)	43 (7.9%)	14 (3.7%)
	Grade 4	1 (0.2%)	4 (0.4%)	2 (0.5%)	5 (0.9%)	2 (0.5%)

Table 72: Grade 3 and 4 Liver Function Test Elevations (SAF; Pooled Analysis)

Laboratory Test		Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
		MARIPOSA (n=421)	Total (n=947)	(n=428)	(n=550)	(n=380)
Increased ALT	Grade 3	26 (6.2%)	47 (5.0%)	10 (2.4%)	8 (1.5%)	4 (1.1%)
	Grade 4	2 (0.5%)	3 (0.3%)	1 (0.2%)	2 (0.4%)	2 (0.5%)
Increased AST	Grade 3	15 (3.6%)	22 (2.3%)	7 (1.7%)	5 (0.95)	2 (0.5%)
	Grade 4	1 (0.2%)	2 (0.2%)	1 (0.2%)	2 (0.4%)	1 (0.3%)

Electrocardiograms (ECGs)

In MARIPOSA, 1 participant (0.3%) in the combination of amivantamab and lazertinib arm and 3 participants (0.7%) in the osimertinib arm had a maximum post-baseline QTcF value >500 msec.

In the all-treated amivantamab+lazertinib group, similar to the combination of amivantamab and lazertinib (MARIPOSA), 3 participants (0.4%) had a maximum post-baseline QTcF value >500 msec.

Among participants treated with lazertinib monotherapy, there were no participants with a maximum post-baseline value of >500 msec.

QT

Table 73: Maximum Post-baseline QTcF Interval (msec) (SAF; Pooled Analysis)

	Amivantamab + Lazertinib		Osimertinib	Lazertinib	Amivantamab
	MARIPOSA (n=421)	Total (n=947)	(n=428)	(n=550)	(n=380)
N	368	839	411	344	333
<=450 msec	302 (82.1%)	705 (84.0%)	340 (82.7%)	324 (94.2%)	305 (91.6%)
>450 to <=480 msec	61 (16.6%)	121 (14.4%)	63 (15.3%)	30 (8.7%)	21 (6.3%)
>480 to <=500 msec	4 (1.1%)	10 (1.2%)	5 (1.2%)	4 (1.2%)	5 (1.5%)
>500 msec	1 (0.3%)	3 (0.4%)	3 (0.7%)	0	2 (0.6%)

Immunogenicity

The incidence of anti-drug antibodies to amivantamab was evaluated in MARIPOSA. All 396 evaluable participants in the amivantamab+lazertinib arm were considered negative for antibodies to amivantamab postdose (MARIPOSA SCS).

2.6.8.5. Safety in special populations

Table 74: Incidence of AEs from amivantamab + lazertinib in the N=947 pool across age categories.

MedDRA Terms	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
Total AEs	530 (100%)	317 (100%)	93 (100%)	7 (100%)
Total SAEs	217 (40.9%)	168 (53.0%)	56 (60.2%)	5 (71.4%)
Fatal	29 (5.5%)	42 (13.2%)	17 (18.3%)	1 (14.3%)
Hospitalization	189 (35.7%)	150 (47.3%)	52 (55.9%)	4 (57.1%)
prolong existing hospitalization	32 (6.0%)	38 (12.0%)	7 (7.5%)	1 (14.3%)
- Life-threatening	26 (4.9%)	37 (11.7%)	10 (10.8%)	1 (14.3%)
- Disability/incapacity	29 (5.5%)	42 (13.2%)	17 (18.3%)	1 (14.3%)
- Other (medically significant)	30 (5.7%)	24 (7.6%)	3 (3.2%)	0
AE leading to drop-out	114 (21.5%)	107 (33.8%)	36 (38.7%)	6 (85.7%)
Psychiatric disorders	81 (15.3%)	64 (20.2%)	19 (20.4%)	0
Nervous system disorders	298 (56.2%)	161 (50.8%)	42 (45.2%)	4 (57.1%)
Accidents and injuries	68 (12.8%)	50 (15.8%)	18 (19.4%)	2 (28.6%)
Cardiac disorders	64 (12.1%)	38 (12.0%)	11 (11.8%)	1 (14.3%)
Vascular disorders	156 (29.4%)	110 (34.7%)	35 (37.6%)	2 (28.6%)
Cerebrovascular disorders	7 (1.3%)	8 (2.5%)	2 (2.2%)	0
Infections and infestations	434 (81.9%)	241 (76.0%)	69 (74.2%)	5 (71.4%)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	107 (20.2%)	64 (20.2%)	23 (24.7%)	2 (28.6%)
<other AE appearing more frequently in older patients>	NA	NA	NA	NA

Table 75: Overall Summary of treatment-emergent Adverse events by subgroup (Age group 1), safety analysis set

	Amivantamab + Lazertinib								
	MARIPOSA			Total			Osimertinib		
		Age (years)			Age (years)			Age (years)	
	Total	<65	≥65	Total	<65	≥65	Total	<65	≥65
Analysis set: Safety	421	233	188	947	530	417	428	237	191
Subjects with 1 or more:									
AEs	421 (100.0%)	233 (100.0%)	188 (100.0%)	947 (100.0%)	530 (100.0%)	417 (100.0%)	425 (99.3%)	234 (98.7%)	191 (100.0%)
Grade 3 or higher AEs	316 (75.1%)	163 (70.0%)	153 (81.4%)	655 (69.2%)	344 (64.9%)	311 (74.6%)	183 (42.8%)	91 (38.4%)	92 (48.2%)
Maximum toxicity grade									
Grade 1	2 (0.5%)	2 (0.9%)	0	15 (1.6%)	10 (1.9%)	5 (1.2%)	50 (11.7%)	32 (13.5%)	18 (9.4%)
Grade 2	103 (24.5%)	68 (29.2%)	35 (18.6%)	277 (29.3%)	176 (33.2%)	101 (24.2%)	192 (44.9%)	111 (46.8%)	81 (42.4%)
Grade 3	259 (61.5%)	146 (62.7%)	113 (60.1%)	517 (54.6%)	296 (55.8%)	221 (53.0%)	136 (31.8%)	64 (27.0%)	72 (37.7%)
Grade 4	23 (5.5%)	9 (3.9%)	14 (7.4%)	49 (5.2%)	19 (3.6%)	30 (7.2%)	16 (3.7%)	11 (4.6%)	5 (2.6%)
Grade 5	34 (8.1%)	8 (3.4%)	26 (13.8%)	89 (9.4%)	29 (5.5%)	60 (14.4%)	31 (7.2%)	16 (6.8%)	15 (7.9%)
Serious AEs	205 (48.7%)	89 (38.2%)	116 (61.7%)	446 (47.1%)	217 (40.9%)	229 (54.9%)	143 (33.4%)	78 (32.9%)	65 (34.0%)
AEs leading to discontinuation of any study agent	147 (34.9%)	59 (25.3%)	88 (46.8%)	263 (27.8%)	114 (21.5%)	149 (35.7%)	58 (13.6%)	30 (12.7%)	28 (14.7%)
AEs leading to discontinuation of Amivantamab	145 (34.4%)	58 (24.9%)	87 (46.3%)	247 (26.1%)	106 (20.0%)	141 (33.8%)	-	-	-
AEs leading to discontinuation of Lazertinib	85 (20.2%)	28 (12.0%)	57 (30.3%)	176 (18.6%)	72 (13.6%)	104 (24.9%)	-	-	-
AEs leading to discontinuation of Osimertinib	-	-	-	-	-	-	58 (13.6%)	30 (12.7%)	28 (14.7%)
AEs leading to drug interruption of any study agent[a]	350 (83.1%)	200 (85.8%)	150 (79.8%)	705 (74.4%)	394 (74.3%)	311 (74.6%)	165 (38.6%)	82 (34.6%)	83 (43.5%)
AEs leading to interruption of Amivantamab[a]	328 (77.9%)	191 (82.0%)	137 (72.9%)	651 (68.7%)	365 (68.9%)	286 (68.6%)	-	-	-
AEs leading to interruption of Lazertinib[a]	299 (71.0%)	171 (73.4%)	128 (68.1%)	575 (60.7%)	324 (61.1%)	251 (60.2%)	-	-	-
AEs leading to interruption of Osimertinib[a]	-	-	-	-	-	-	165 (38.6%)	82 (34.6%)	83 (43.5%)
AEs leading to dose reduction of any study agent	249 (59.1%)	147 (63.1%)	102 (54.3%)	422 (44.6%)	242 (45.7%)	180 (43.2%)	23 (5.4%)	13 (5.5%)	10 (5.2%)
AEs leading to reduction of Amivantamab	193 (45.8%)	114 (48.9%)	79 (42.0%)	289 (30.5%)	168 (31.7%)	121 (29.0%)	-	-	-
AEs leading to reduction of Lazertinib	176 (41.8%)	102 (43.8%)	74 (39.4%)	313 (33.1%)	176 (33.2%)	137 (32.9%)	-	-	-
AEs leading to reduction of Osimertinib	-	-	-	-	-	-	23 (5.4%)	13 (5.5%)	10 (5.2%)
AEs leading to death[b]	34 (8.1%)	8 (3.4%)	26 (13.8%)	89 (9.4%)	29 (5.5%)	60 (14.4%)	31 (7.2%)	16 (6.8%)	15 (7.9%)

