30 January 2025
EMA/61503/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rybrevant

International non-proprietary name: Amivantamab

Procedure No. EMEA/H/C/005454/X/0014

Note

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

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List of abbreviations

1L	first-line
2L	second-line
3L	third line
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARR	administration related reaction
AST	aspartate aminotransferase
AUC_{1week}	area under the concentration-time curve for 1 week after dose
$AUC_{D1\text{-}DX}$	area under the concentration-time curve from Day 1 to Day X
BICR	blinded independent central review
BMI	body mass index
BW	body weight
$C_{avg,1st\ cycle}$	predicted average concentration in Cycle 1
CBR	clinical benefit rate
CCO	clinical cutoff
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
CL	(linear) clearance
C_{max}	maximum observed concentration
$C_{max,1st\ dose}$	predicted peak concentration after first dose (Cycle 1 Day 1 dose)
$C_{max,max}$	predicted maximum peak concentration
(c)MET	(cellular) mesenchymal epithelial transition
CP	carboplatin and pemetrexed
CTCAE	common terminology criteria for AEs
C_{trough}	trough concentration
$C_{trough,max}$	predicted maximum trough concentration
CV	coefficient of variation
C*x*D*y*	Cycle *x* Day *y*
DDI	drug-drug interaction
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DS	drug susbstance
DVT	deep venous thrombosis
ECLIA	electrochemilumineSCence-based immunoassay
ECOG	Eastern Cooperative Oncology Group
EGF(R)	epidermal growth factor (receptor)
EGFRm	EGFR mutation(s)
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
exon 19del	exon 19 deletion
exon 20ins	exon 20 insertion
F	absolute bioavailability
FAS	full analysis set
FOIA	Freedom of Information Act
HA	Health Authority
HC	high concentration
HR	hazard ratio
ICH	International Council on Harmonisation
ICR	independent central review
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G
ILD	interstitial lung disease
INV	investigator
IRR	infusion related reactions
IV	intravenous

Ka	first-order subcutaneous absorption rate constant
L858R	(exon 21) L858R substitution
LARR	local administration related reaction
LC	low concentration
MA	marketing authorization
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Meso ACale Discovery
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not estimable
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
popPK	population pharmacokinetics
PRO	patient-reported outcome
PT	preferred term
Q*x*W	every *x* weeks
QD	once daily
QW	once weekly
rHuPH20	recombinant human hyaluronidase PH20
RMP	Risk Management Plan
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
TASQ	Therapy Administration Satisfaction Questionnaire
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTR	time to response
US	United States
USPI	United States Prescribing Information
V_1	volume of distribution in the ventral compartment
V_2	volume of distribution in the peripheral compartment
VTE	venous thromboembolic (event)

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International N.V. submitted on 29 May 2024 extensions of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (solution for injection), two new strengths of 1600 mg and 2240 mg and a new route of administration (subcutaneous use).

The MAH applied for the following indication for Rybrevant new strengths and new pharmaceutical form:

Rybrevant subcutaneous formulation is indicated:

- in combination with lazertinib 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.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-002573-PIP01-19 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 MAH 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. Scientific advice

In April 2022, the CHMP provided Scientific advice to the Applicant regarding the proposed development plan for amivantamab as a subcutaneous formulation. The Scientific advice covered various aspects including:

-study design elements of the non-inferiority study PALOMA-3

-the design of the bridging study PALOMA-2 to support approval of the SC formulation across amivantamab IV indications

-whether the overall data from the planned studies could support approval for the administration of amivantamab SC for the current and foreseen amivantamab IV indications.

The CHMP agreed with the dose selection strategy and study design for the proposed studies of amivantamab SC, however proposed an alternative co-primary endpoint. Further recommendations were provided regarding specific study design elements. The recommendations were taken into consideration and implemented as appropriate. The CHMP considered that the data on non-inferiority demonstrated from the Phase 3 study, along with additional evidence from the Phase 2 study, could support approval for the administration of amivantamab SC for the treatment of EGFRm NSCLC.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Gabriele Maurer

The application was received by the EMA on	29 May 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	17 October 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	26 October 2024
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one cell banking site in the USA between 14 March 2022 and 15 March 2022. The outcome of the inspection carried out was issued on 12 September 2022.	24 February 2022
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	30 December 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	30 January 2025

a marketing authorisation to Rybrevant on	

2. Scientific discussion

2.1. Problem statement

Rybrevant (amivantamab) is currently approved:

- in combination with lazertinib 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.
- in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

The line extension for amivantamab SC is intended to support administration under a Q2W dosing schedule which corresponds to the following indications:

- in combination with lazertinib 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.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

The rationale for the new route of administration for amivantamab (SC injection) is to improve both patient and healthcare provider experience with amivantamab with a decrease in the rate of infusion related reactions (IRRs), decreased healthcare resource utilization, and lower incidence of any potential access-related complications, all while maintaining efficacy.

2.1.1. Disease or condition

Advanced NSCLC is a serious terminal illness that accounts for approximately 20% of all cancer mortality and, until recently, had a median OS of approximately 1 year. In patients with metastatic disease, driver mutations are observed in approximately 60% of adenocarcinomas (Herbst 2018).

The most frequently identified EGFR mutations, exon 19del and exon 21 L858R substitution, are found in approximately 85% of patients with activating EGFR mutations (Harrison 2020). In up to 10% of EGFR-mutated NSCLC, EGFR is activated through one of a group of heterogenous, in frame base pair insertions in EGFR exon 20, collectively referred to as exon 20 insertion mutations (exon 20ins) (Vyse 2019).

2.1.2. Management

EGFR TKIs such as osimertinib have shown to be effective as first-line treatment in the presence of EGFR exon 19del and exon 21 L858R substitution mutations, while they are ineffective against EGFR exon 20ins mutations. Platinum based chemotherapy (to be followed by single agent chemotherapy after disease progression) is currently the standard of care once emergence of resistance renders treatment with osimertinib ineffective and is the first-line treatment for EGFR exon 20ins mutated NSCLC (Hendriks 2023; NCCN 2023).

2.1.3. About the product

Amivantamab SC is a liquid, sterile concentrate for manual SC injection. It is presented at a nominal amivantamab concentration of 160 mg/mL, formulated with rHuPH20 at a nominal concentration of 2,000 U/mL (~20 µg/mL) in a single use vial.

Amivantamab is a low-fucose, fully human, bispecific IgG1 based antibody directed against the EGF and MET receptors, produced by CHO cells using recombinant DNA technology.

rHuPH20 is a neutral pH-active human hyaluronidase that depolymerizes hyaluronan under physiologic conditions and acts as a spreading factor in vivo.

The proposed dosing regimen is as follows:

Table 1: Recommended dosage of Rybrevant subcutaneous formulation

Body weight at baseline*	Recommended dose	Dosing schedule
Less than 80 kg	1600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards
Greater than or equal to 80 kg	2240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards

* Dose adjustments not required for subsequent body weight changes.

Table 2: Recommended dose modifications for adverse reactions

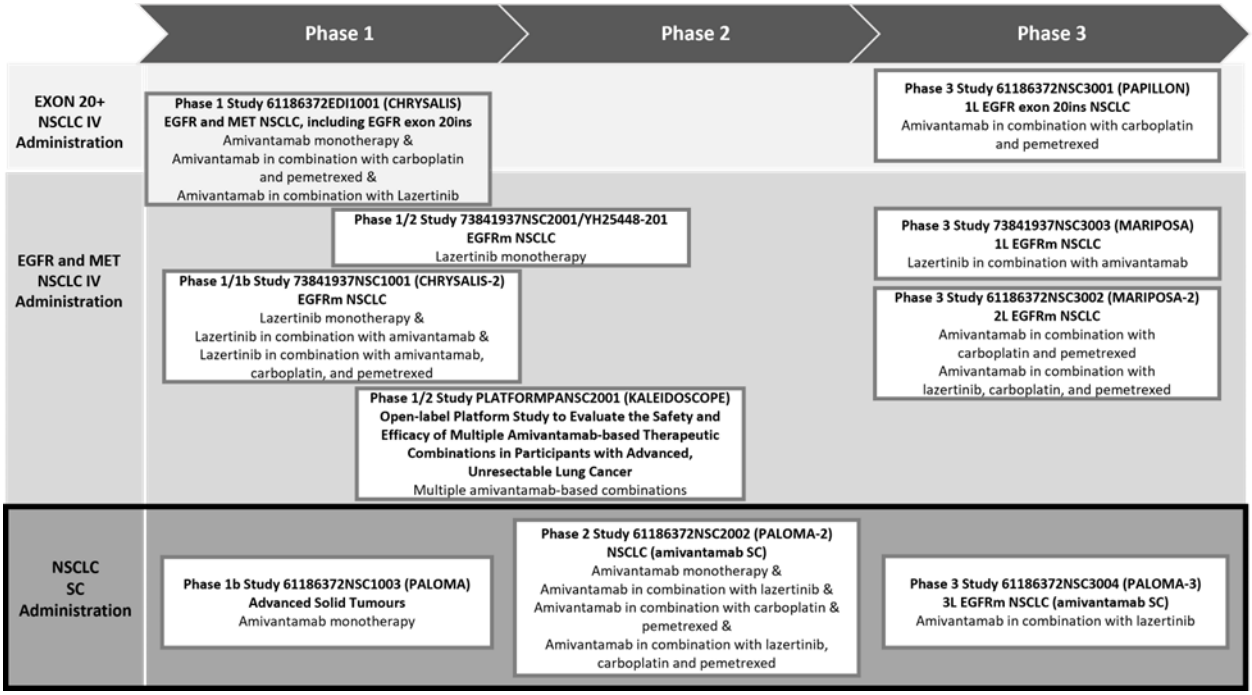
Dose*	Dose after 1st interruption for adverse reaction	Dose after 2nd interruption for adverse reaction	Dose after 3rd interruption for adverse reaction
1600 mg	1050 mg	700 mg	DiSContinue Rybrevant subcutaneous formulation
2240 mg	1600 mg	1050 mg	

* Dose at which the adverse reaction occurred

2.2. Type of Application and aspects on development

The amivantamab SC formulation has been investigated in 3 studies. The SC formulation of amivantamab is evaluated in the ongoing Phase 1b PALOMA, the Phase 2 PALOMA-2, and the Phase 3 PALOMA-3 studies. An overview of the Applicant's amivantamab (IV and SC) NSCLC clinical development program is presented below:

Figure 1: Clinical Development Program for Amivantamab in Patients with Locally Advanced or Metastatic NSCLC



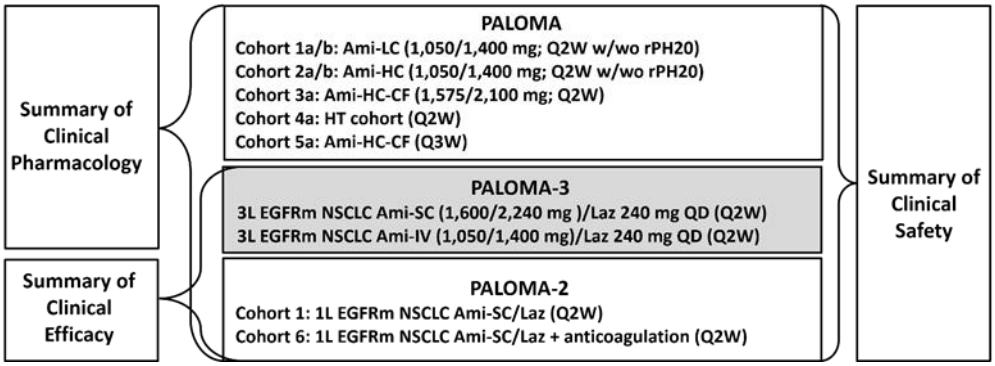
Note: All studies are ongoing.

Note: the studies supporting the proposed product information update are presented in the black box.

1L: first-line; 2L: second-line; 3L: third-line; EGFRm: epidermal growth factor receptor with exon 19 deletions or exon 21 L858R substitution mutations; exon 20ins: exon 20 insertion; IV: intravenous; NSCLC: non-small cell lung cancer; SC: subcutaneous

The primary PK, efficacy, and safety data to support the proposed submission are derived from the ongoing Phase 3 PALOMA-3 study. Supportive PK, efficacy, and safety data are derived from Cohorts 1 and 6 (Q2W) of the ongoing Phase 2 PALOMA 2 study. Additional supportive PK, PD, and safety data are derived from Cohorts 1a/b, 2a/b, 3a, 4a, and 5a of the ongoing Phase 1 PALOMA study.

Figure 2: Overview of the Clinical Studies Supporting the Proposed Product Information Update



1L: first-line; 3L: third-line; Ami: amivantamab; EGFRm: epidermal growth factor receptor with exon 19 deletions or exon 21 L858R substitution mutations; HC: high concentration; IV: intravenous; Laz: lazertinib; LC: low concentration; NSCLC: non-small cell lung cancer; QD: once daily; QxW: every x weeks; SC: subcutaneous; w/wo: with or without.

2.3. Quality aspects

2.3.1. Introduction

Amivantamab, the active substance contained in Rybrevant, is a fully human immunoglobulin G1 (IgG1)-based bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal epidermal transition (MET) receptors, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

The current commercial formulation of Rybrevant is a 350 mg concentrate for solution for infusion in vial (EU/1/21/1594/001). The purpose of this line extension (LE) application is to extend the current marketing authorisation of Rybrevant to introduce a new pharmaceutical form, 2 new strengths and a new route of administration consisting of a 160 mg/mL solution for subcutaneous (SC) injection: 10 mL vial containing 1600 mg of amivantamab and 14 mL vial containing 2240 mg of amivantamab.

To facilitate subcutaneous (SC) delivery of amivantamab, the finished product is formulated with recombinant human hyaluronidase (rHuPH20) which is an excipient already used for several monoclonal antibodies (MAbs) as permeation enhancer for SC administration. The other excipients are EDTA disodium salt dihydrate, glacial acetic acid, L-methionine, polysorbate 80, sodium acetate trihydrate, sucrose and water for injections.

2.3.2. Active Substance

2.3.2.1. General information

Amivantamab is a low-fucose, fully human IgG1-based EGFR-MET bispecific antibody.

No major modifications have been made to Module 3.2.S.1 for this new submission, except for the introduction of new text and figures describing the structure and nomenclature for the parenteral antibody intermediates. The text in this section is assessed to be acceptable.

2.3.2.2. Manufacture, characterisation and process controls

Manufacturers

The amivantamab active substance is, for the new formulation, manufactured at Janssen Sciences Ireland UC in Cork, Ireland (Stages 6 to 14).

The new manufacturer of the parenteral MAbs (Stage 1-5) is supported by adequate GMP documentation.

All sites involved in manufacture and control of the active substance operate in accordance with GMP.

Manufacturing process and process controls

Amivantamab (JNJ-61186372) is a bispecific antibody which is generated through Fab-arm exchange (FAE) involving 2 independent parental antibodies. During FAE the heavy chain and linked light chain pair (half-antibody) of one parental antibody is exchanged with a heavy chain and linked light chain pair of the other parental antibody, creating a bispecific antibody.

Both parental antibodies, JNJ-55986736 (anti-EGFR MAb) and JNJ-55944083 (anti-cMET MAb), are manufactured in separate 5-stage processes at SBL. The 2 parental antibodies are combined in a single 9-stage bispecific antibody manufacturing process which is performed at JSI.

The description of the manufacturing process is acceptable and at the same level as the original process previously performed at Biogen Inc and Janssen Sciences. Some differences exist between the processes, e.g. the size of the bioreactors during Stage 1. For all process stages, acceptable overview figures and tables are presented, indicating in-process controls (IPCs), process parameters (targets and proven acceptable ranges (PARs)) and critical process parameters (CPPs).

For reprocessing, no changes have been performed in connection with the submission. The original procedures still apply, and the same documents, including verification protocols, remain in the dossier. The approach is regarded as acceptable.

The batch numbering system for Stages 1-5 at SBL is only briefly described but is found to be acceptable.

The manufacturing process and the descriptive documents are essentially the same for the two parenteral antibodies (Stages 1-5), with only minor parameter differences between the two for Stage 2.

For Stages 6-14, performed at Janssen-Cilag, the process is in general considered to be the same.

Control of materials

The current cell lines, for monospecific anti-EGFR and anti-cMET parental antibodies, respectively, are CHO cell lines.

For the expression constructs the source of the coding sequences and the creation of the expression constructs are well described, for both antibodies. With this line extension no changes have been introduced in these descriptions or in the creation of both the cell lines. the

No animal-derived materials (ADMs) of any kind were used in the creation of the manufacturing cell lines, except for Foetal Bovine Serum (FBS) and Advanced DMEM/F12 medium used during methylcellulose cloning, several generations prior to the generation of the master cell bank (MCB). ADMs were not used in production of the MCB and working cell bank (WCB) and are not used in the production process.

Details on the preparation, storage, and testing are given. It is assessed that no changes have been introduced in these descriptions with this LE.

During the anti-EGFR MAb and anti-cMET manufacturing processes, the age of the cell culture is defined by the number of days from the WCB thaw to the end of the 15,000-L bioreactor run. Creation of the extended banks assured that the cells were cultured and tested beyond the limit of *in vitro* cell age (LIVCA)

A complete listing of the compendial raw materials utilised in the manufacture of the active substance is presented, with acceptable compendial citations indicated (Ph. Eur. & USP/NF). All compendial raw materials are derived from animal-free sources.

A complete listing of the non-compendial raw materials utilised in the manufacture of the active substance is presented. Specifications for non-compendial raw materials are acceptably listed. All non-compendial raw materials are derived from animal-free sources.

The content of this section is assessed to be acceptable.

Control of critical step and intermediates

<u>Intermediate Specifications/Justifications</u>

The release and stability specifications for the concentrated Protein A eluates are part of an integrated control strategy to ensure product quality and process consistency. These specifications were derived

from compendial guidelines, product and process knowledge, prior experience with other monoclonal and bispecific antibody products, and statistical analysis of release and stability data. The justifications including background data are assessed to be acceptable.

IPC tests

Definitions of IPC test procedures are acceptably described. An IPC is a test, check, or measurement made during the course of manufacturing to monitor, and, if necessary, adjust the process to ensure the resulting active substance or finished product will comply with its specification. There are 3 types of IPCs: (1) an IPC with an acceptance criterion, (2) IPC with an action limit, and (3) an IPC with a predefined instruction.

IPCs are established based on the control of active substance critical quality attributes (CQAs) and/or process requirements at critical steps and intermediates to ensure product quality and process consistency during the active substance manufacturing process. It is assessed that sufficiently detailed descriptions of IPCs and the justification of their acceptance criteria or predefined instructions are provided.

Lists of IPCs with acceptance criteria and action limits used are acceptably provided. They include the process step/stage in which the IPC test is performed, the test, and the associated acceptance criterion. It is assessed that the IPCs are correctly included in the process description documents.

Process validation and/or evaluation

Process Validation

For process validation (PV), four consecutive commercial-scale batches were manufactured and released for each parental antibody (Stage 1-5), and four consecutive commercial-scale, active substance batches were manufactured for the active substance (Stage 6-14). It is acknowledged that the PV results demonstrate that the process exhibited consistent process performance and met all PV acceptance criteria for the IPCs and process parameters. Deviations are acceptably described, and it is concluded that there was no impact on product quality, process performance, or the validity of the study due to theses exceptions. Based upon the results, it is assessed that the manufacturing process is validated.

Impurity Clearance

It is acknowledged that the impurities were demonstrated to be reduced to acceptable levels. It is assessed that the procedure and data are acceptably presented and discussed.

Chromatography Resin & Ultrafiltration Membrane Lifetime Verification

Reduced scale studies have been performed to set a number for the maximum use of the chromatography resins. The studies and their results are acceptably described.

The chromatography resin lifetime limits will also be verified during commercial processing through the periodic monitoring of process and product quality related impurity levels and chromatographic performance (chromatographic profile and yield).

The ultrafiltration membranes are re-used in accordance with site specific procedures that define routine testing requirements and acceptance criteria for re-use.

Continued Process Verification (CPV)

A CPV program to collect and analyse product and process data for detecting unplanned departures from the process as designed is outlined. The data that will be collected includes all release tests, relevant IPCs, additional product quality attributes as required and relevant CPPs. The data collected

will be statistically trended and reviewed, and statistically-relevant alert limits will be established, once a sufficient number of batches have been produced. Observation of unexpected process trends will be investigated for any potential impact to product CQAs or process economics. The approach and procedure described is assessed to be acceptable.

Reprocessing

The following reprocessing points have been identified for validation for reprocessing.

Reduced-scale process validation data supporting reprocessing at these points is provided. It is acknowledged that these validation studies demonstrate that these stages do not impact product quality. Reprocessing must be completed within the established hold times. To confirm findings from the reduced-scale reprocessing, verification studies will be performed during the first commercial-scale batch that requires reprocessing. The approach is assessed to be acceptable.

Process Intermediate Hold Time

It is assessed that acceptable hold points evaluation has been performed, to validate biochemical stability of process intermediates under conditions representative of the commercial-scale manufacturing process. All sampled intermediates were demonstrated to be biochemically stable at the hold conditions that were evaluated. All vessels used during the active substance manufacturing process were successfully validated to maintain integrity with respect to microbial contamination. PARs for hold times associated with each process intermediate are acceptably justified; they are the minimum time demonstrated between biochemical stability and microbial control of the hold vessel. These validated hold times are correctly transferred to the process description.

Shipping Qualification

Parental antibody concentrated Protein A eluate and active substance shipping qualification was performed for insulated shippers at minimum and maximum shipping loads. It is acknowledged that the qualification demonstrated the shippers maintained the acceptable temperature for the duration of the transport. It is also shown that the shippers and their contents maintained structural integrity during shipment.

Manufacture process development

Active Substance Manufacturing Process History

The process development history for active substance manufacturing is acceptably presented. Initially, the parental antibodies were produced in bioreactors using a manufacturing process at Biogen, NC, USA, and further processed in Stages 6-14 at JSI, Ireland.

Subsequently, the parental antibodies were produced in bioreactors, at WuXi Biologics, China, and further processed at WuXi. Finally parental antibody manufacturing process was performed in bioreactors at SBL, Korea, and further processed at JSI. These changes were made to accommodate clinical supply requirements and to meet projected commercial demand.

The active substance production development history, including the process changes made to improve or streamline the process, is acceptably summarised, showing all active substance batches manufactured to date and the disposition of each batch.

Process Comparability

Analytical comparability studies were performed to evaluate the changes introduced in the active substance and finished product.

Hence, it is agreed that overall the comparability statement is acceptable.

Manufacturing Process Development

In section 3.2.S.2.6 extensive background information is presented and justifications for the PARs are acceptably provided. The materials and equipment, and the observed ranges for process parameters used throughout process development, clinical process and PV batches are provided with CPPs highlighted in bold text. The description of the process ranges corresponds to the process description provided in Section 3.2.S.2.2.

Separate development documents for each stage are acceptably presented, with process parameter justifications, description of material attributes and comparisons of manufacturing results from development and commercial scale manufacturing.

CPP assessment

The CPP identification process is described. During this process, an initial list of presumptive critical process parameters (pCPPs) is identified based on development data, scientific knowledge and manufacturing process understanding. These pCPPs are then further evaluated in development studies to assess their actual impact to CQAs. Each process parameter is evaluated for its potential effect on each CQA, and the associated degree of knowledge uncertainty, which then are combined to determine the criticality of the PP. The identification process and the results are assessed to be acceptably described. The CPPs identified is correctly transferred to the process descriptions.

Characterisation

Elucidation of structure and other characteristics

The analytical characterisation was in general performed as described in the original dossier, with the corresponding results. Minor differences were observed but are assessed to be of no concern.

The characterisation included a comprehensive analysis of the biochemical, biophysical, and biological properties of amivantamab using a wide variety of orthogonal techniques. In addition, the charge, size and glycoform variants of amivantamab were fully characterised and the post-translational modification (PTM) CQAs were identified using forced degradation studies. The methodology and results of the characterisation is assessed to be acceptably presented.

Impurities

As with any complex protein therapeutics, active substance batches of amivantamab contain low levels of product- and process-related impurities in addition to potential microbial and viral contaminants. The result of the characterisation of the product-related impurities in active substance is acceptably presented. Process-related impurities are discussed. A summary of the product- and process-related impurities is acceptably presented in this section. Minor differences to the original dossier are observed, but is assessed to be of no concern.

2.3.2.3. Specification

Specification

The release and stability specifications for the active substance include control of identity, purity and impurities, potency and other general tests. They are adequately justified. These active substance specifications are aligned with the amivantamab subcutaneous (SC) finished product specifications and were derived from compendial guidelines, product and process knowledge, prior experience with other MAb products, and statistical analysis of active substance release and stability data. The active substance acceptance criteria for most attributes were adjusted slightly to align with the finished

product acceptance criteria, as there were no meaningful changes in the levels during finished product manufacturing.

A summary of the proposed active substance specifications is presented. This includes the actual minimum/maximum ranges. Statistical analysis was performed on these data to set the commercial acceptance criteria.

Release and stability data for the clinical and PV batches used in justification of the acceptance criteria are provided. The detailed justification of specification for each of the quality attributes are acceptably provided.

The specifications are acceptable.

Analytical Procedures

The method descriptions for the analytical procedures used for batch release and stability testing of the amivantamab active substance are acceptably presented.

Validation of Analytical Procedures

For the active substance specific analytical procedures the validations of the analytical procedures are assessed to be qualified for testing of amivantamab process intermediates and active substance.

It is noted that the active substance is tested for endotoxin using the compendial Limulus Amebocyte Lysate (LAL) test based on Ph. Eur. 2.6.14. The Applicant has described its efforts and plans to develop and implement an endotoxin assay based on recombinant Factor C (instead of animal lysate) which are acknowledged.

Batch Analyses

Batch analyses results for the clinical and process validation batches of the amivantamab active substance are acceptable.

Reference standards

The procedures for establishing the reference standards are acceptably described. A process has been established to prepare and qualify each reference material (RM) generated using the active substance release assays and additional characterisation methods, to demonstrate consistency, continuity, and traceability from one RM batch to the next. A process has also been established to requalify RMs on an annual basis to demonstrate stability and monitor any potential drift.

Container closure

The container closure system for antibody intermediates and active substance remains unchanged. Acceptable descriptions are presented for the containers, including representative container and closure drawings with nominal dimensions. Container closure integrity was evaluated by bioburden testing after exposure to typical storage and shipping process followed by multiple freeze/thaw cycles.

The container closure system meets the compendial requirements described and also comply with the European requirements on extractables and leachables. The results of a study demonstrated that the container closure system integrity is maintained during freezing, storage, thawing, and shipping of materials. This is endorsed.

The content of this section is assessed to be acceptable.

2.3.2.4. Stability

A shelf life is claimed for the active substance, JNJ-55986736 and JNJ-55944083 intermediates. Stability data are provided for both active substance and antibody intermediates.

Antibody Intermediates shelf-life claim

The stability data from these batches were used to establish the shelf life of the intermediates. The shelf life is based on stability data generated at the -storage condition. A statistical trending approach for analysing the real time stability data was utilised for projecting the shelf life as per ICH Guideline Q1E: Evaluation of Stability Data. Stability data obtained from accelerated (-20 ± 5 °C) and stressed (5 ± 3 °C) storage conditions were also presented in support of the shelf-life claim.

The results indicate that there are no significant trend on stability when batches are stored at the recommended storage condition. The data presented provide the justification for the active substance shelf-life claims when stored frozen. This is endorsed.

In addition, freeze/thaw cycling studies were performed, and the results support the stability of active substance during potential freeze/thaws.

Active substance shelf-life claim

The stability data from these batches were used to establish the shelf life of active substance. The shelf life for the active substance is based on stability data generated at the storage condition. A statistical trending approach for analysing the real time stability data was utilised for projecting the shelf life as per ICH Guideline Q1E: Evaluation of Stability Data. Stability data obtained from accelerated (-20 ± 5 °C) and stressed (5 ± 3 °C) storage conditions were also presented in support of the shelf-life claim.

The results indicate that there are no significant trend on stability when active substance batches are stored at the recommended storage condition. The data presented provide the justification for the active substance shelf-life claim when stored frozen. This is endorsed.

In addition, freeze/thaw cycling studies were performed, and the results support the stability of active substance during potential freeze/thaws that may be encountered during transportation, storage, and handling.

Summary of shelf-life claims

In summary, the shelf-life claim of proposed for active substance, JNJ-55986736 and JNJ-55944083 are assessed to be acceptable.

Post-approval stability protocols

The Applicant commits to continuing the stability studies as indicated in Section S.7.1, and to place batches into the stability monitoring program each year that the intermediates are manufactured. Confirmed out-of-specification (OOS) results obtained will be reported to the Health Authority, as appropriate. This is endorsed.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The amivantamab SC 160 mg/mL finished product is supplied as a sterile liquid in a single use vial. The active substance is formulated with recombinant human hyaluronidase (rHuPH20), EDTA disodium salt

dihydrate, glacial acetic acid, L-methionine, polysorbate 80, sodium acetate trihydrate, sucrose and water for injections. There are no novel excipients in the formulation.

1600 mg finished product

Each finished product vial contains 1600 mg of amivantamab at a 10 mL nominal fill volume. The primary packaging consists of a 25R Type I glass vial with an elastomeric closure and an aluminium seal with a flip off cap. The finished product contains no preservative and is for single use only.

2240 mg finished product

Each finished product vial contains 2240 mg of amivantamab at a 14.0 mL nominal fill. The primary packaging consists of a 25 mL Type I glass vial with an elastomeric closure and an aluminium seal with a flip-

off cap. The finished product contains no preservative and is for single use only.

The composition of the finished product along with the function and grade of the excipients used in preparation of the finished product are shown.

The description of the finished product is satisfactory and all the components of the presentation as intended for the marketing have been clearly stated.

Additionally, a brief description has been given on the primary packaging material. A more detailed description is included in section P7.

Pharmaceutical development

The Applicant has satisfactorily described the components of the finished product, which are the same as those used for the formulation of the active substance, except for the addition of rHuPH20. Although rHuPH20 is not a novel excipient, it has been extensively described in Module 3.2.A.3, including manufacturing process, characterisation, controls, impurities, stability and viral safety assessment.

All excipients are of non-animal origin, and except for rHuPH20. All the excipients are of pharmacopeial grade, and the same as those used in the active substance formulation. rHuPH20 is a recombinant enzyme, produced by genetically engineered CHO cells. Halozyme is responsible for the manufacture, testing, and release of rHuPH20 Bulk Enzyme.

The finished product is intended for SC administration. To facilitate this type of delivery, the finished product was co-formulated with rHuPH20. Forced degradation studies, which included an evaluation of oxidation induced by peracetic acid and photo stress and an evaluation of deamidation and isomerisation induced by heat stress, were performed to determine if the addition of rHuPH20 had any impact on the degradation of amivantamab, under stressed conditions. Three active substance batches and three finished product batches were exposed to increasing levels of stress to compare the rates and degradation pathways of amivantamab with and without rHuPH20. The results indicate that the presence of rHuPH20 has no impact on the degradation of amivantamab.

The primary reason for developing and optimising the amivantamab SC finished product was to significantly reduce the burden of administration time on the patient associated with IV administration. Development studies were performed for a final formulation with 160 mg/mL amivantanab active substance and the corresponding finished product. The selection of the formulation composition was based on the results of a high throughput formulation screening. The lead formulation was further tested for robustness against manufacturing, processing, and shipping stress, using freeze-thaw (F/T), metal spiking and peroxide stress, photostability, excipient level boundary and distribution/shipping studies. Based on the outcome of all these studies, the finished product formulation was optimised to achieve an amivantanab concentration of 160 mg/mL allowing SC delivery and two single-vial liquid dosage form presentations.

It is noted that the SmPC for the new formulation Rybrevant 160 mg/ml contain the same warning for exposure to light in section 6.4 as for the already approved Rybrevant presentation.

The physical properties of the finished product formulation are density, pH, osmolality, viscosity and glass transition temperature of frozen active substance.

The manufacturing process for amivantamab finished product and its associated control strategy were developed based on a Quality Target Product Profile (QTPP) and platform manufacturing experience with the liquid filled vial at the commercial manufacturing facility Cilag AG, Switzerland. A QTPP has been presented, and links to the CQAs have been included. A formal risk assessment was performed according to internal procedures to establish an appropriate set of controls for the CQAs. The control elements (parametric controls, material controls, IPC tests, release testing, stability testing, characterisation testing, process validation, and procedural controls) are placed at control points that have a major influence on product performance to specifications for CQAs. This approach is acceptable.

Criticality assessment was performed on all the finished product process steps of the manufacturing process, with associated parameters that could potentially impact a CQA. Justifications for the IPC acceptance criteria are provided and are considered satisfactory.

In-process tests were performed on clinical finished product batches manufactured at Cilag. All IPC results met the acceptance criteria. The critical steps and the in-process controls for amivantamab finished product, and their acceptance criteria are listed.

The container closure system used for finished product is a 25R Type I glass blow back vial closed with a fluoropolymer film coated stopper and an aluminum seal with flip-off cap, as described in *3.2.P.7 Container Closure System*. Studies to determine the extractables and potential leachables from the stopper have been conducted and are based on the FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics.

The finished product contains no preservatives and is manufactured using an aseptic process that includes sterilisation by filtration. Container closure integrity tests (CCITs) were used to validate the integrity of the container closure system, and its ability to prevent microbial contamination of the final product.

The finished product was evaluated for in-use stability and compatibility with materials that are in direct contact with the finished product during preparation and SC administration: polypropylene (PP), polyethylene (PE), acrylonitrile butadiene styrene (ABS), polyurethane (PU), polycarbonate (PC), polyvinyl chloride (PVC), acrylic, silicone rubber, and stainless steel (SS) under storage conditions for 24 hours at 2-8 °C followed by 24 hours at 30 °C for periods up to 48 hours. Additionally, aged finished product (stored at 2-8°C for 21 months since its manufacturing date) was evaluated for in-use stability and compatibility with ancillaries composed of PP, PE, ABS, PU, PC, PVC, acrylic, silicone rubber, and SS for 48 hours (24 hours at 2-8 °C followed by 24 hours at 30 °C) in the dosing syringe. All the in-use and compatibility data show that the finished product is compatible with ancillaries composed of PP, PE, ABS, PU, PC, PVC, acrylic, silicone rubber, and SS.

2.3.3.2. Manufacture of the product and process controls

Manufacture

The amivantamab finished product for SC administration is manufactured by Cilag AG Schaffhausen, Switzerland.

All sites responsible for manufacture and control of the finished product operate in accordance with GMP.