Key: AE = Adverse Event
Amivantamab and lazertinib total group includes subjects from studies 61186372EDI1001(CHRYSALIS), 73841937NSC3003(MARIPOSA) and 73841937NSC1001(CHRYSALIS-2).
Osimertinib group includes subjects from study 73841937NSC3003(MARIPOSA).
[a] Excludes infusion related reactions.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: The data cut for 61186372EDI1001(CHRYSALIS) was March 20th 2021, 60% subjects discontinued study treatment prior to March 2020

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Table 76: Summary of treatment-emergent Adverse events by subgroup (Race) in Amivantamab + Lazertinib combination treatment group, safety analysis set

	Amivantamab + Lazertinib								
	MARIPOSA			CHRYSALIS + CHRYSALIS-2			Total		
		Race			Race			Race	
	Total	Asian	Non-Asian	Total	Asian	Non-Asian	Total	Asian	Non-Asian
Analysis set: Safety	419	248	171	523	321	202	942	569	373
Subjects with 1 or more:									
AEs	419 (100.0%)	248 (100.0%)	171 (100.0%)	523 (100.0%)	321 (100.0%)	202 (100.0%)	942 (100.0%)	569 (100.0%)	373 (100.0%)
Grade 3 or higher AEs	314 (74.9%)	176 (71.0%)	138 (80.7%)	337 (64.4%)	188 (58.6%)	149 (73.8%)	651 (69.1%)	364 (64.0%)	287 (76.9%)
Maximum toxicity grade									
Grade 1	2 (0.5%)	2 (0.8%)	0	13 (2.5%)	13 (4.0%)	0	15 (1.6%)	15 (2.6%)	0
Grade 2	103 (24.6%)	70 (28.2%)	33 (19.3%)	173 (33.1%)	120 (37.4%)	53 (26.2%)	276 (29.3%)	190 (33.4%)	86 (23.1%)
Grade 3	258 (61.6%)	148 (59.7%)	110 (64.3%)	256 (48.9%)	146 (45.5%)	110 (54.5%)	514 (54.6%)	294 (51.7%)	220 (59.0%)
Grade 4	22 (5.3%)	11 (4.4%)	11 (6.4%)	26 (5.0%)	13 (4.0%)	13 (6.4%)	48 (5.1%)	24 (4.2%)	24 (6.4%)
Grade 5	34 (8.1%)	17 (6.9%)	17 (9.9%)	55 (10.5%)	29 (9.0%)	26 (12.9%)	89 (9.4%)	46 (8.1%)	43 (11.5%)
Serious AEs	203 (48.4%)	117 (47.2%)	86 (50.3%)	241 (46.1%)	138 (43.0%)	103 (51.0%)	444 (47.1%)	255 (44.8%)	189 (50.7%)
AEs leading to discontinuation of any study agent	145 (34.6%)	73 (29.4%)	72 (42.1%)	116 (22.2%)	65 (20.2%)	51 (25.2%)	261 (27.7%)	138 (24.3%)	123 (33.0%)
AEs leading to discontinuation of Amivantamab	143 (34.1%)	72 (29.0%)	71 (41.5%)	102 (19.5%)	59 (18.4%)	43 (21.3%)	245 (26.0%)	131 (23.0%)	114 (30.6%)
AEs leading to discontinuation of Lazertinib	84 (20.0%)	47 (19.0%)	37 (21.6%)	91 (17.4%)	51 (15.9%)	40 (19.8%)	175 (18.6%)	98 (17.2%)	77 (20.6%)
AEs leading to discontinuation of Osimertinib	-	-	-	0	0	0	0	0	0
AEs leading to drug interruption of any study agent[a]	348 (83.1%)	208 (83.9%)	140 (81.9%)	352 (67.3%)	205 (63.9%)	147 (72.8%)	700 (74.3%)	413 (72.6%)	287 (76.9%)
AEs leading to interruption of Amivantamab[a]	326 (77.8%)	198 (79.8%)	128 (74.9%)	320 (61.2%)	189 (58.9%)	131 (64.9%)	646 (68.6%)	387 (68.0%)	259 (69.4%)
AEs leading to interruption of Lazertinib[a]	297 (70.9%)	170 (68.5%)	127 (74.3%)	276 (52.8%)	156 (48.6%)	120 (59.4%)	573 (60.8%)	326 (57.3%)	247 (66.2%)
AEs leading to interruption of Osimertinib[a]	-	-	-	0	0	0	0	0	0
AEs leading to dose reduction of any study agent	247 (58.9%)	145 (58.5%)	102 (59.6%)	171 (32.7%)	93 (29.0%)	78 (38.6%)	418 (44.4%)	238 (41.8%)	180 (48.3%)
AEs leading to reduction of Amivantamab	191 (45.6%)	116 (46.8%)	75 (43.9%)	96 (18.4%)	62 (19.3%)	34 (16.8%)	287 (30.5%)	178 (31.3%)	109 (29.2%)
AEs leading to reduction of Lazertinib	175 (41.8%)	102 (41.1%)	73 (42.7%)	135 (25.8%)	67 (20.9%)	68 (33.7%)	310 (32.9%)	169 (29.7%)	141 (37.8%)
AEs leading to reduction of Osimertinib	-	-	-	0	0	0	0	0	0
AEs leading to death[b]	34 (8.1%)	17 (6.9%)	17 (9.9%)	55 (10.5%)	29 (9.0%)	26 (12.9%)	89 (9.4%)	46 (8.1%)	43 (11.5%)

Key: AE = Adverse Event
Amivantamab and lazertinib total group includes subjects from studies 73841937NSC3003(MARIPOSA), 61186372EDI1001(CHRYSALIS) and 73841937NSC1001(CHRYSALIS-2).
[a] Excludes infusion related reactions.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: Race is based on investigator reported data recorded on eCRF page.
Note: If race was not reported, then that subject is excluded from this table.
Note: If multiple races were reported, then that subject is excluded from this table.
Note: The data cut for 61186372EDI1001(CHRYSALIS) was March 20th 2021, 60% subjects discontinued study treatment prior to March 2020
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Table 77: Summary of treatment-emergent Adverse events by subgroup (sex) in Amivantamab + Lazertinib combination treatment group, safety analysis set

TSFAE01BYSGSEXa: Summary of Treatment-emergent Adverse Events by Subgroup (Sex) in Amivantamab and Lazertinib Combination Treatment Group ; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab + Lazertinib								
	MARIPOSA			CHRYSALIS + CHRYSALIS-2			Total		
		Sex			Sex			Sex	
	Total	Male	Female	Total	Male	Female	Total	Male	Female
Analysis set: Safety	421	153	268	526	204	322	947	357	590
Subjects with 1 or more:									
AEs	421 (100.0%)	153 (100.0%)	268 (100.0%)	526 (100.0%)	204 (100.0%)	322 (100.0%)	947 (100.0%)	357 (100.0%)	590 (100.0%)
Grade 3 or higher AEs	316 (75.1%)	113 (73.9%)	203 (75.7%)	339 (64.4%)	140 (68.6%)	199 (61.8%)	655 (69.2%)	253 (70.9%)	402 (68.1%)
Maximum toxicity grade									
Grade 1	2 (0.5%)	1 (0.7%)	1 (0.4%)	13 (2.5%)	8 (3.9%)	5 (1.6%)	15 (1.6%)	9 (2.5%)	6 (1.0%)
Grade 2	103 (24.5%)	39 (25.5%)	64 (23.9%)	174 (33.1%)	56 (27.5%)	118 (36.6%)	277 (29.3%)	95 (26.6%)	182 (30.8%)
Grade 3	259 (61.5%)	92 (60.1%)	167 (62.3%)	258 (49.0%)	109 (53.4%)	149 (46.3%)	517 (54.6%)	201 (56.3%)	316 (53.6%)
Grade 4	23 (5.5%)	11 (7.2%)	12 (4.5%)	26 (4.9%)	8 (3.9%)	18 (5.6%)	49 (5.2%)	19 (5.3%)	30 (5.1%)
Grade 5	34 (8.1%)	10 (6.5%)	24 (9.0%)	55 (10.5%)	23 (11.3%)	32 (9.9%)	89 (9.4%)	33 (9.2%)	56 (9.5%)
Serious AEs	205 (48.7%)	80 (52.3%)	125 (46.6%)	241 (45.8%)	102 (50.0%)	139 (43.2%)	446 (47.1%)	182 (51.0%)	264 (44.7%)
AEs leading to discontinuation of any study agent	147 (34.9%)	51 (33.3%)	96 (35.8%)	116 (22.1%)	49 (24.0%)	67 (20.8%)	263 (27.8%)	100 (28.0%)	163 (27.6%)
AEs leading to discontinuation of Amivantamab	145 (34.4%)	51 (33.3%)	94 (35.1%)	102 (19.4%)	42 (20.6%)	60 (18.6%)	247 (26.1%)	93 (26.1%)	154 (26.1%)
AEs leading to discontinuation of Lazertinib	85 (20.2%)	31 (20.3%)	54 (20.1%)	91 (17.3%)	41 (20.1%)	50 (15.5%)	176 (18.6%)	72 (20.2%)	104 (17.6%)
AEs leading to discontinuation of Osimertinib	-	-	-	0	0	0	0	0	0
AEs leading to drug interruption of any study agent[a]	350 (83.1%)	128 (83.7%)	222 (82.8%)	355 (67.5%)	132 (64.7%)	223 (69.3%)	705 (74.4%)	260 (72.8%)	445 (75.4%)
AEs leading to interruption of Amivantamab[a]	328 (77.9%)	126 (82.4%)	202 (75.4%)	323 (61.4%)	123 (60.3%)	200 (62.1%)	651 (68.7%)	249 (69.7%)	402 (68.1%)
AEs leading to interruption of Lazertinib[a]	299 (71.0%)	112 (73.2%)	187 (69.8%)	276 (52.5%)	105 (51.5%)	171 (53.1%)	575 (60.7%)	217 (60.8%)	358 (60.7%)
AEs leading to interruption of Osimertinib[a]	-	-	-	0	0	0	0	0	0
AEs leading to dose reduction of any study agent	249 (59.1%)	90 (58.8%)	159 (59.3%)	173 (32.9%)	66 (32.4%)	107 (33.2%)	422 (44.6%)	156 (43.7%)	266 (45.1%)
AEs leading to reduction of Amivantamab	193 (45.8%)	71 (46.4%)	122 (45.5%)	96 (18.3%)	39 (19.1%)	57 (17.7%)	289 (30.5%)	110 (30.8%)	179 (30.3%)
AEs leading to reduction of Lazertinib	176 (41.8%)	68 (44.4%)	108 (40.3%)	137 (26.0%)	51 (25.0%)	86 (26.7%)	313 (33.1%)	119 (33.3%)	194 (32.9%)
AEs leading to reduction of Osimertinib	-	-	-	0	0	0	0	0	0
AEs leading to death[b]	34 (8.1%)	10 (6.5%)	24 (9.0%)	55 (10.5%)	23 (11.3%)	32 (9.9%)	89 (9.4%)	33 (9.2%)	56 (9.5%)

Key: AE = Adverse Event

Amivantamab and lazertinib total group includes subjects from studies 73841937NSC3003(MARIPOSA), 61186372EDI1001(CHRYSALIS) and 73841937NSC1001(CHRYSALIS-2).

[a] Excludes infusion related reactions.

[b] AEs leading to death are based on AE outcome of Fatal.