The finished product solution is sterile filtered and aseptically filled into vials, which are stoppered and finally capped. The vials stored at 5±3°C. The manufacturing process has been described in sufficient detail in the dossier. A flow-chart of the process, indicating the critical steps (IPCs), has been provided.

Process controls

The critical steps of the finished product manufacturing process, the process parameters (critical and non-critical) and their PARs for the amivantamab finished product have been identified and presented, and they are considered to be relevant for the process validation. The assigned critical steps and the IPCs have been provided and they are considered acceptable.

Validation of the process steps was performed to demonstrate control of the finished product manufacturing process. Those aspects of the process that were validated met one or more of the following five types of pre-determined criteria: acceptance criteria for IPCs, acceptable ranges for CPPs, acceptance criteria for all finished product release and stability testing, acceptance criteria for all process characterisation.

The formulation of the commercial finished product and the commercial manufacturing process are considered to be justified and the reproducibility is demonstrated by the manufacturing of consecutive finished product process validation compounded batches that were filled into consecutive finished product batches.

Process validation/verification

The maximum allowable processing times, including hold times, for the manufacturing process were validated. The maximum validated hold times at 2-8°C, controlled room temperature (CRT) of 15-25 °C and ambient light conditions during the manufacturing process were established during manufacturing of the finished product PV runs.

All process characterisation, finished product release and characterisation sampling tests met the release acceptance criteria and PV specifications for all quality attributes.

Media fills were performed to qualify the aseptic filling process and demonstrate that the procedures and environmental conditions in the commercial manufacturing facility were capable of supporting aseptic processing of the finished product. The results of the three most recent semi-annual re-qualification runs of 2017/2018 show that the media fill runs were successfully performed, demonstrating that the aseptic handling procedures and environmental conditions for the line are appropriate for the production of the finished product.

An extractable and leachable risk assessment for polymeric product contact materials (PCMs) used for the finished product manufacturing process was performed. The results show that the use of polymeric PMCs poses minimal risk to patient safety.

Validation reports on filters used during the manufacturing process, as well as validation reports on sterilisation of equipment, components and stoppers, depyrogenation of glass vials and decontamination of filling isolators has been provided in the dossier.

Qualification of finished product shipping was evaluated through qualification of the shipping systems used for transportation through the supply chain. Information pertaining to shipping lanes and qualification of shipping systems can be found in *3.2.P.3.5 Process Validation and/or Evaluation* and is considered acceptable.

The Applicant performs CPV where data from manufactured batches, during commercial production, are reviewed periodically to verify that the validated state is maintained. This is acceptable.

Overall, the finished product manufacturing process is considered validated.

2.3.3.3. Product specification

Specifications

The battery of tests listed on the finished product specification for release and stability is acceptable and in line with ICH Q6B. It includes control of identity, purity and impurities, potency and other general tests.

The specifications and acceptance criteria for non-compendial methods for release and stability testing of finished product are based on statistical analyses and the specification for Rybrevant solution for infusion. Many acceptance criteria are the same due to the established comparability between active substance used for the IV and SC formulations. The Applicant has provided an overview of release and stability ranges (actual ranges of clinical batches and calculated tolerance intervals) and the proposed acceptance criteria for both 1600 and 2240 mg finished product presentations. This is endorsed. Release and stability data for PV batches are also within the proposed acceptance criteria for all specifications.

For the non-compendial specifications and acceptance criteria not already approved, the justifications of specifications/acceptance criteria were assessed. The acceptance criteria reflect the batch and stability data. The justification of specifications is acceptable.

The finished product is well controlled with adequately justified specifications and acceptance criteria.

Analytical procedures

The analytical procedures used for release and stability testing of amivantamab 160 mg/mL finished product are listed in the finished product specification. These are the same methods used for release and stability testing of active substance. All analytical methods, except identity of amivantamab, identity of rHuH20, rHuPh20 Activity, Polysorbate 80, Tests for Particulate matter (Visible foreign, Sub-visible and Visible Translucent) and Sterility are identical to the methods used for release and stability testing of Rybrevant IV finished product.

All non-compendial methods specific for amivantamab 160 mg/mL active substance and finished product have been adequately described. System suitability criteria for the methods have been set to ensure that the obtained methods can be considered valid. This is acceptable.

Validation of analytical procedures

Analytical procedures for identity of amivantamab and of rHuPH20 were validated.

Activity of rHuPH20 analytical procedure was validated.

Polysorbate 80 content analytical procedure was validated.

Particulate Matter (Visible Translucent) analytical procedure has been validated.

The Sterility analytical procedure is compendial but a few changes has been made to the method at the testing sites and thus a method verification report has been submitted. This is endorsed. The method including the changes has been verified to be suitable for testing of sterility in amivantamab 160 mg/mL finished product.

The non-compendial analytical procedures which were already approved for Rybrevant solution for infusion have all been revalidated at the relevant testing sites with amivantamab 160 mg/mL, to assure that the hyaluronidase of the SC formulation does not interfere with the methods.

All validation of non-compendial analytical procedures is acceptable and are in line with ICH Q2. Stability indicating studies were conducted by Halozyme, which is the manufacturer of rHuPH20.

Batch analyses

Batch analysis results have been presented. The batch results are all well within specification limits, and the results confirm consistency and uniformity of the product, indicating that the manufacturing process is under control.

Characterisation of impurities

The product-related impurities identified in amivantamab finished product are the same as those identified in active substance, except for the presence of translucent particles.

Process-related impurities and contaminants of finished product are the same as those listed and evaluated for active substance in the respective active substance sections of the dossier.

No elemental impurities above the calculated permitted daily exposure (PDE) for parenteral finished products were identified.

A risk assessment for nitrosamines has been provided. This evaluation considers finished product formulation components including active substance, raw materials and excipients, primary container, manufacturing process and equipment for the potential presence of nitrosamine and for risk factors potentially inducing formation of nitrosamines. No nitrosating agent is used in the manufacturing process of the active substance and finished product. No nitrosamine is identified as a potential impurity from the active substance or finished product manufacturing process. Hence, this assessment determines the risk for presence of nitrosamines to be negligible. This statement is endorsed.

Excipients - rHuPH20

Rybrevant 160 mg/mL mg solution for injection finished product is formulated with recombinant hyaluronidase, a skin permeation enhancer that facilitates subcutaneous delivery. RHuPH20 is produced in CHO cells.

The Applicant has submitted relevant data regarding source, history and generation of the cell substrate.

rhuPH20 from the same supplier (Halozyme) has already been commercially registered within the EU as a biological excipient (permeation enhancer) when co-formulated with other biological therapeutics. Additionally, it has been commercialised since 2005 in the United States. A complete Module 3.2.A.3 dossier for rHuPH20 is provided.

The Applicant has submitted extensive documentation regarding manufacturers, description of the manufacturing process, control of materials, process validation, characterisation, impurity testing, stability and viral safety assessment. The batches have been assessed against purity and characterisation of a reference standard. This is accepted.

Stability data is provided forrHuPH20 bulk enzyme batches at the long-term storage condition. A photostability study was performed and the results show the test articles exposed to light did not meet the acceptance criteria demonstrating the impact of light on the bulk enzyme. Therefore, handling and storage of the rHuPH20 is controlled to protect from direct light exposure. Based on the above, "protect from light" is included in the recommended storage conditions of rHuPH20. This is endorsed.

Container closure system

The choice of primary packaging (25R Type I glass vial with a bromobutyl rubber stopper, aluminium seal and flip-off cap) is considered justified based on the fact that the finished product is a solution for injection, intended to be administered subcutaneously.

Additionally, the secondary packaging (an opaque paperboard carton) is justified, as the finished product is light sensitive, and the glass vials transmits light to the finished product. The secondary packaging is therefore protecting the finished product against light-induced degradation.

The stability data demonstrates that the container closure also provide adequate protection from microbial contamination. The container closure system is therefore considered to be suitable for its intended use.

The type I glass vial comply with Ph. Eur. 3.2.1 and USP <660>, and the bromobutyl rubber stopper comply with Ph. Eur. 3.2.9 and/or USP <381>. The depyrogenation and sterilisation methods were appropriately validated.

The primary and secondary packaging used in the stability studies to support the shelf life are representative of the packaging proposed for routine storage of the finished product. This is acceptable.

2.3.3.4. Stability of the product

The claimed shelf-life of amivantamab 160 mg/mL SC finished product is 18 months when stored at the recommended storage condition of 5 $\pm$ 3^0C and protected from light.

Stability data at long-term storage conditions 5±3°C for up to 24 months on clinical batches have been provided. These conclusions are endorsed and the overall comparability statement is acceptable.

Finished product placed on stability studies was stored in primary packaging (vials) representative of the packaging used commercially. Manufacturing dates of all the batches placed on stability have been provided.

The Applicant submitted data regarding rHuPH20 activity studies performed at long term storage conditions 5±3°C and at accelerated and stressed storage conditions 25 °C/60% RH and 40°C/75% RH. Photostability studies have been performed supporting the storage condition "protect from light". The studies demonstrate that the surrogate package representative of the commercial secondary package will provide finished product with adequate protection from the effects of light conditions as specified in ICH Q1B.

Additionally, a temperature cycling study was performed to investigate stability of finished product following temperature fluctuations during transportation. The stability data is acceptable and the claimed shelf-life of 18 months for the finished product when stored at 5±3°C (unopened vial).

Regarding the prepared syringe, chemical and physical in-use stability has been demonstrated up to 24 hours at 2 to 8°C followed by up to 24 hours at 15 to 30°C. From a microbiological point of view, unless the method of dose preparation precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user.

2.3.3.5. Adventitious agents

Non-viral adventitious agents

The evaluation document for non-viral agents remains unchanged. The conclusions reached are assessed to be applicable.

The Applicant describes that the safety of amivantamab regarding adventitious agents is assured through the design and control of the manufacturing process. Transmissible spongiform encephalopathy infectivity risk is excluded by omission of animal-derived raw materials from the production process and the cell bank preparation. No animal-derived materials, have been used to prepare the Master Cell Bank or Working Cell Banks or are used during the production of the active substance. This is endorsed.

Mycoplasma and microbial bioburden are controlled through use of a sanitary process design and appropriate in-process testing. Bioburden and endotoxin contamination is also evaluated as part of routine release testing and 0.2 µm filtration steps throughout the process minimise the risk of microbial contamination.

Viral adventitious agents

The evaluation document for viral agents is similar to the document used before the submission. The conclusions reached are assessed to be applicable.

These studies demonstrate that the active substance manufacturing process yields acceptable viral clearance to assure viral safety of the amivantamab product. This is endorsed.

rhuPH20

During PPQ, the unclarified harvest was tested on each PPQ batch using the viral *in vitro* assay, viral *in vivo* assay, and Transmission Electron Microscopy (TEM). The PPQ assessments demonstrated that the rHuPH20 process controls provide effective adventitious viral safety.

Viral safety testing of the MCB, WCB and End-of-Production (EOP) cells for the manufacturing process was carried out according to ICH Q5A.

Overall adventitious agents safety of Rybrevant is considered sufficiently assured.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The Rybrevant dossier is acceptably structured and of acceptable quality.

Manufacturing, preparation and testing of cell banks, including LIVCA, are acceptably presented. The information on manufacture of the active substance is found acceptable. Differences between the different versions of the manufacturing process used during development are clearly described. Comparability between process versions has been demonstrated.

Characterisation of amivantamab was performed using an extensive panel of appropriate state-of-the art methods.

The development and manufacture of the finished product has been sufficiently described and justifies the chosen formulation as well as the commercial manufacturing process.

Acceptable information was provided to support the use of rhuPH20 excipient.

The control of the active substance and finished product has been presented in a satisfactory way.

The stability results support the proposed shelf-life for parenteral antibody intermediates, active substance and finished product.

Acceptable information has been provided to ensure safety of the product with regards to adventitious agents.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Rybrevant is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, this line extension application for Rybrevant is considered approvable from the quality point of view.

2.3.6. Recommendation(s) for future quality development

None.

2.4. Non-clinical aspects

2.4.1. Introduction

No new non-clinical data was submitted in this application.

To support amivantamab SC administration the applicant refers to toxicology studies in cynomolgus monkey submitted in the original MAA.

2.4.2. Toxicology

No new toxicology studies were conducted. A 2-weeks local tolerance study and 6-weeks and 13-weeks repeat dose toxicology studies were submitted and assessed in original MAA support this application. In the local tolerance study cynomolgus monkeys were administrated SC weekly with 125 mg/kg amivantamab with or without the excipient rHuPH20 (2000 U/mL).

2.4.3. Ecotoxicity/environmental risk assessment.

Amivantamab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no environmental risk assessment for amivantamab is required.

2.4.4. Discussion on non-clinical aspects

No new non-clinical data have been submitted to support this extension application which is considered acceptable. The toxicological studies included in the original MAA is considered to support the SC administration of amivantamab. The assessment of the study revealed a good tolerability at the injection sites in cynomolgus monkeys. In the 6-weeks and 13-weeks repeated-dose studies the animals were dosed IV up to 120 mg/kg/week with amivantamab. In addition to standard toxicological evaluations, safety pharmacology assessment of the cardiovascular, respiratory, and central nervous systems was included in the studies. The assessment of these studies revealed no apparent safety signals or no dose-limiting toxicities and no clear target organs toxicity. Minor findings observed in the gastrointestinal tract, liver and kidney were considered non-adverse. The safety margins in these two studies were approximately 6 times AUC and 8 times Cmax.

All prior non-clinical data for rybrevant have been reviewed in previous procedures and therefore no re-assessment of the non-clinical data has been performed.

The information in sections 4.6 and 5.3 of the SmPC remains unchanged.

The active substance is a protein, the use of which is not expected to alter the concentration or distribution of the substance in the environment. Therefore, amivantamab is not expected to pose a risk to the environment.

2.4.5. Conclusion on the non-clinical aspects

No new non-clinical data was submitted for the current application. This is considered acceptable.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Study ID/Participant Population	**Dose Regimen**	**Reported PK Parameters**
Study 61186372NSC3004 (PALOMA-3) in participants with EGFRm locally advanced or metastatic NSCLC after progression on osimertinib and platinum-based chemotherapy	*Arm A (28-day cycles): Amivantamab SC* Cycle 1: 1600 mg (2240 mg if BW ≥80 kg) on Days 1, 8, 15, and 22. Cycles 2+: 1600 mg (2240 mg if BW ≥80 kg) on Days 1 and 15. *Arm B (28-day cycles): Amivantamab IV* Cycle 1: 1050 mg (1400 mg if BW ≥80 kg) on Days 1 to 2 (split dose), 8, 15, and 22 Cycles 2+: 1050 mg (1400 mg if BW ≥80 kg) on Days 1 and 15. *Arms A and B* Lazertinib oral 240 mg once daily.	*Amivantamab* Co-primary: C2D1 Ctrough, C2D1-15 AUC Co-secondary: C4D1 Ctrough, model predicted C4D1-15 AUC *Lazertinib*: sparse sampling
Study 61186372NSC2002 (PALOMA-2) in participants with EGFRm locally advanced or metastatic NSCLC (Cohorts 1 and 6)	<u>Cohorts 1 and 6 (28-day cycles):</u> Amivantamab SC Cycle 1: 1600 mg (2240 mg if BW ≥80 kg) QW. Cycles 2+: 1600 mg (or 2240 mg if BW ≥80 kg) on Days 1 and 15. Lazertinib oral 240 mg once daily. <u>Cohort 6:</u> Prophylactic-dose anticoagulation per local guidelines.	*Amivantamab* C2D1: Ctrough C4D1 (Cohort 6 only): Ctrough, Cmax, tmax, AUC *Lazertinib*: sparse sampling
Study 61186372NSC1003 (PALOMA) in participants with advanced solid malignancies	*Part 1* <u>Cohorts 1a and 1b (28-day cycles)</u>: Amivantamab SC Cycle 1: 1050 mg (1400 mg if BW ≥80 kg) on Days 1 (Days 1-2 in case of split dosing), 8, 15, and 22. Cycles 2+: 1050 mg (1400 mg if BW ≥80 kg) on Days 1 and 15.	*Amivantamab* C1D1: Cmax, tmax, AUC C2D1: Ctrough, Cmax, tmax, AUC C4D1: Ctrough

Study ID/Participant Population	Dose Regimen	Reported PK Parameters
	Part 2 Cohorts 2a and 2b (28-day cycles): Amivantamab SC 1050 mg (1400 mg if BW ≥80 kg); regimen as in Part 1. Cohort 3a (28-day cycles): Amivantamab SC 1600 mg (2240 mg if BW ≥80 kg); regimen as in Part 1. Cohort 4a (28-day cycles): Amivantamab SC 1600 mg (2240 mg if BW ≥80 kg); regimen as in Part 1. Cohort 5a (21-day cycles): Amivantamab SC Cycle 1: 2560 mg (3360 mg if BW ≥80 kg) on Days 1, 8, and 15. Cycles 2+: 2560 mg (3360 mg if BW ≥80 kg) on Day 1.	

2.5.2. Clinical pharmacology

The pharmacokinetic (PK) and anti-drug antibodies (ADA) data for the amivantamab program across the clinical trials using the intravenous (IV) formulation has been described and assessed previously. This overview will thus focus on the differences and/or new information regarding the subcutaneous (SC) formulation. The approval of the new SC formulation of amivantamab (1600mg and 2240mg, solution for injection) is supported by data from two studies (PALOMA-3, pivotal; PALOMA-2, supportive) in NSCLC and from one study (PALOMA, dose-finding) in advanced solid malignancies

Amivantamab SC is formulated with recombinant human hyaluronidase PH20 (rHuPH20 2,000 U/mL, ~20 µg/mL). rHuPH20 is a neutral pH-active human hyaluronidase that works locally and transiently to degrade hyaluronan ((HA), a naturally occurring glycoaminoglycan found throughout the body) in the extracellular matrix of the subcutaneous space by cleaving the linkage between the two sugars (N-acetylglucosamine and glucuronic acid), which comprise HA.

Non-inferiority in PK, as primary endpoint, after SC versus IV (PALOMA-3) is intended to support line extension with the same indications as currently approved under a Q2W dosing schedule for amivantamab IV.

2.5.2.1. Pharmacokinetics

Methods

Bioanalysis

A validated and cross validated MSD ECLIA method was used to determine amivantamab PK concentrations in human serum samples. This is the same assay used to assess amivantamab IV in the

current and previous submissions. Lazertinib was quantified using a previously reported LC-MS/MS method.

Immunogenicity

Multitiered strategies were employed to characterise the antibodies to amivantamab and rHuPH20. Validation cutpoints were used unless stated otherwise.

The amivantamab antidrug antibody (ADA) assay was the same as in previous submissions for PALOMA and Chinese samples of PALOMA-2 and PALOMA-3 (MTD207). For samples collected and analyzed outside of China from PALOMA-2 and PALOMA-3, the assay was updated to increase drug tolerance (MTD269).

Briefly, in both methods, samples were pretreated with acid, followed by an incubation with biotinylated-amivantamab. Dissociated ADA were then captured on NeutraAvidin-coated magnetic particles, captured using a magnet and washed. Bound ADA were eluted from the bead complex by a second acid treatment. The biotin-amivantamab bound ADA were then incubated in the presence of Sulfo-TAG™-amivantamab and transferred to a blocked MSD-streptavidin plate. The biotin-amivantamab in the complex binds to the streptavidin in the wells before detection by chemilumineSCence (ECL).

The method modification consisted of an increase in the biotin-drug concentration and an increase in capture NeutrAvidin beads concentration. Precision, sensitivity, selectivity and drug tolerance were evaluated for the updated method. At high positive control (HPC) (100 ng/mL), drug tolerance was 1000 µg/mL and at low positive control (LPC) (5.0 ng/mL) 100 µg/mL. HPC drug tolerance was improved, compared to 400 µM in MTD207, which at LPC stayed the same.

A validated ECLIA method was used for the detection of antibodies to rHuPH20 in human plasma from PALOMA, PALOMA-2, and PALOMA-3 studies. Briefly, the sample was incubated simultaneously with biotinylated-rHuPH20 and Sulfo-Tag-rHuPH20. The biotin-rHuPH20 was captured on a streptavidin coated MSD assay plate, unbound proteins were washed away before detection by ECL.

PK analysis

Standard non-compartmental analysis was performed, in particular for the co-primary endpoints of the pivotal study PALOMA-3.

Population PK analysis

A population PK (popPK) analysis was performed using the nonlinear mixed effect modelling software NONMEM (version 7.4). The FOCE method with the INTERACTION option was used.

The starting model was informed by previously developed popPK models for amivantamab following IV administration.

Data

The popPK model for amivantamab following IV and SC (mainly Q2W) administration was developed based on IV PK data from Study CHRYSALIS monotherapy cohorts (PK cutoff date 26 February 2021; 413 participants) and Study PALOMA-3 (PK cutoff date 03 January 2024; 207 participants), and SC PK data from Study PALOMA Cohorts 2a, 3a, 4a, 5a (target SC formulation HC-CF only; PK cutoff date 30 October 2023; 81 participants), Study PALOMA-2 Cohorts 1 and 6 (PK cutoff date 15 November 2023; 121 participants), and Study PALOMA-3 (PK cutoff date 03 January 2024; 204 participants). In total, the popPK analysis included 21860 measurable amivantamab serum concentrations from 1016 participants with EGFR-mutated NSCLC and 10 participants with other advanced carcinomas. Among them, 16696 (76.4%) and 5164 (23.6%) measurable amivantamab serum concentrations were

collected from 620 (60.4%) participants who received amivantamab IV and 406 (39.6%) participants who received amivantamab SC, respectively. Measurable amivantamab serum concentrations (261 [1.2%]) from 39 (3.8%) participants (22 participants from Study PALOMA Cohort 4a and 17 participants from Study PALOMA-3) were collected after SC administration of drug products manufactured with GEN2 drug substance. The remaining PK data were collected after administration of drug products manufactured with GEN1 drug substance. Because the percentage of post-treatment BQL samples was low (<1%), the BQL samples were omitted.

Model

Amivantamab PK after IV and SC administration was described using a 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination and a first-order process with lag time for SC absorption. The model was parameterized in terms of CL, V_1, Q, V_2, V_{max}, K_m, K_a, ALAG, and F. Inter-individual variability (IIV) was quantified on CL, V_1, V_2, and K_a assuming log-normal distributions and on F assuming normal distribution after logit transformation. The residual variability (RUV) was both proportional and additive.

Given the robustness of the amivantamab IV models with covariates, all covariate relationships from the IV models were retained in the new model. Only limited covariate testing on SC absorption parameters (F and K_a) was conducted, as well as evaluation of GEN1 versus GEN2 drug substance process, on F, K_a and CL. The final model included body weight, sex, age, and albumin as covariates on CL, body weight and sex as covariates on V_1, body weight as covariate on V_2 (shared scaling exponent for V_1 and V_2), age as covariate on K_a ($p<0.001$), and BMI as covariate on F ($p<0.001$). GEN1 versus GEN2 drug substance had no significant impact on the PK based on the prespecified p-value of 0.01.

The population parameter estimates in the final model are presented in Table 3 , summary statistics of individual (secondary) PK parameters (derived based on post hoc parameter estimates) for 396 SC participants with NSCLC from Studies PALOMA, PALOMA-2, and PALOMA-3 are presented in Table 5, and prediction corrected VPCs, with and without observed data, stratified by route of administration, are presented in Figure 3.

Table 4: Parameter estimates in the final population PK model on pooled data from the CHRYSALIS, PALOMA, PALOMA-2, and PALOMA-3 studies.

	Final Model (run70) Condition Number: 73.65	
Parameter	**Estimate (RSE%[i])**	**Shrinkage (%)[j]**
Fixed effect		
F	0.683 (1.6)	-
BMI on LF[a]	-0.0363 (21.7)	-
K_a (h^{-1})	0.0172 (4.1)	-
Age on K_a[b]	-0.521 (34)	-
ALAG (h)	8.44 (10)	-
CL (L/h)	0.00889 (1.6)	-
Weight on CL[c]	0.48 (9.5)	-
Albumin on CL[c]	-0.52 (15)	-
Age on CL[c]	-0.218 (23.3)	-
Sex=Male on CL[c]	0.206 (12.5)	-
V_1 (L)	2.63 (1.3)	-
Weight on V_1 and V_2[d,e]	0.421 (8.3)	-
Sex=Male on V_1[d]	0.121 (17.9)	-
V_2 (L)	2.41 (2.2)	-
Q (L/h)	0.0373 (2.3)	-
V_{max} (mg/h)	0.751 (4.1)	-
K_m (µg/mL)	18.4 (21.5)	-
IIV		
F (SD)[f]	0.109 (7.4)	20.8
K_a (CV%)[g]	25.4 (31.5)	12.8
CL (CV%)[g]	25.4 (3)	10.7
V_1 (CV%)[g]	19.6 (2.2)	18.9
V_2 (CV%)[g]	47.4 (3.1)	21.7
Correlation F ~K_a	0.895 (0.0401)	-
Correlation F ~V_1	-0.229 (0.0324)	-
Correlation V_1 ~K_a	-0.631 (0.0203)	-
Residual variability[h]		
Proportional error	0.144 (0.3)	-
Additive error (µg/mL)	23.3 (0.6)	-

ALAG=subcutaneous absorption delay time; ALB=albumin; BMI=body mass index; CL=linear clearance; CV=coefficient of variation; F=subcutaneous bioavailability; IIV=interindividual variability; K_a=first-order subcutaneous absorption rate constant; K_m=Michaelis-Menten constant (amivantamab concentration at half maximum velocity of the nonlinear clearance); LF=logit transformation of the typical value of F; NONMEM=nonlinear mixed effects modeling; popPK=population pharmacokinetics; Q=intercompartmental clearance; RSE=relative standard error; SC=subcutaneous; TV=typical value; V_1=volume of distribution in the central compartment; V_2=volume of distribution in the peripheral compartment; V_{max}=maximum velocity of the nonlinear clearance; WT=weight.

[a] BMI effect on the typical value of F was modeled as follows: $TVF=\frac{1}{1+e^{-(LF+(BMI-24)\times\theta_{bmi,f})}}$, where TV stands for "typical value," LF is the logit transformation of θ_F in a typical participant with baseline BMI of 24 kg/m^2, and $\theta_{bmi,f}$ is the BMI coefficient for SC bioavailability. BMI was calculated as weight/(height^2).

[b] Age effect on the typical value of K_a was modeled as follows: $TVK_a=\theta_{Ka}\times(AGE/63)^{\theta age,Ka}$, where θ_{Ka} is the absorption rate constant in a typical participant with baseline age of 63 years, $\theta_{age,Ka}$ is the age coefficient for absorption rate constant.

[c] Weight, albumin, age, and sex effects on the typical value of clearance were modeled as follows: $TVCL=\theta_{CL}\times(WT/60)^{\theta wt,CL}\times(ALB/40)^{\theta alb,CL}\times(AGE/63)^{\theta age,CL}\times(1+\theta_{sex,CL}\times sex)$, where θ_{CL} is the clearance value in a typical female participant with baseline WT of 60 kg, ALB level of 40 g/L, age of 63 years, $\theta_{wt,CL}$, $\theta_{alb,CL}$, and $\theta_{age,CL}$ are the weight, albumin, and age coefficients for clearance respectively, sex is an indicator variable for

female (sex=0; reference category) or male (sex=1) participants, and $\theta_{sex,CL}$ is the multiplicative term for male sex effect on clearance.

[d] Weight and sex effects on the typical value of V_1 was modeled as follows: $TVV1=\theta_{V1}\times(WT/60)^{\theta_{wt,V}}\times(1+\theta_{sex,V1}\times sex)$, where θ_{V1} is the central volume of distribution value in a typical female participant with baseline weight of 60 kg, and $\theta_{wt,V}$ is the weight coefficient for V_1 and V_2, sex is an indicator variable for female (sex=0; reference category) or male (sex=1) participants, and $\theta_{sex,V1}$ is the multiplicative term for male sex effect on central volume of distribution.

[e] Weight effect on the typical value of V_2 was modeled as follows: $TVV2=\theta_{V2}\times(WT/60)^{\theta_{wt,V}}$, where θ_{V2} is the peripheral volume of distribution value in a typical participant with baseline weight of 60 kg, and $\theta_{wt,V}$ is the weight coefficient for V_1 and V_2.

[f] IIV of bioavailability was reported on standard deviation scale and calculated as $\sqrt{VAR}\cdot\theta_F\cdot(1-\theta_F)$ (Samtani 2009), where VAR represents the variance estimate for logit normally distributed random effects as returned by NONMEM and θ_F was the SC bioavailability in a typical participant with baseline BMI of 24 kg/m^2.

[g] IIV was estimated in relative percentage scale, calculated as $(e^{var}-1)^{1/2}\times100\%$, where var represents the variance estimate for log-normally distributed random effects as returned by NONMEM.

[h] Residual variability was estimated as THETAs in standard deviation.

[i] RSE%=(standard error of estimate/estimate)×100%; IIV RSE%=(standard error of estimate/variance estimate)/2×100%.

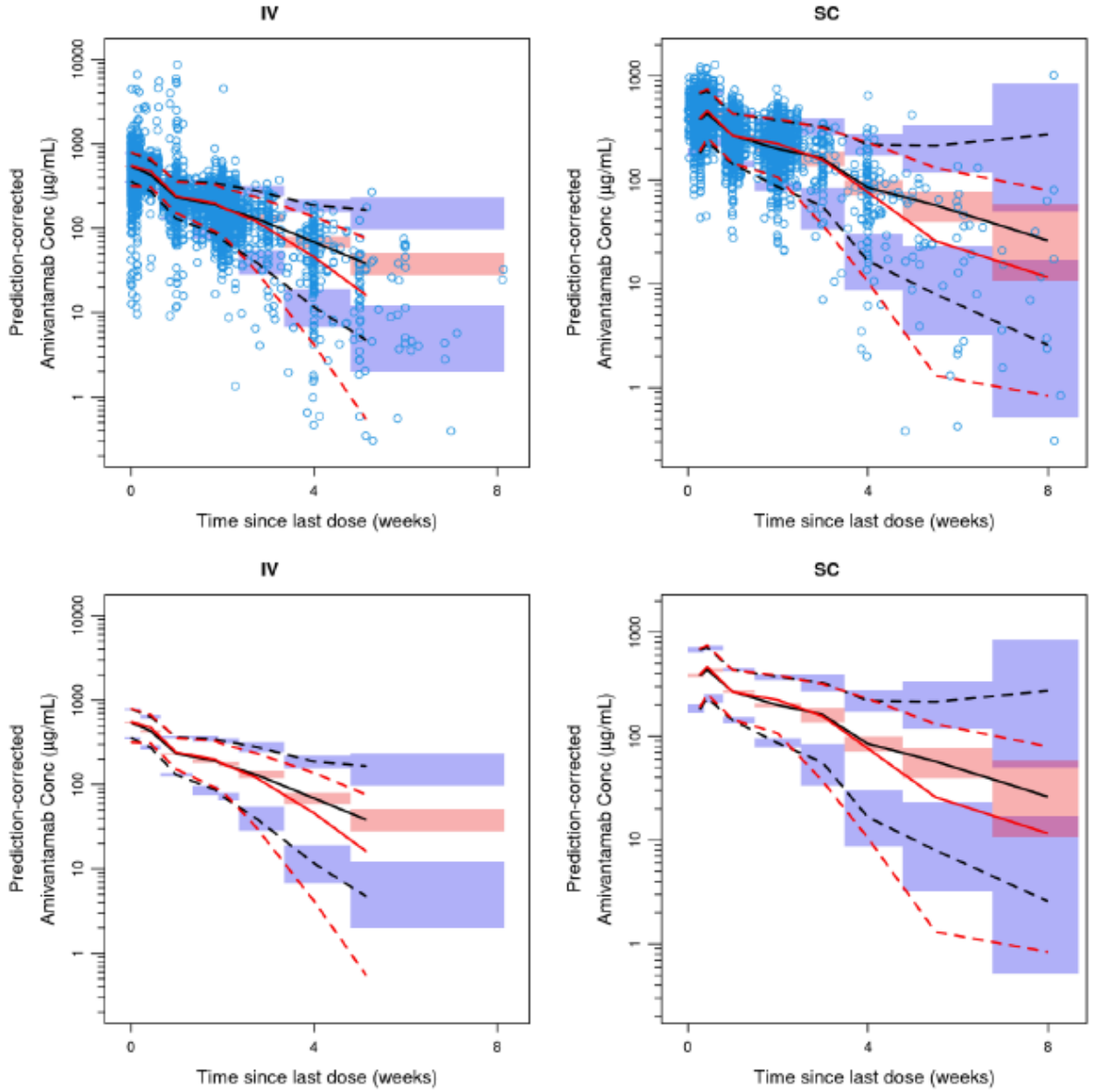
[j] Shrinkage for IIV F and K_a were calculated using the η values of SC participants as 1- SD(η)/ $\sqrt{VAR}$, where VAR represents the variance estimate as returned by NONMEM.

Table 5: Summary statistics of individual PK parameters derived based on post hoc parameter estimates, for SC participants with NSCLC from Studies PALOMA, PALOMA-2, and PALOMA-3.

	PALOMA (N=71)	PALOMA-2 (N=121)	PALOMA-3 (N=204)	Overall (N=396)
SC bioavailability				
Mean (CV%)	0.690 (12.6%)	0.662 (13.9%)	0.673 (13.4%)	0.673 (13.5%)
Median [Min, Max]	0.684 [0.483, 0.859]	0.675 [0.255, 0.869]	0.694 [0.340, 0.829]	0.685 [0.255, 0.869]
Geo. mean (geo. CV%)	0.685 (13.0%)	0.655 (16.0%)	0.666 (14.9%)	0.666 (14.9%)
Volume of distribution at steady state [L]				
Mean (CV%)	5.56 (24.6%)	6.47 (28.0%)	5.60 (22.7%)	5.86 (26.0%)
Median [Min, Max]	5.34 [3.55, 12.2]	6.00 [4.02, 16.1]	5.36 [3.39, 11.0]	5.66 [3.39, 16.1]
Geo. mean (geo. CV%)	5.42 (22.2%)	6.27 (24.5%)	5.47 (22.1%)	5.69 (23.8%)
Linear clearance (L/day)				
Mean (CV%)	0.219 (28.6%)	0.238 (27.4%)	0.233 (24.9%)	0.232 (26.4%)
Median [Min, Max]	0.214 [0.127, 0.468]	0.226 [0.133, 0.451]	0.224 [0.113, 0.423]	0.223 [0.113, 0.468]
Geo. mean (geo. CV%)	0.211 (27.7%)	0.230 (26.9%)	0.226 (24.6%)	0.224 (26.0%)
Terminal half-life associated with linear clearance (Day)				
Mean (CV%)	20.0 (36.0%)	21.8 (38.6%)	18.8 (32.6%)	19.9 (36.1%)
Median [Min, Max]	18.0 [9.27, 46.5]	20.1 [9.26, 63.8]	18.0 [7.80, 41.4]	18.6 [7.80, 63.8]
Geo. mean (geo. CV%)	19.0 (33.5%)	20.5 (35.9%)	17.9 (32.7%)	18.8 (34.3%)

CV=coefficient of variation; Geo=geometric; IV=intravenous; N=number of participants; PK=pharmacokinetic; SC=subcutaneous.