Note: The data cut for 61186372EDI1001(CHRYSALIS) was March 20th 2021, 60% subjects discontinued study treatment prior to March 2020

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Table 78: Summary of treatment-emergent Adverse events by subgroup (history of smoking) in Amivantamab + Lazertinib combination treatment group, safety analysis set

TSFAE01BYSGSMKa: Summary of Treatment-emergent Adverse Events by Subgroup (History of Smoking) in Amivantamab and Lazertinib Combination Treatment Group ; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab + Lazertinib								
	MARIPOSA			CHRYSALIS + CHRYSALIS-2			Total		
		Smoking History			Smoking History			Smoking History	
	Total	Yes	No	Total	Yes	No	Total	Yes	No
Analysis set: Safety	421	129	292	521	201	320	942	330	612
Subjects with 1 or more:									
AEs	421 (100.0%)	129 (100.0%)	292 (100.0%)	521 (100.0%)	201 (100.0%)	320 (100.0%)	942 (100.0%)	330 (100.0%)	612 (100.0%)
Grade 3 or higher AEs	316 (75.1%)	97 (75.2%)	219 (75.0%)	335 (64.3%)	134 (66.7%)	201 (62.8%)	651 (69.1%)	231 (70.0%)	420 (68.6%)
Maximum toxicity grade									
Grade 1	2 (0.5%)	1 (0.8%)	1 (0.3%)	13 (2.5%)	6 (3.0%)	7 (2.2%)	15 (1.6%)	7 (2.1%)	8 (1.3%)
Grade 2	103 (24.5%)	31 (24.0%)	72 (24.7%)	173 (33.2%)	61 (30.3%)	112 (35.0%)	276 (29.3%)	92 (27.9%)	184 (30.1%)
Grade 3	259 (61.5%)	83 (64.3%)	176 (60.3%)	256 (49.1%)	103 (51.2%)	153 (47.8%)	515 (54.7%)	186 (56.4%)	329 (53.8%)
Grade 4	23 (5.5%)	5 (3.9%)	18 (6.2%)	26 (5.0%)	9 (4.5%)	17 (5.3%)	49 (5.2%)	14 (4.2%)	35 (5.7%)
Grade 5	34 (8.1%)	9 (7.0%)	25 (8.6%)	53 (10.2%)	22 (10.9%)	31 (9.7%)	87 (9.2%)	31 (9.4%)	56 (9.2%)
Serious AEs	205 (48.7%)	57 (44.2%)	148 (50.7%)	238 (45.7%)	97 (48.3%)	141 (44.1%)	443 (47.0%)	154 (46.7%)	289 (47.2%)
AEs leading to discontinuation of Amivantamab	145 (34.4%)	44 (34.1%)	101 (34.6%)	99 (19.0%)	42 (20.9%)	57 (17.8%)	244 (25.9%)	86 (26.1%)	158 (25.8%)
AEs leading to discontinuation of Lazertinib	85 (20.2%)	30 (23.3%)	55 (18.8%)	88 (16.9%)	42 (20.9%)	46 (14.4%)	173 (18.4%)	72 (21.8%)	101 (16.5%)
AEs leading to discontinuation of Osimertinib	-	-	-	0	0	0	0	0	0
AEs leading to drug interruption of any study agent[a]	350 (83.1%)	103 (79.8%)	247 (84.6%)	351 (67.4%)	133 (66.2%)	218 (68.1%)	701 (74.4%)	236 (71.5%)	465 (76.0%)
AEs leading to interruption of Amivantamab[a]	328 (77.9%)	96 (74.4%)	232 (79.5%)	320 (61.4%)	119 (59.2%)	201 (62.8%)	648 (68.8%)	215 (65.2%)	433 (70.8%)
AEs leading to interruption of Lazertinib[a]	299 (71.0%)	89 (69.0%)	210 (71.9%)	272 (52.2%)	109 (54.2%)	163 (50.9%)	571 (60.6%)	198 (60.0%)	373 (60.9%)
AEs leading to interruption of Osimertinib[a]	-	-	-	0	0	0	0	0	0
AEs leading to dose reduction of any study agent	249 (59.1%)	74 (57.4%)	175 (59.9%)	173 (33.2%)	79 (39.3%)	94 (29.4%)	422 (44.8%)	153 (46.4%)	269 (44.0%)
AEs leading to reduction of Amivantamab	193 (45.8%)	59 (45.7%)	134 (45.9%)	96 (18.4%)	43 (21.4%)	53 (16.6%)	289 (30.7%)	102 (30.9%)	187 (30.6%)
AEs leading to reduction of Lazertinib	176 (41.8%)	52 (40.3%)	124 (42.5%)	137 (26.3%)	64 (31.8%)	73 (22.8%)	313 (33.2%)	116 (35.2%)	197 (32.2%)
AEs leading to reduction of Osimertinib	-	-	-	0	0	0	0	0	0
AEs leading to death[b]	34 (8.1%)	9 (7.0%)	25 (8.6%)	53 (10.2%)	22 (10.9%)	31 (9.7%)	87 (9.2%)	31 (9.4%)	56 (9.2%)

Key: AE = Adverse Event
Amivantamab and lazertinib total group includes subjects from studies 73841937NSC3003(MARIPOSA), 61186372EDI1001(CHRYSALIS) and 73841937NSC1001(CHRYSALIS-2).
[a] Excludes infusion related reactions.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: The data cut for 61186372EDI1001(CHRYSALIS) was March 20th 2021, 60% subjects discontinued study treatment prior to March 2020

Modified from: [tsfae01bysgsmka.rtf] [xcp_oncology/z61186372_73841937/dbr_dwh_mariposa/re_iss_mariposa/tsfae01bysga.sas] 30NOV2023, 12:10

2.6.8.6. Immunological events

Not applicable to lazertinib. The incidence of anti-drug antibodies to amivantamab was evaluated in MARIPOSA. All 396 evaluable participants in the amivantamab+lazertinib arm were considered negative for antibodies to amivantamab postdose (MARIPOSA SCS).

2.6.8.7. Safety related to drug-drug interactions and other interactions

Following administration of 240 mg lazertinib with a high-fat meal in study YH25448-101, there was no clinically relevant change in lazertinib plasma exposure as compared to administration in fasting conditions, lazertinib GMRs (90% CI) for C_{max} and AUC_{last} were 0.9337 (0.8266, 1.0546) and 1.1416 (1.0666, 1.2220). Lazertinib can be taken with or without food.

The co-administration of 240 mg lazertinib with rifampin (strong CYP3A4 inducer) decreased lazertinib plasma exposure, lazertinib GMRs (90% CI) for C_{max} and $AUC_{0\text{-}120h}$ were 0.28 (0.23, 0.34) and 0.17 (0.14, 0.19) respectively. The co-administration of lazertinib with strong CYP3A4 inducers should be avoided. The co-administration of 160 mg lazertinib with itraconazole (strong CYP3A4 inhibitor)

increased lazertinib plasma exposure by less than 50%, lazertinib GMRs (90% CI) for C_{max} and AUC_{0-120h} were 1.19 (1.08, 1.30) and 1.46 (1.39, 1.53) respectively. No lazertinib dose adjustment is required for co-administration with CYP3A4 inhibitors.

The co-administration of midazolam (CYP3A4 substrate) with 160 mg lazertinib increased midazolam plasma exposure by less than 50%, the midazolam GMRs (90% CI) for C_{max} and AUC_{0-last} were 1.39 (1.23, 1.58) and 1.47 (1.34, 1.60) respectively. The co-administration of rosuvastatin (BCRP substrate) with 160 mg lazertinib increased rosuvastatin plasma exposure by approximately 2-fold, the rosuvastatin GMRs (90% CI) for C_{max} and AUC_{0-last} were 2.24 (1.82, 2.76) and 2.02 (1.70, 2.40) respectively. For sensitive CYP3A4 or BCRP substrates with narrow therapeutic index, monitor for adverse reactions as increased plasma exposure of co-administered CYP3A4 or BCRP substrates may increase the risk of exposure-related toxicity. The co-administration of metformin (OCT1 substrate) with 160 mg lazertinib did not increase metformin plasma exposure, the metformin GMRs (90% CI) for C_{max} and AUC_{0-last} were 0.81 (0.72, 0.91) and 0.94 (0.83, 1.07) respectively suggesting no dose adjustment is required.

A retrospective PK analysis from Study YH25448-201 in NSCLC participants concluded that there was no clinically relevant change in lazertinib plasma exposure when co-administered with gastric acid reducing agents and no dose adjustment is required (MARIPOSA).

2.6.8.8. Discontinuation due to adverse events

Discontinuations due to adverse events

Table 79: Most Commonly (≥2%) Reported Adverse Events Leading to Treatment Discontinuation (SAF; Pooled Analysis)

Adverse Event	MARIPOSA (n=421)			Total (n=947)			Osi (n=428)	Laz (n=550)	Ami (n=380)
	Discontinue			Discontinue			Discontinue		
	Any n (%)	Ami n (%)	Laz n (%)	Any n (%)	Ami n (%)	Laz n (%)	Osi n (%)	Laz n (%)	Ami n (%)
≥1 AE leading to discontinuation	147 (34.9)	145 (34.4)	85 (20.2)	263 (27.8)	247 (26.1)	176 (18.6)	58 (13.6)	62 (11.3)	26 (6.8)
IRR	19 (4.5)	19 (4.5)	0	32 (3.4)	32 (3.4)	1 (0.1)	0	0	4 (1.1)
Paronychia	14 (3.3)	14 (3.3)	2 (0.5)	18 (1.9)	18 (1.9)	3 (0.3)	0	1 (0.2)	2 (0.5)
Rash	11 (2.6)	10 (2.4)	3 (0.7)	13 (1.4)	11 (1.2)	4 (0.4)	0	0	0
Pneumonia	8 (1.9)	8 (1.9)	8 (1.9)	24 (2.5)	24 (2.5)	23 (2.4)	3 (0.7)	4 (0.7)	6 (1.6)

Dose interruption/reduction due to adverse effects

Table 80: Most Commonly (≥5%) Reported Adverse Events Leading to Drug Interruption (SAF; Pooled Analysis)

Adverse Event	MARIPOSA (n=421)			Total (n=947)			Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	Interrupt			Interrupt			Interrupt	Interrupt	Interrupt
	Any	Ami	Laz	Any	Ami	Laz	Osi	Laz	Ami
≥1 AE leading to drug interruption	350 (83.1 %)	328 (77.9 %)	299 (71.0 %)	705 (74.4 %)	651 (68.7 %)	575 (60.7 %)	165 (38.6%)	193 (35.1%)	287 (75.5%)
Rash	104	95	76	155	135	115	4	14	14
Paronychia	91	84	65	141	121	107	4	5	11
COVID-19	63	58	38	93	79	58	36	17	4 (1.1%)
Dermatitis acneiform	50 (11.9	49 (11.6	37 (8.8%)	72 (7.6%)	66 (7.0%)	55 (5.8%)	1 (0.2%)	5 (0.9%)	11 (2.9%)
ALT	30	25	27	53	45	47	12	12	6 (1.6%)
Hypoalbumi	25	23	15	48	43	29	0	1	0
AST	23	19	22	42	35	39	11	9	4 (1.1%)
Asthenia	18	12	11	47	34	33	1	7	5 (1.3%)
Vomiting	9	7	4	44	36	13	2	5	38
Nausea	8	4	7	44	33	17	2	4	67
Dyspnea	7	3	5	34	29	17	4	7	88
Cough	6	4	4	12	10	5	0	0	21
Pyrexia	4	2	2	20	15	8	1	3	31
Hypotensio	3	3	0	12	12	0	0	1	24
Chest	0	0	0	16	16	0	0	0	42
Chills	0	0	0	24	24	0	0	2	92
Flushing	0	0	0	7	7	0	0	0	60

Adverse events leading to dose reduction

Table 81: Most Commonly (≥5%) Reported Adverse Events Leading to Dose Reduction (SAF; Pooled Analysis)

Adverse Event	MARIPOSA (n=421)			Total (n=947)			Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	Reduce			Reduce			Reduce	Reduce	Reduce
	Any	Ami	Laz	Any	Ami	Laz	Osi	Laz	Ami
≥1 AE leading to dose reduction	249 (59.1 %)	193 (45.8 %)	176 (41.8 %)	422 (44.6 %)	289 (30.5 %)	313 (33.1 %)	23 (5.4%)	91 (16.5%)	39 (10.3%)
Rash	84 (20.0 %)	62 (14.7 %)	42 (10.0 %)	120 (12.7 %)	81 (8.6%)	71 (7.5%)	2 (0.5%)	12 (2.2%)	2 (0.5%)
Paronychia	80 (19.0 %)	59 (14.0 %)	48 (11.4 %)	120 (12.7 %)	78 (8.2%)	75 (7.9%)	1 (0.2%)	1 (0.2)	10 (2.6%)
Dermatitis acneiform	38 (9.0%)	26 (6.2%)	27 (6.4%)	64 (6.8%)	42 (4.4%)	46 (4.9%)	0	2 (0.4%)	13 (3.4%)

2.6.8.9. Post marketing experience

There are currently no post-marketing data on the combination of amivantamab and lazertinib.

Postmarketing data for lazertinib monotherapy has been accruing since the first marketing approval in 2021. Based on the 925,932 units of 80 milligram tablets distributed in South Korea from launch to 31 May 2023, the estimated exposure to lazertinib is 845.6 patient-years. The postmarketing safety profile of lazertinib monotherapy is consistent with the safety information provided in the product information. No new major safety issues have been identified.

2.6.9. Discussion on clinical safety

The experimental arm from pivotal trial MARIPOSA (amivantamab + lazertinib) is the key dataset to describe the adverse reactions profile for this regimen in section 4.8 of the SmPC. On account of the size of this safety dataset (n=421), sufficient follow-up and overall consistent results with the larger pool of patients treated with amivantamab and lazertinib ("total" pool, n=947), this is endorsed. The ADR frequencies reported in the Lazcluze SmPC (in section 4.8) correspond to the above-mentioned safety dataset, without taking into consideration investigator causality. As per the last revision of the EMA anticancer guidelines (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-anticancer-medicinal-products-revision-6_en.pdf), all-causality AE frequencies are expected to be least biased measure of ADR frequency, so this approach to report ADR frequencies is endorsed.

Safety datasets and exposure: The five datasets (ami+lazer arm of MARIPOSA, n=421; ami+lazer "total" pool including CHRYSALIS AND CHRYSALIS-2, n=947; osimertinib arm of MARIPOSA, n=428; lazertinib monotherapy pool, n=550; and amivantamab monotherapy pool, n=380) presented for the assessment of safety of lazertinib as monotherapy and in combination with amivantamab are considered appropriately sized and with enough follow-up for a preliminary characterization of the safety profile of this novel regimen, considering the intended indication for lazertinib is in combination with amivantamab.