Figure 3: Prediction-corrected visual predictive check for time since last dose stratified by route of administration for the final population PK model.



CI=confidence interval; Conc=concentration; IV=intravenous; pcVPC=prediction-corrected visual predictive check; SC=subcutaneous.

Solid red lines represent the median, and dashed red lines represent 5th and 95th percentiles of the prediction-corrected observed values. Solid black lines represent the median, and dashed black lines represent 5th and 95th percentiles of the prediction-corrected simulated values based on 1,000 simulations. Pink and blue shaded areas represent the 95% CI of the median, 5th and 95th percentiles of the prediction-corrected simulated values. Blue circles represent the prediction-corrected observed values. The blue circles were removed in the bottom panel to facilitate visualization.

Simulations

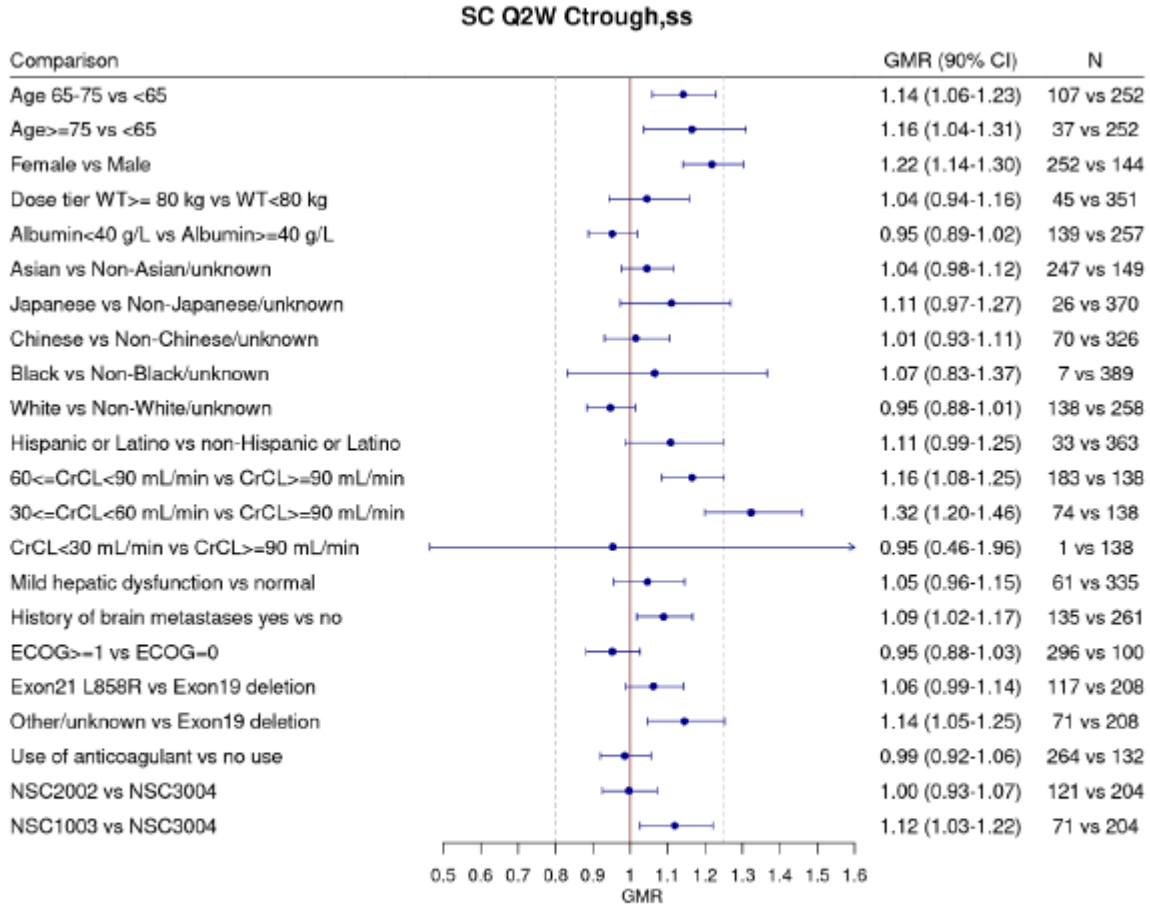
Simulations were conducted for the 396 SC participants with NSCLC, from studies PALOMA, PALOMA-2, and PALOMA-3, based on their individual parameter estimates, assuming nominal doses. Summary statistics of relevant exposure metrics are presented in Table 6. The mean serum $AUC_{1\text{-week}}$ was approximately 3.5-fold higher after the Cycle 2 Day 1 (C2D1) dose, following weekly dosing, compared to the first dose. Steady state was reached by Week 13; median time to reach peak concentration at steady state was 3 days. The mean serum $AUC_{1\text{-week}}$ was approximately 2.4-fold higher at steady state compared to the first dose.

Table 6: Summary of simulated amivantamab exposure for the SC Q2W regimen using individual parameter estimates of participants with NSCLC, from studies PALOMA, PALOMA-2, and PALOMA-3.

	SC (Q2W) regimen: 1600/2240 mg QW in Cycle 1, and Q2W from Cycle 2 onwards; 28-days per cycle (N=396; PALOMA studies)
$AUC_{1\text{-week,1st dose}}$ (µg/mL*h)	
Median [min, max]	22000 [4230, 42500]
G_{mean} (GCV)	21400 (33.5%)
$AUC_{1\text{-week,C2D1}}$ (µg/mL*h)	
Median [min, max]	76600 [18400, 156000]
G_{mean} (GCV)	74300 (29.3%)
$AUC_{1\text{-week,ss}}$ (µg/mL*h)	
Median [min, max]	54300 [10100, 121000]
G_{mean} (GCV)	52300 (33.5%)
$AUC_{tau,ss}$ (µg/mL*h)	
Median [min, max]	95800 [18500, 226000]
G_{mean} (GCV)	93400 (34.5%)
$T_{max,ss}$ (day)	
Median [min, max]	3.04 [1.79, 4.25]
G_{mean} (GCV)	3.05 (13.7%)

A comparison of amivantamab exposure metrics ($C_{trough,ss}$, $C_{max,max}$, and $C_{max,ss}$) across subgroups of interests was conducted (on the simulations conducted for the 396 SC participants with NSCLC) using forest plots, i.e., by presenting the estimated geometric mean ratio (GMR) and its 90% CI for the exposure metrics for a given covariate stratum relative to the reference stratum. Subgroups were considered to have comparable exposure if the estimated GMR and 90% CI limits were not entirely outside the 80% to 125% range. The forest plot of $C_{trough,ss}$ is presented in Figure 4.

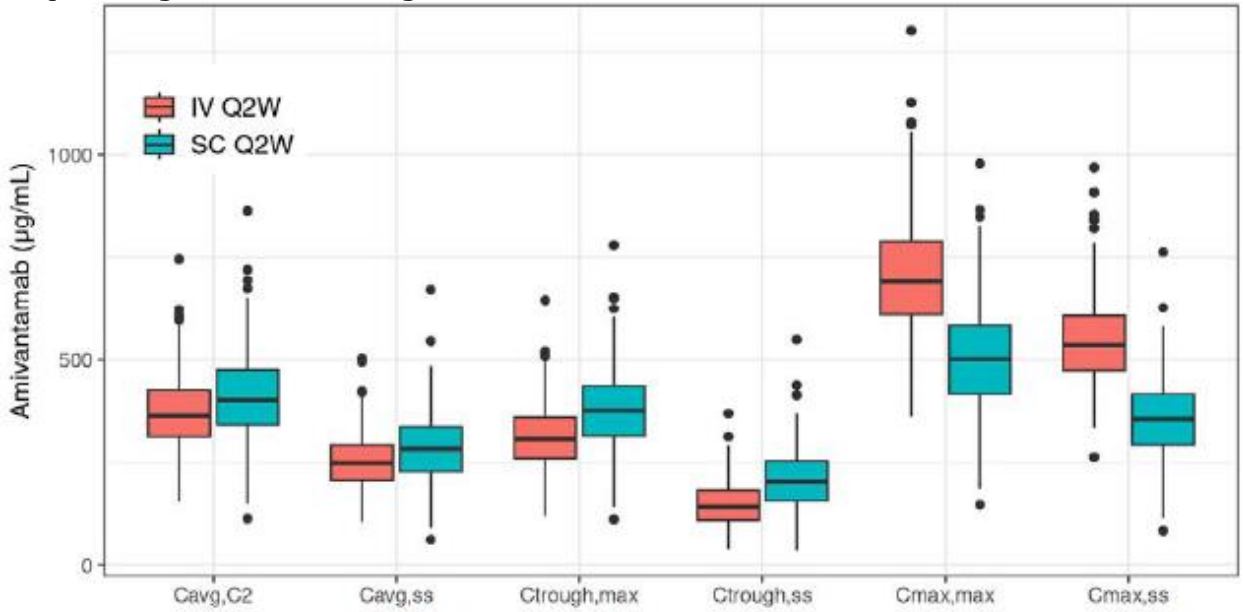
Figure 4: Forest plot of simulated $C_{trough,ss}$ using individual parameter estimates of participants with NSCLC, from studies PALOMA, PALOMA-2, and PALOMA-3.



CI=confidence interval; CrCL=creatinine clearance; $C_{trough,ss}$=trough concentration at steady state; ECOG=Eastern Cooperative Oncology Group; GMR=geometric mean ratio; N=number of participants; NSC1003=Study PALOMA; NSC2002=Study PALOMA-2; NSC3004=Study PALOMA-3; Q2W=every 2 weeks; SC=subcutaneous; vs=versus; WT=body weight.

Further simulations were conducted to compare the selected SC regimen with the approved IV regimen. Participants in PALOMA-3 with available individual parameter estimates from the final model (N=204 for SC and N=207 for IV) were assumed to have received nominal doses of amivantamab per their assigned administration route, and the PK metrics of interest were derived from their simulated PK profiles. Comparisons of PK metrics are presented in Figure 5. The PK covariates including sex, age, body weight, and albumin were balanced between the simulated IV and SC participants.

Figure 5: Comparison of simulated PK metrics of the SC Q2W weight-tiered dose regimen to IV Q2W weight-tiered dose regimen.



$C_{avg,C2}$=average concentration in Cycle 2 Day 1 to Day 15; $C_{avg,ss}$=average concentration at steady state from Day 1 to Day 15; $C_{max,max}$=maximum peak concentration (ie, peak concentration after Cycle 2 Day 1 dose); $C_{max,ss}$=peak concentration at steady state; $C_{trough,max}$=maximum trough concentration (ie, Cycle 2 Day 1 predose); $C_{trough,ss}$=trough concentration at steady state; IV=intravenous; PK=pharmacokinetics; Q2W=every 2 weeks; SC=subcutaneous.

Absorption

Based on the individual parameter estimates for 396 participants with NSCLC who received amivantamab SC from studies PALOMA-3, PALOMA-2, and PALOMA, the geometric mean bioavailability of amivantamab co-formulated with rHuPH20 was 66.6%.

The median time for amivantamab SC to reach Cmax is approximately 3 days after administration. Cmax (SD) was 562 (135) µg/mL at cycle 2 day 1 (C2D1) after SC administration of 1600 mg amivantamab (2240 mg ≥80 kg) QW in cycle 1 (28d), Q2W thereafter (PALOMA cohort 4a,Table 8).

The exposure of the excipient rHuPH20 administered SC was not measured based on previous reports of low systemic bioavailability (Kirschbrown 2019).

PALOMA (Study 61186372NSC1003)

PALOMA was a phase 1b study in participants with advanced solid malignancies where PK was a primary objective, with Cycle 2 Day 1 Ctrough being the PK parameter of choice. Selection of formulation and dose for SC amivantamab is based on this study. No formal statistical hypothesis testing was intended and there was no IV arm in this study.

Four different formulations of amivantamab were studied (Table 7), with different concentrations of amivantamab with or without rHuPH20, all given by SC injection in the abdomen. The high concentration (HC) formulation of amivantamab (160 mg/mL) with rHuPH20 was selected for further development. Regarding the drug substance, see at the end of the absorption section.

Table 7: PALOMA Cohorts, Doses and Formulations

Cohort	SC Dose	Amivantamab concentration	Drug substance GEN1/GEN2	rHuPH20
1a	1050 mg (1400 mg ≥80 kg)	50 mg/mL	GEN 1	Yes 110000 U/mL
1b	1050 mg (1400 mg ≥80 kg)	50 mg/mL	GEN 1	No
2a	1050 mg (1400 mg ≥80 kg)	160 mg/mL	GEN 1	Yes 2000 U/mL
2b	1050 mg (1400 mg ≥80 kg)	160 mg/mL	GEN 1	No
3a	1600 mg (2240 mg ≥80 kg)	160 mg/mL	GEN 1	Yes 2000 U/mL
4a	1600 mg (2240 mg ≥80 kg)	160 mg/mL	GEN 2	Yes 2000 U/mL
5a	2560 mg (3360 mg ≥80 kg)	160 mg/mL	GEN 1	Yes 2000 U/mL

QW in cycle 1 (28d), Q2W thereafter except cohort 5a QW in cycle 1 (21d), Q3W thereafter

PK parameters and concentration time profile for the different cohort are presented in Table 8 and Figure 6. The Tmax occurred at a median of 70 to 96 hours after the first dose and 46 to 70 hours after the Cycle 2 Day 1 dose. In all cohorts, mean serum amivantamab concentration increased over time until Cycle 2 Day 1. After Cycle 2 Day 1, mean serum amivantamab concentration decreased slightly and then remained stable until the last timepoints measured. Mean C2D1 Ctrough generally increased with dose level, with Cohort 5a showing higher exposure than Cohort 3a/4a and Cohorts 1a/1b/2a/2b. Bioavailability was calculated using historic data for iv posologies of amivantamab (61186372EDI1001, Q2W: gmean AUC=135488 µg.h/mL, n=33; Q3W gmean AUC=211365 µg.h/mL, n=12). Bioavailability at C2D1 (gmean) was 58.1, 51.8, 75.0, 54.8, 113, 112 and 149% in cohorts 1a, 1b, 2a, 2b, 3a, 4a and 5a, respectively.

Table 8: Amivantamab PK parameters after SC administration (PALOMA)

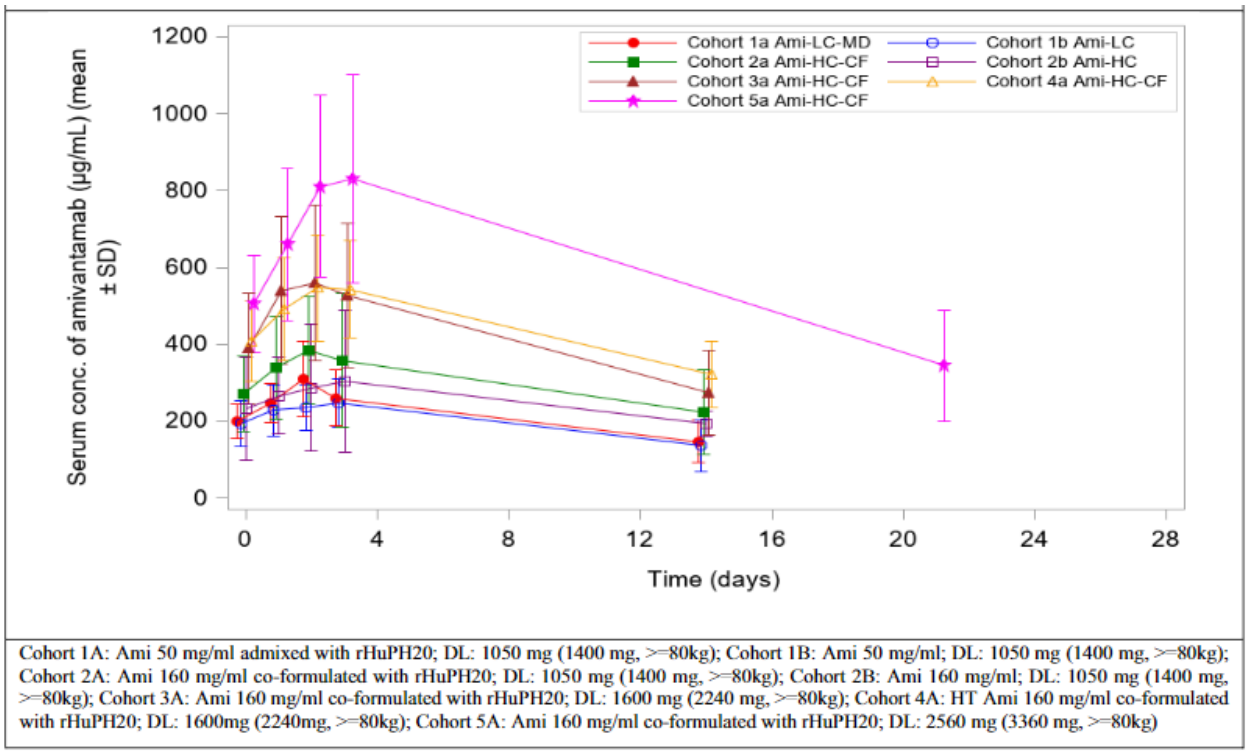
Pharmacokinetics of Amivantamab (mean [SD], t_{max}: median [range])	Cohort 1a Ami-LC-MD	Cohort 1b Ami-LC	Cohort 2a Ami-HC-CF	Cohort 2b Ami-HC	Cohort 3a Ami-HC-CF	Cohort 4a Ami-HC-CF	Cohort 5a Ami-HC-CF
Cycle 1 Day 1							
n	8	8	8	8	25[a]	35[b]	25[c]
C_{max} (µg/mL)	84.7 (20.0)	67.4 (24.8)	179 (106)	93.9 (68.1)	183 (82.0)	147 (54.1)	271 (89.4)
t_{max} (h)	72.03 (46.78 - 169.85)	73.64 (69.50 - 211.63)	70.86 (67.00 - 165.28)	96.88 (22.40 - 190.70)	70.30 (46.13 - 193.00)	70.88 (46.17 - 197.58)	70.50 (22.25 - 192.13)
$AUC_{0\text{-}168h}$ (µg.h/mL)	10817 (2477)	9322 (4439)	19041 (9497)	9871 (6471)	22753 (9560)	19834 (7345)	34532 (12139)
Cycle 2 Day 1							
n	6	6[d]	8	4[e]	14[f]	28[g]	17[h]
C_{trough} (µg/mL)	200 (44.9)	193 (59.9)	272 (97.3)	233 (133)	390 (145)	407 (104)	505 (125)
C_{max} (µg/mL)	311 (98.3)	255 (67.7)	396 (141)	335 (143)	608 (196)	562 (135)	922 (256)
t_{max} (h)	46.26 (44.05 - 48.15)	69.30 (24.20 - 73.17)	46.47 (22.05 - 70.50)	69.05 (46.72 - 335.42)	48.33 (23.42 - 73.80)	47.92 (45.57 - 73.33)	70.39 (22.93 - 72.18)
AUC_{τ} (µg.h/mL)	78674 (24472)	70246 (22061)	101609 (44036)	74300 (23630)	153578 (45952)	151788 (38619)	314539 (77368)
Cycle 4 Day 1							
n	5	4	5	-	10	14	9
C_{trough} (µg/mL)	119 (66.9)	152 (89.3)	195 (83.1)	-	401 (137)	224 (80.6)	257 (150)

[a] n=22 for $AUC_{0\text{-}168h}$., [b] n=33 for $AUC_{0\text{-}168h}$., [c] n=23 for $AUC_{0\text{-}168h}$, [d] n=5 for AUC_{τ}.[e] n=5 for C_{max} and t_{max}, [f] n=13 for C_{max}, and t_{max}, and n=11 for AUC_{τ},[g] n=29 for C_{max} and t_{max}, and n=26 for AUC_{τ}, [h] n=16 for C_{max} and t_{max}, and n=15 for AUC_{τ}

Cohort 1a: Ami-LC-MD 50 mg/ml admixed with rHuPH20; DL: 1050 mg (1400 mg, >=80kg); Cohort 1b: Ami-LC 50 mg/ml; DL: 1050 mg (1400 mg, >=80kg); Cohort 2a: Ami-HC-CF 160 mg/ml co-formulated with rHuPH20; DL: 1050 mg (1400 mg, >=80kg); Cohort 2b: Ami-HC 160 mg/ml; DL: 1050 mg (1400 mg, >=80kg); Cohort 3a: Ami-HC-CF 160 mg/ml co-formulated with rHuPH20; DL: 1600 mg (2240 mg, >=80kg); Cohort 4a: HT/GEN2 Ami-HC-CF 160 mg/ml co-formulated with rHuPH20; DL: 1600mg (2240mg, >=80kg); Cohort 5a: Ami-HC-CF 160 mg/ml co-formulated with rHuPH20; DL: 2560 mg (3360 mg, >=80kg)

Note: PK data cutoff 5 March 2024, clinical cut off 30 October 2023.

Figure 6: Mean concentration-time profiles of amivantamab after SC administration on cycle 2 day 1 (PALOMA)



Cohort 1A: Ami 50 mg/ml admixed with rHuPH20; DL: 1050 mg (1400 mg, >=80kg); Cohort 1B: Ami 50 mg/ml; DL: 1050 mg (1400 mg, >=80kg); Cohort 2A: Ami 160 mg/ml co-formulated with rHuPH20; DL: 1050 mg (1400 mg, >=80kg); Cohort 2B: Ami 160 mg/ml; DL: 1050 mg (1400 mg, >=80kg); Cohort 3A: Ami 160 mg/ml co-formulated with rHuPH20; DL: 1600 mg (2240 mg, >=80kg); Cohort 4A: HT Ami 160 mg/ml co-formulated with rHuPH20; DL: 1600mg (2240mg, >=80kg); Cohort 5A: Ami 160 mg/ml co-formulated with rHuPH20; DL: 2560 mg (3360 mg, >=80kg)

All participants were negative for antibodies to amivantamab post-dose. Nine participants (11.4%) were positive for treatment-emergent antibodies to rHuPH20, with titers up to 5120. The amivantamab PK profiles of these subject did not suggest an impact on amivantamab PK.

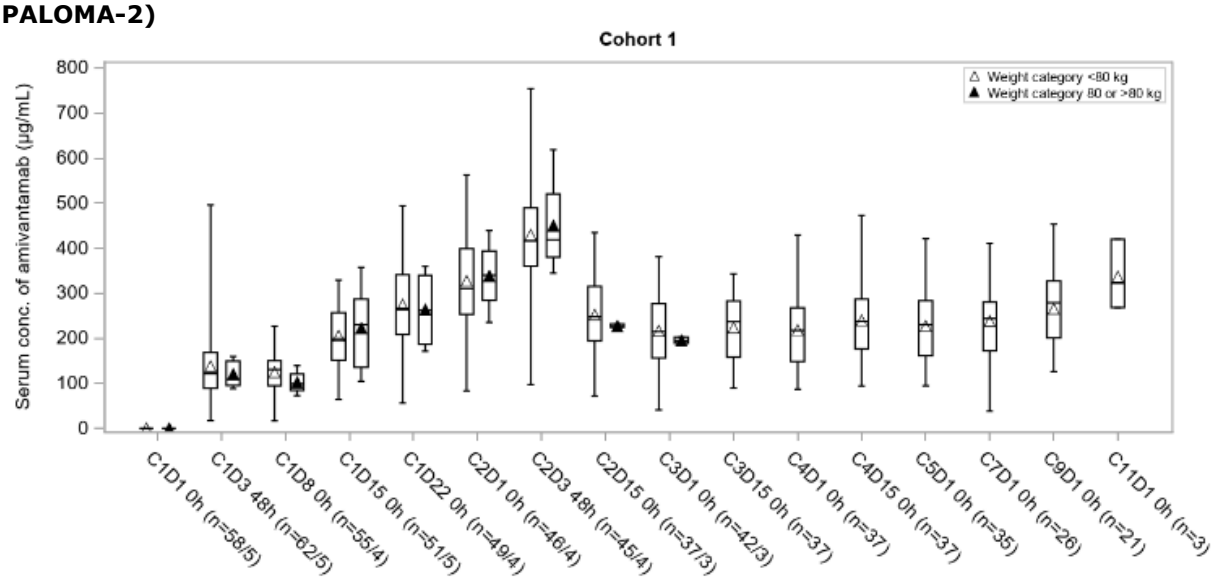
PALOMA-2 (Study 61186372NSC2002)

PALOMA-2 is an ongoing open-label, non-randomised, Phase 2 study to evaluate the safety, efficacy, and PK of amivantamab SC administered via manual injection in multiple combinations and treatment settings of participants with EGFR-mutated locally advanced or metastatic NSCLC. Characterisation of PK, with C2D1 Ctrough, was a secondary endpoint. Immunogenicity characterisation and lazertinib quantification were exploratory objectives.

In PALOMA-2 cohorts 1 and 6, amivantamab (material GEN1) was administered by manual SC injection in the abdomen at doses of 1600 mg (2240 mg if BW ≥80 kg) in cycle 1 QW, and Q2W from cycle 2, for 28-day cycles. Lazertinib was given orally 240 mg QD with or without food. In cohort 6, prophylactic anticoagulation was also given.

PK was available for 50 participants in Cohort 1 and 42 participants in Cohort 6 for Cycle 2 Day 1 mean Ctrough (SD), which was 328 (105) µg/mL in cohort 1 and 373 (100) µg/mL in cohort 6. Amivantamab concentrations by timepoint and cohort were also presented stratified by BW category, as exemplified for cohort 1 (Figure 7).

Figure 7: Box plot of serum amivantamab concentration by weight category for cohort 1 – (PALOMA-2)



Lazertinib exposure appeared similar between the 2 treatment arms (data not shown).

No treatment-emergent antibodies to amivantamab were observed. Eight participants in China were not evaluable due to concentrations above the drug tolerance limit (> 1000 µg/mL) and were excluded, while all samples analysed outside of China were within the assay drug tolerance limit.

13 participants (11.1%) were positive for treatment-emergent antibodies to recombinant human hyaluronidase PH20 (rHuHP20).

PALOMA-3 (Study 61186372NSC3004)

The primary objective for the EU regions was to assess the pharmacokinetic non-inferiority of amivantamab SC (Cycle 2 Day 1 and AUCD1-D15 at Cycle 2) via manual injection versus amivantamab IV. Amivantamab SC would be considered non-inferior to IV if the lower bound of the 90% CI for the ratio of the geometric means of pre-dose on Cycle 2 Day 1 [or C4D1 Ctrough for non-EU] and AUCD1-D15 in Cycle 2 was at least 80% (non-inferiority margin of 20%). In non-EU regions, non-inferiority of Ctrough at Cycle 4 Day 1 was a primary endpoint.

Lazertinib 240 mg was taken orally once daily with or without food. The amivantamab dosing schedule followed a 28-day cycle and was as follows:

Arm A: SC by manual injection into the abdomen

Cycle 1: 1600 mg (2240 mg if BW ≥80 kg) on Days 1, 8, 15, and 22.

From cycle 2: 1600 mg (2240 mg if BW ≥80 kg) on Day 1 and 15 of each subsequent 28-day cycle

Arm B: IV infusion

Cycle 1: 1050 mg (1400 mg if BW ≥80 kg) on Days 1 and 2 (split dose), 8, 15, and 22.

From cycle 2: 1050 mg (1400 mg if BW ≥80 kg) on Days 1 and 15 of each subsequent 28-day cycle.

Amivantamab GEN1 was given, 26 participants in PALOMA 3 switched from GEN1 after reaching Cycle 4 Day 1 or later, depending on when GEN2 was available.

Demographics and baseline disease characteristics were well balanced between the 2 treatment arms. 88% had BW <80 kg. The median (range) BW of the 418 enrolled participants was 63.2 kg (33-150).

The data cutoff date for this submission was 03 January 2024, when the last enrolled participant completed the Cycle 4 Day 1 visit. The PK evaluable dataset consisted of 206 subjects in the SC arm and 208 in the IV arm. The number of evaluable participants was however lower for the primary and secondary endpoints, ranging from 62.9 to 77.7% for C2D1 and C2 AUCD1-15, and was much lower for C4D1 (46.7 to 47.6%). Major protocol deviations were identified in 53 participants (25.7%) in the amivantamab SC+lazertinib and in 73 participants (34.4%) in the amivantamab IV+lazertinib. Any deviations to dose administration were considered a major protocol deviation, resulting in a higher number of major protocol deviations. The deviations for each of the EU co-primary endpoints are summarised in Table 9 and Table 10.

Table 9: Drop out from co-primary endpoint C2D1 Ctrough (PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Safety	206	210	416
Subjects who dropped out and excluded from evaluable PK analysis set[a]	46 (22.3%)	68 (32.4%)	114 (27.4%)
Reason for dropout from the PK primary endpoint evaluable analysis set for C_{trough} and EU Only	46 (22.3%)	68 (32.4%)	114 (27.4%)
PK Sample not available	40 (19.4%)	47 (22.4%)	87 (20.9%)
Injection/Infusion interrupted	1 (0.5%)	23 (11.0%)	24 (5.8%)
Drug delayed within the cycle	2 (1.0%)	6 (2.9%)	8 (1.9%)
Dose reduction	4 (1.9%)	2 (1.0%)	6 (1.4%)
Dose withdrawn	1 (0.5%)	1 (0.5%)	2 (0.5%)

Key: IV=Intravenous; SC=Subcutaneous
Note: Subjects can be counted in more than one category.
[a] The definition of PK primary endpoint evaluable analysis set is that all randomized participants who receive all doses in Cycle 1, without dose modifications and provide Cycle 2 Day 1 Ctrough
Note: Percentages are calculated with the number of subjects in the safety analysis set in each treatment group as the denominators
Note: This table includes subjects who dropped out or were excluded from the PK Evaluable Analysis Set, and does not account for subjects who may have been excluded from the analysis due to below quantifiable serum concentrations

Table 10: Drop out from co-primary endpoint C2 AUCD1-15 (PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Safety	206	210	416
Subjects who dropped out and excluded from evaluable PK analysis set[a]	56 (27.2%)	78 (37.1%)	134 (32.2%)
Reason for dropout from the PK primary endpoint evaluable analysis set for cycle 2 AUC_{D1-D15}	56 (27.2%)	78 (37.1%)	134 (32.2%)
PK Sample not available	33 (16.0%)	47 (22.4%)	80 (19.2%)
Injection/Infusion interrupted	1 (0.5%)	24 (11.4%)	25 (6.0%)
Participants with Cycle delay	14 (6.8%)	11 (5.2%)	25 (6.0%)
Dose reduction	9 (4.4%)	8 (3.8%)	17 (4.1%)
Drug delayed within the cycle	7 (3.4%)	8 (3.8%)	15 (3.6%)
Dose withdrawn	1 (0.5%)	1 (0.5%)	2 (0.5%)

Key: IV=Intravenous; SC=Subcutaneous
Note: Subjects can be counted in more than one category.
[a] The definition of PK primary endpoint evaluable analysis set is all randomized participants who receive all doses without modifications up to Cycle 2 Day 1, and provide all necessary PK samples to derive primary PK endpoint Cycle 2 AUCD1-D15
Note: Percentages are calculated with the number of subjects in safety analysis set in each treatment group as the denominators
This table includes subjects who dropped out or were excluded from the PK Evaluable Analysis Set, and does not account for subjects who may have been excluded from the analysis due to below quantifiable serum concentrations

Overall, amivantamab SC resulted in non-inferior PK parameters compared with amivantamab IV (Table 11). As a low number of participants were evaluable for the Cycle 4 Ctrough co-primary endpoint (non-EU), a hybrid endpoint was implemented using the population PK model.

Table 11: Summary of PK Results of Amivantamab SC Versus Amivantamab IV (PALOMA-3)

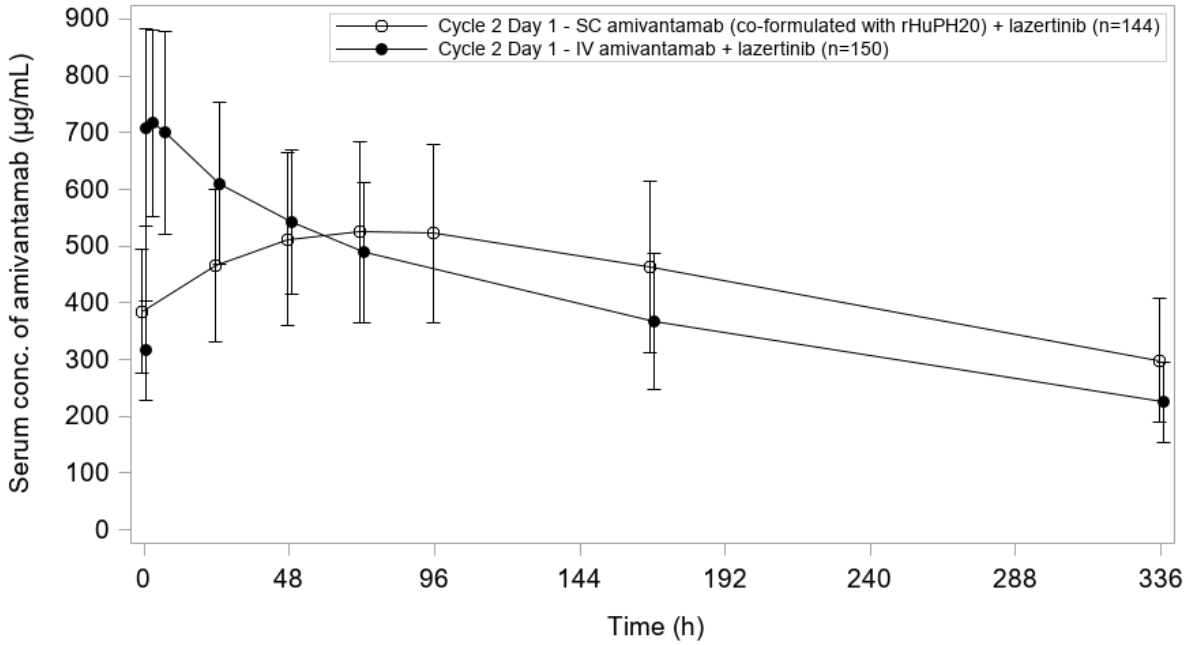
Parameter	Geometric Mean Arm A (SC) (Test)	Arm B (IV) (Reference)	Geometric Mean Ratio	90% CI
Cycle 2 Day 1 C_{trough}, µg/mL [EU co-primary]				
N	160	142	-	-
C_{trough}, µg/mL	335	293	1.145	1.040 – 1.261
Cycle 2 AUC_{D1-D15}, µg·h/mL [co-primary]				
N	140	132		
AUC_{D1-D15}, µg·h/mL	135861	131704	1.032	0.976 – 1.090
Observed Cycle 4 Day 1 C_{trough}, µg/mL [non-EU co-primary]				
N	98	98		
C_{trough}, µg/mL	206	144	1.427	1.266 – 1.610
Hybrid (Observed and Model-Predicted) Cycle 4 Day 1 C_{trough}, µg/mL [non-EU co-primary]				
N	157[a]	134 [a]		
C_{trough}, µg/mL	205	145	1.417	1.294 – 1.551
Model-Predicted Cycle 4 AUC_{D1-D15}, µg·h/mL [secondary]				
N	150	132		
AUC_{D1-D15}, µg·h/mL	97414	88280	1.104	1.045 – 1.165

Arm A: amivantamab SC 1600 mg (2240 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+ and lazertinib 240 mg PO QD. Arm B: amivantamab IV 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+ and lazertinib 240 mg PO QD. AUCD1-D15=area under the concentration-time curve from Day 1 to 15; BW=body weight; CI=confidence interval; Ctrough=trough concentration; IV=intravenous; N=number of observations;

PK=pharmacokinetic; PO=orally; Q2W=every 2 weeks; QD=daily; QW=every week; SC=subcutaneous. [a] SC n=59 and IV n=36 are model-predicted.