Median duration of treatment in the ami+lazer and osi arms of MARIPOSA was similar (~18 months).

The fact that aggregated safety data from lazertinib monotherapy (n=550) and amivantamab monotherapy (n=380) from akin NSCLC clinical settings are available allows for a better characterisation of the safety profile of the combination, as some AEs might exhibit and additive or potentiating effect from the individual components of the combination, others might have a more clear relation to one of the components, and some might be expected within the specific disease setting (e.g., cough, dyspnoea).

AEs: As expected in this clinical setting, and considering the median duration of treatment across the provided datasets, nearly all patients experienced AEs. The adjudication of treatment-related AEs implies risk of investigator bias (particularly on account of the partial blinding of the MARIPOSA trial), so the assessment of safety for amivantamab + lazertinib (ami + lazer) in the intended setting will focus on all-cause frequencies, i.e., regardless of investigator-adjudicated causality to study treatment.

Unless otherwise stated, the frequencies of AEs in the following paragraphs concern the ami+lazer arm from MARIPOSA (n=421).

Common AEs (≥20%): For ami + lazer, AEs that occurred with an incidence ≥20% in MARIPOSA included paronychia (68%), infusion-related reaction (IRR)(63%), rash (62%), hypoalbuminemia (49%), venous thromboembolism (37%), ALT increased (37%), peripheral oedema (36%), dermatitis

acneiform (29%), stomatitis (29%), constipation (29%), diarrhoea (29%), AST increased (29%), COVID-19 (26%), decreased appetite (25%), pruritus (24%), anaemia (23%), nausea (21%). Although the frequency of some of these AEs might have an additive effect from each of the regimen components (e.g. ALT/AST increased, anaemia), others have a clear relation to individual components (e.g. peripheral oedema/hypoalbuminemia, IRRs/chills most likely attributable to amivantamab, while paraesthesias most often happened with lazertinib). A minority of the common symptoms reported as AEs are expected and likely attributable to the disease setting, e.g. cough and dyspnoea.

Grade ≥3 AEs: High-grade AEs occurred in 75% of patients in the ami+lazer arm from MARIPOSA (and 69% of the ami+lazer pool), exhibiting a worrisome additive pattern, as the proportion for these AEs in each of the amivantamab monotherapy and lazertinib monotherapy pools was ~42% (and 43% in the osimertinib arm). As expected, most of these high-grade AEs were Grade 3 events (259/316=82%), but importantly, when the subcategorization by grades is assessed, it becomes apparent that, across all safety datasets, grade 5 AEs were slightly more common than grade 4 events. The most common (incidence ≥5%) ≥G3 AEs from ami+lazer were: rash (15%), paronychia (11%), pulmonary embolism (8%), acneiform dermatitis (8%), IRR (6%), hypoalbuminemia (5%) and ALT increased (5%).

Skin toxicity events (rash, paronychia, acneiform dermatitis) can be medically managed (recommendation to limit sun exposure, to consider prophylactic therapy with oral antibiotic, prescriptions of topical and or oral corticosteroids) and mitigated by dose interruptions/reductions (as described in section 4.2 and 4.4 of the SmPC).

VTEs: Venous thromboembolism events (VTEs), which happened in about a third of patients treated with ami+lazer in the MARIPOSA (37%) and total pool (29%), constitute the main AESI and safety concern for this regimen. Most VTEs were pulmonary embolism, accounting for the severity/seriousness of these events: nearly a third of VTEs were high-grade or serious. Due to this unexpected finding, an urgent safety measure was triggered for the clinical pipeline of this combination regimen, recommending the use of prophylactic anticoagulation during the first four months of treatment with ami+lazer. This approach was already followed in the PALOMA-3 trial (RCT of amivantamab IV + lazertinib vs. amivantamab SC + lazertinib in a 3L+ setting).

It is noted that none of the MARIPOSA or PALOMA-3 studies were designed to investigate the required duration of anticoagulation. PALOMA-3 was also performed in a later-line setting where the duration of AL combination treatment was considerably shorter than anticipated in the first line setting.

Furthermore, the duration of prophylactic therapy in PALOMA-3 was at the investigators'/treating physicians' discretion. It was recommended for four months but not mandatory. Interestingly, the median duration of prophylactic therapy was 5.11 months, i.e., longer than the median duration of study treatment (4.65 and 4.12 months for amivantamab SC vs. IV, respectively) and longer than the recommended four months.

Prophylactic anticoagulants significantly decreased the risk of VTE in PALOMA-3 participants (9.6% VTEs in patients with anticoagulants vs. 21.0% in patients without). Only a minority (137/335 [40.9%]), though, discontinued anticoagulants after four months, making it difficult to draw any conclusions on the risk of experiencing a VTE while still on AL treatment but after discontinuing anticoagulants. Data do, thus, not suffice to recommend only four months of prophylactic anticoagulants. The risk may also differ depending on mode of administration.

Prophylactic anticoagulants are both safe and do effectively mitigate the risk of VTE during AL treatment. A warning was implemented in the SmPC 4.4, emphasising that patients treated with AL should receive prophylactic anticoagulants with DOACs or LMWHs. Furthermore, patients should be monitored for signs and symptoms of VTE and treated as clinically indicated in the event of a VTE. For patients who are clinically circulatory unstable, AL treatment should be temporarily withheld and

resumed only when the patient is clinically stable. In the event of a recurrent VTE, despite appropriate anticoagulation, amivantamab should be discontinued but lazertinib monotherapy can be continued.

VTE was also added to the RMP as an important identified risk associated with AL combination treatment and prophylactic anticoagulation identified as a measure to minimise this risk.

On account of their frequency, paresthesia (34%), diarrhoea (29%) and stomatitis (29%) are also considered AESIs for the combination of amivantamab and lazertinib. The same is valid for hepatotoxicity. Dose modifications recommendations have been included in section 4.2 for all these ADRs as well as further descriptions of those ADRs in section 4.8 of the SmPC.

Pneumonitis/ILD is also considered an AESIs for the combination (3.1%). A warning has been included in section 4.4 of the SmPC to monitor for symptoms indicative of ILD/pneumonitis and in case of confirmed symptoms to permanently discontinue Lazcluze (interruption and discontinuation also described in section 4.2 of the SmPC).

Eye disorders, including keratitis, occurred in 2.6% in the AL arm. Recommendation that Patients presenting with worsening eye symptoms should promptly be referred to an ophthalmologist and should discontinue use of contact lenses until symptoms are evaluated has been included in section 4.4 of the SmPC.

SAEs: The proportion of patients with SAEs from ami+lazer (49%) is almost additive in relation to its individual components (ami 29%, lazer 30%). The most common SAE for ami+lazer was pulmonary embolism (PE), accounting for ~13% of all SAEs in MARIPOSA (26 out of 205). The summary table of SAEs shows that the highest proportion of serious PE occurs in the lazertinib arm (3.8%) vs. the amivantamab (2.4%) and osimertinib (2.3%) arms, suggesting that the main causal relation is to lazertinib. The other SAEs (pleural effusion, pneumonia, dyspnoea) may be related to baseline disease, but the amount of cases in which dyspnoea might eventually be attributed to PE is uncertain, particularly since some patients may die before diagnosing takes place.