There is substantial overlap of amivantamab concentrations in participants in the amivantamab SC+lazertinib arm and participants in the amivantamab IV+lazertinib arm at similar timepoints, with the exception of the higher concentrations observed on the first day after IV administration, as depicted for cycle 2 (Figure 8). Lazertinib exposure appeared similar between the 2 treatment arms.

Figure 8: Mean Serum Concentration-time Curves of Amivantamab for Cyle 2 (PALOMA-3)



For both administration routes, following the BW tiered posology, subjects >80 kg had PK parameters in the same range as subjects <80 kg (Table 12).

Table 12: Amivantamab PK Parameters by Weight Group

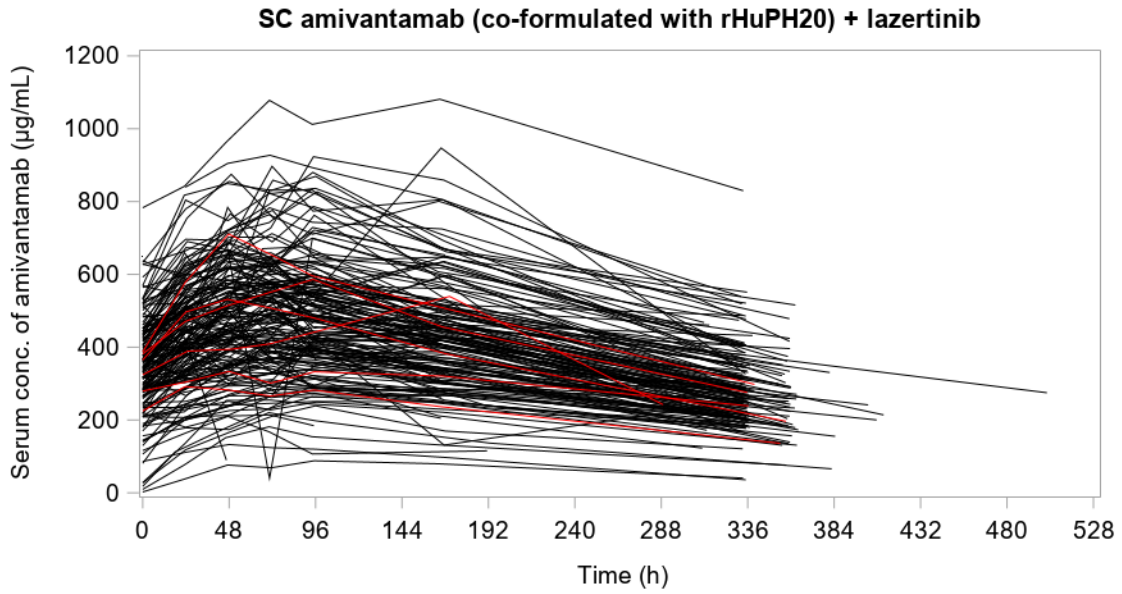
Pharmacokinetics of amivantamab (arithmetic mean [SD])	Weight category <80 kg, SC amivantamab (co-formulated with rHuPH20) + lazertinib	Weight category <80 kg, IV amivantamab + lazertinib	Weight category 80 kg or >80 kg, SC amivantamab (co-formulated with rHuPH20) + lazertinib	Weight category 80 kg or >80 kg, IV amivantamab + lazertinib
Cycle 2 Day 1				
n	142[a]	124[b]	18[c]	19[d]
Observed C_{trough}, µg/mL	366 (123)	316 (103)	354 (89.2)	305 (71.3)
Observed $AUC_{(D1-D15)}$, µg.h/mL	142684 (43842)	136640 (33728)	138501 (43672)	129081 (24160)
Cycle 4 Day 1				
n	140[e]	115[f]	17[g]	19[h]
Observed C_{trough}, µg/mL	225 (90.2)	164 (66.5)	215 (68.0)	150 (71.7)
Model-predicted C_{trough}, µg/mL	221 (79.9)	160 (60.0)	166 (27.5)	128 (25.2)
Observed and Model-predicted C_{trough}, µg/mL	223 (86.1)	163 (64.6)	201 (62.4)	144 (62.9)
Model-predicted $AUC_{(D1-D15)}$, µg.h/mL	102041 (30236)	91630 (23234)	98881 (27690)	87511 (20657)

[a] n=125 for Observed $AUC_{(D1-D15)}$.
[b] n=113 for Observed $AUC_{(D1-D15)}$.
[c] n=15 for Observed $AUC_{(D1-D15)}$.
[d] n=18 for Observed C_{trough}.
[e] n=133 for Model-predicted $AUC_{(D1-D15)}$, n=86 for Observed C_{trough}, and n=54 for Model-predicted C_{trough}.
[f] n=113 for Model-predicted $AUC_{(D1-D15)}$, n=84 for Observed C_{trough}, and n=31 for Model-predicted C_{trough}.
[g] n=12 for Observed C_{trough} and n=5 for Model-predicted C_{trough}.
[h] n=14 for Observed C_{trough} and n=5 for Model-predicted C_{trough}.

Treatment-emergent ADA were observed in 1 (0.6%) participant with a titer of 1:20 in the SC arm, while none was positive in the IV arm. Participants for whom ADA samples had drug concentrations greater than the assay drug tolerance limit (>200 µg/mL for China and >1,000 µg/mL non-China) were not considered evaluable (n=18 for amivantamab SC+lazertinib and n=11 amivantamab IV+lazertinib). Overall, the baseline screening false positive rate was 1.0%.

Among the 193 rHuPH20 immunogenicity-evaluable participants, 7 were positive at baseline, but did not boost post-baseline. Treatment-emergent antibodies to rHuPH20 were observed in 15 (7.8%) participants. The highest titer was 1:80 in 2 subjects. 7 subjects were positive at the timepoint of their last samples, while the remaining 9 subjects had transient antibodies to rHuPH20. PK profiles stratified by antibodies to rHuPH20 status are presented in Figure 9. Overall immunogenicity to rHuPH20 across studies is presented in Table 13.

Figure 9: Serum Amivantamab Concentrations at Cycle 2 Day 1 by rHuPH20 ADA Status (PALOMA-3)



All samples (including samples excluded from descriptive statistics) are shown in the plot. Red lines represent participants with positive rHuPH20 ADA status at Cycle 2 Day 1.

Table 13: Summary of the Incidence of Antibodies to rHuPH20

Study Number	Participants With Appropriate Samples[a]	Participants Positive for Treatment-emergent Antibodies to rHuPH20[b,c]	Participants Negative for Treatment-emergent Antibodies to rHuPH20[d]
61186372NSC1003 (PALOMA)			
Cohort 1a	8	1 (12.5)	7 (87.5)
Cohort 2a	9	2 (22.2)	7 (77.8)
Cohort 3a	21	2 (9.5)	19 (90.5)
Cohort 4a	19	1 (5.3)	18 (94.7)
Cohort 5a	22	3 (13.6)	19 (86.4)
Total	79	9 (11.4)	70 (88.6)
61186372NSC2002 (PALOMA-2)			
Cohort 1	66	9 (13.6)	57 (86.4)
Cohort 6	51	4 (7.8)	47 (92.2)
Total	117	13 (11.1)	104 (88.9)
61186372NSC3004 (PALOMA-3)			
amivantamab SC + lazertinib arm	193	15 (7.8)	178 (92.2)

rHuPH20=recombinant human hyaluronidase; SC=subcutaneous.

[a] Participants with appropriate samples had 1 or more samples obtained after their first rHuPH20 administration.

[b] Denominator is number of participants with appropriate samples for antibodies to rHuPH20.

[c] Participants positive for treatment-emergent antibodies to rHuPH20 includes all participants who were positive (treatment-boosted or treatment-induced) at any time after their first rHuPH20 administration. Participants with baseline positive samples and without 2-fold increased titer after treatment are not considered treatment-boosted.

[d] Includes all participants with negative samples at all times and excludes participants who were treatment-emergent positive at any time.

GEN1 vs GEN2 amivantamab

Amivantamab was produced by 2 different production processes using the same cell line; GEN1 process and GEN2 process.

Drug products manufactured with both GEN1 and GEN2 drug substances were used to support clinical studies PALOMA, PALOMA 2, and PALOMA 3. GEN2 material is intended to be used in the commercial SC product (no change for the IV product at present).

Table 14: PK Parameters of Amivantamab GEN1 and GEN2

PK Parameter	GEN2	GEN1	GMR (90% CI)
	Geometric Mean		
Cycle 2 Day 1			
C_{trough} (µg/mL)	396	364	1.086 (0.922 - 1.279)
C_{max} (µg/mL)	548	580	0.944 (0.816 - 1.093)
AUC_{τ} (µg.h/mL)	147533	147070	1.03 (0.855 - 1.178)

AUC_{τ}=area under the plasma concentration-time curve from time of administration up to the end of the dose interval; CI=confidence interval; C_{max}=maximum observed serum (or other biological fluids) concentration; C_{trough}=observed serum (or other biological fluids) concentration immediately prior to the next administration; ; GMR=geometric mean ratio; PK=pharmacokinetic.

A comparison of GEN1 and GEN2 showed Cycle 4 Day 1 C_{trough} was comparable, with 217 µg/mL for GEN2 and 206 µg/mL for GEN1, with GMR of 1.05 (90%CI 0.887-1.251).

Distribution

Based on the individual parameter estimates for 396 participants with NSCLC who received amivantamab SC from studies PALOMA-3, PALOMA-2, and PALOMA, the geometric mean (geometric CV%) of total volume of distribution (V1+V2) was 5.69 L (23.8%) (Table 5).

Elimination

The geometric mean (geometric CV%) of individual parameter estimates of nonspecific linear clearance from the model was 0.224 L/day (26.0%), associated with a terminal half-life of 18.8 days (34.3%) (Table 5).

Special populations

In the population PK analysis, BMI was identified as a statistically significant covariate on SC bioavailability (F) and age was identified as a statistically significant covariate on absorption rate (K_a). When BMI increased from 17.8 to 32.1 kg/m2, F decreased from 73% to 62%, suggesting that obesity may be associated with a small and not clinically meaningful decrease in F. When age increased from 43 to 78 years, K_a decreased from 0.021 to 0.015 h^{-1} corresponding to a minimal increase of $T_{max,ss}$

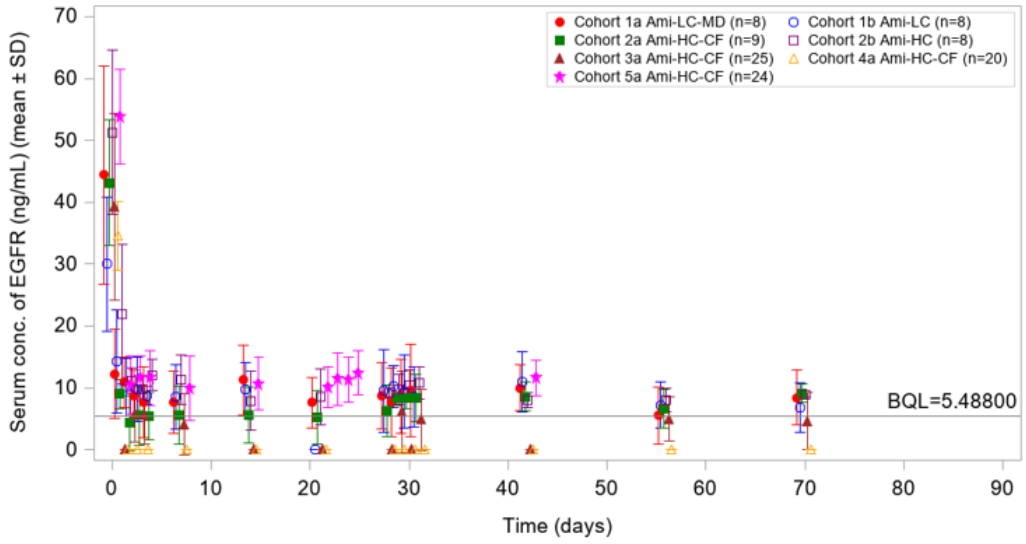
(from 3.0 to 3.5 days for SC Q2W). This suggests that absorption may be slightly slower in older individuals, but the extent of absorption was not affected by age.

Consistent with previous findings from IV administration of amivantamab, with weight-tiered dosage, no further dose adjustments are needed for any other covariates/special populations.

2.5.2.2. Pharmacodynamics

In Study PALOMA, serial serum EGFR and cMET concentrations were collected to assess target engagement. After SC administration of amivantamab, mean serum EGFR and cMET concentrations decreased substantially, reaching near complete saturation after the full first dose, and remained suppressed for the duration of treatment for all cohorts (Figure 10 and Figure 11). Saturation of the serum soluble targets as a surrogate for whole body target engagement was established previously with amivantamab IV. The saturation of EGFR and cMET appears comparable between GEN1 and GEN2 drug substances. No PD data are available for Studies PALOMA-3 and PALOMA-2.

Figure 10: Mean (±SD) serum concentrations of EGFR (study PALOMA)



BQL=below quantification limit; BW=body weight; EGFR=epidermal growth factor receptor; GEN1=low titer drug substance; GEN2=high titer drug substance; HC=high concentration (160 mg/mL); HC-CF=high concentration co-formulated with rHuPH20; LC=low concentration (50 mg/mL); LC-MD=low concentration mix-and-deliver with rHuPH20; LLOQ=lower limit of quantification; Q2W=every 2 weeks; Q3W=every 3 weeks; QW=every week; SC=subcutaneous; SD=standard deviation.

LLOQ is 5.48800 ng/mL.

Cohort 1a: GEN1 amivantamab LC-MD SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.

Cohort 1b: GEN1 amivantamab LC SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.

Cohort 2a: GEN1 amivantamab HC-CF SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.

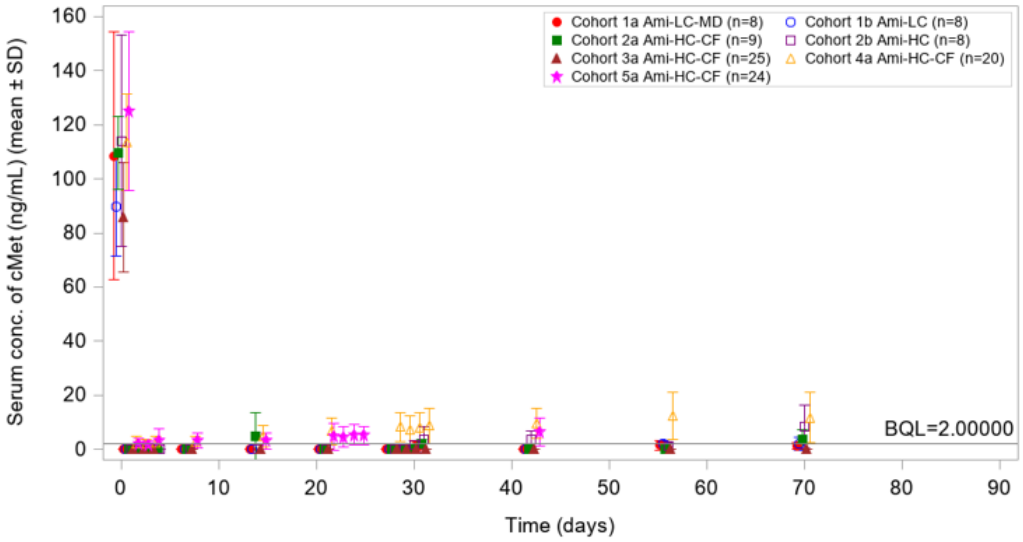
Cohort 2b: GEN1 amivantamab HC SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.

Cohort 3a: GEN1 amivantamab HC-CF SC 1600 mg (2240 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.

Cohort 4a: GEN2 amivantamab HC-CF SC 1600 mg (2240 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.

Cohort 5a: GEN1 amivantamab HC-CF SC 2560 mg (3360 mg if BW ≥80 kg) QW in Cycle 1 and Q3W in Cycles 2+.

Figure 11: Mean serum concentrations of cMET (study PALOMA)



BQL=below quantification limit; BW=body weight; cMET=cleaved hepatocyte growth factor receptor gene; conc.=concentrations; GEN1=low titer drug substance; GEN2=high titer drug substance; HC=high concentration (160 mg/mL); HC-CF=high concentration co-formulated with rHuPH20; LC=low concentration (50 mg/mL); LC-MD=low concentration mix-and-deliver with rHuPH20; LLOQ=lower limit of quantification; Q2W=every 2 weeks; Q3W=every 3 weeks; QW=every week; SC=subcutaneous; SD=standard deviation.
LLOQ is 2.0000 ng/mL.
Cohort 1a: GEN1 amivantamab LC-MD SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.
Cohort 1b: GEN1 amivantamab LC SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.
Cohort 2a: GEN1 amivantamab HC-CF SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.
Cohort 2b: GEN1 amivantamab HC SC 1050 mg (1400 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.
Cohort 3a: GEN1 amivantamab HC-CF SC 1600 mg (2240 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.
Cohort 4a: GEN2 amivantamab HC-CF SC 1600 mg (2240 mg if BW ≥80 kg) QW in Cycle 1 and Q2W in Cycles 2+.
Cohort 5a: GEN1 amivantamab HC-CF SC 2560 mg (3360 mg if BW ≥80 kg) QW in Cycle 1 and Q3W in Cycles 2+.

Exposure-response analysis

The strategy for the development of amivantamab SC assumes that the SC regimens can provide sufficient efficacy if the C_{trough} is noninferior to the approved IV regimens. Therefore, the exposure-response (E-R) analysis focused on safety endpoints and was conducted on data from participants who received amivantamab SC in study PALOMA-3. The E-R relationships for all safety endpoints (binary endpoints) were evaluated using bar plots, stratified by exposure quartiles.

Event rates of hypoalbuminemia and paronychia slightly increased with increase of exposure. There were no apparent relationships for other endpoints, including administration-related reaction, rash, nausea, constipation, stomatitis, and interstitial lung disease, with exposure. Analysis of venous thromboembolic event (VTE) rate was not conducted due to an event rate being <10%.

2.5.3. Discussion on clinical pharmacology

Methods

The ECLIA for amivantamab, MS method for lazertinib, and the original ADA assay for amivantamab were adequately validated and showed adequate performance of the within study validation.

The updated amivantamab ADA assay MTD269 was used for non-Chinese samples in studies PALOMA-2 and PALOMA-3. In these, the screening false positive rate was lower than 5%, ie 0.6 and 1%,

respectively. This indicates the validation cutpoint is not adequate for use in these studies. This deviation could be study specific, but could also be caused by the method update, where no new cutpoint was determined. Of note, the false positive rate is within the acceptable range for samples from PALOMA-2 and 3 analysed in China using the "old" method. In consequence, study samples analysed with MTD269 are at risk of not being screened positive (see below in the absorption discussion for mitigation).

The rHuPH20 antibody method is adequately validated and cross-validated using state of the art methodology and shows adequate sensitivity and lack of interference. Study sample analysis was adequate for rHuPH20 antibodies.

The population PK model for amivantamab following IV and SC administration was used to derive PK endpoints at Cycle 4 ($C_{trough,C4D1}$ and $AUC_{D1\text{-}D15,C4}$) for noninferiority tests in study PALOMA-3. That would normally be considered a high impact model analysis; however, since CHMP advised against the use of a Cycle 4 parameter as co-primary endpoint (EMA/SA/0000080094), the co-primary endpoints for EU were C_{trough} pre-dose on Cycle 2 Day 1 ($C_{trough,C2D1}$) and Cycle 2 $AUC_{D1\text{-}D15}$, and the statistical analyses of these endpoints did not require support by the population PK model. Hence, the model analysis has low impact in the current procedure (is mainly descriptive), and the above-mentioned simulations are out-of-scope and not reported.

The starting model for amivantamab following IV and SC (mainly Q2W) administration was informed by previously developed population PK models for amivantamab following IV administration. The same structural model for disposition and elimination was used (2-compartment model with parallel linear and nonlinear elimination), adding a first-order absorption with lag time for SC administration. All covariate relationships from the IV models (for disposition and elimination) were retained in the IV+SC model. In addition, covariates were evaluated on SC absorption parameters (F and K_a): BMI was identified as a covariate on F (a higher BMI is associated with a decrease in bioavailability), and age was identified as a covariate on K_a (a higher age is associated with a slightly slower absorption rate). Both BMI and age are common covariates for SC absorption of mAbs and neither of the covariates are considered to have a clinically relevant effect on the exposure of amivantamab following SC administration. Since only a limited number of participants received product containing GEN2 process material, the applicant conducted a separate covariate testing to evaluate potential PK differences between GEN1 and GEN2 process material. The effect of process material on CL, F, and K_a was tested individually; the effect was not statistically significant on any of the parameters ($p=0.01$).

Disposition and elimination population parameter estimates in the final IV+SC model are overall similar to those reported for the previously developed IV models, except for K_m (the Michaelis-Menten constant) which is much higher in the IV+SC model compared to the IV models (18.4 µg/mL compared to 1.86 µg/mL in the MARIPOSA analysis (see procedure EMEA/H/C/005454/II/0013) and 3.71 in the PAPPILON and MARIPOSA-2 analyses (see procedures EMEA/H/C/005454/II/0010 and EMEA/H/C/005454/II/0011), respectively). The higher estimate indicates that there is more information on the nonlinear elimination in the SC data than in the IV data alone. A larger between-subject variability in exposure is expected following SC administration than following IV administration. This could potentially lead to more subjects with concentrations in the nonlinear range after SC administration than after IV administration, even if noninferiority is achieved with respect to the geometric mean values. In the side-by-side comparison of individual predictions of PK metrics for participants in PALOMA-3, following SC and IV administration, respectively, lower through concentrations following SC administration are not a major issue.

The η-shrinkage is around 20% for several parameters (F, V_1, and V_2), which implies that the true variability in the population is likely slightly larger than the variability reported based on post-hoc estimates. Nevertheless, since total volume of distribution and terminal elimination half-life are derived

parameters, it is acceptable to base information on these parameters (in section 5.2 of the SmPC) on individual (post-hoc) parameter estimates. The reported estimate of linear CL can be based on individual parameter estimates, since it reflects the clearance in the target patient population, considering both covariate distributions and correlation between covariates, and it uses the same method as the reported terminal half-life. The same argument can also apply to the reported estimate of SC bioavailability.

The pcVPC stratified on route of administration indicate that the model overpredicts concentrations at later time points, following both SC and IV administrations. However, since amivantamab is administered every second week, the focus should be on the first two weeks after dose, and the model provides adequate predictions of concentrations up to 3-4 weeks after dose. The overpredictions at later time points are hence not considered an issue.

The forest plots demonstrated that the study PALOMA-2 Cohorts 1 and 6 (population similar to the study MARIPOSA population) had similar exposure as the study PALOMA-3 population, supporting the extrapolation of PK noninferiority from study PALOMA-3 population to study MARIPOSA population.

Absorption

PALOMA provides support for the dose selection for SC administration of amivantamab and the selection of the formulation including rHuPH20. The dose of 1600 mg (2240 mg≥80 kg) was selected for the posologies given Q2W after cycle 1 and used without further modifications in the later studies PALOMA-2 and PALOMA-3. The calculated bioavailabilities in PALOMA are only indicative as they are comparisons between studies. Ctrough at C2D1 was in a similar range across all three PALOMA studies.

The exposure of amivantamab SC appears to increase in a less than a dose proportional manner after the first dose. Furthermore, Km is much higher in the IV+SC model compared to the IV models, implying that PK may not be dose proportional between the lower SC dose of 1050 mg (1400 mg ≥80 kg) and the proposed SC dose of 1600 mg (2240 mg ≥80 kg).

It is agreed that PK data show a reasonable comparability between the processes GEN1 and GEN2, even if slightly out of standard BE margins. This together with analytical comparability is sufficient to support the use of GEN2 material in the commercial product.

The design of PALOMA-3 and particularly the choice of co-primary PK endpoints were the topic of a scientific advice (EMA/SA/0000080094). The study design and the EU endpoints are in line with the given advice to demonstrate non-inferiority of the selected dose of amivantamab SC vs IV. The PK of the excipient rHuPH20 was not investigated in this study, which is acceptable, given its low systemic exposure, as reported in the literature. As lazertinib does not have an impact on the PK of amivantamab, the results of this study can be extrapolated to the monotherapy setting.

As noted in the scientific advice, it is unsurprising to note the number of major protocol deviations as the PK endpoints were to be determined in patients who did not deviate from the planned posology. This is acceptable. Of note, the proportion of missing data due to interruption of infusion or injection was higher for the IV arm, which is expected. This also contributes to the higher missingness in the IV arm.

It is agreed that PK non-inferiority of amivantamab SC vs IV has been demonstrated for the totality of the dataset for amivantamab GEN1. Additionally, data stratified by BW supports both SC posologies (1600 mg for < 80kg and 2240 mg for ≥ 80 kg), which is also in line with data from PALOMA-2 stratified by BW.

The section 5.2 of the SmPC presents data from PALOMA-3 for the two co-primary endpoints. It was clarified that these (EU endpoints) were the basis for the demonstration of non-inferiority.

All three PALOMA studies used slow SC injection in the abdomen. This is adequately reflected in section 4.2 of the SmPC where the recommendation is to inject in the abdomen over approximately 5 minutes as no data are available for other injection sites.

The lack of data on rHuPH20 exposure is acceptable, given previous reports of lack of systemic exposure.

It is agreed that immunogenicity against amivantamab was low in PALOMA, in line with previous data with IV administration, however some uncertainty remains on the results from PALOMA-2 and PALOMA-3 due to the use of a low cutpoint. Taking into consideration the low immunogenicity of amivantamab IV, even if the immunogenicity of amivantamab after SC administration was slightly higher, it is still expected to be low and to lack clinical relevance, and this has been reflected in section 5.1 of the SmPC.

No impact of treatment-emergent antibodies to rHuPH20 on the PK of amivantamab was observed in any of the studies.

No difference in amivantamab ADA between GEN1 and GEN2 was noted in PALOMA, however the sample size is quite limited. It is unclear what cutpoint was used for the individual patients as different types of cancer had different cutpoints in the validation, and this study has a mixed population. This is an additional uncertainty. However, the data is consistent with previous conclusions that amivantamab has low immunogenicity. Immunogenicity data is adequately reflected in section 5.1 of the SmPC.

Distribution

The geometric mean total volume of distribution (5.69 L (23.8%)) indicates that amivantamab SC is confined in the vascular system with limited extravascular tissue distribution as observed with amivantamab IV.

Elimination

The parameters presented in section 5.2 of the SmPC, the estimated geometric mean (% CV) linear CL and associated-terminal half-life (0.224 L/day (26.0%) and 18.8 days (34.3%) are acceptable.

Special populations

The SmPC text in section 4.2 regarding renal and hepatic impairment is identical to that of the IV product, which is acceptable. In section 5.2, the data presented is from the popPK analysis for the SC formulation only, with the same conclusions as for the IV product. The route of administration (RoA) is not expected to affect the PK in patients with organ impairment. Thus for consistency, the reference to Rybrevant subcutaneous formulation was replaced with amivantamab only, without specification of RoA.

Missed dose

The SmPC text in section 4.2 regarding missed dose is different from that of the IV product. For the SC formulation it is stated that if a dose is missed between Weeks 1 to 4, it should be administered within 24 hours, while if a dose is missed from Week 5 onward, it should be administered within 7 days. Otherwise, the missed dose should not be administered, and the next dose should be administered per the usual dosing schedule. This strategy is reasonable, given the alterations of the PK profile when amivantamab is administered SC compared with IV.

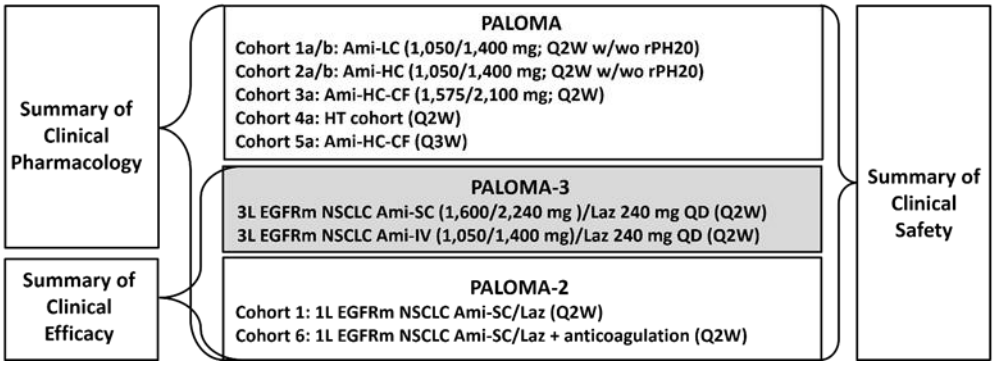
2.5.4. Conclusions on clinical pharmacology

The PK of amivantamab after subcutaneous administration is well-described and non-inferiority to IV amivantamab has been demonstrated for the proposed Q2W posology. The lack of interaction between amivantamab and lazertinib (see procedure EMEA/H/C/005454/II/0013) ensures extrapolation to all other indications with Q2W treatment with amivantamab.

2.5.5. Clinical efficacy

In support of the use of amivantamab SC for the treatment of NSCLC, this section presents efficacy results from the pivotal Phase 3 PALOMA 3 study and from Cohort 1 and Cohort 6 (Q2W) of the Phase 2 PALOMA-2 study.

Figure 12: Overview of the Clinical Studies



The pivotal Phase 3 study PALOMA-3 is presented in the grey shaded box.

1L: first-line; 3L: third-line; Ami: amivantamab; EGFRm: epidermal growth factor receptor with exon 19 deletions or exon 21 L858R substitution mutations; HC: high concentration; IV: intravenous; Laz: lazertinib; LC: low concentration; NSCLC: non-small cell lung cancer; QD: once daily; QxW: every x weeks; SC: subcutaneous; w/wo: with or without

2.5.5.1. Dose response study(ies)

The selection of the recommended RP2D for amivantamab SC Q2W were based on the totality of PK, PD, and safety data from the PALOMA study.

A preliminary PK modeling and simulation, supported by observed data, was used to determine a Q2W target dose that was predicted to achieve non-inferior steady state exposure levels as observed at the IV Q2W RP2D level. The amivantamab SC Q2W RP2D was determined to be 1,600 mg for participants with a BW <80 kg and 2,240 mg for participants with a BW ≥80 kg. This proposed dose was studied and confirmed in PALOMA Cohort 3a, in which the resulting exposure was non-inferior to those observed for the approved IV Q2W dose.

In addition, soluble EGFR and MET saturation, which serves as a surrogate for total body target engagement, was observed at this dose.

The SC Q2W RP2D was subsequently studied in PALOMA-3 and PALOMA-2 Q2W cohorts. Additionally, data from the PALOMA study demonstrated the feasibility of a single day- infusion of amivantamab SC for the first dose, with a lower incidence of IRRs (18.7% overall and 0 Grade ≥3) than previously reported with amivantamab IV (65.9% overall and 2.3% Grade ≥3).

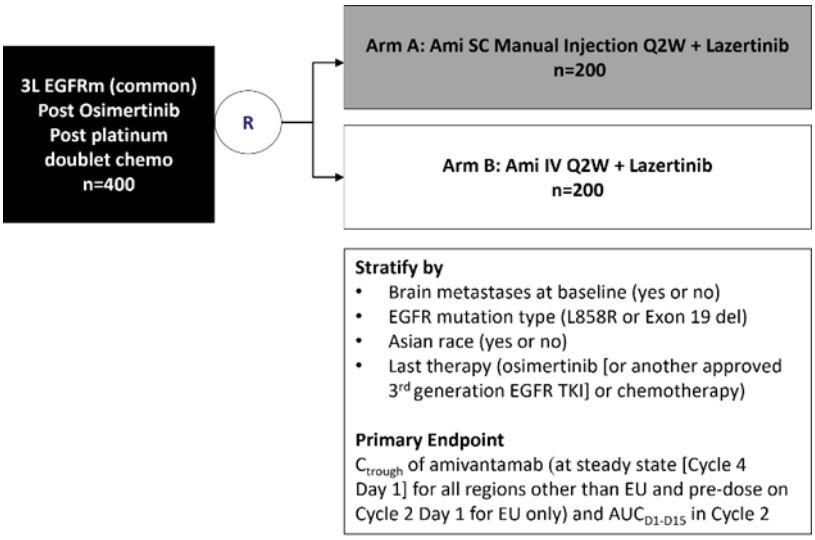
On this basis the studied SC Q2W dose was 1,600 (BW <80 kg)/2240 (BW ≥80 kg) mg amivantamab on Cycle 1 Days 1, 8, 15 and 22, then on Days 1 and 15 of each 28-day cycle starting at Cycle 2.