AEs leading to death: As expected, the main cause of death across all the safety datasets was progressive disease. At CCO, 34 patients (8.1%) in the ami+lazer arm died due to TEAEs. Four cases were considered related to the study treatment by the investigator (two cases of myocardial infarction, one case of sudden death, and one case of pneumonitis).

AEs leading to treatment discontinuation: The proportion of patients who discontinued either amivantamab or lazertinib in the ami+lazer arm from MARIPOSA (35%) or the total pool (28%) is outstanding and nearly triples that in any of the monotherapy pools (osimertinib 14%, lazertinib 11% or amivantamab 7%). From the data provided, the most common causes for permanent discontinuation of ami+lazer was IRR, paronychia and rash.

AEs leading to treatment interruption/reduction: It seems that amivantamab-specific AEs were the cause for most treatment interruptions, as these occurred in ~80% of the ami+lazer pools, noting 76% of the amivantamab monotherapy pool, 35% in the lazertinib pool and 39% in the osimertinib pool. From the data presented, it seems most interruptions or reductions for ami/lazer are attributable to amivantamab-specific AEs: rash, paronychia and acneiform dermatitis.

AEs in special populations: Although the incidence of overall AEs was similar in both <65 and ≥65 subpopulations, older patients (≥ 65 years of age) reported more Grade 3 or higher adverse events compared to patients < 65 years of age (81% vs. 70%). While the rates of drug interruptions and dose reductions were similar, the rate of adverse events leading to any treatment discontinuation was higher in patients ≥ 65 years of age compared to patients < 65 years of age (47% vs. 25%).This is reflected in section 4.8 of the SmPC.

2.6.10. Conclusions on the clinical safety

The safety dataset is sufficiently large to describe the safety profile of amivantamab + lazertinib (AL) combination treatment. The toxicity with AL combination treatment is significantly increased compared to both the well characterised toxicity of amivantamab monotherapy and the toxicity profile of lazertinib monotherapy. This includes pronounced increased incidence of grade ≥3 (60% versus 14-20%) and SAE (49% versus 33-35%). Moreover, VTE has been identified as a new adverse reaction for the combination of lazertinib and amivantamab. This risk is mitigated by the use of concomitant prophylactic anticoagulant therapy throughout treatment.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 82: Summary of safety concerns

Important Identified Risks	Venous thromboembolic (VTE) events*
Important Potential Risks	Hepatotoxicity
	Impaired fertility and embryofetal toxicity
Missing Information	None

* Applies only to the combination of lazertinib and amivantamab.

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Venous thromboembolic (VTE) events*	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. • Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	are provided in SmPC Sections 4.2 and 4.4, and PL Section 2. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. • Legal status **Additional risk minimization measures:** • None	
Hepatotoxicity	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.8 • PL Section 4 • Recommendations regarding the management of hepatotoxicity (ie, criteria for treatment interruption and dose reduction) are provided in SmPC Section 4.2. • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Impaired fertility and embryofetal toxicity	**Routine risk minimization measures:** • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • The potential harmful effects of lazertinib on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 weeks after the last dose of LAZCLUZE, are provided in SmPC Section 4.6 and PL Section 2. • Patients should notify their doctor immediately about a potential or confirmed pregnancy before and during treatment with LAZCLUZE, as described in PL Section 2. • Legal status **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• None	

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant 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 Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.05.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lazcluze (Lazertinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

3.1.1. Disease or condition

The approved new indication is*:*

Lazcluze in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) EGFR exon 19 deletions or exon 21 L858R substitution mutations.

Among patients with NSCLC of adenocarcinoma histology, the most prevalent of these driver mutations that are actionable are those that result in the activation of EGFR, which are identified in approximately 15% of Western patients (Pao 2011) and up to 50% of Asian patients (Jänne 2006). The most frequently identified EGFR mutations, exon 19 deletions and exon 21 L858R substitution mutations, are seen in approximately 85% of patients with NSCLC harbouring activating EGFR mutations (Gazdar 2009; Harrison 2020).

Advanced NSCLC is a progressive, deadly disease. In this disease setting, the aim of treatment is to prolong progression-free survival and overall-survival, and/or to improve symptoms.

3.1.2. Available therapies and unmet medical need

The current standard of care for the first-line treatment of EGFRm NSCLC is a third-generation EGFR TKI, most commonly osimertinib. Osimertinib have demonstrated improved PFS and OS in comparison with previous generations of TKIs.

Despite the improved initial disease control, almost all patients treated with first-line osimertinib will develop resistance, and there are no approved targeted therapies for treatment of these patients once resistance has developed. While osimertinib represents a significant advance over earlier EGFR TKIs, there is a need to improve first-line treatment prior to the development of resistance in order to improve treatment outcomes beyond what is seen with available therapies.

3.1.3. Main clinical studies

The pivotal study for this application is MARIPOSA study. This is an ongoing, randomized, multicentre Phase 3 study planned as three arm study to compare the combination of amivantamab and lazertinib (AL in arm A) with osimertinib (O in arm B) and with lazertinib (L in arm C), respectively.

The ITT population consists of 1074 participants randomized 2:2:1(429 to AL, 429 to O, and 216 to L).

Since Osimertinib monotherapy represents the present standard of care, evaluation of AL combination in comparison with O was type 1 error-controlled. Lazertinib shares mechanism of action with Osimertinib. The comparison of AL with L was not included in the hypothesis testing and was intended to allow for the evaluation of mono-components contribution to AL.

All patients in MARIPOSA tested positive for either of the two relevant EGFR mutations: Exon 19 deletions or Exon 21 L858R substitution mutations. The primary endpoint was PFS by BICR and the key secondary endpoint was OS.

3.2. Favourable effects

Upon median duration of follow-up of 22 months and reaching 61% of PFS events, the study met its primary endpoint at the time of the final analysis for **BICR-PFS** (DCO 11-AUG-2023), showing superiority of amivantamab + lazertinib over the comparator osimertinib with a statistically significant treatment effect (**HR=0.70 [95% CI: 0.58, 0.85]**, p=0.0002). The median PFS in the amivantamab + lazertinib arm was 23.72m compared with a median PFS of 16.59m in the osimertinib arm.

The PFS benefit was consistent across all pre-defined subgroups.

Noting OS maturity of ~25% of events, the key secondary endpoint **OS** difference was not statistically significant at the time of the primary analysis for PFS and the OS curves first crossed after 12 months in favour of the amivantamab + lazertinib arm. The HR for OS is 0.80 (0.61, 1.05) with a p-value of 0.1099.

At the updated OS analysis (CCO 13 May 2024) with additionally 9 months FU (totally 31 months median FU) and 129 more events in the entire study, the HR was 0.77 (0.61, 0.96) p 0.0185. Median survival was not reached with AL combination compared with 37.32 (32.53, NE) months with O. Maturity was still limited with 33% events in AL arm compared with 41% events in O arm and 37% events in L arm.