2.5.5.2. Main study(ies)

PALOMA-3 Study

This is a Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy.

Figure 13: Schematic Overview of the PALOMA-3 Study



Ami=amivantamab; AUCD1-D15=area under the curve Day1-Day15; Ctrough=trough concentration; EGFR=epidermal growth factor receptor; EGFRm=epidermal growth factor receptor mutated; exon 19del=exon 19 deletion; L858R=exon 21 L858R substitution; IV=intravenous; 3L=third line; R=randomized; SC=subcutaneous; Q2W=every 2 weeks; TKI=tyrosine kinase inhibitor

Cycles are 28 days.
Cycle 1 for IV: Days 1-2 (Day 2 applies to IV split dose only), 8, 15, and 22. Cycle 1 for SC: Days 1, 8, 15, and 22
Cycle 2 for all: Days 1, 15

Methods

Study Participants

The study participants are patients with NSCLC with Exon 19 deletions and Exon 21 L858R mutations in EGFR who have progressed on or after both a third generation TKI and platinum-based chemotherapy.

Key eligibility criteria for inclusion in the study were as follows:

- ≥18 years of age (or the legal age of consent in the jurisdiction in which the study took place) at the time of informed consent.

- Histologically or cytologically confirmed, advanced, or metastatic locally NSCLC characterized by either EGFR Exon 19del or Exon 21 L858R mutation.
- Have progressed on or after osimertinib (or another approved 3rd generation EGFR-TKI) and
- platinum-based chemotherapy.
- Have measurable lesion according to RECIST v1.1.
- Have ECOG performance status 0 or 1.
- With adequate organ and bone marrow function.

Participants having received cytotoxic, investigational, or targeted therapies beyond one regimen of platinum-based chemotherapy and EGFR inhibitors were excluded from participation in the study.

Treatments

To study the non-inferiority of amivantamab SC versus IV the following treatment regimens were administered:

- Amivantamab SC+lazertinib arm: up to Cycle 2 Day 1, amivantamab was administered subcutaneously via manual injection once weekly at a dose of 1600 mg (2240 mg if body weight was ≥80 kg). Starting at Cycle 2, amivantamab was administered subcutaneously by manual injection at a dose of 1600 mg (2240 mg if BW was ≥80 kg) on Day 1 and 15 of each 28-day cycle. Lazertinib was administered once daily at a dose of 240 mg.
- Amivantamab IV+lazertinib arm: up to Cycle 2 Day 1, amivantamab was administered intravenously (with the first dose split over Days 1-2) once weekly at a dose of 1050 mg (1400 mg if body weight was ≥80 kg). Starting at Cycle 2, amivantamab was administered intravenously at a dose of 1050 mg (1400 mg if body weight was ≥80 kg) on Day 1 and 15 of each 28-day cycle. Lazertinib was administered once daily at a dose of 240 mg.

Study treatment was planned to be continued until documented clinical or radiographic progression.

Objectives

The primary objective was to assess the pharmacokinetic non-inferiority of amivantamab SC (Ctrough at Cycle 4 Day 1 or Cycle 2 Day 1 and AUCD1-D15 at Cycle 2) via manual injection versus amivantamab IV.

Key secondary objectives were to assess efficacy (ORR and PFS) and safety of the different administrations.

Outcomes/endpoints

Primary endpoints

The co-primary PK non-inferiority endpoints are defined as follows:
- Ctrough on Cycle 4 Day 1 (non-EU and other applicable regions)
- Ctrough pre-dose on Cycle 2 Day 1 (EU and other applicable regions)
- AUCD1-D15 in Cycle 2 (for all regions)

If the "non-inferiority" of the amivantamab SC relative to amivantamab IV was claimed and the lower bounds of the 90% CI for the ratio of the geometric means of amivantamab SC vs amivantamab IV

were at least 80% (non-inferiority margin of 20%) for both Ctrough and AUCD1-D15 in Cycle 2, then non-inferiority based on key secondary endpoints were tested.

Secondary endpoints
-ORR

-PFS

-Safety

Other Secondary Objectives

- To assess amivantamab pharmacokinetics and immunogenicity to amivantamab or rHuPH20 in participants treated with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B)

- Patient-Reported-Outcome (PRO)

Exploratory endpoints

-OS

-Patient-Reported-Outcome (PRO)

Sample size

Number of Participants (planned and analysed)

Approximately, 400 eligible participants were to be randomised 1:1 between amivantamab SC+lazertinib and amivantamab IV+lazertinib.

The sample size of 400 participants was selected to accommodate the assessment of the key secondary efficacy endpoint of ORR. With a 1:1 randomisation, the sample size of 400 participants (200 participants per arm) would provide a power of 80% to demonstrate the "non-inferiority" of amivantamab SC compared with amivantamab IV (both on a background of lazertinib), with a non-inferiority margin of 60% and a one-sided alpha of 0.025, assuming the true ORR is the same for both treatment arms.

The efficacy analyses for the study were performed on the Full Analysis Set (all participants who were randomised in the study).

A total of 418 participants were actually randomised in the study in 1:1 ratio between arms A and B.

Randomisation and blinding (masking)

Due to differences in safety profile, safety monitoring, premedication requirements, and administration, blinded study treatment and a placebo control was not used.

Statistical methods

Statistical hypotheses

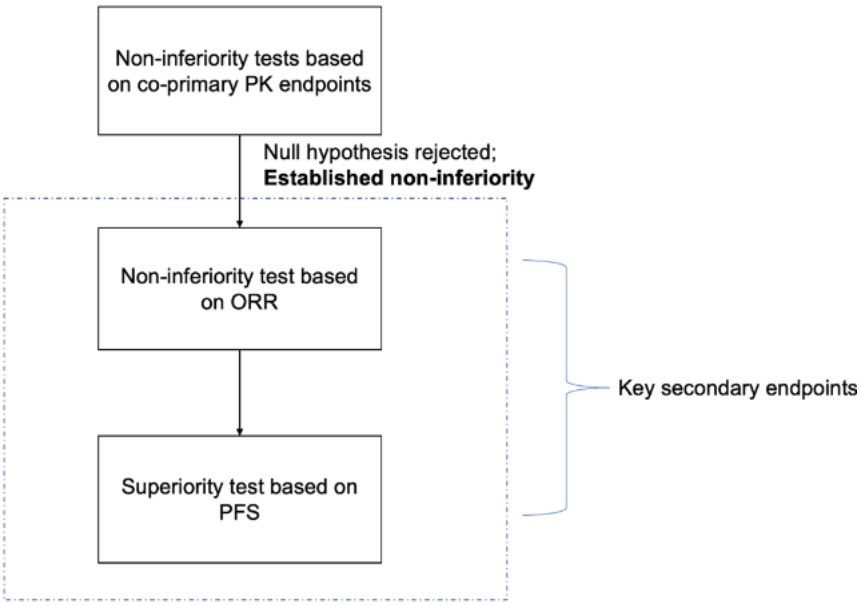
The primary statistical hypothesis of this study was that amivantamab SC-CF, administered via manual injection at the RP2D was non-inferior to amivantamab IV based on the co-primary pharmacokinetics endpoints, C trough (at steady state [Cycle 4 Day 1] for all regions other than EU and others accepting

Cycle 2 Day 1 and pre-dose on cycle 2 Day 1 for EU and any applicable region) and AUC D1-D15 in Cycle 2.

The hypotheses were that the lower bounds of the 90% CI for the ratio of the geometric means of amivantamab SC-CF vs amivantamab IV would be at least 80% (non-inferiority margin of 20%) for both C trough (at steady state of amivantamab on Cycle 4 Day 1 for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and AUC D1-D15 in Cycle 2.

To control familywise Type I error rate at a two-sided significance level of 0.05, a hierarchical procedure for hypothesis testing between primary PK endpoints and key secondary efficacy endpoints was implemented.

Figure 14: Primary and Key Secondary Endpoints Testing Strategy



Justification of Non-inferiority Margins

For the co-primary pharmacokinetic endpoints, C trough (at steady state on Cycle 4 Day 1 for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 day 1 for EU and any applicable region) and AUC D1-D15 in cycle 2, the non-inferiority of amivantamab SC-CF relative to amivantamab IV is defined using a non-inferiority margin of at least 80% of the ratio of geometric mean of C trough (at steady state on Cycle 4 Day 1 for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 day 1 for EU and any applicable region) and AUC D1-D15 in cycle 2. Since these are PK endpoints, the selection of non-inferiority margin and the choice of alpha level follow the convention for bioequivalence studies.

In a previous clinical study (73841937NSC1001), of 50 participants with locally advanced or metastatic NSCLC with EGFR Exon 19del or Exon 21 L858R mutations whose disease had progressed on or after treatment with osimertinib and platinum-based chemotherapy and who were treated with the combination of amivantamab IV and lazertinib, an ORR of 32.1% (95% CI:23.3%, 41.8%) was observed.

On this basis the key secondary hypothesis defines the clinical non-inferiority of amivantamab SC-CF relative to amivantamab IV using a 60% retention of the lower bound (23.3%) of the 95% CI of ORR from previous clinical study 73841937NSC1001.

Endpoints and Estimands

Table 15: Intercurrent events in the ORR analysis

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment switching to other anticancer therapy	**Hypothetical strategy**: use best overall response until subsequent anti-cancer therapy

Progression-free Survival (PFS)

Definition: PFS is defined as the time from randomisation until the date of objective disease progression or death, whichever comes first, based on RECIST v1.1. Participants who have not progressed or have not died at the time of analysis will be censored at their last evaluable RECIST v1.1 assessment date.

Table 16: Key Censoring Rules for PFS

Situation	Censoring Rule
No evaluable baseline or postbaseline disease assessment	Censored at the date of randomization
Lost to follow-up or withdraw from study	Censored at the date of last evaluable disease assessment
No documented disease progression or death	Censored at the date of last evaluable disease assessment
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visits

* If no evaluable disease assessment before the consecutive missed/unevaluable visits, participants will be censored at the date of randomization.

Estimand

The components Study Treatment and Population are similar as for the primary estimand.

Variable: time to event, PFS

Population-level summary: odds ratio for amivantamab SC-CF vs amivantamab IV.

Table 17: Intercurrent events and their corresponding strategies

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not study treatment discontinuation had occurred
Study treatment switching to other anticancer therapy	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not started subsequent anticancer therapies
Death	**Composite Variable strategy:** death being a component of the variable

Results

Participant flow

Table 18: Summary of Screen Failures; All Analysis Set (Study PALOMA-3)

	Total
Analysis set: All	635
Screen failures	217 (34.2%)
Reason for discontinuation during screening	
Failure to meet eligibility criteria	199 (31.3%)
Withdrawal by subject	5 (0.8%)
Adverse event	3 (0.5%)
Death	2 (0.3%)
Progressive disease	2 (0.3%)
Other	6 (0.9%)

Recruitment

Study Period: This study was initiated on 05 August 2022 (the date that the first participant was screened) and is currently ongoing. This clinical study report describes data through a clinical cutoff date (CCO) of 03 January 2024 (the date of the last observation recorded as part of the database for the final analysis of the primary endpoint).

Disposition of Participants

Table 19: Study Disposition; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Full	206	212	418
Subjects randomized	206 (100.0%)	212 (100.0%)	418 (100.0%)
Subjects randomized but not treated	0	2 (0.9%)	2 (0.5%)
Subjects treated	206 (100.0%)	210 (99.1%)	416 (99.5%)
Subjects still on the study	156 (75.7%)	141 (66.5%)	297 (71.1%)
Subjects completed study participation [a]	43 (20.9%)	62 (29.2%)	105 (25.1%)
Subjects discontinued the study	7 (3.4%)	9 (4.2%)	16 (3.8%)
Reason for termination			
Withdrawal by Subject	7 (3.4%)	8 (3.8%)	15 (3.6%)
Lost to Follow-Up	0	1 (0.5%)	1 (0.2%)

Key: IV=Intravenous; SC=Subcutaneous
[a] Completed: if a subject had died before the end of study

Table 20 : Treatment Disposition; Safety Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Safety	206	210	416
Discontinued all study agents	114 (55.3%)	114 (54.3%)	228 (54.8%)
Discontinued any study agents	114 (55.3%)	118 (56.2%)	232 (55.8%)
Reason for discontinuation of Amivantamab			
Progressive Disease	87 (42.2%)	84 (40.0%)	171 (41.1%)
Adverse Event	21 (10.2%)	27 (12.9%)	48 (11.5%)
Subject Refused Further Study Treatment	4 (1.9%)	5 (2.4%)	9 (2.2%)
Physician Decision	2 (1.0%)	1 (0.5%)	3 (0.7%)
Reason for discontinuation of Lazertinib			
Progressive Disease	85 (41.3%)	83 (39.5%)	168 (40.4%)
Adverse Event	23 (11.2%)	25 (11.9%)	48 (11.5%)
Subject Refused Further Study Treatment	4 (1.9%)	5 (2.4%)	9 (2.2%)
Physician Decision	2 (1.0%)	2 (1.0%)	4 (1.0%)

Key: IV=Intravenous; SC=Subcutaneous

Protocol Deviations

Table 21: Summary of Subjects With Major Protocol Deviations; Full Analysis Set (Study JNJ-PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Full	206	212	418
Subjects with major protocol deviations	53 (25.7%)	73 (34.4%)	126 (30.1%)
Received wrong treatment or incorrect dose	18 (8.7%)	5 (2.4%)	23 (5.5%)
Entered but did not satisfy criteria	8 (3.9%)	5 (2.4%)	13 (3.1%)
Received a disallowed concomitant treatment	0	1 (0.5%)	1 (0.2%)
Other	37 (18%)	65 (30.7%)	102 (24.4%)

Note: Subjects may appear in more than one category.

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Conduct of the study

Changes in Study Conduct

Table 22: Key Changes Implemented with Global Protocol Amendments to PALOMA-3

Amendment Number (Date)	Key Changes
Amendment 1 (25 August 2022)	The primary changes and reasons for this amendment included: • Changes to the primary endpoint (and corresponding changes to the secondary endpoint) following advice from EMA. • Implementation of the AESI of VTE, as well as associated measures for monitoring and prophylaxis of these events. • Overall survival was added as an exploratory endpoint to explore the direct measure of clinical benefit in the study population. • Changes were made to Inclusion Criterion 3 to allow for global enrollment to the trial, recognizing heterogeneous access to osimertinib.
Amendment 2 (27 October 2022)	The primary change and reasons for this amendment was: • Part 2 of the study was removed due to the global impact of the OBDS availability.
Amendment 3 (11 August 2023)	The primary change and reason for this amendment was: • To clarify risk mitigation strategies for VTE among patients treated with a combination of amivantamab and lazertinib.
Amendment 4 (21 November 2023)	The primary change and reason for this amendment was: • An amendment was written to implement the model-predicted Cycle 4 Day 1 C_{trough} using the population PK model for participants who are $AUC_{D1\text{-}D15}$ PK evaluable in Cycle 2 and would not be PK evaluable based on an observed Cycle 4 Day 1 C_{trough}. This was done, following interactions with health authorities, to address the issue of the low number of participants evaluable for Cycle 4 C_{trough}.

AESI= adverse event of special interest; EMA= European Medicines Agency; OBDS= O Body Delivery System; VTE= venous thromboembolic

Baseline data

Demographic Characteristics

Table 23: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Full	206	212	418
Age, years			
N	206	212	418
Mean (SD)	60.8 (9.76)	61.4 (10.71)	61.1 (10.25)
Median	61.0	62.0	61.0
Range	(35; 82)	(29; 81)	(29; 82)
<50	28 (13.6%)	29 (13.7%)	57 (13.6%)
50-64	105 (51.0%)	91 (42.9%)	196 (46.9%)
65-74	55 (26.7%)	70 (33.0%)	125 (29.9%)
>=75	18 (8.7%)	22 (10.4%)	40 (9.6%)
Age Group 1, years			
N	206	212	418
<65	133 (64.6%)	120 (56.6%)	253 (60.5%)
>=65	73 (35.4%)	92 (43.4%)	165 (39.5%)
Age Group 2, years			
N	206	212	418
<75	188 (91.3%)	190 (89.6%)	378 (90.4%)
>=75	18 (8.7%)	22 (10.4%)	40 (9.6%)
Sex			
N	206	212	418
Female	138 (67.0%)	141 (66.5%)	279 (66.7%)
Male	68 (33.0%)	71 (33.5%)	139 (33.3%)
Undifferentiated	0	0	0
Unknown	0	0	0
Race [a]			
N	206	212	418
American Indian or Alaska Native	0	0	0
Asian	126 (61.2%)	129 (60.8%)	255 (61.0%)
Black or African American	1 (0.5%)	3 (1.4%)	4 (1.0%)
Native Hawaiian or other Pacific Islander	0	0	0
White	78 (37.9%)	77 (36.3%)	155 (37.1%)
Multiple	0	1 (0.5%)	1 (0.2%)
Not Reported	1 (0.5%)	2 (0.9%)	3 (0.7%)
Unknown	0	0	0

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Ethnicity			
N	206	212	418
Hispanic or Latino	12 (5.8%)	19 (9.0%)	31 (7.4%)
Not Hispanic or Latino	191 (92.7%)	191 (90.1%)	382 (91.4%)
Not Reported	3 (1.5%)	2 (0.9%)	5 (1.2%)
Unknown	0	0	0
Weight, kg			
N	206	212	418
Mean (SD)	63.5 (13.65)	62.8 (15.90)	63.2 (14.82)
Median	61.8	60.1	61.0
Range	(35; 130)	(33; 150)	(33; 150)
[<80 kg]	184 (89.3%)	184 (86.8%)	368 (88.0%)
[>=80 kg]	22 (10.7%)	28 (13.2%)	50 (12.0%)
Height, cm			
N	206	212	418
Mean (SD)	162.4 (9.00)	162.4 (9.05)	162.4 (9.01)
Median	162.0	161.3	162.0
Range	(141; 185)	(143; 191)	(141; 191)
Body mass index, kg/m^2			
N	206	212	418
Mean (SD)	23.96 (3.909)	23.65 (4.822)	23.80 (4.394)
Median	23.54	23.00	23.23
Range	(12.9; 41.0)	(13.3; 48.8)	(12.9; 48.8)
Baseline ECOG score			
N	206	212	418
0	58 (28.2%)	61 (28.8%)	119 (28.5%)
1	148 (71.8%)	151 (71.2%)	299 (71.5%)
Unknown	0	0	0
History of smoking			
N	206	212	418
Yes	65 (31.6%)	67 (31.6%)	132 (31.6%)
No	141 (68.4%)	145 (68.4%)	286 (68.4%)
Unknown	0	0	0

Key: IV=Intravenous; SC=Subcutaneous; ECOG = Eastern Cooperative Oncology Group
[a] Based on investigator reported data recorded on eCRF page.

Baseline Disease Characteristics

Table 24: Summary of Baseline Disease Characteristics; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Full	206	212	418
Time since initial lung cancer diagnosis (months)			
N	206	212	418
Mean (SD)	40.414 (26.1357)	39.399 (25.2365)	39.899 (25.6578)
Median	34.513	33.725	34.316
Range	(2.76; 191.34)	(6.05; 156.85)	(2.76; 191.34)
Time since metastatic disease diagnosis (months)			
N	206	212	418
Mean (SD)	36.417 (24.2781)	34.392 (20.9185)	35.390 (22.6320)
Median	32.723	29.700	31.244
Range	(0.85; 168.97)	(0.56; 142.55)	(0.56; 168.97)
Number of prior lines of systemic therapy			
N	206	212	418
Mean (SD)	2.3 (0.71)	2.2 (0.69)	2.3 (0.70)
Median	2.0	2.0	2.0
Range	(1; 5)	(1; 4)	(1; 5)
Mutation Type [a]			
N	206	212	418
Exon 19del	135 (65.5%)	138 (65.1%)	273 (65.3%)
Exon 21 L858R	71 (34.5%)	74 (34.9%)	145 (34.7%)
History of brain metastasis[a]			
N	206	212	418
Present	70 (34.0%)	72 (34.0%)	142 (34.0%)
Absent	136 (66.0%)	140 (66.0%)	276 (66.0%)
Initial diagnosis NSCLC subtype			
N	206	212	418
Adenocarcinoma	204 (99.0%)	207 (97.6%)	411 (98.3%)
Large cell carcinoma	1 (0.5%)	1 (0.5%)	2 (0.5%)
Squamous cell carcinoma	1 (0.5%)	3 (1.4%)	4 (1.0%)
Other	0	1 (0.5%)	1 (0.2%)
Cancer stage at initial diagnosis			
N	206	212	418
0	0	0	0
IA	5 (2.4%)	8 (3.8%)	13 (3.1%)
IB	5 (2.4%)	7 (3.3%)	12 (2.9%)
IIA	1 (0.5%)	2 (0.9%)	3 (0.7%)
IIB	7 (3.4%)	6 (2.8%)	13 (3.1%)
IIIA	9 (4.4%)	11 (5.2%)	20 (4.8%)
IIIB	11 (5.3%)	2 (0.9%)	13 (3.1%)
IIIC	1 (0.5%)	1 (0.5%)	2 (0.5%)
IV	167 (81.1%)	174 (82.1%)	341 (81.6%)
Not Reported	0	1 (0.5%)	1 (0.2%)
Location of metastasis at screening [b]			
N	206	212	418
Bone	112 (54.4%)	128 (60.4%)	240 (57.4%)
Liver	51 (24.8%)	46 (21.7%)	97 (23.2%)
Brain	70 (34.0%)	72 (34.0%)	142 (34.0%)
Lymph Node	125 (60.7%)	118 (55.7%)	243 (58.1%)
Adrenal Gland	19 (9.2%)	32 (15.1%)	51 (12.2%)
Lung	147 (71.4%)	141 (66.5%)	288 (68.9%)
Other	99 (48.1%)	96 (45.3%)	195 (46.7%)
Last therapy before randomization			
N	206	212	418
Osimertinib	91 (44.2%)	96 (45.3%)	187 (44.7%)
Chemotherapy	115 (55.8%)	116 (54.7%)	231 (55.3%)
Cancer stage at screening			
N	206	212	418
IIIA	0	0	0
IIIB	1 (0.5%)	0	1 (0.2%)
IIIC	2 (1.0%)	0	2 (0.5%)
IV	203 (98.5%)	212 (100.0%)	415 (99.3%)

Key: IV=Intravenous; SC=Subcutaneous; 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.
Note: Any patient receiving both chemotherapy and osimertinib is listed under chemotherapy

Numbers analysed

Number of Participants Analysed

Table 25: Number of Subjects in Each Analysis Set; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	Total
Analysis set: Full	206	212	418
Safety analysis set	206 (100.0%)	210 (99.1%)	416 (99.5%)
Other PK Evaluable	206 (100.0%)	208 (98.1%)	414 (99.0%)

Key: IV=Intravenous; SC=Subcutaneous

Table 26: Number of Evaluable Participants for the Primary and Secondary PK Endpoints

Endpoint	Amivantamab SC+lazertinib	Amivantamab IV+lazertinib
Cycle 2 Day 1 C_{trough}	160 (77.7%)	142 (67.6%)
Cycle 2 Day 1 $AUC_{(D1-D15)}$,	140 (68.0%)	132 (62.9%)
Observed Cycle 4 Day 1 C_{trough}	98 (47.6%)	98 (46.7%)
Hybrid[a] Cycle 4 Day 1 C_{trough}	157 (76.2%)	134 (63.8%)
Predicted Cyclce 4 AUC_{D1-D15}	150 (72.8%)	132 (62.9%)

[a] Using observed values for PK evaluable participants and model-predicted values for participants who were PK unevaluable at Cycle 4 Day 1 if the participant had sufficient PK samples to calculate Cycle 2 AUC_{D1-D15}.

Exposure

The median duration of treatment in the amivantamab SC+lazertinib arm was 4.65 months (4.12 months [range: 0.0; 12.5] for amivantamab SC and 4.60 months [range: 0.1; 13.2] for lazertinib).

Outcomes and estimation

As of the CCO date of 03 January 2024, the median duration of follow-up was 7.26 (range: 0.1+; 13.4) months in the amivantamab SC+lazertinib arm and 6.54 (range: 0.4+; 14.4) months in the amivantamab IV+lazertinib arm.

The outcome of the primary PK endpoint is described in section clinical pharmacology.

Secondary Endpoints

Efficacy

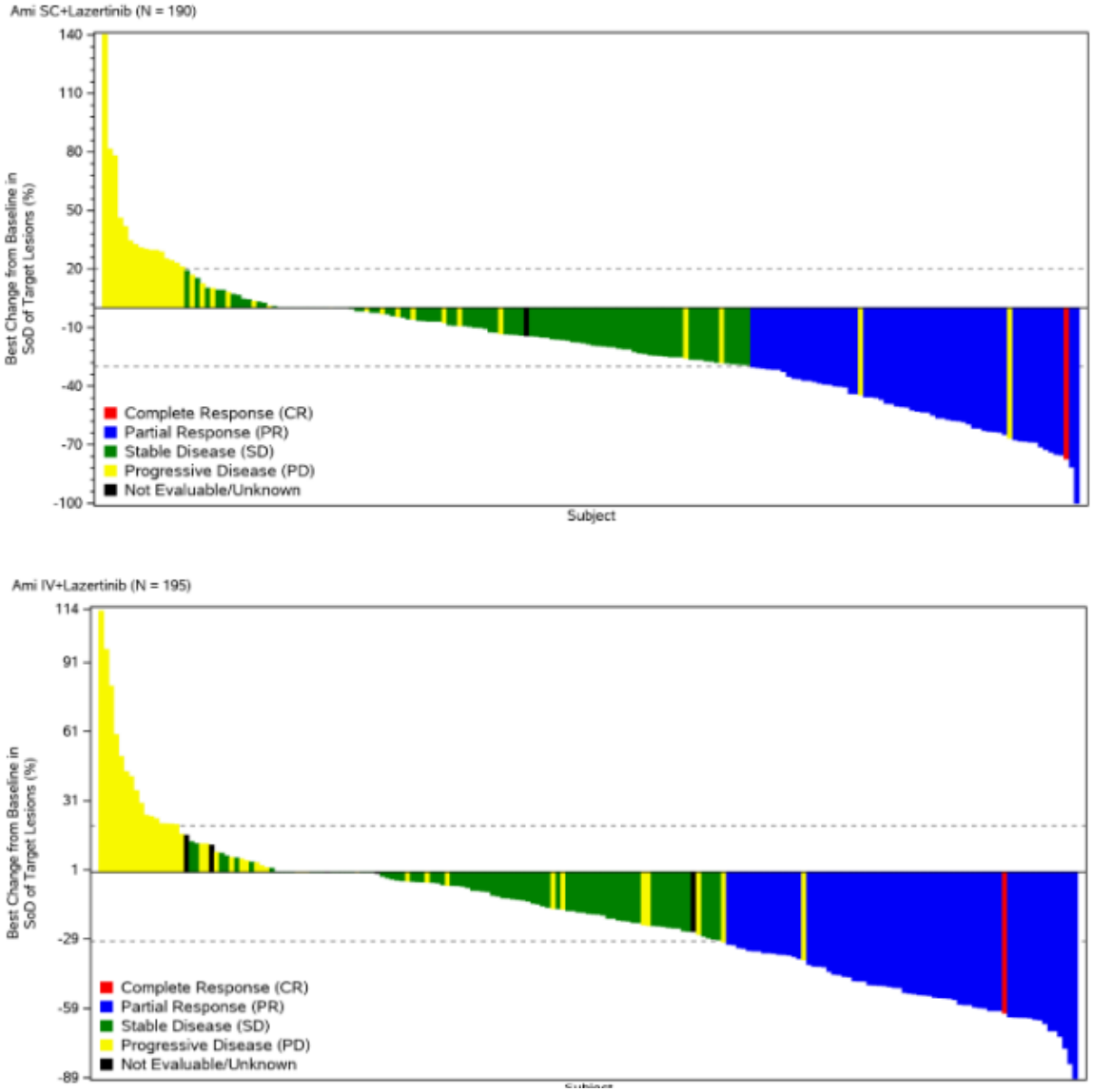
Objective Response Rate

Table 27: Summary of Objective Response Rate Based on RECIST 1.1 Criteria by Investigator Assessment; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib
Analysis set: Full	206	212
Objective response rate (CR + PR)	62 (30.1%)	69 (32.5%)
95% CI	(23.9%, 36.9%)	(26.3%, 39.3%)
Ami SC + Lazertinib vs Ami IV + Lazertinib		
Relative risk (95% CI)[a]		0.92 (0.70, 1.23)
p-value[b]		0.0014
Best Overall Response		
Complete Response (CR)	1 (0.5%)	1 (0.5%)
Partial Response (PR)	61 (29.6%)	68 (32.1%)
Stable Disease (SD)	93 (45.1%)	81 (38.2%)
Progressive Disease (PD)	37 (18.0%)	42 (19.8%)
Not Evaluable (NE)	14 (6.8%)	20 (9.4%)

Key: IV=Intravenous; SC=Subcutaneous
[a] Farrington-Manning estimates of the relative risk of Ami SC + Lazertinib over Ami IV + lazertinib and associated CI are provided
[b] P-value is from Farrington-Manning test for the non-inferiority hypothesis that Ami SC + Lazertinib retains at least 60% of ORR in Ami IV + Lazertinib.
Note: CR and PR do not have to be confirmed. Percent of Responder/Non-responder is based on the number of subjects with measurable disease at baseline.

Figure 15: Waterfall Plot of Best Percentage Change From Baseline in Sum of Diameters (SoD) of Target Lesions at Baseline - Investigator; Full Analysis Set (Study PALOMA-3)



Confirmed Objective Response Rate

An analysis of ORR based on confirmed PR or CR showed similar results with an ORR of 26.7% (95% CI: 20.8%, 33.3%) in the amivantamab SC+lazertinib arm and an ORR of 26.9% (95% CI: 21.0%, 33.4%) in the amivantamab IV+lazertinib arm. The relative risk for confirmed responses in the amivantamab SC+lazertinib arm compared to the amivantamab IV+lazertinib arm was 0.99 (95% CI: 0.72,1.36; nominal p-value = 0.0009).

Table 28: Summary of Time to Response - Investigator; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib
Analysis set: Full	206	212
Responders (CR + PR)	62	69
Time to response (months)		
N	62	69
Mean (SD)	2.13 (1.368)	1.97 (1.426)
Median	1.49	1.48
Range	(1.2; 6.9)	(1.2; 9.9)
<=2	45 (72.6%)	58 (84.1%)
<=4	55 (88.7%)	62 (89.9%)
<=6	60 (96.8%)	67 (97.1%)
<=8	62 (100.0%)	68 (98.6%)
<=10	62 (100.0%)	69 (100.0%)

Key: IV=Intravenous; SC=Subcutaneous; CR=Complete Response; PR=Partial Response
Note: Percentages are based on the number of subjects who achieved CR or PR.
Note: CR and PR do not have to be confirmed.

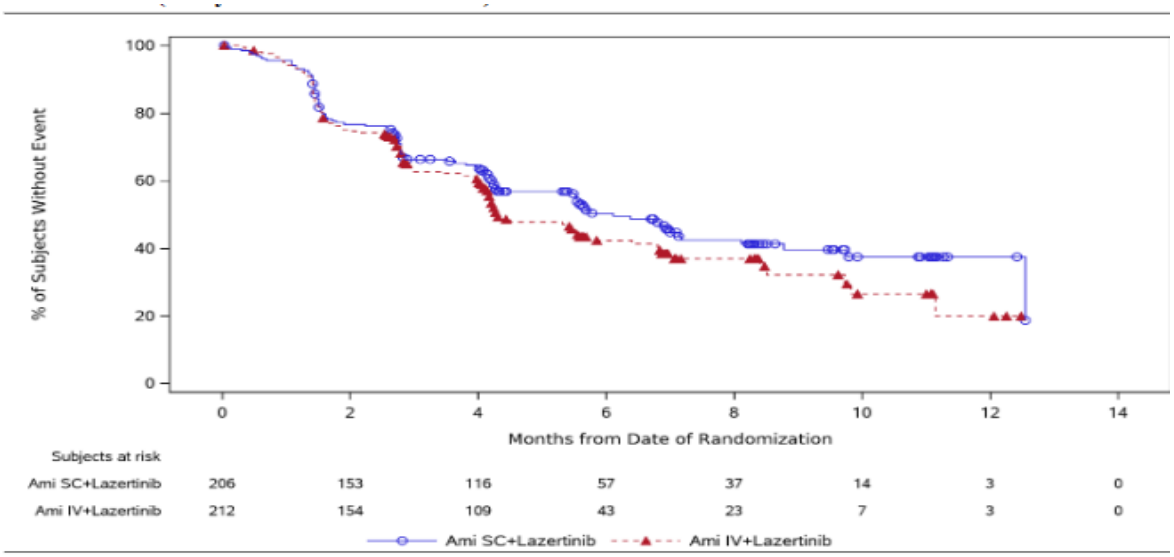
Progression-free Survival

Table 29: Summary of Progression-free Survival by Investigator –Stratified Analysis; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib
Analysis set: Full	206	212
Event	103 (50.0%)	116 (54.7%)
Censored	103 (50.0%)	96 (45.3%)
Time to event (months)		
25th percentile (95% CI)	2.66 (1.54, 2.79)	2.04 (1.54, 2.79)
Median (95% CI)	6.11 (4.30, 8.11)	4.30 (4.14, 5.72)
75th percentile (95% CI)	12.55 (12.55, NE)	11.14 (8.51, NE)
Range	(0.0+, 12.6+)	(0.0+, 12.5+)
6-month event-free rate (95% CI)	0.50 (0.43, 0.58)	0.42 (0.35, 0.50)
12-month event-free rate (95% CI)	0.37 (0.28, 0.46)	0.20 (0.08, 0.35)
Ami SC + Lazertinib vs Ami IV + Lazertinib		
p-value[a]		0.2006
Hazard ratio (95% CI)[b]		0.84 (0.64, 1.10)

Key: IV=Intravenous; SC=Subcutaneous
[a] p-value is from a log-rank test stratified by [brain metastases at baseline (yes versus no), EGFR mutation (L858R versus Exon 19del), race (Asian versus Non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] versus chemotherapy)].
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors active treatment.
Note: + = censored observation, NE = not estimable

Figure 16: Kaplan-Meier Plot for Progression-free Survival by Investigator Assessment; Full Analysis Set (Study PALOMA-3)



Key: IV=Intravenous; SC=Subcutaneous

Overall Survival

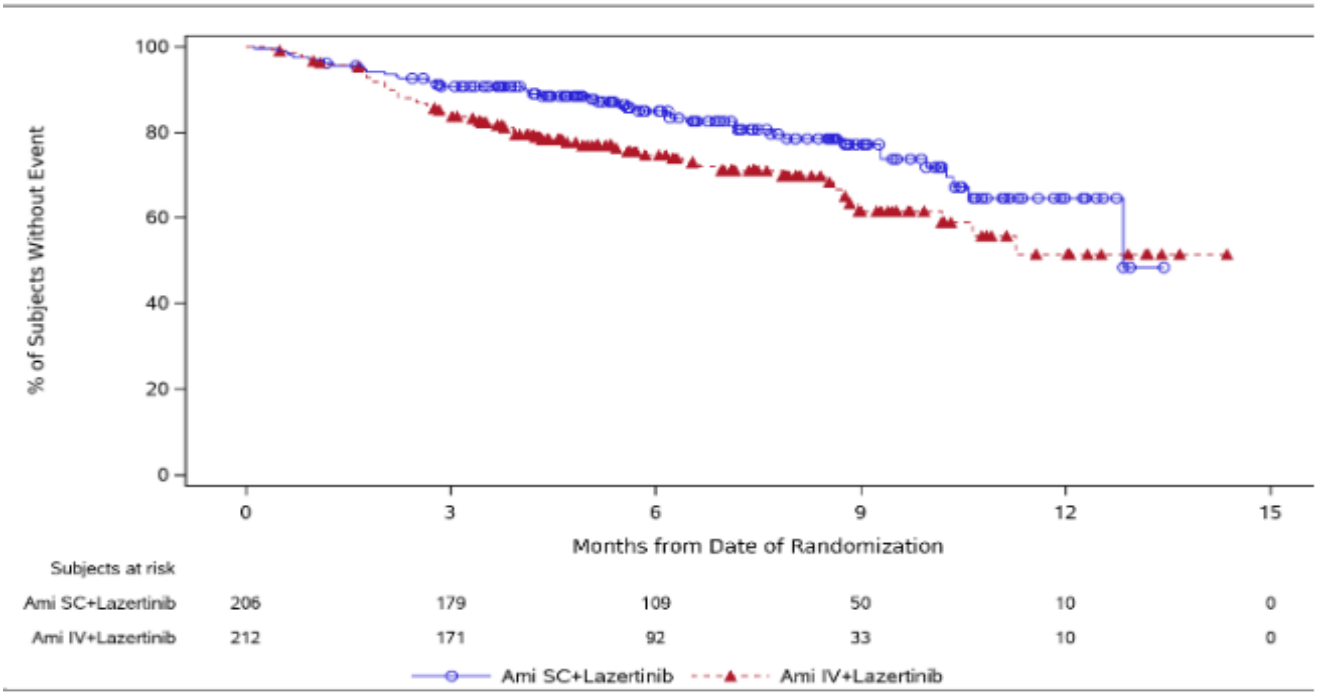
At the time of the CCO of 03 January 2024, after a median follow-up of 7.00 months 43 events (20.9%) in the amivantamab SC+lazertinib arm and 62 events (29.2%) in the amivantamab IV+lazertinib were observed.

Table 30: Summary of Overall Survival – Stratified Analysis; Full Analysis Set (Study PALOMA-3)

	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib
Analysis set: Full	206	212
Event	43 (20.9%)	62 (29.2%)
Censored	163 (79.1%)	150 (70.8%)
Time to event (months)		
25th percentile (95% CI)	9.30 (7.16, 10.58)	5.75 (3.91, 8.61)
Median (95% CI)	12.85 (12.85, NE)	NE (10.18, NE)
75th percentile (95% CI)	NE (12.85, NE)	NE (NE, NE)
Range	(0.1, 13.4+)	(0.4, 14.4+)
6-month event-free rate (95% CI)	0.85 (0.79, 0.89)	0.75 (0.68, 0.80)
9-month event-free rate (95% CI)	0.77 (0.69, 0.83)	0.62 (0.51, 0.70)
12-month event-free rate (95% CI)	0.65 (0.52, 0.74)	0.51 (0.37, 0.64)
Ami SC + Lazertinib vs Ami IV + Lazertinib		
p-value [a]		0.0169
Hazard ratio (95% CI) [b]		0.62 (0.42, 0.92)

Key: IV=Intravenous; SC=Subcutaneous
[a] p-value is from a log-rank test stratified by [brain metastases at baseline (yes versus no), EGFR mutation (L858R versus Exon 19del), race (Asian versus Non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] versus chemotherapy].
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors active treatment.
Note: + = censored observation, NE = not estimable

Figure 17: Kaplan-Meier Plot of Overall Survival; Full Analysis Set (Study PALOMA-3)



Key: IV=Intravenous; SC=Subcutaneous

Patient-reported Outcomes

Table 31: Summary of Modified TASQ Assessment and Change From Baseline Over Time During Study; Full Analysis Set (Study PALOMA-3)

	Measured Value								Change From Baseline						
	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
Analysis set: Full															
Amivantamab SC + Lazertinib	206														
Amivantamab IV + Lazertinib	212														
Convenience Domain Score															
Amivantamab SC + Lazertinib															
Baseline	193	84.65	15.040	1.083	87.50	25.0	100.0								
Cycle 3 Day 1	146	85.10	14.704	1.217	87.50	25.0	100.0	84.16	146	0.94	15.612	1.292	0.00	-75.0	37.5
End Of Treatment	61	82.58	16.968	2.173	87.50	25.0	100.0	82.58	61	0.00	20.412	2.614	0.00	-62.5	50.0
Amivantamab IV + Lazertinib															
Baseline	195	65.58	23.577	1.688	62.50	0.0	100.0								
Cycle 3 Day 1	125	71.70	19.710	1.763	75.00	0.0	100.0	65.00	125	6.70	19.478	1.742	0.00	-37.5	50.0
End Of Treatment	56	62.50	23.955	3.201	62.50	0.0	100.0	62.72	56	-0.22	26.596	3.554	0.00	-62.5	50.0
Impact on Activities of Daily Living Domain Score															
Amivantamab SC + Lazertinib															
Baseline	193	58.5	24.30	1.75	50.0	0	100								
Cycle 3 Day 1	146	56.0	23.36	1.93	50.0	0	100	57.5	146	-1.5	28.95	2.40	0.0	-75	75
End Of Treatment	61	55.7	22.54	2.89	50.0	0	100	57.0	61	-1.2	29.02	3.72	0.0	-75	75
Amivantamab IV + Lazertinib															
Baseline	195	38.8	20.48	1.47	50.0	0	100								
Cycle 3 Day 1	125	38.4	20.22	1.81	50.0	0	100	41.6	125	-3.2	26.94	2.41	0.0	-100	50
End Of Treatment	56	36.6	22.34	2.99	25.0	0	100	39.3	56	-2.7	25.53	3.41	0.0	-75	50
Physical Impact Domain Score															
Amivantamab SC + Lazertinib															
Baseline	193	86.9171	11.30429	0.81370	91.6667	41.667	100.000								
Cycle 3 Day 1	146	85.5023	12.18687	1.00859	87.5000	50.000	100.000	86.8151	146	-1.3128	11.77244	0.97429	0.0000	-50.000	33.333
End Of Treatment	61	83.0601	15.13574	1.93793	83.3333	41.667	100.000	90.3005	61	-7.2404	14.22988	1.82195	-8.3333	-50.000	25.000
Amivantamab IV + Lazertinib															
Baseline	195	93.5470	10.01273	0.71703	100.0000	50.000	100.000								
Cycle 3 Day 1	125	92.6000	11.31062	1.01165	100.0000	50.000	100.000	93.8000	125	-1.2000	11.67550	1.04429	0.0000	-41.667	33.333

	Measured Value								Change From Baseline						
End Of Treatment	N	Mean	SD	SE	Med	Min	Max	Base Mean	N	Mean	SD	SE	Med	Min	Max
	56	91.3690	12.20245	1.63062	91.6667	50.000	100.000	92.5595	56	-1.1905	13.24102	1.76941	0.0000	-33.333	50.000
Psychological Impact Domain Score															
Amivantamab SC + Lazertinib															
Baseline	193	88.9	18.37	1.32	100.0	0	100								
Cycle 3 Day 1	146	87.0	19.08	1.58	100.0	0	100	88.5	146	-1.5	17.67	1.46	0.0	-50	75
End Of Treatment	61	84.8	21.05	2.70	100.0	0	100	88.5	61	-3.7	21.81	2.79	0.0	-75	25
Amivantamab IV + Lazertinib															
Baseline	195	71.2	25.85	1.85	75.0	0	100								
Cycle 3 Day 1	125	79.2	22.39	2.00	75.0	0	100	69.6	125	9.6	29.58	2.65	0.0	-50	100
End Of Treatment	56	75.4	25.00	3.34	75.0	0	100	69.2	56	6.3	29.87	3.99	0.0	-100	75
Treatment Satisfaction Domain Score															
Amivantamab SC + Lazertinib															
Baseline	193	79.92	16.488	1.187	87.50	25.0	100.0								
Cycle 3 Day 1	146	80.48	15.810	1.308	87.50	12.5	100.0	78.85	146	1.63	16.032	1.327	0.00	-62.5	50.0
End Of Treatment	61	72.54	20.003	2.561	75.00	25.0	100.0	79.10	61	-6.56	21.843	2.797	0.00	-75.0	50.0
Amivantamab IV + Lazertinib															
Baseline	195	70.51	20.005	1.433	75.00	12.5	100.0								
Cycle 3 Day 1	125	74.80	18.307	1.637	75.00	25.0	100.0	72.20	125	2.60	17.339	1.551	0.00	-37.5	50.0
End Of Treatment	56	60.71	20.702	2.766	62.50	12.5	100.0	64.96	56	-4.24	15.499	2.071	0.00	-37.5	25.0

Key: IV=Intravenous; SC=Subcutaneous; SD=standard deviation; SE=standard error
Note: N for measured value is the number of subjects with a non-missing value for the Questionnaire at the specified timepoint. N for Change from baseline is the number of subjects with non-missing values at both baseline and the postbaseline timepoint.
Change from "baseline" would be change from Cycle 1 Day 1. For Amivantamab IV subjects who received split dose, Cycle1 Day 2 will be the baseline if the questionnaires were completed on that visit.

Ancillary analyses

N/A

2.5.5.3. Summary of main efficacy results

For the PK co-primary and secondary endpoints, see the clinical pharmacology section.

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 32: Summary of efficacy for trial PALOMA-3

Title: PALOMA-3			
Design	Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non- small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy.		
Hypothesis	Non-inferiority		
Treatments groups	A		Amivantamab SC+lazertinib arm
	B		Amivantamab IV+lazertinib arm
Endpoints and definitions	Co-Primary endpoint	Ctrough at Cycle 2 Day 1 and AUCD1-D15 at Cycle 2	Refer to clinical pharmacology section
	Secondary	ORR	

Title: PALOMA-3				
	Secondary	PFS		
Database lock	03 January 2024			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point deSCription	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	A (SC) arm	B (IV) arm	
	Number of subjects	206	212	
	Secondary endpoint ORR	30.1%	32.5%	RR (95%CI) 0.92 (0.70;1.23)
	95%CI	23.9%-36.9%	26.3%-39.3%	
	Secondary endpoint PFS (months)	6.11	4.30	HR (95%CI) 0.84 (0.64;1.1)
	95%CI	4.30;8.11	4.14;5.72	

2.5.5.4. In vitro biomarker test for patient selection for efficacy

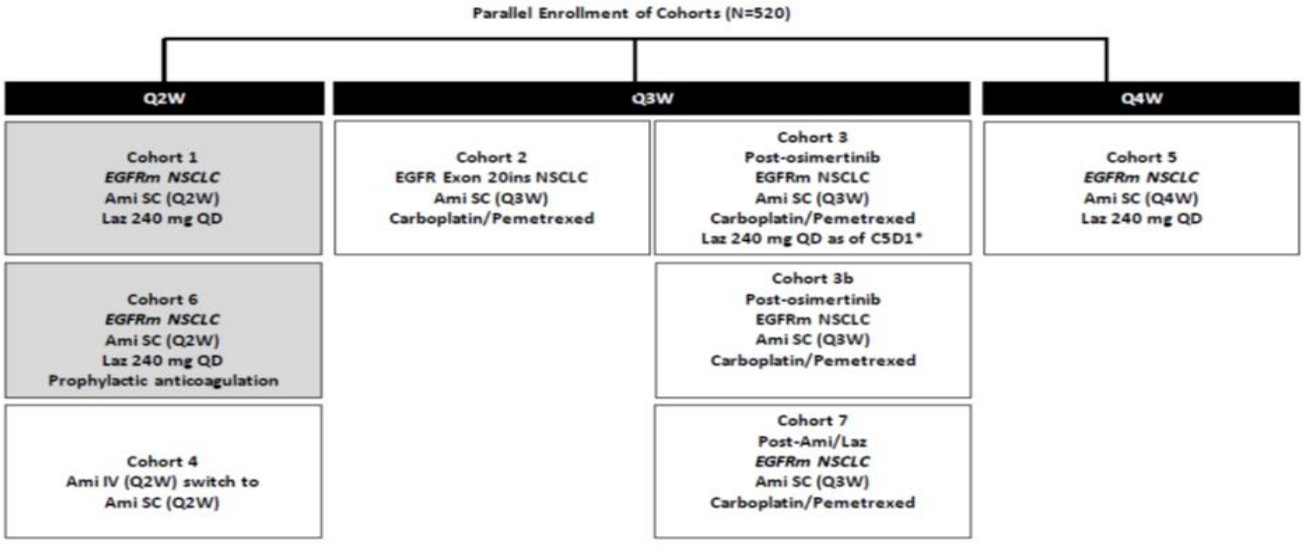
Similar biomarker testing strategy was used for patient selection into PALOMA-3 study and PALOMA-2 study as in the previous studies. The recommendations for biomarker testing are sufficiently addressed in the section 4.2 of the SmPC: "Before initiation of amivantamab SC, EGFR mutation status in tumour tissue or plasma specimens must be established using a validated test method. If no mutation is detected in a plasma specimen, tumour tissue should be tested if available in sufficient amount and quality due to the potential for false negative results using a plasma test. Once EGFR mutation status has been established, testing does not need to be repeated".

2.5.5.5. Supportive study(ies)

PALOMA-2

PALOMA-2 is an ongoing Phase 2, open-label, parallel cohort, interventional study evaluating the efficacy, safety, and PK of amivantamab SC administered via manual injection in multiple combinations and treatment settings of participants with EGFR-mutated locally advanced or metastatic NSCLC that have been previously treated with amivantamab IV. Cohorts 1 and 6 are relevant for this application.

Figure 18: Schematic Overview of the PALOMA-2 Study



Ami=amivantamab; C=cycle; D=day; EGFR= epidermal growth factor receptor; EGFRm NSCLC=epidermal growth factor receptor with EGFR mutations; exon 20ins=exon 20 insertions; IV=intravenous; 1L=first line; 2L=second line; Laz=lazertinib; N=number; NSCLC=non-small cell lung cancer; QD=once daily; Q2W=every 2 weeks;; SC=subcutaneous; SCE=Summary of Clinical Efficacy; VTE=venous thromboembolic (events)

Note: Cohorts 1 and 6 support Q2W dosing and are discussed in this SCE; information is presented in the grey text boxes. Due to the increased risk of VTE events in participants receiving the combination of amivantamab and lazertinib, the protocol was amended to both recommend prophylactic-dose anticoagulation as per local guidelines for the first 4 months of therapy for all study participants in Cohort 1, and to add Cohort 6, which required mandatory prophylactic-dose anticoagulation for all study participants.

Methods

Study participants.

Both cohorts 1 and 6 assessed the combination of amivantamab SC (Q2W) and lazertinib in participants with treatment-naïve locally advanced or metastatic NSCLC harboring an EGFR exon 19del or exon 21 L858R mutation; participants in Cohort 6 received additional mandatory prophylactic anticoagulation.

Treatments

- **Cohorts 1 and 6:** The combination of amivantamab SC (Q2W) and lazertinib

Participants received amivantamab SC on Cycle 1 Days 1, 8, 15, and 22 and on Day 1 and 15 of each subsequent 28-day cycle, starting with Cycle 2. Amivantamab SC (160 mg/mL co-formulated with rHuPH20) (Q2W) will be administered by manual injection at 1,600 mg (2,240 mg if BW ≥80 kg).

Lazertinib was given 240 mg orally QD.

Results

Table 33: Summary of Efficacy Results (PALOMA-2: Cohorts 1 and 6)

	Cohort 1		Cohort 6		Cohort 1 + 6	
	Investigator (N=68)	ICR (N=68)	Investigator (N=45)	ICR (N=45)	Investigator (N=113)	ICR (N=113)
ORR (confirmed CR + confirmed PR)						
N % ORR (95% CI)	46 67.6% (55.2, 78.5)	49 72.1% (59.9, 82.3)	29 64.4% (48.8, 78.1)	33 73.3% (58.1, 85.4)	75 66.4% (56.9, 75.0)	82 72.6% (63.4, 80.5)
TTR						
Median TTR (months) (95% CI)	1.87 (1.4, 5.3)	-	1.87 (1.6, 3.8)	-	1.87 (1.4, 5.3)	
CBR						
N % CBR (95% CI)	59 86.8% (76.4, 93.8)	60 88.2% (78.1, 94.8)	42 93.3% (81.7, 98.6)	43 95.6% (84.9, 99.5)	101 89.4% (82.2, 94.4)	103 91.2% (84.3, 95.7)
CBR: clinical benefit rate; CI: confidence interval; ICR: independent central review; ORR: objective response rate; TTR: time to response						

2.5.6. Discussion on clinical efficacy

The primary efficacy data to support the proposed SC formulation and administration are derived from the ongoing Phase 3 PALOMA-3 study. Supportive efficacy data are submitted from the ongoing Phase 2 PALOMA 2 study Cohorts 1 and 6 (Q2W).

PALOMA-3

PALOMA-3 was designed to demonstrate "non-inferiority" (by which is rather meant PK equivalence) of the new SC formulation versus IV formulation in terms of pharmacokinetic metrics as well as for pharmacodynamic metrics and safety profile when given in Q2W regimen. The PALOMA-3 study informs section 5.2 of the SmPC (*Pharmacokinetic properties*), while section 5.1 of the SmPC remains identical to the IV formulation for the applied indications.

Study design and conduct

The population chosen is represented by the patients with advanced/metastatic NSCLC with EGFR exon 19del and exon 21 L858R substitution later line of therapy, i.e after progression on or after both a third generation TKI and platinum-based chemotherapy.

All patients had measurable disease at inclusion.

Objectives, endpoints and estimands

The primary endpoint was to assess non-inferiority of amivantamab SC as demonstrated by PK metrics measured when the last enrolled participant completed the Cycle 4 Day 1 visit and provided the last required serum amivantamab PK sample to perform the primary analysis. The cut off for primary analysis was 03 January 2024.

Secondary endpoints included in hierarchical testing were ORR and PFS

Sample size

The sample size was calculated to establish non-inferiority of amivantamab SC to amivantamab IV based on the co-primary pharmacokinetics endpoints. The sample size of 400 participants would provide a power of 80% to demonstrate the "non-inferiority" of amivantamab SC compared with amivantamab IV (both on a background of lazertinib), with a non-inferiority margin of 60% and a one-sided alpha of 0.025, assuming the true ORR is the same for both treatment arms.

The sample size was acceptable.

Of note, neither 73841937NSC1001 nor PALOMA-3 included a placebo-controlled arm, while amivantamab was given in combination with lazertinib. Thus, the effect size of amivantamab (i.e., the contribution to the sum efficacy) cannot be isolated.

Statistical plan

Since the study primary point estimates are PK endpoints, the selection of non-inferiority margin and the choice of alpha level follow the convention for bioequivalence studies. No interim analysis was projected. There were no planned subgroup analyses.

In essence, in PALOMA-3 the "non-inferiority" margin for ORR is a margin of clinical equivalence between the two regimens.

Given the PK and overall outcomes, this is not an issue. PALOMA-3 is a model to establish PK equivalence and does not support an indication in the studied population.

Changes in planned study conduct and analyses

As of the CCO of 03 January 2024, there were no changes in the planned analyses for the study.

There were four protocol amendments. The most important protocol amendment PA1, including change of the primary endpoint to pharmacokinetic parameters was introduced on 25 August 2022, closely to the approval of the original protocol 12 April 2022, following advice from EMA.

PA4 to amend the model for calculation of Ctrough on Cycle 4 Day 1 due to low number of participants evaluable for Cycle 4 Ctrough was introduced before the clinical cutoff date (CCO) of 03 January 2024, also following interactions with health authorities. The justification of the reasons for these amendments is acceptable.

The study was initiated on 05 August 2022 and is currently ongoing.

Totally 418 participants were randomised 1:1 between arms, 206 in SC arm and 212 in IV arm and represents the full analysis set (FAS) the basis for primary and secondary efficacy endpoints analysis. Totally 416 participants received at least one dose of treatment with two participants randomized to IV arm not being treated.

No important numerical imbalance in study discontinuation between arms is observed.

Demographics, baseline and disease characteristics were balanced between the two treatment arms. The last therapy prior randomisation consisted of osimertinib for 45% of participants and chemotherapy for 55% of participants. A small numerical imbalance is observed in the proportion of patients receiving prior lines of systemic therapy with higher proportion receiving three prior lines (39.8% vs 30.25) in the SC versus IV arm.

Results

PK results are discussed in the clinical pharmacology section.

ORR was 30.1% for the amivantamab SC+lazertinib regimen and 32.5% for the amivantamab IV+lazertinib regimen. The relative risk was 0.92 (95% CI: 0.70, 1.23). The lower bound of the 95% CI (0.70) indicated at least 70% retention of the ORR seen with the reference treatment. Thus, the pre-defined clinical "non-inferiority" criterion was met.

Further, the analyses of the time-related efficacy endpoints PFS, DoR and OS showing nominal better point estimates favouring the combination with SC amivantamab supports the conclusion that the SC regimen is not clinically inferior to the IV regimen.

Results from the supportive study PALOMA-2 (cohorts 1 and 6) are in line with the results of the pivotal trial.

Extrapolation of the PALOMA-3 results on bridging to the amivantamab monotherapy setting and generally to the Q2W SC regimen

Bridging between IV and SC amivantamab formulation, when given in combination with lazertinib, has been demonstrated in terms of PK non-inferiority with support from similarity in efficacy and safety data based on PALOMA-3 study. No separate study to bridge the SC and IV amivanatamab formulation when given as monotherapy has been performed; however, since there is no PK interaction between amivantamab and lazertinib, the results can be extrapolated to all other indications with Q2W treatment with amivantamab.

The applied indications for amivantamab SC are identical to those for amivantamab IV when administered in Q2W regimen, which was deemed acceptable. Therefore, the final approved wording of the indication for amivantamab SC is as follows:

Amivantamab in combination with lazertinib 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.

Amivantamab as monotherapy is indicated for the treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations, after failure of platinum-based therapy.

2.5.7. Conclusions on the clinical efficacy

Non-inferiority was shown for PK metrics, in line with prespecified criteria. ORR, PFS and OS data support that the SC regimen is not clinically inferior to the approved IV regimen. Since there is no PK interaction between amivantamab and lazertinib, the results from study PALOMA-3 support the use of amivantamab SC in the applied, and all future, indications when administered in Q2W regimen.

2.5.8. Clinical safety

In support of the use of amivantamab SC for the treatment of NSCLC, pivotal safety data were obtained from the safety population of the PALOMA-3 study, in which amivantamab (Q2W, IV or SC) is used in combination with lazertinib. Supportive safety data were obtained from Cohorts 1 and 6 of the PALOMA-2 study, in which amivantamab (Q2W, SC) is used in combination with lazertinib.

Data from the PALOMA-3 and PALOMA-2 (Cohort 1 and 6) were also pooled per type of treatment.

Additional supportive safety data were obtained from the PALOMA study, in which amivantamab SC is used as monotherapy.

Table 34: Number of Participants Included in the Safety Analysis Set

IV	SC			
PALOMA-3		Combined PALOMA-3 and PALOMA-2	PALOMA-2	PALOMA
Ami IV	Ami SC	Ami SC (P-3) combined with Cohorts 1 and 6 (P-2)	Cohorts 1 and 6	All Cohorts
210	206	331	125	105

Table 35: Overview of the Clinical Studies Included in the SCS

Study Name Study Number Status	Study Design	Role in SCS CCO	Population	Treatment	Number of Subjects	Median Total Duration of Treatment
PALOMA-3 61186372NSC3004 Ongoing	A Phase 3, open-label, randomized non-inferiority study	**Pivotal** 03 January 2024	Participants with EGFRm (EGFR Exon 19del or Exon 21 L858R mutation) advanced or metastatic NSCLC after progression on osimertinib and chemotherapy	Arm A: Amivantamab SC Q2W + lazertinib Arm B: Amivantamab IV Q2W + lazertinib	N=206 N=210	4.65 months 4.12 months
PALOMA-2 61186372NSC2002 Ongoing	A Phase 2, open-label, parallel cohort, interventional study	**Supportive** 06 January 2024	Cohort 1: participants with treatment-naïve locally advanced or metastatic NSCLC harboring an EGFR Exon 19del or Exon 21 L858R mutation	Cohort 1: Amivantamab SC Q2W + lazertinib	N=68	9.61 months
			Cohort 6: participants with treatment-naïve locally advanced or metastatic NSCLC harboring an EGFR Exon 19del or Exon 21 L858R mutation treated with prophylactic anticoagulation	Cohort 6: Amivantamab SC Q2W + lazertinib	N=57	6.05 months
PALOMA 61186372NSC1003 Ongoing	A Phase 1b, open-label, non-randomized study	**Supportive** 30 October 2023	Participants with advanced solid malignancies	Cohort 3a: Ami-HC-CF Q2W	N=25	2.5 months
				Cohort 4a (GEN2[1]): Ami-HC-CF Q2W	N=22 N=25	1.4 months 1.4 months

Ami=amivantamab; CCO=clinical cut off; CF=co-formulated with rHuPH20; HC=high concentration; IV=intravenous; LC=lower concentration; SC=subcutaneous; SCS=summary of clinical safety

2.5.8.1. Patient exposure

Subject Disposition

Table 36: Treatment Disposition; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Analysis set: Safety	210	206	125	331
Subjects ongoing any study agent	96 (45.7%)	92 (44.7%)	104 (83.2%)	196 (59.2%)
Discontinued all study agents	114 (54.3%)	114 (55.3%)	21 (16.8%)	135 (40.8%)
Discontinued any study agents	118 (56.2%)	114 (55.3%)	25 (20.0%)	139 (42.0%)
Reason for discontinuation of Amivantamab				
Progressive Disease	84 (40.0%)	87 (42.2%)	7 (5.6%)	94 (28.4%)
Adverse Event	27 (12.9%)	21 (10.2%)	15 (12.0%)	36 (10.9%)
Subject Refused Further Study Treatment	5 (2.4%)	4 (1.9%)	3 (2.4%)	7 (2.1%)
Physician Decision	1 (0.5%)	2 (1.0%)	0	2 (0.6%)
Reason for discontinuation of Lazertinib				
Progressive Disease	83 (39.5%)	85 (41.3%)	7 (5.6%)	92 (27.8%)
Adverse Event	25 (11.9%)	23 (11.2%)	11 (8.8%)	34 (10.3%)
Subject Refused Further Study Treatment	5 (2.4%)	4 (1.9%)	3 (2.4%)	7 (2.1%)
Physician Decision	2 (1.0%)	2 (1.0%)	0	2 (0.6%)

Key: IV=Intravenous; SC=Subcutaneous

Summary of exposure

Table 37: Summary of Exposure to Study Agent; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib			Amivantamab SC + Lazertinib								
	PALOMA-3			PALOMA-3			PALOMA-2 Cohort 1 and 6			Combined		
	Any[a]	Amivantamab IV	Lazertinib	Any[a]	Amivantamab SC	Lazertinib	Any[a]	Amivantamab SC	Lazertinib	Any[a]	Amivantamab SC	Lazertinib
Analysis Set: Safety	210	210	210	206	206	206	125	125	125	331	331	331
Duration of treatment (months)												
N	210	210	210	206	206	206	125	125	125	331	331	331
Mean (SD)	4.44 (3.046)	4.03 (3.029)	4.29 (2.969)	5.12 (3.345)	4.66 (3.262)	5.04 (3.303)	7.13 (2.920)	6.66 (2.909)	7.10 (2.907)	5.88 (3.332)	5.42 (3.276)	5.82 (3.309)
Median	4.12	3.68	3.75	4.65	4.12	4.60	6.80	6.47	6.80	5.72	5.32	5.59
Range	(0.0; 13.2)	(0.0; 12.9)	(0.0; 13.2)	(0.1; 13.2)	(0.0; 12.5)	(0.1; 13.2)	(0.5; 12.9)	(0.0; 12.5)	(0.5; 12.9)	(0.1; 13.2)	(0.0; 12.5)	(0.1; 13.2)
Cumulative duration of treatment (months)												
>=3	132 (62.9%)	120 (57.1%)	127 (60.5%)	140 (68.0%)	129 (62.6%)	140 (68.0%)	109 (87.2%)	106 (84.8%)	109 (87.2%)	249 (75.2%)	235 (71.0%)	249 (75.2%)
>=6	56 (26.7%)	52 (24.8%)	52 (24.8%)	68 (33.0%)	64 (31.1%)	64 (31.1%)	88 (70.4%)	82 (65.6%)	86 (68.8%)	156 (47.1%)	146 (44.1%)	150 (45.3%)
>=9	19 (9.0%)	18 (8.6%)	18 (8.6%)	34 (16.5%)	28 (13.6%)	32 (15.5%)	45 (36.0%)	34 (27.2%)	45 (36.0%)	79 (23.9%)	62 (18.7%)	77 (23.3%)
>=12	4 (1.9%)	2 (1.0%)	4 (1.9%)	7 (3.4%)	4 (1.9%)	7 (3.4%)	2 (1.6%)	1 (0.8%)	2 (1.6%)	9 (2.7%)	5 (1.5%)	9 (2.7%)
Cumulative dose (mg)												

	Amivantamab IV + Lazertinib		Amivantamab SC + Lazertinib								
	PALOMA-3		PALOMA-3			PALOMA-2 Cohort 1 and 6			Combined		
	Any[a]	Amivantamab IV	Lazertinib	Any[a]	Amivantamab SC	Lazertinib	Any[a]	Amivantamab SC	Lazertinib	Any[a]	Amivantamab SC	Lazertinib
N		210	210		206	206		125	125		331	331
Mean (SD)		11696.24 (7331.392)	26815.24 (18833.767)		19117.25 (10862.364)	29094.76 (18594.382)		24665.60 (9556.546)	45047.68 (19870.145)		21212.55 (10717.814)	35119.27 (20570.305)
Median		11200.00	23640.00		17600.00	25560.00		25472.00	44640.00		20768.00	32640.00
Range		(16.8; 43400.0)	(240.0; 94800.0)		(1600.0; 67200.0)	(720.0; 87360.0)		(1600.0; 44800.0)	(3360.0; 86400.0)		(1600.0; 67200.0)	(720.0; 87360.0)
Total dose days												
N			210			206			125			331
Mean (SD)			119.4 (84.19)			138.2 (90.20)			201.6 (85.49)			162.1 (93.55)
Median			107.5			120.5			201.0			155.0
Range			(1; 395)			(3; 385)			(14; 367)			(3; 385)
Relative dose intensity (%)												
N		210	210		206	206		125	125		331	331
Mean (SD)		89.25 (18.490)	83.94 (20.054)		91.94 (12.173)	85.58 (16.040)		99.96 (1.121)	92.85 (9.728)		94.97 (10.378)	88.32 (14.417)
Median		98.94	91.75		98.63	90.43		100.00	97.77		100.00	93.88
Range		(1.2; 100.4)	(11.3; 100.0)		(25.0; 100.5)	(15.8; 100.0)		(87.6; 100.5)	(59.9; 100.0)		(25.0; 100.5)	(15.8; 100.0)

Key: IV=Intravenous; SC=Subcutaneous
[a.] Duration of treatment for subjects who received 'any' study drug in combination arm is the maximum duration of amivantamab IV + lazertinib or amivantamab SC+ lazertinib received.
Note: Relative dose intensity is actual divided by prescribed cumulative doses after that multiply by 100%
Note: The mean value of the treatment duration varies, Amivantamab IV first dosing is split into Cycle 1 Day 1 and Day 2 (duration will be counted two days) whereas Amivantamab SC will be just 1 day for each subject.
Lazertinib is collected on the interval basis, if the start date is before the clinical cut off date, the entire exposure interval will be included even though the end date is beyond clinical cut off.