3.3. Uncertainties and limitations about favourable effects

The impact of amivantamab + lazertinib over osimertinib on OS has not been statistically established. The final OS analysis planned per protocol when 490 deaths overall (all treatment arms combined) and 390 deaths from the AL and O arms combined is anticipated in November 2025. The final OS data will be submitted by the MAH as a post authorisation measure **(REC).**

3.4. Unfavourable effects

Common AEs: Almost all patients experienced AEs. For amivantamab + lazertinib, AEs that occurred with an incidence ≥20% in MARIPOSA included paronychia (68%), infusion-related reaction (IRR)(63%), rash (62%), hypoalbuminemia (49%), venous thromboembolism (VTE)(37%), ALT increased (37%), peripheral oedema (36%), dermatitis acneiform (29%), stomatitis (29%), constipation (29%), diarrhoea (29%), AST increased (29%), COVID-19 (26%), decreased appetite (25%), pruritus (24%), anaemia (23%), nausea (21%).

High-grade (≥G3) AEs occurred in 75% of patients in the ami+lazer arm from MARIPOSA. The most common ≥G3 AEs from ami+lazer were: rash (15%), paronychia (11%), VTEs (11%, almost all pulmonary embolism), acneiform dermatitis (8%), IRR (6%), hypoalbuminemia (5%) and ALT increased (5%).

AESIs: Rash/paronychia, IRR, pneumonitis/ILD, VTE events, hepatotoxicity, stomatitis, diarrhoea, peripheral neuropathy (paresthesia), hypoalbuminemia and peripheral oedema are considered AESIs from the combination of amivantamab + lazertinib.

SAEs: The proportion of patients with SAEs from ami+lazer was 49%. The most common SAE for ami+lazer was pulmonary embolism (PE), accounting for ~13% of all SAEs in MARIPOSA (26 out of 205). Other common SAEs were pleural effusion, pneumonia and dyspnoea.

AEs leading to death: As expected, the main cause of death across all the safety datasets was progressive disease. At CCO, 34 patients (8.1%) in the ami+lazer arm died due to TEAEs. Four cases

were considered related to the study treatment by the investigator (two cases of myocardial infarction, one case of sudden death, and one case of pneumonitis).

AEs leading to treatment discontinuation: The proportion of patients who discontinued either amivantamab or lazertinib in the ami+lazer arm from MARIPOSA was 35%, nearly tripling that in any of the monotherapy pools (osimertinib 14%, lazertinib 11% or amivantamab 7%). The most common causes for permanent discontinuation of ami+lazer were IRR, paronychia and rash.

AEs leading to treatment interruption/reduction: It seems that amivantamab-specific AEs were the cause for most treatment interruptions, as these occurred in ~80% of the ami+lazer pools, noting 76% of the amivantamab monotherapy pool, 35% in the lazertinib pool and 39% in the osimertinib pool.

3.5. Uncertainties and limitations about unfavourable effects

Data from PALOMA-3 indicate that, as anticipated, prophylactic anticoagulation will reduce the VTE risk. Therefore as a risk minimisation measure prophylactic anticoagulation should be given while on treatment as indicated in sections 4.2 and 4.4 of the SmPC.

3.6. Effects table

Table 83: Effects Table for study MARIPOSA

Effect	Short Description	Unit	Treatment Ami+Lazer n=429	Control Osimertinib n=429	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median BICR-PFS	Progression free survival by blinded independent central review	Months	23.7 95% CI 19.1, 27.7 HR 0.70 95% CI 0.58, 0.85	16.6 95% CI 14.8, 18.5	Primary PFS analysis, DCO 11 Aug 2023 Stat. significant for AL vs. O.	CSR
Median OS	Overall survival	Months	NE 95% CI NE, NE HR 0.77 95% CI 0.61, 0.96	37.3 95% CI 32.5, NE	OS updated analysis, DCO 13 May 2024 Not stat. significant for AL vs. O. Immature data.	CSR
Unfavourable Effects						
AEs	Any adverse event	%	100	99		SCS, ISS
≥G3 AEs	Grade 3 or higher AEs	%	75	43		SCS, ISS

Effect	Short Description	Unit	Treatment Ami+Lazer n=429	Control Osimertinib n=429	Uncertainties/ Strength of evidence	References
SAEs	Serious AEs	%	49	33		SCS, ISS
G5 AEs	AEs leading to death	%	8	7		SCS, ISS
AEs discount	AEs leading to discontinuation	%	35	14		SCS, ISS
AEs interrupt	AEs leading to interruption	%	83	39		SCS, ISS
AEs reduction	AEs leading to dose reduction	%	59	5		SCS, ISS
Rash	Rash and dermatitis acneiform	% All % G3-4%	89 27	47 1		SCS, ISS
IRR	Infusion related reactions	% All % G3-4%	63 6	0		SCS, ISS
Nail toxicity	Mostly paronychia	% All % G3-4%	71 11	33 1		SCS, ISS
VTE	Venous thromboembolism	% All % G3-4%	37 11	8 3		SCS, ISS
Hepatotoxicity		% All % G3-4%	47 9	25 4		SCS, ISS

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the primary analysis (final analysis for PFS and interim for OS) MARIPOSA study has demonstrated a statistically significant PFS gain with amivantamab in combination with lazertinib (AL) (HR 0.70 (95% CI; 0.58, 0.85); p-value 0.0002) versus osimertinib, in patients with EGFR mutations positive advanced NSCLC in first line setting. The size of this effect is deemed clinically relevant in accordance with precedent.

At the time of the interim analysis, OS was trending towards a benefit, with an upper bound of the 85% CI at 1.05, indicating that any detrimental effect is unlikely. A data update at approximately 35% maturity shows an OS HR 0.77 (0.61, 0.96) with a nominal p 0.0185. This provides reassurance that there will be no detrimental effect and is indicative that a positive final OS result may be likely. The applicant will submit final OS data to fulfil the CHMP Recommendation, the final CSR is anticipated by November 2025 (REC).

The safety dataset is sufficiently large to describe the safety profile of AL combination treatment. The toxicity associated with AL treatment is significantly increased compared to both the well characterised toxicity of amivantamab monotherapy and the toxicity profile of lazertinib monotherapy. This includes pronounced increased incidences of grade ≥3 TEAEs (60% versus 14-20%) and SAEs (49% versus 33-35%).

VTE was identified as a new ADR for AL treatment, with an incidence of 37.3% (11.7% grade ≥3, 10.9% SAEs), including two fatal cases (0.5%). VTE is a significant toxicity but should be minimised by the recommendation for prophylactic anticoagulant therapy throughout the whole treatment.

3.7.2. Balance of benefits and risks

Overall, a clinically relevant PFS gain has been shown. A detrimental effect on OS may be ruled out, and a positive final OS result may be considered likely. There is considerable additional toxicity. However, the most common adverse effects are anticipated to be reversible, and PRO outcomes do not seem to indicate a clinically meaningful deterioration. An increased risk of VTE has been shown when lazertinib is combined with amivantamab; however, this has been demonstrated to be manageable with the recommendation for prophylactic anticoagulant therapy throughout the duration of treatment.

Consequently, the beneficial effect of lazertinib in combination with amivantamab outweighs the risks.

3.8. Conclusions

The overall benefit/risk balance of Lazcluze in combination with amivantamab for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations is positive. The MAH will submit final OS data by November 2025 (REC).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lazcluze is favourable in the following indication(s):

Lazcluze in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

The CHMP therefore recommends the granting of the marketing authorisation 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).

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Lazertinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).