2.5.8.2. Adverse events

Summary of Treatment-emergent Adverse Events

Table 38: Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Analysis set: Safety	210	206	125	331
Subjects with 1 or more:				
AEs	209 (99.5%)	204 (99.0%)	125 (100.0%)	329 (99.4%)
Related AEs[a]	206 (98.1%)	196 (95.1%)	125 (100.0%)	321 (97.0%)
Related to Amivantamab[a]	205 (97.6%)	194 (94.2%)	125 (100.0%)	319 (96.4%)
Related to Lazertinib[a]	200 (95.2%)	192 (93.2%)	125 (100.0%)	317 (95.8%)
Grade 3 or greater AEs	118 (56.2%)	107 (51.9%)	59 (47.2%)	166 (50.2%)
Related Grade 3 or greater AEs[a]	82 (39.0%)	79 (38.3%)	46 (36.8%)	125 (37.8%)
Related to Amivantamab[a]	77 (36.7%)	69 (33.5%)	42 (33.6%)	111 (33.5%)
Related to Lazertinib[a]	64 (30.5%)	66 (32.0%)	40 (32.0%)	106 (32.0%)
Maximum toxicity grade				
Grade 1	9 (4.3%)	7 (3.4%)	5 (4.0%)	12 (3.6%)
Grade 2	82 (39.0%)	90 (43.7%)	61 (48.8%)	151 (45.6%)
Grade 3	96 (45.7%)	92 (44.7%)	51 (40.8%)	143 (43.2%)
Grade 4	12 (5.7%)	8 (3.9%)	6 (4.8%)	14 (4.2%)
Grade 5	10 (4.8%)	7 (3.4%)	2 (1.6%)	9 (2.7%)
Serious AEs	64 (30.5%)	59 (28.6%)	31 (24.8%)	90 (27.2%)
Related serious AEs[a]	34 (16.2%)	33 (16.0%)	20 (16.0%)	53 (16.0%)
Related to Amivantamab[a]	33 (15.7%)	29 (14.1%)	18 (14.4%)	47 (14.2%)
Related to Lazertinib[a]	26 (12.4%)	27 (13.1%)	16 (12.8%)	43 (13.0%)
AEs leading to dose reduction	52 (24.8%)	63 (30.6%)	59 (47.2%)	122 (36.9%)
AEs leading to dose reduction of Amivantamab	25 (11.9%)	34 (16.5%)	47 (37.6%)	81 (24.5%)
AEs leading to dose reduction of Lazertinib	45 (21.4%)	55 (26.7%)	43 (34.4%)	98 (29.6%)
AEs leading to drug interruption[b]	127 (60.5%)	127 (61.7%)	78 (62.4%)	205 (61.9%)
AEs leading to interruption of Amivantamab[b]	101 (48.1%)	105 (51.0%)	71 (56.8%)	176 (53.2%)
AEs leading to interruption of Lazertinib[b]	112 (53.3%)	113 (54.9%)	58 (46.4%)	171 (51.7%)
AEs leading to discontinuation of study agent	29 (13.8%)	26 (12.6%)	16 (12.8%)	42 (12.7%)
AEs leading to discontinuation of Amivantamab	28 (13.3%)	23 (11.2%)	16 (12.8%)	39 (11.8%)
AEs leading to discontinuation of Lazertinib	26 (12.4%)	25 (12.1%)	12 (9.6%)	37 (11.2%)
AEs leading to death[c]	10 (4.8%)	7 (3.4%)	2 (1.6%)	9 (2.7%)
Related AEs leading to death[a,c]	4 (1.9%)	3 (1.5%)	0	3 (0.9%)
Related to Amivantamab[a,c]	3 (1.4%)	3 (1.5%)	0	3 (0.9%)
Related to Lazertinib[a,c]	3 (1.4%)	3 (1.5%)	0	3 (0.9%)
AEs related to COVID-19[d]	23 (11.0%)	18 (8.7%)	6 (4.8%)	24 (7.3%)

Key: AE = adverse event; IV=Intravenous; SC=Subcutaneous
[a] An AE is assessed by the investigator as related to study agent.
[b] Excludes infusion/administration related reactions.
[c] AEs leading to death are based on AE outcome of Fatal.
[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.

Grade 3 or Higher Treatment-emergent Adverse Events

Table 39: Number of Subjects with Toxicity Grade 3 or Higher Treatment emergent Adverse Events With Frequency of at Least 2% in Any Treatment Group by System Organ Class and Preferred Term (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Analysis set: Safety	210	206	125	331
Subjects with 1 or more grade >=3 AEs	118 (56.2%)	107 (51.9%)	59 (47.2%)	166 (50.2%)
System organ class Preferred term				
Skin and subcutaneous tissue disorders	23 (11.0%)	30 (14.6%)	29 (23.2%)	59 (17.8%)
Dermatitis acneiform	12 (5.7%)	18 (8.7%)	11 (8.8%)	29 (8.8%)
Rash	8 (3.8%)	8 (3.9%)	12 (9.6%)	20 (6.0%)
Infections and infestations	22 (10.5%)	19 (9.2%)	13 (10.4%)	32 (9.7%)
Paronychia	3 (1.4%)	8 (3.9%)	4 (3.2%)	12 (3.6%)
Pneumonia	7 (3.3%)	3 (1.5%)	4 (3.2%)	7 (2.1%)
Metabolism and nutrition disorders	17 (8.1%)	21 (10.2%)	7 (5.6%)	28 (8.5%)
Hypoalbuminaemia	8 (3.8%)	9 (4.4%)	3 (2.4%)	12 (3.6%)
Hypokalaemia	2 (1.0%)	5 (2.4%)	2 (1.6%)	7 (2.1%)
Respiratory, thoracic and mediastinal disorders	12 (5.7%)	18 (8.7%)	3 (2.4%)	21 (6.3%)
Pneumonitis	3 (1.4%)	6 (2.9%)	0	6 (1.8%)
Gastrointestinal disorders	13 (6.2%)	13 (6.3%)	7 (5.6%)	20 (6.0%)
Stomatitis	5 (2.4%)	1 (0.5%)	4 (3.2%)	5 (1.5%)
General disorders and administration site conditions	11 (5.2%)	14 (6.8%)	4 (3.2%)	18 (5.4%)
Oedema peripheral	1 (0.5%)	6 (2.9%)	2 (1.6%)	8 (2.4%)
Fatigue	5 (2.4%)	3 (1.5%)	1 (0.8%)	4 (1.2%)
Investigations	11 (5.2%)	9 (4.4%)	7 (5.6%)	16 (4.8%)
Alanine aminotransferase increased	8 (3.8%)	6 (2.9%)	3 (2.4%)	9 (2.7%)
Aspartate aminotransferase increased	3 (1.4%)	2 (1.0%)	3 (2.4%)	5 (1.5%)
Blood and lymphatic system disorders	23 (11.0%)	9 (4.4%)	5 (4.0%)	14 (4.2%)
Anaemia	5 (2.4%)	4 (1.9%)	2 (1.6%)	6 (1.8%)
Lymphopenia	17 (8.1%)	1 (0.5%)	2 (1.6%)	3 (0.9%)
Injury, poisoning and procedural complications	8 (3.8%)	6 (2.9%)	0	6 (1.8%)
Infusion related reaction[a]	8 (3.8%)	1 (0.5%)	0	1 (0.3%)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined

Key: AE = adverse event; IV=Intravenous; SC=Subcutaneous
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 25.1.
[a] Infusion related reaction reported in PALOMA-3 Amivantamab SC arm and Administration related reaction reported in the PALOMA-2 are considered as a systemic reaction related to subcutaneous administration. Administration related reaction from PALOMA-2 is displayed as Infusion related reaction in this table.

2.5.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 40: Number of Subjects With Treatment-emergent Serious Adverse Events With Frequency of at Least 2% in Any Treatment Group by System Organ Class and Preferred Term; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Analysis set: Safety	210	206	125	331
Subjects with 1 or more SAEs	64 (30.5%)	59 (28.6%)	31 (24.8%)	90 (27.2%)
System organ class Preferred term				
Respiratory, thoracic and mediastinal disorders	15 (7.1%)	19 (9.2%)	5 (4.0%)	24 (7.3%)
Pneumonitis	6 (2.9%)	9 (4.4%)	1 (0.8%)	10 (3.0%)
Infections and infestations	18 (8.6%)	14 (6.8%)	9 (7.2%)	23 (6.9%)
Pneumonia	7 (3.3%)	3 (1.5%)	4 (3.2%)	7 (2.1%)
Injury, poisoning and procedural complications	2 (1.0%)	5 (2.4%)	3 (2.4%)	8 (2.4%)
Infusion related reaction[a]	2 (1.0%)	0	3 (2.4%)	3 (0.9%)
VaSCular disorders	9 (4.3%)	3 (1.5%)	4 (3.2%)	7 (2.1%)
Deep vein thrombosis	4 (1.9%)	2 (1.0%)	3 (2.4%)	5 (1.5%)

Key: SAE = serious adverse event; IV=Intravenous; SC=Subcutaneous
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 25.1.
[a] Infusion related reaction reported in PALOMA-3 Amivantamab SC arm and Administration related reaction reported in the PALOMA-2 are considered as a systemic reaction related to subcutaneous administration. Administration related reaction from PALOMA-2 is displayed as Infusion related reaction in this table.

Deaths

Table 41: 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 IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Analysis set: Safety	210	206	125	331
Subjects with 1 or more AEs leading to death	10 (4.8%)	7 (3.4%)	2 (1.6%)	9 (2.7%)
System organ class Preferred term				
Infections and infestations	1 (0.5%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Pneumonia	0	1 (0.5%)	0	1 (0.3%)
Pneumonia viral	0	1 (0.5%)	0	1 (0.3%)
Sepsis	0	0	1 (0.8%)	1 (0.3%)
Urosepsis	1 (0.5%)	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (1.9%)	3 (1.5%)	0	3 (0.9%)
Pneumonitis	3 (1.4%)	1 (0.5%)	0	1 (0.3%)
Respiratory disorder	0	1 (0.5%)	0	1 (0.3%)
Respiratory failure	1 (0.5%)	1 (0.5%)	0	1 (0.3%)
Cardiac disorders	1 (0.5%)	1 (0.5%)	1 (0.8%)	2 (0.6%)
Cardiac arrest	0	1 (0.5%)	1 (0.8%)	2 (0.6%)
Acute myocardial infarction	1 (0.5%)	0	0	0
General disorders and administration site conditions	2 (1.0%)	1 (0.5%)	0	1 (0.3%)
Sudden death	1 (0.5%)	1 (0.5%)	0	1 (0.3%)
Asthenia	1 (0.5%)	0	0	0
Nervous system disorders	2 (1.0%)	0	0	0
Cerebral infarction	2 (1.0%)	0	0	0

Key: AE = adverse event; IV=Intravenous; SC=Subcutaneous
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 25.1.

Adverse Events of Special Interest

Table 42: Number of Subjects With Treatment-emergent Adverse Events of Special Interest by Special Interest Category and Preferred Term; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Analysis set: Safety	210	206	125	331
Subjects with 1 or more AEs of special interest	197 (93.8%)	178 (86.4%)	116 (92.8%)	294 (88.8%)
Special interest category Preferred term				
Rash	167 (79.5%)	166 (80.6%)	115 (92.0%)	281 (84.9%)
Rash	91 (43.3%)	95 (46.1%)	76 (60.8%)	171 (51.7%)
Dermatitis acneiform	69 (32.9%)	64 (31.1%)	49 (39.2%)	113 (34.1%)
Rash maculo-papular	10 (4.8%)	11 (5.3%)	8 (6.4%)	19 (5.7%)
Rash pustular	5 (2.4%)	7 (3.4%)	10 (8.0%)	17 (5.1%)
Folliculitis	6 (2.9%)	4 (1.9%)	5 (4.0%)	9 (2.7%)
Dermatitis	8 (3.8%)	4 (1.9%)	4 (3.2%)	8 (2.4%)
Erythema	6 (2.9%)	4 (1.9%)	4 (3.2%)	8 (2.4%)
Rash papular	1 (0.5%)	5 (2.4%)	0	5 (1.5%)
Erythema multiforme	0	0	4 (3.2%)	4 (1.2%)
Skin lesion	4 (1.9%)	1 (0.5%)	3 (2.4%)	4 (1.2%)
Papule	1 (0.5%)	1 (0.5%)	2 (1.6%)	3 (0.9%)
Rash erythematous	1 (0.5%)	3 (1.5%)	0	3 (0.9%)
Rash macular	0	1 (0.5%)	2 (1.6%)	3 (0.9%)
Skin exfoliation	1 (0.5%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Acne	4 (1.9%)	1 (0.5%)	1 (0.8%)	2 (0.6%)
Acne varioliformis	0	2 (1.0%)	0	2 (0.6%)
Dermatitis infected	0	1 (0.5%)	0	1 (0.3%)
Perineal rash	1 (0.5%)	1 (0.5%)	0	1 (0.3%)
Rash follicular	0	1 (0.5%)	0	1 (0.3%)
Rash pruritic	0	1 (0.5%)	0	1 (0.3%)
Infusion Related Reaction[a]	138 (65.7%)	27 (13.1%)	19 (15.2%)*	46 (13.9%)*
Infusion Related Reaction[a]	138 (65.7%)	27 (13.1%)	19 (15.2%)*	46 (13.9%)*
Venous Thromboembolic Event	30 (14.3%)	19 (9.2%)	16 (12.8%)	35 (10.6%)
Deep vein thrombosis	11 (5.2%)	5 (2.4%)	8 (6.4%)	13 (3.9%)
Pulmonary embolism	9 (4.3%)	6 (2.9%)	3 (2.4%)	9 (2.7%)
Venous thrombosis limb	3 (1.4%)	3 (1.5%)	3 (2.4%)	6 (1.8%)
Embolism	3 (1.4%)	2 (1.0%)	3 (2.4%)	5 (1.5%)
Embolism venous	3 (1.4%)	3 (1.5%)	1 (0.8%)	4 (1.2%)
Thrombosis	1 (0.5%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Subclavian vein thrombosis	0	1 (0.5%)	0	1 (0.3%)
Superficial vein thrombosis	0	1 (0.5%)	0	1 (0.3%)
Pulmonary infarction	1 (0.5%)	0	0	0
Venous thrombosis	3 (1.4%)	0	0	0
Local Administration Related Reaction	0	20 (9.7%)	0	20 (6.0%)
Administration Related Reaction[b]	0	20 (9.7%)	0	20 (6.0%)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Pneumonitis/Interstitial Lung Disease	7 (3.3%)	12 (5.8%)	2 (1.6%)	14 (4.2%)
Pneumonitis	6 (2.9%)	9 (4.4%)	1 (0.8%)	10 (3.0%)
Interstitial lung disease	1 (0.5%)	3 (1.5%)	1 (0.8%)	4 (1.2%)

Key: AE = adverse event; IV=Intravenous; SC=Subcutaneous
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 25.1.
[a] Infusion related reaction reported in PALOMA-3 Amivantamab SC arm and Administration related reaction reported in the PALOMA-2 are considered as a systemic reaction related to subcutaneous administration. Administration related reaction from PALOMA-2 is displayed as Infusion related reaction in this table.
[b] Administration related reaction reported in PALOMA-3 Amivantamab SC arm is considered as a local reaction related to subcutaneous administration. In PALOMA-2, LARRs were not reported separately from ARRs.
[*] Including one subject who had only local redness and swelling without any systemic reactions.

IRR/ARR

The incidence of IRR/ARR was substantially lower in the amivantamab SC arm compared with the amivantamab IV arm of the PALOMA-3 study. The incidence of IRR/ARR with amivantamab SC was also substantially lower compared with prior studies with amivantamab IV (62.9% in MARIPOSA).

In PALOMA-3, the incidence of IRR/ARRs was substantially lower in the amivantamab SC arm (13.1%) compared with the amivantamab IV arm (65.7%). Most IRR/ARRs were Grade 1 or 2; no Grade 4 or 5 IRR/ARRs were reported. The incidence of Grade 3 IRR/ARRs was generally low and lower in the amivantamab SC arm (1 participant [0.5%]) compared with the amivantamab IV arm (8 participants [3.8%]). Serious IRRs were reported for 2 (1.0%) participants, both in the amivantamab IV arm. The incidence of IRR/ARRs leading to interruption of any study treatment was substantially lower in the amivantamab SC arm (1.0%) compared with the amivantamab IV arm (55.2%). IRRs leading to discontinuation of any study treatment were reported for 4 (1.9%) participants, all in the amivantamab IV arm.

The majority of IRR/ARR events occurred at Cycle 1. The median time to first onset of IRR/ARR s was 107.0 (range: 2; 2056) minutes in the amivantamab SC arm and 55.0 (range: 0, 395) minutes in the amivantamab IV arm. The median duration of IRR/ARR s, relative to the dose prior to the IRR/ARR event, was 124.0 (range: 15; 600) minutes in the amivantamab SC arm and 68.0 (range: 0; 3013) minutes in the amivantamab IV arm). Most administration-related reactions (98%) were Grades 1 or 2 in severity.

The incidence of LARRs was low in the amivantamab SC arm (9.7%) and all events were Grade 1 or Grade 2. No LARRs were reported in the amivantamab IV arm.

In PALOMA-2 (Cohorts 1 and 6 combined), ARRs were reported for 15.2% of participants. All ARRs were Grade 1 or 2. Serious ARRs were reported for 2.4% of participants. None of the ARRs led to study treatment discontinuation.

The median time to first onset of ARRs was 138.0 (range: 19; 434) minutes. The median duration of ARR was 60.0 (range: 10; 190) minutes.

VTE

VTE events is a risk identified with the combination of amivantamab and lazertinib during the MARIPOSA study, in 1L patients with EGFR mutated NSCLC. Consequently, prophylactic anticoagulation

was recommended for the first 4 months of treatment in all ongoing studies of amivantamab in combination with lazertinib.

The criteria for classifying a participant as having received full, partial, or no prophylactic anticoagulation were as follows:

- any participant who received anticoagulation prior to or at C1D1 plus a 3-day window and continued without interruption until progression, death, withdrawal from the study, occurrence of VTE, or C5D1 was considered to have received **full prophylactic anticoagulation**.
- any participant who received prophylactic anticoagulant prior to C5D1 and had interruption was considered to have received **partial prophylactic anticoagulation.**
- participants who never took prophylactic anticoagulation during the first 4 months of amivantamab and lazertinib combination treatment were part of the **no prophylactic anticoagulation group.**

The uptake of prophylactic anticoagulation in PALOMA-3 was high and comparable between the 2 treatment arms with 164 (79.6%) and 171 (81.4%) participants on (full or partial) anticoagulation in the amivantamab SC and IV arm, respectively.

Overall, 49 (11.8%) participants experiencing VTE events. Despite similar rates of anticoagulation use, the incidence of VTE events was lower in the amivantamab SC arm (9.2%) compared with the amivantamab IV arm (14.3%). Most VTE events were Grade 1 or Grade 2. Grade 3 VTE events were reported in 2 participants (1.0%) in the amivantamab SC arm and in 6 participants (2.9%) in the amivantamab IV arm. One Grade 4 VTE event (in the amivantamab IV arm) and no Grade 5 VTE events were reported.

Serious VTE events were reported for 4 (1.9%) and 7 (3.3%) participants in the amivantamab SC and IV arm, respectively. Study treatment discontinuation due to VTE was reported for 2 participants (1.0%), both in the amivantamab IV arm. The median time to first onset of VTE events was 43 (range: 17; 170) days for amivantamab SC and 88.5 (range: 12; 325) days for amivantamab IV.

Notably, the incidence of VTE events was significantly reduced in the participants who received full and partial anticoagulation, respectively, as compared with participants who received no anticoagulation. This was observed in both IV and SC arms.

The incidence of VTE events for participants who received no anticoagulation was lower in the amivantamab SC arm (16.7%), with all VTE reactions reported as Grade 1-2 and serious VTE reactions reported in 4.8% of these patients compared with the amivantamab IV arm (25.6%) (with Grade 3 VTE reactions reported in 10% and serious VTE reactions reported in 8% of these patients).

The incidence of bleeding events was higher in participants who received anticoagulation (20.9% on full and 40.0% on partial) compared to those who did not (12.3%), which is expected with anticoagulation therapy (Raskob 2018). The majority of bleeding events were Grade 1 or Grade 2. Overall, there was only 1 (0.2%) discontinuation due to a bleeding event.

In **PALOMA-2, Cohort 1,** in which prophylactic anticoagulation was recommended, 48 participants (70.6%) were on anticoagulation (32.3% on full anticoagulation and 38.2% on partial anticoagulation) and 20 participants (29.4%) did not receive anticoagulation. VTE events were reported for 12 participants (17.6%). Serious VTE events were reported for 4 (5.9%) participants. No study treatment discontinuation due to VTE event was reported. The median time to first onset of VTE event was 123.5 (range: 4; 284) days.

The incidence of bleeding events was higher in participants who received anticoagulation (27.3% on full and 30.8% on partial) compared to those who did not (20.0%). All bleeding events were Grade 1 or Grade 2, non-serious, and none of the bleeding events led to treatment discontinuation.

In **PALOMA-2 Cohort 6,** in which prophylactic anticoagulation was mandatory, all 57 participants were on anticoagulation (84.2% on full anticoagulation and 15.8% on partial anticoagulation). VTE events were reported for 4 participants (7.0%). A serious VTE event was reported for 1 (1.8%) participant. VTE led to study drug interruption for 1 participant (1.8%). The median time to first onset of VTE event was 130.0 (43; 183) days.

Bleeding events were experienced by 33.3% of participants who received full anticoagulation and by 88.9% of participants who received partial anticoagulation. All bleeding events were Grade 1 or Grade 2. Two participants (on full anticoagulation) had serious bleeding events. One participant had a bleeding event that led to treatment discontinuation.

Table 43: Overall Summary of Treatment-emergent Adverse Events VTEs; Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Analysis set: Safety	210	206	125	331
Subjects with 1 or more:				
VTEs	30 (14.3%)	19 (9.2%)	16 (12.8%)	35 (10.6%)
Related VTEs [a]	22 (10.5%)	16 (7.8%)	14 (11.2%)	30 (9.1%)
Related to Amivantamab[a]	22 (10.5%)	16 (7.8%)	13 (10.4%)	29 (8.8%)
Related to Lazertinib[a]	21 (10.0%)	16 (7.8%)	12 (9.6%)	28 (8.5%)
Grade 3 or higher VTEs	7 (3.3%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Related Grade 3 or higher VTEs[a]	6 (2.9%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Related to Amivantamab[a]	6 (2.9%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Related to Lazertinib[a]	5 (2.4%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Maximum toxicity grade				
Grade 1	7 (3.3%)	1 (0.5%)	1 (0.8%)	2 (0.6%)
Grade 2	16 (7.6%)	16 (7.8%)	14 (11.2%)	30 (9.1%)
Grade 3	6 (2.9%)	2 (1.0%)	1 (0.8%)	3 (0.9%)
Grade 4	1 (0.5%)	0	0	0
Grade 5	0	0	0	0
Serious VTEs	7 (3.3%)	4 (1.9%)	5 (4.0%)	9 (2.7%)
Related serious VTEs[a]	5 (2.4%)	4 (1.9%)	5 (4.0%)	9 (2.7%)
Related to Amivantamab[a]	5 (2.4%)	4 (1.9%)	5 (4.0%)	9 (2.7%)
Related to Lazertinib[a]	5 (2.4%)	4 (1.9%)	5 (4.0%)	9 (2.7%)
VTEs leading to dose reduction	1 (0.5%)	1 (0.5%)	0	1 (0.3%)
VTEs leading to dose reduction of Amivantamab	1 (0.5%)	1 (0.5%)	0	1 (0.3%)
VTEs leading to dose reduction of Lazertinib	0	0	0	0
VTEs leading to drug interruption	7 (3.3%)	5 (2.4%)	3 (2.4%)	8 (2.4%)
VTEs leading to interruption of Amivantamab	6 (2.9%)	4 (1.9%)	3 (2.4%)	7 (2.1%)
VTEs leading to interruption of Lazertinib	6 (2.9%)	4 (1.9%)	1 (0.8%)	5 (1.5%)
VTEs leading to diSContinuation of study agent	2 (1.0%)	0	0	0
VTEs leading to diSContinuation of Amivantamab	2 (1.0%)	0	0	0
VTEs leading to diSContinuation of Lazertinib	2 (1.0%)	0	0	0
VTEs leading to death [b]	0	0	0	0

	Amivantamab IV + Lazertinib	Amivantamab SC + Lazertinib		
	PALOMA-3	PALOMA-3	PALOMA-2 Cohort 1 and 6	Combined
Related VTEs leading to death[a,b]	0	0	0	0
Related to Amivantamab[a,b]	0	0	0	0
Related to Lazertinib[a,b]	0	0	0	0

Key: VTE=Venous Thromboembolic Event; IV=Intravenous; SC=Subcutaneous
[a] A VTE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: VTEs include all Embolic and thrombotic events, venous (SMQ), Thrombosis and Embolism events.

Table 44: Number of Subjects With Treatment-emergent VTEs by Preferred Term and Use of Anticoagulants; Safety Analysis Set (Study Integrated Safety Summary)

Table

	Amivantamab IV + Lazertinib				Amivantamab SC + Lazertinib								
	PALOMA-3				PALOMA-3				PALOMA-2 Cohort 1 and 6				
	Total	On Anticoagulation	Partial Anticoagulation	No Anticoagulation	Total	On Anticoagulation	Partial Anticoagulation	No Anticoagulation	Total	On Anticoagulation	Partial Anticoagulation	No Anticoagulation	Total
Safety Analysis Set	210	112	59	39	206	108	56	42	125	70	35	20	331
Subjects with 1 or more VTEs	30 (14.3%)	14 (12.5%)	6 (10.2%)	10 (25.6%)	19 (9.2%)	7 (6.5%)	5 (8.9%)	7 (16.7%)	16 (12.8%)	6 (8.6%)	6 (17.1%)	4 (20.0%)	35 (10.6%)
Preferred term													
Deep vein thrombosis	11 (5.2%)	5 (4.5%)	3 (5.1%)	3 (7.7%)	5 (2.4%)	1 (0.9%)	2 (3.6%)	2 (4.8%)	8 (6.4%)	2 (2.9%)	3 (8.6%)	3 (15.0%)	13 (3.9%)
Pulmonary embolism	9 (4.3%)	5 (4.5%)	1 (1.7%)	3 (7.7%)	6 (2.9%)	2 (1.9%)	2 (3.6%)	2 (4.8%)	3 (2.4%)	1 (1.4%)	1 (2.9%)	1 (5.0%)	9 (2.7%)
Venous thrombosis limb	3 (1.4%)	1 (0.9%)	0	2 (5.1%)	3 (1.5%)	0	3 (5.4%)	0	3 (2.4%)	1 (1.4%)	2 (5.7%)	0	6 (1.8%)
Embolism	3 (1.4%)	1 (0.9%)	1 (1.7%)	1 (2.6%)	2 (1.0%)	1 (0.9%)	0	1 (2.4%)	3 (2.4%)	1 (1.4%)	2 (5.7%)	0	5 (1.5%)
Embolism venous	3 (1.4%)	0	2 (3.4%)	1 (2.6%)	3 (1.5%)	2 (1.9%)	0	1 (2.4%)	1 (0.8%)	1 (1.4%)	0	0	4 (1.2%)
Pulmonary infarction	1 (0.5%)	0	0	1 (2.6%)	0	0	0	0	0	0	0	0	0
Venous thrombosis	3 (1.4%)	2 (1.8%)	0	1 (2.6%)	0	0	0	0	0	0	0	0	0
Subclavian vein thrombosis	0	0	0	0	1 (0.5%)	1 (0.9%)	0	0	0	0	0	0	1 (0.3%)
Superficial vein thrombosis	0	0	0	0	1 (0.5%)	0	0	1 (2.4%)	0	0	0	0	1 (0.3%)
Thrombosis	1 (0.5%)	1 (0.9%)	0	0	2 (1.0%)	0	1 (1.8%)	1 (2.4%)	1 (0.8%)	1 (1.4%)	0	0	3 (0.9%)

Key: VTE=Venous Thromboembolic Event; IV=Intravenous; SC=Subcutaneous
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. Adverse events are coded
25.1.
On Prophylactic Anticoagulation: Any subject who had anticoagulation prior or at C1D1 plus 3 days window and continue without interruption until progre
the study, occurrence of VTE or C5D1.
Partial Prophylactic Anticoagulation: Any subject who was on prophylactic anticoagulant prior to C5D1 and had interruption.
No Prophylactic Anticoagulation: Subjects who never took prophylactic anticoagulation during first 4 months of amivantamab and lazertinib combination t

Rash

The incidence of rash (grouped term) was similar between the amivantamab SC and amivantamab IV arms.

In **PALOMA-3**, rash was reported with a similar incidence in the amivantamab SC arm (80.6%) compared with the amivantamab IV arm (79.5%). Most rash events were Grade 1 or 2. The incidence of Grade 3 rash was similar between the amivantamab SC arm (13.6%) and the amivantamab IV arm (11.0%). One participant in each treatment arm experienced Grade 4 rash. No Grade 5 rash was reported.

The median duration of rash events was 26.5 (range: 1; 270) days in the amivantamab SC arm and 25.0 (range: 1; 278) days in the amivantamab IV arm.

In **PALOMA-2 (Cohorts 1 and 6 combined)**, rash was reported for 92.0% of participants. Most rash events were Grade 1 or 2. No Grade 4 or 5 rash was reported. Grade 3 rash was reported for 21.6% of participants. Serious rash was reported for 2 participants. Rash led to study treatment discontinuation in 2 participants.

The median time to first onset of rash was 14.0 (range: 1; 143) days.

The results of the **pooled analysis** are consistent with the observations from the individual studies. Rash (including dermatitis acneiform), pruritus, and dry skin have occurred in patients treated with Rybrevant (either intravenous or subcutaneous formulation) in combination with lazertinib. **Rash** occurred in 87% of patients, leading to discontinuation of Rybrevant in 0.7% of patients. Most cases were Grade 1 or 2, with Grade 3 and Grade 4 reactions occurring in 23% and 0.1% of patients, respectively**.**

Pneumonitis/ILD

The incidence of pneumonitis/ILD (grouped term) was low and similar between the amivantamab SC and amivantamab IV arms, and in line with historical data.

In **PALOMA-3**, the incidence of pneumonitis/ILD was similar between the amivantamab SC arm (12 participants [5.8%]) and the amivantamab IV arm (7 participants [3.3%]). Most pneumonitis/ILD events were Grade 1 or 2. Grade 3 and 4 pneumonitis/ILD was reported for 3 and 4 participants, respectively, all in the amivantamab SC arm. Grade 5 pneumonitis/ILD was reported for 1 and 3 participants in the amivantamab SC arm and IV arms, respectively. Pneumonitis/ILD led to study treatment discontinuation in 10 and 7 participants in the amivantamab SC and IV arms, respectively.

The median time to first onset of pneumonitis/ILD was 73.0 (range: 10; 166) days for amivantamab SC and 83.0 (range: 8; 251) days for amivantamab IV.

In **PALOMA-2 (Cohorts 1 and 6 combined)**, 2 participants reported pneumonitis/ILD, 1 Grade 2 and 1 Grade 3. Both events led to study treatment discontinuation.

The results of the **pooled analysis** are consistent with the observations from the individual studies.

Adverse Drug Reactions

The selection of new ADRs for amivantamab SC is based on the data from the PALOMA-3 SC arm and PALOMA-2 Cohorts 1 and 6 and takes into consideration prior experience with amivantamab IV.

Based on this methodology, 32 PTs were identified for amivantamab SC. The ADRs determined for amivantamab SC have all been previously identified in prior amivantamab IV ADR determinations, with 2 exceptions:

- Systemic administration related reaction[2]
- Injection site reaction

These 2 ADRs were driven by SC mode of administration. Systemic administration relation reactions are systemic reactions triggered by the introduction of a new therapeutic protein, akin to IRRs observed with amivantamab IV administration. Injection site reactions are local phenomenon defined as a constellation of symptoms, including pain, dryness, urticaria, hematoma, and hemorrhage.

In addition, 3 new PTs were identified and added to pre-existing amivantamab IV ADR grouped terms:

- Fatigue (grouped term) had 1 new PT added (malaise)
- Other eye disorders (grouped term) had 1 new PT added (lacrimation increased)
- Venous thromboembolism (grouped term) had 1 new PT added (subclavian vein thrombosis)

In Table 45, data from the PALOMA-3 SC arm and PALOMA-2 Cohorts 1 and 6 were pooled. Frequency of occurrence was calculated for each ADR term using this pooled population (n=331).

Table 45: Incidence of Treatment emergent Adverse Drug Reactions (ADRs) for Amivantamab SC by System Organ Class, Preferred Term and Toxicity Grade (Study 61186372NSC2002 - Cohort 1 and 6, Study 61186372NSC3004)

			All Subjects (N=331)	
System Organ Class (SOC)	Adverse Drug Reaction	Frequency (all grades)	All Grades (%)	Grade 3-4 (%)
Skin and subcutaneous tissue disorders	Rash[a]	Very common	280 (84.6%)	56 (16.9%)
	Nail toxicity[a]	Very common	207 (62.5%)	12 (3.6%)
	Dry skin[a]	Very common	74 (22.4%)	1 (0.3%)
	Pruritus	Very common	70 (21.1%)	0
Metabolism and nutrition disorders	Hypoalbuminaemia	Very common	156 (47.1%)	12 (3.6%)
	Decreased appetite	Very common	76 (23.0%)	2 (0.6%)
	Hypocalcaemia	Very common	52 (15.7%)	0
	Hypokalaemia	Very common	36 (10.9%)	7 (2.1%)
	Hypomagnesaemia	Common	25 (7.6%)	0
Gastrointestinal disorders	Stomatitis[a]	Very common	140 (42.3%)	5 (1.5%)
	Nausea	Very common	92 (27.8%)	1 (0.3%)
	Constipation	Very common	74 (22.4%)	0
	Diarrhoea	Very common	71 (21.5%)	4 (1.2%)
	Vomiting	Very common	61 (18.4%)	2 (0.6%)
	Abdominal pain[a]	Common	25 (7.6%)	1 (0.3%)
	Haemorrhoids	Common	22 (6.6%)	0
General disorders and administration site conditions	Oedema[a]	Very common	117 (35.3%)	8 (2.4%)
	Fatigue[a]	Very common	113 (34.1%)	9 (2.7%)
	Pyrexia	Very common	35 (10.6%)	0
	Injection site reactions[a]	Common	26 (7.9%)	0
Investigations	Alanine aminotransferase increased	Very common	93 (28.1%)	9 (2.7%)
	Aspartate aminotransferase increased	Very common	83 (25.1%)	5 (1.5%)
	Blood alkaline phosphatase increased	Common	27 (8.2%)	1 (0.3%)
MuSCuloskeletal and connective tissue disorders	Myalgia	Very common	62 (18.7%)	1 (0.3%)

[2] Systemic ARR represents the PTs of ARR from PALOMA-2 and IRR from the Amivantamab SC arm of PALOMA-3

System Organ Class (SOC)	Adverse Drug Reaction	Frequency (all grades)	All Subjects (N=331) All Grades (%)	All Subjects (N=331) Grade 3-4 (%)
Eye disorders	Other eye disorders[a]	Very common	49 (14.8%)	2 (0.6%)
	Visual impairment[a]	Common	8 (2.4%)	0
	Growth of eyelashes[a]	Common	5 (1.5%)	0
	Keratitis	Uncommon	2 (0.6%)	0
Injury, poisoning and procedural complications	Systemic administration related reactions	Very common	46 (13.9%)	1 (0.3%)
Nervous system disorders	Dizziness[a]	Very common	37 (11.2%)	0
VaSCular disorders	Venous thromboembolism[a,*]	Very common	34 (10.3%)	3 (0.9%)
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[a]	Common	14 (4.2%)	8 (2.4%)

[a] Preferred terms are displayed as adverse drug reaction groupings.
[*] Assessed as ADR for Amivantamab and Lazertinib combination only.
Adverse events are coded using MedDRA Version 25.1.
Frequency category: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Table 49 summarises the ADRs as presented in SmPC section 4.8.

Table 46: Adverse reactions for Rybrevant (either intravenous or subcutaneous formulation) when received in combination with lazertinib (N=752)

System Organ Class Adverse Reaction	**Frequency category**	**Any grade (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders			
Hypoalbuminaemia*	Very common	48	4.5
Decreased appetite		24	0.8
Hypocalcaemia		19	1.2
Hypokalaemia		13	2.7
Hypomagnesaemia	Common	6	0
Nervous system disorders			
Paraesthesia*, [a]	Very common	29	1.3
Dizziness*		12	0
Eye disorders			
Other eye disorders*	Very common	19	0.5
Visual impairment*	Common	3.6	0
Keratitis		1.7	0.3
Growth of eyelashes*		1.7	0
Vascular disorders			
Venous thromboembolism			
Amivantamab intravenous*, [b]	Very common	37	11
Amivantamab subcutaneous*, [c]	Very common	11	0.9
Respiratory, thoracic, and mediastinal disorders			
Interstitial lung disease*	Common	3.6	1.7
Gastrointestinal disorders			
Stomatitis*	Very common	43	2.0
Constipation		26	0
Diarrhoea		26	1.7
Nausea		24	0.8
Vomiting		15	0.5
Abdominal pain*		10	0.1
Haemorrhoids	Common	8	0.1
Hepatobiliary disorders			
Hepatotoxicity*	Very common	43	7
Skin and subcutaneous tissue disorders			
Rash*	Very common	87	23

System Organ Class (SOC)	Adverse Drug Reaction	Frequency (all grades)	All Subjects (N=331) All Grades (%)	All Subjects (N=331) Grade 3-4 (%)
Nail toxicity*			67	8
Dry skin*			25	0.7
Pruritus			23	0.3
Palmar-plantar erythrodysaesthesia syndrome		Common	3.9	0.1
Urticaria			1.6	0
Musculoskeletal and connective tissue disorders				
Myalgia		Very common	15	0.5
Muscle spasms			13	0.4
General disorders and administration site conditions				
Oedema*		Very common	42	2.7
Fatigue*			35	3.5
Pyrexia			11	0
Injection site reactions*[, c, d]		Common	8	0
Injury, poisoning, and procedural complications				
Infusion-/Administration-related reactions				
Amivantamab intravenous[b, e]		Very common	63	6
Amivantamab subcutaneous[c, f]		Very common	14	0.3

* Grouped terms.
[a] Applicable only to lazertinib.
[b] Frequency based on amivantamab intravenous study only (MARIPOSA [N=421]).
[c] Frequency based on amivantamab subcutaneous studies only (PALOMA-2 cohorts 1 and 6 [N=125] and PALOMA-3 subcutaneous arm [N=206]).
[d] Injection site reactions are local signs and symptoms associated with subcutaneous mode of administration.
[e] Infusion-related reactions are systemic signs and symptoms associated with infusion of amivantamab intravenous.
[f] Administration-related reactions are systemic signs and symptoms associated with administration of amivantamab subcutaneous.

2.5.8.4. Laboratory findings

In **PALOMA-3**, no clinically meaningful changes during treatment were observed and results were generally comparable between treatment arms for most of the hematology laboratory parameters.

In **PALOMA-2 (Cohorts 1 and 6 combined)**, changes in hematology values were generally consistent with the established safety profile for amivantamab, and no clinically meaningful deleterious effects on hematology were observed during the treatment period. Grade ≥3 lymphocyte count decreased was observed in 8.3% of participants.

Chemistry

In **PALOMA-3**, there were no clinically meaningful changes in chemistry laboratory parameters during treatment and results were generally comparable between treatment arms. Changes in clinical chemistry values were generally consistent with the established safety profile for amivantamab. There was an increase in the rate of alkaline phosphatase increased in the amivantamab SC arm (48.3% in the amivantamab SC arm vs 38.0% in the amivantamab IV arm) and an increase in the rate of hyponatremia in the amivantamab IV arm (42.9% in the amivantamab SC arm vs 53.4% in the amivantamab IV arm).

In **PALOMA-2 (Cohorts 1 and 6)**, changes in clinical chemistry values were generally consistent with the established safety profile for amivantamab, and no clinically meaningful deleterious effects on clinical chemistry were observed during the treatment period. Grade ≥3 hyponatremia was observed in 10.4% of participants.

2.5.8.5. Safety in special populations

Separate analyses of TEAEs were performed to evaluate potential differences in the safety of amivantamab SC in comparison to amivantamab IV among subgroups defined by intrinsic factors (age, sex, race, weight, history of brain metastases, mutation type and ECOG performance status Score), as well as subgroups defined by the extrinsic factor of history of smoking. These subgroup analyses were conducted using integrated data from the PALOMA-3 and PALOMA-2 studies.

Age of <65 Years or ≥65 Years

There was a similar distribution between amivantamab SC and amivantamab IV of participants <65 years of age (65.9% versus 56.7%) and participants ≥65 years of age (34.1% versus 43.3%).

Table 47: Overall Summary of Treatment-emergent Adverse Events by Subgroup (Age Group 1); Safety Analysis Set (Study Integrated Safety Summary)

	Amivantamab IV + Lazertinib			Amivantamab SC + Lazertinib								
	PALOMA-3			PALOMA-3			PALOMA-2 Cohort 1 and 6			Combined		
		Age (years)			Age (years)			Age (years)			Age (years)	
	Total	<65	≥65	Total	<65	≥65	Total	<65	≥65	Total	<65	≥65
Analysis set: Safety	210	119	91	206	133	73	125	85	40	331	218	113
Subjects with 1 or more:												
AEs	209 (99.5 %)	119 (100.0 %)	90 (98.9 %)	204 (99.0 %)	133 (100.0 %)	71 (97.3 %)	125 (100.0 %)	85 (100.0 %)	40 (100.0 %)	329 (99.4 %)	218 (100.0 %)	111 (98.2 %)
Related AEs [a]	206 (98.1 %)	116 (97.5 %)	90 (98.9 %)	196 (95.1 %)	127 (95.5 %)	69 (94.5 %)	125 (100.0 %)	85 (100.0 %)	40 (100.0 %)	321 (97.0 %)	212 (97.2 %)	109 (96.5 %)
Related to Amivantamab[a]	205 (97.6 %)	116 (97.5 %)	89 (97.8 %)	194 (94.2 %)	127 (95.5 %)	67 (91.8 %)	125 (100.0 %)	85 (100.0 %)	40 (100.0 %)	319 (96.4 %)	212 (97.2 %)	107 (94.7 %)
Related to Lazertinib[a]	200 (95.2 %)	114 (95.8 %)	86 (94.5 %)	192 (93.2 %)	123 (92.5 %)	69 (94.5 %)	125 (100.0 %)	85 (100.0 %)	40 (100.0 %)	317 (95.8 %)	208 (95.4 %)	109 (96.5 %)
Grade 3 or greater AEs	118 (56.2 %)	57 (47.9 %)	61 (67.0 %)	107 (51.9 %)	67 (50.4 %)	40 (54.8 %)	59 (47.2 %)	38 (44.7 %)	21 (52.5 %)	166 (50.2 %)	105 (48.2 %)	61 (54.0 %)
Related Grade 3 or greater AEs[a]	82 (39.0 %)	35 (29.4 %)	47 (51.6 %)	79 (38.3 %)	48 (36.1 %)	31 (42.5 %)	46 (36.8 %)	31 (36.5 %)	15 (37.5 %)	125 (37.8 %)	79 (36.2 %)	46 (40.7 %)
Related to Amivantamab[a]	77 (36.7 %)	33 (27.7 %)	44 (48.4 %)	69 (33.5 %)	43 (32.3 %)	26 (35.6 %)	42 (33.6 %)	28 (32.9 %)	14 (35.0 %)	111 (33.5 %)	71 (32.6 %)	40 (35.4 %)
Related to Lazertinib[a]	64 (30.5 %)	29 (24.4 %)	35 (38.5 %)	66 (32.0 %)	41 (30.8 %)	25 (34.2 %)	40 (32.0 %)	29 (34.1 %)	11 (27.5 %)	106 (32.0 %)	70 (32.1 %)	36 (31.9 %)
Maximum toxicity grade												
Grade 1	9 (4.3 %)	8 (6.7%)	1 (1.1 %)	7 (3.4 %)	5 (3.8%)	2 (2.7 %)	5 (4.0%)	3 (3.5%)	2 (5.0%)	12 (3.6 %)	8 (3.7%)	4 (3.5 %)
Grade 2	82 (39.0 %)	54 (45.4 %)	28 (30.8 %)	90 (43.7 %)	61 (45.9 %)	29 (39.7 %)	61 (48.8 %)	44 (51.8 %)	17 (42.5 %)	151 (45.6 %)	105 (48.2 %)	46 (40.7 %)
Grade 3	96 (45.7 %)	44 (37.0 %)	52 (57.1 %)	92 (44.7 %)	58 (43.6 %)	34 (46.6 %)	51 (40.8 %)	36 (42.4 %)	15 (37.5 %)	143 (43.2 %)	94 (43.1 %)	49 (43.4 %)

	Amivantamab IV + Lazertinib			Amivantamab SC + Lazertinib								
	PALOMA-3			PALOMA-3			PALOMA-2 Cohort 1 and 6			Combined		
		Age (years)			Age (years)			Age (years)			Age (years)	
	Total	<65	≥65	Total	<65	≥65	Total	<65	≥65	Total	<65	≥65
Grade 4	12 (5.7%)	8 (6.7%)	4 (4.4%)	8 (3.9%)	6 (4.5%)	2 (2.7%)	6 (4.8%)	2 (2.4%)	4 (10.0%)	14 (4.2%)	8 (3.7%)	6 (5.3%)
Grade 5	10 (4.8%)	5 (4.2%)	5 (5.5%)	7 (3.4%)	3 (2.3%)	4 (5.5%)	2 (1.6%)	0	2 (5.0%)	9 (2.7%)	3 (1.4%)	6 (5.3%)
Serious AEs	64 (30.5%)	35 (29.4%)	29 (31.9%)	59 (28.6%)	37 (27.8%)	22 (30.1%)	31 (24.8%)	18 (21.2%)	13 (32.5%)	90 (27.2%)	55 (25.2%)	35 (31.0%)
Related serious AEs[a]	34 (16.2%)	17 (14.3%)	17 (18.7%)	33 (16.0%)	20 (15.0%)	13 (17.8%)	20 (16.0%)	13 (15.3%)	7 (17.5%)	53 (16.0%)	33 (15.1%)	20 (17.7%)
Related to Amivantamab[a]	33 (15.7%)	16 (13.4%)	17 (18.7%)	29 (14.1%)	18 (13.5%)	11 (15.1%)	18 (14.4%)	11 (12.9%)	7 (17.5%)	47 (14.2%)	29 (13.3%)	18 (15.9%)
Related to Lazertinib[a]	26 (12.4%)	13 (10.9%)	13 (14.3%)	27 (13.1%)	15 (11.3%)	12 (16.4%)	16 (12.8%)	10 (11.8%)	6 (15.0%)	43 (13.0%)	25 (11.5%)	18 (15.9%)
AEs leading to dose reduction	52 (24.8%)	22 (18.5%)	30 (33.0%)	63 (30.6%)	37 (27.8%)	26 (35.6%)	59 (47.2%)	40 (47.1%)	19 (47.5%)	122 (36.9%)	77 (35.3%)	45 (39.8%)
AEs leading to dose reduction of Amivantamab	25 (11.9%)	9 (7.6%)	16 (17.6%)	34 (16.5%)	20 (15.0%)	14 (19.2%)	47 (37.6%)	32 (37.6%)	15 (37.5%)	81 (24.5%)	52 (23.9%)	29 (25.7%)
AEs leading to dose reduction of Lazertinib	45 (21.4%)	21 (17.6%)	24 (26.4%)	55 (26.7%)	32 (24.1%)	23 (31.5%)	43 (34.4%)	27 (31.8%)	16 (40.0%)	98 (29.6%)	59 (27.1%)	39 (34.5%)
AEs leading to drug interruption[b]	127 (60.5%)	67 (56.3%)	60 (65.9%)	127 (61.7%)	76 (57.1%)	51 (69.9%)	78 (62.4%)	52 (61.2%)	26 (65.0%)	205 (61.9%)	128 (58.7%)	77 (68.1%)
AEs leading to interruption of Amivantamab[b]	101 (48.1%)	55 (46.2%)	46 (50.5%)	105 (51.0%)	62 (46.6%)	43 (58.9%)	71 (56.8%)	48 (56.5%)	23 (57.5%)	176 (53.2%)	110 (50.5%)	66 (58.4%)
AEs leading to interruption of Lazertinib[b]	112 (53.3%)	58 (48.7%)	54 (59.3%)	113 (54.9%)	70 (52.6%)	43 (58.9%)	58 (46.4%)	36 (42.4%)	22 (55.0%)	171 (51.7%)	106 (48.6%)	65 (57.5%)
AEs leading to discontinuation of study agent	29 (13.8%)	11 (9.2%)	18 (19.8%)	26 (12.6%)	14 (10.5%)	12 (16.4%)	16 (12.8%)	9 (10.6%)	7 (17.5%)	42 (12.7%)	23 (10.6%)	19 (16.8%)
AEs leading to discontinuation of Amivantamab	28 (13.3%)	11 (9.2%)	17 (18.7%)	23 (11.2%)	13 (9.8%)	10 (13.7%)	16 (12.8%)	9 (10.6%)	7 (17.5%)	39 (11.8%)	22 (10.1%)	17 (15.0%)
AEs leading to discontinuation of Lazertinib	26 (12.4%)	10 (8.4%)	16 (17.6%)	25 (12.1%)	14 (10.5%)	11 (15.1%)	12 (9.6%)	6 (7.1%)	6 (15.0%)	37 (11.2%)	20 (9.2%)	17 (15.0%)
AEs leading to death[c]	10 (4.8%)	5 (4.2%)	5 (5.5%)	7 (3.4%)	3 (2.3%)	4 (5.5%)	2 (1.6%)	0	2 (5.0%)	9 (2.7%)	3 (1.4%)	6 (5.3%)
Related AEs leading to death[a,c]	4 (1.9%)	2 (1.7%)	2 (2.2%)	3 (1.5%)	1 (0.8%)	2 (2.7%)	0	0	0	3 (0.9%)	1 (0.5%)	2 (1.8%)
Related to Amivantamab[a,c]	3 (1.4%)	2 (1.7%)	1 (1.1%)	3 (1.5%)	1 (0.8%)	2 (2.7%)	0	0	0	3 (0.9%)	1 (0.5%)	2 (1.8%)

	Amivantamab IV + Lazertinib			Amivantamab SC + Lazertinib								
	PALOMA-3			PALOMA-3			PALOMA-2 Cohort 1 and 6			Combined		
		Age (years)			Age (years)			Age (years)			Age (years)	
	Total	<65	≥65	Total	<65	≥65	Total	<65	≥65	Total	<65	≥65
Related to Lazertinib[a,c]	3 (1.4 %)	2 (1.7%)	1 (1.1 %)	3 (1.5 %)	1 (0.8%)	2 (2.7 %)	0	0	0	3 (0.9 %)	1 (0.5%)	2 (1.8 %)
AEs related to COVID-19[d]	23 (11.0 %)	11 (9.2%)	12 (13.2 %)	18 (8.7 %)	13 (9.8%)	5 (6.8 %)	6 (4.8%)	4 (4.7%)	2 (5.0%)	24 (7.3 %)	17 (7.8%)	7 (6.2 %)

Key: AE = adverse event; IV=Intravenous; SC=Subcutaneous
[a] An AE is assessed by the investigator as related to study agent.
[b] Excludes infusion/administration related reactions.
[c] AEs leading to death are based on AE outcome of Fatal.
[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.

Age of <75 Years or ≥75 Year

Most participants were <75 years of age (amivantamab SC: 90.0 %, amivantamab IV: 89.5%). The size of the subgroup of participants ≥75 years of age was too small to allow for meaningful comparison of TEAEs.

Overall, there were no clinically meaningful differences in the TEAE profile for subgroups defined by age, sex, race, weight, history of brain metastasis, mutation type, ECOG performance status Score, and history of smoking

2.5.8.6. Immunological events

In PALOMA-3, treatment-emergent antibodies to amivantamab were observed in 1 (0.6%) participant out of 175 immunogenicity-evaluable participants in the amivantamab SC arm. Of the 182 immunogenicity-evaluable participants in the amivantamab IV arm, no treatment-emergent antibodies to amivantamab were observed. Among the 193 immunogenicity-evaluable participants in the amivantamab SC arm, treatment-emergent antibodies to rHuPH20 were observed in 15 (7.8%) participants.

In **PALOMA-2 (Cohorts 1 and 6 combined)**, no treatment-emergent antibodies to amivantamab SC were observed among 110 immunogenicity-evaluable participants. Among the 117 participants who received amivantamab SC and had appropriate samples, 13 participants (11.1%) were positive for treatment-emergent antibodies to rHuHP20.

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

The risk of VTE is synergistically increased when combining amivantamab and lazertinib (see above and Rybrevant II/13)

2.5.8.8. Discontinuation due to adverse events

Treatment-emergent Adverse Events Leading to Dose Reduction

In PALOMA-3, the incidence of TEAEs leading to dose reduction of any study treatment was 30.6% in the amivantamab SC arm (16.5% for amivantamab and 26.7% for lazertinib) and 24.8% in the amivantamab IV arm (11.9% for amivantamab and 21.4% for lazertinib). The most frequently

reported (≥5% of participants in either treatment arm) TEAEs leading to dose reduction were rash, paronychia, and dermatitis acneiform.

In PALOMA-2 (Cohorts 1 and 6 combined), the incidence of TEAEs leading to dose reduction of any study treatment was 47.2% (37.6% for amivantamab and 34.4% for lazertinib), with rash, dermatitis acneiform, and paronychia being reported the most frequently (≥5% of participants).

The results of the pooled analysis are consistent with the observations from the individual studies.

Treatment-emergent Adverse Events Leading to Study Drug Interruption

In PALOMA-3, the incidence of TEAEs (other than IRRs) leading to interruption of at least 1 study treatment was comparable between the amivantamab SC arm (61.7% [51.0% for amivantamab and 54.9% for lazertinib]) and the amivantamab IV arm (60.5% [48.1% for amivantamab and 53.3% for lazertinib]). The most frequently reported TEAEs (≥5% of participants in either treatment arm) leading to study drug interruption were rash, dermatitis acneiform, paronychia, and COVID-19).

In PALOMA-2 (Cohorts 1 and 6 combined), the incidence of TEAEs leading to interruption of any study treatment was 62.4% (56.8% for amivantamab and 46.4% for lazertinib), with rash, dermatitis acneiform, and paronychia being reported the most frequently (≥5% of participants).

The results of the pooled analysis are consistent with the observations from the individual studies.

Treatment-emergent Adverse Events Leading to Study Treatment Discontinuation

In PALOMA-3, the incidence of TEAEs leading to study treatment discontinuation was comparable between the amivantamab SC arm (12.6% [11.2% for amivantamab and 12.1% for lazertinib]) and the amivantamab IV arm (13.8% [13.3% for amivantamab and 12.4% for lazertinib]). The most frequently reported TEAE (≥3% of participants in either treatment arm) leading to study treatment discontinuation was pneumonitis.

In PALOMA-2 (Cohorts 1 and 6 combined), the incidence of TEAEs leading to study treatment discontinuation was 12.8% (12.8% for amivantamab and 9.6% for lazertinib). At the PT level, no TEAEs leading to study treatment discontinuation were reported for more than 2 participants.

2.5.8.9. Post marketing experience

There is currently no post marketing experience with amivantamab SC monotherapy or in combination with lazertinib or CP.

Post marketing information for amivantamab IV monotherapy has been accruing since the first approval in 2021. Based on 32,848,379 milligrams distributed worldwide from launch to 30 November 2023, the estimated exposure to amivantamab is 2,682 treatment courses. The postmarketing safety profile of amivantamab monotherapy is consistent with the safety information provided in the product information. No major safety issues have been identified.

2.5.9. Discussion on clinical safety

The overall safety data for the amivantamab SC given in combination with lazertinib derive from the PALOMA-3 and PALOMA-2 studies, respectively, presented separately and pooled together. In addition, to support bridging to the amivantamab IV, safety data in PALOMA-3 were presented head-to head for the SC and IV arm.

The safety analysis set (SAF) in PALOMA-3 consists of 206 participants in SC arm and 210 participants in IV arms, respectively; in PALOMA-2 SAF consists of 125 participants that received at least 1 dose of

amivantamab SC Q2W+Lazertinib. Pooled together the SAF for the participants treated with amivantamab SC Q2W+ Lazertinib in PALOMA-3 and PALOMA-2 consists of totally 331 participants.

In PALOMA-3 similar proportion of participants between arms discontinued study treatment due to progressive disease or due to adverse events. Distribution of discontinuation per reason is similar between arms.

Exposure

At the clinical cutoff date (CCO) of 03 January 2024 in PALOMA-3 the median duration of treatment was similar between the amivantamab SC arm (3.68 months) and the amivantamab IV arm (3.75 months). In PALOMA-2 the median duration of treatment in first line setting was 6.80 months. The median follow-up was 8.64 months in PALOMA-2 while in PALOMA-3 was 7.26 months in the amivantamab SC +lazertinib arm and 6.54 months in the amivantamab IV+lazertinib arm.

Adverse events/TEAEs

The most frequent adverse events of any grade with amivanatamb SC+lazertinib were rash, nail toxicity, hypoalbuminaemia, stomatitis, oedema, fatigue, alanine aminotransferase increased, nausea, aspartate aminotransferase increased, decreased appetite, dry skin, constipation, diarrhoea, and pruritus. This is similar to what is seen with IV administration.

In terms of TEAES, the incidence of SAEs, Grade ≥3 TEAE and TEAEs leading to death was comparable between the amivantamab SC+lazertinib arm and the amivantamab IV+lazertinib arm, although slightly higher numerical incidence is observed in the IV arm.

In PALOMA-3 the overall safety profile appears similar between SC and IV arm. The most frequently reported adverse events have a similar distribution between arms.

TEAEs were generally managed in the two treatment arms with treatment interruptions and dose reductions. The incidence of TEAEs leading to dose reductions was slightly higher in the SC arm (30.6%) compared with the IV arm (24.8%). On the other hand, a slightly higher incidence of TEAES that led to discontinuation of any study treatment in was observed in the IV arm (13.8%) compared with SC arm (12.6%).

SAEs

In PALOMA-3, SAEs were reported with a similar incidence in the amivantamab SC arm (28.6%) compared with the amivantamab IV arm (30.5%). The most frequently reported SAEs (in ≥3% of participants in either treatment arm) with amivantamab SC+lazertinib and amivantamab IV +lazertinib were pneumonitis (4.4% and 2.9%, respectively) and pneumonia (1.5% and 3.3%, respectively).

TEAEs Leading to Death

In PALOMA-3, TEAEs leading to death were reported in 7 participants [3.4%]) in the SC arm and 10 participants [4.8%] in the IV arm. Pneumonitis was among the most frequently reported TEAEs leading to death across treatment arms, leading to death in 1 participant (0.5%) in the SC arm and 3 participants (1.4%) in the IV arm. Among the TEAEs leading to death, cerebral infarction and acute myocardial infarction were reported only in the IV arm. TEAEs leading to death were considered related to study treatment in 3 (1.5%) participants in the SC arm and 4 (1.9%) participants in the IV arm.

In PALOMA-2 (Cohorts 1 and 6 combined), TEAEs leading to death were observed in 2 participants (1.6%) and were cardiac arrest and sepsis, both considered not related to study treatment.

TEAEs leading to dose reduction

In PALOMA-3, the incidence of TEAEs leading to dose reduction of any study treatment was numerically higher (30.6%) in the SC arm than in the IV arm (24.8%). The most frequently reported TEAEs that led to dose reduction in both PALOMA-3 and PALOMA-2 study were skin and nail related adverse events (rash, dermatitis acneiform, and paronychia).

AEs Leading to Study Drug Interruption

In PALOMA-3, the incidence of TEAEs (other than IRRs) leading to interruption of at least 1 study treatment was comparable between the SC arm and the IV arm. The most frequently reported TEAEs that led to study drug interruption were rash, dermatitis acneiform, paronychia in both PALOMA-3 and PALOMA-2 study.

AEs Leading to Study Treatment Discontinuations

In PALOMA-3, the incidence of TEAEs and SAEs leading to study treatment discontinuation was comparable between the amivantamab SC arm (12.6% TEAEs, 8.7% SAEs) and the amivantamab IV arm (13.8% TEAEs, 9.5% SAEs). The most frequently reported TEAE and SAEs leading to study treatment discontinuation was pneumonitis.

AESI

IRR/ARR and LARR

The incidence of IRR/ARRs was lower in the SC arm compared with the IV arm of the PALOMA-3 study, 13.1% vs 65.7%. The LARRs were reported only for the SC arm in 9.7% of the participants. Only Grade 1 or Grade 2 were reported.

The majority of IRR events occurred at Cycle 1. Most IRRs were Grade 1 or 2 while no Grade 4 or 5 IRRs were reported. The incidence of Grade 3 IRRs was lower in the SC arm (0.5%) compared with the IV arm (3.8%). Serious IRRs and IRR leading to study treatment discontinuation were reported only for the IV arm. The incidence of the IRRs leading to interruption of any study treatment was higher in the IV arm compared with the SC arm, 55.2% vs 1%.

In PALOMA-2 (Cohorts 1 and 6 combined), ARRs were reported for 15.2% of participants, with similar characteristics as for SC arm in PALOMA-3.

Premedications with antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of ARRs with Rybrevant SC formulation. Injections should be interrupted at the first sign of ARRs. Additional supportive medicinal products (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated (see section 4.4).

- Grade 1 3 (mild severe): Upon recovery of symptoms, Rybrevant SC formulation injections can be resumed. Concomitant medicinal products should be administered at the next dose, including dexamethasone (20 mg) or equivalent.

- Recurrent Grade 3 or Grade 4 (life threatening): Rybrevant should be permanently discontinued (see sections 4.2 and 4.4 of the SmPC).

VTE

VTE is a known risk for the amivatamab+lazertinib combination observed in MARIPOSA study.

Prophylactic Anticoagulant Use

Following a safety signal from the MARIPOSA study in 1L patients with EGFR-positive NSCLC, all study participants in PALOMA-3 were recommended to receive prophylactic anticoagulants as per local guidelines during the first 4 months of combination therapy.

A similar proportion of participants between arms received full prophylactic anticoagulant medication (52.4% and 53.3% in SC and IV arm respectively), or partial prophylactic anticoagulant medication (26.6% and 28% in SC and IV arm respectively). The prophylactic anticoagulation had approximately 1 month longer duration in the SC than in IV arm.

Notably, in PALOMA-3 the incidence of VTE events was lower in the SC arm (9.2%) compared with the IV arm (14.3%).

Both in PALOMA-2 and -3, the incidence of VTE events was reduced in participants who received full and partial anticoagulation, respectively, as compared to participants who received no anticoagulation. The incidence of VTE events for participants who received no anticoagulation was lower in the amivantamab SC arm compared with the amivantamab IV arm.

The incidence of bleeding events was corelated with the incidence and length of given anticoagulation and is acceptable. Data from PALOMA-3 and MARIPOSA studies suggest that anticoagulation considerably reduces the VTE risk occurring when amivantamab is used with lazertinib in combination (see assessment of Rybrevant II/13).

As for the IV formulation, a warning in sections 4.2 and 4.4 of the SmPC was added to add recommendations on how to manage VTE including instructions on the use of prophylactic anticoagulants.

Warnings on insterstitial lung disease, skin and nails reaction and eye disorders included in section 4.4 and 4.2 of the IV formulation are also applicable to the SC presentation.

ADRs

Currently, the analysis of the ADR for amivantamab SC is based exclusively on the data from the PALOMA-3 SC arm and PALOMA-2 Cohorts 1 and 6 (N=331).

According to the recommendations of the SmPC guideline and the mock-up of 4.8 in the Appendix 3 guideline clinical evaluation anticancer medicinal products- summary product characteristics 4.8, the information on ADRs in 4.8 should wherever possible be based on the pooled safety data across the clinical trials. Therefore, for the amivantamab+Lazertinib combination, the ADRs presented in section 4.8 reflect exposure to amivantamab (either IV or SC formulation) in 752 patients from the Mariposa, Paloma-3 and Paloma-2 cohort 1 and 6.

As for the monotherapy setting, only data from the IV formulation are available and presented in a separate table. The safety profile of amivantamab is well characterised and mechanistically based on its dual MET and EGFR inhibition. There is no PK interaction between amivantamab and lazertinib,. The similar exposure between SC and IV dosing justifies the extrapolation of safety in monotherapy for the IV formulation to the SC formulation.

The clinically relevant differences in the ADRs between IV and SC formulations observed in the studies with amivantamab+lazertinib combination in terms of administration-related reactions (63% for intravenous vs. 14% for subcutaneous) and VTE (37% for intravenous vs. 11% for subcutaneous) were appropriately highlighted in section 4.8.

Special populations

There were no clinically meaningful differences in the TEAE profile for subgroups defined by age, sex, race, weight, history of brain metastasis, mutation type, ECOG performance status Score, and history of smoking.

2.5.10. Conclusions on the clinical safety

Similar exposure across PK metrics was shown for the amivantamb SC to the amivantamab IV (both in combination with lazertinib) in PALOMA-3, which suggest general consistency of the safety data between the SC and IV arm. Differences are seen in the incidence of VTE and ARR/IRR in favour of SC arm. This is adequately reflected in the product information. The lack of PK interaction between amivantamab and lazertinib justifies extrapolation of safety between treatments with and without lazertinib.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table SVIII.1: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 amivantamab and lazertinib.

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. 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) 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Hepatotoxicity	**Routine risk minimization measures:** • SmPC Section 4.8 • PL Section 4 • Legal status. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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 EGFR inhibition on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of RYBREVANT, are provided in SmPC Section 4.6 and PL Section 2. • Patients should notify their doctor or nurse immediately about a potential or confirmed pregnancy before and during treatment with RYBREVANT, as described in PL Section 2. • Legal status. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

* Applies only to the combination of amivantamab and lazertinib.

2.6.4. Conclusion

The CHMP considered that the risk management plan version 6.1 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Rybrevant 350mg. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The line extension for amivantamab solution for injection includes all current and future approved indications for amivantamab IV with Q2W dosing schedules.

Presently this includes:

-in combination with lazertinib 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.

-as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations, after failure of platinum-based therapy

3.1.2. Available therapies and unmet medical need

The claimed added benefits that amivantamab SC would address (in comparison to already available amivantamab IV) is a less invasive and faster administration. The full benefit of this is somewhat limited by the need for medically observed administration.

3.1.3. Main clinical studies

The pivotal study to support SC administration is PALOMA-3, an open-label, randomized, Phase 3 study to compare the PK, efficacy, and safety of combining oral lazertinib with amivantamab SC administered via manual injection versus amivantamab IV. This pivotal study aimed to assess the PK "noninferiority" (=pharmacokinetic equivalence to establish a PK bridge) of amivantamab SC (Arm A) versus amivantamab IV (Arm B).

This study was performed in patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease has progressed on or after treatment with osimertinib and platinum-based chemotherapy.

The primary objective for the EU regions was to assess the pharmacokinetic "non-inferiority" of amivantamab SC (Ctrough at Cycle 2 Day 1 and AUCD1-D15 at Cycle 2) via manual injection versus amivantamab IV.

Key secondary objectives were to assess efficacy (ORR and PFS) and safety of the different routes of administration.

3.2. Favourable effects

- The co-primary endpoints (Ctrough at Cycle 2 Day 1 and AUCD1-D15 at Cycle 2) were met: geometric mean ratio (90% CI) of amivantamab SC/IV was 1.145 (1.040-1.261) for Cycle 2 Day1 Ctrough and 1.032 (0.976-1.090) for Cycle 2 AUCD1-D15. The corresponding lower limit of the 90% CI for both co-primary endpoints were above the prespecified non-inferiority margin of 0.8, and thus PK non-inferiority of SC over IV was established.
- ORR was the secondary endpoint included in the hierarchical testing. ORR amivantamab SC+lazertinib was 30.1% in comparison with 32.5% for amivantamab IV+lazertinib suggesting equivalence.
- PFS analysis showed nominally better median PFS in the SC arm 6.11 months compared with 4.30 months in the IV arm. The HR was 0.84 (95% CI: 0.64, 1.10, nominal p-value= 0.2006).

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

The overall safety data for the amivantamab SC given in combination with lazertinib are derived from PALOMA-3 and PALOMA-2 study. In addition, to support bridging to the amivantamab IV, safety data in PALOMA-3 were presented head-to head for the SC and IV arm.

In PALOMA-3 the overall safety profile appears similar between SC and IV arms.

In terms of TEAES, the incidence of SAEs, Grade ≥3 TEAE and TEAEs leading to death was comparable between the amivantamab SC+lazertinib arm and the amivantamab IV+lazertinib arm, although slightly higher numerical incidence is observed in the IV arm.

Similar to the IV product, the most frequent adverse reactions of any grade with amivantamab SC were rash, nail toxicity, hypoalbuminemia, stomatitis, oedema, fatigue, alanine aminotransferase increased, nausea, aspartate aminotransferase increased, decreased appetite, dry skin, constipation, diarrhoea, and pruritus.

TEAEs were generally managed in the two treatment arms with treatment interruptions and dose reductions. The incidence of TEAEs leading to dose reductions was slightly higher in the SC arm (30.6%) compared with the IV arm (24.8%). On the other hand, a slightly higher incidence of TEAES that led to discontinuation of any study treatment in was observed in the IV arm (13.8%) compared with SC arm (12.6%).

In terms of AESI, local administration related reaction (LARR) was the new identified AESIs for the amivantamab SC arm. The incidence of IRR/ARRs was lower in the SC arm compared with the IV arm of the PALOMA-3 study, 65.7% vs 13.1%. The LARRs were reported only for the SC arm in 9.7% of the participants.

VTE is a risk for the amivantamab+lazertinib combination initially observed in the MARIPOSA study.

Following the safety signal on VTE identified in the MARIPOSA study, all study participants in PALOMA-3 were recommended to receive prophylactic anticoagulants as per local guidelines.

In terms of the relevance of the type of administration SC or IV on the risk for VTE, in PALOMA-3 the incidence of VTE events was lower in the SC arm (9.2%) compared with the IV arm (14.3%), although

a similar proportion of participants between arms received full prophylactic anticoagulant medication, or partial prophylactic anticoagulant medication. In addition, the incidence of VTE events for participants who received no anticoagulation was lower in the amivantamab SC arm compared with the amivantamab IV arm.

The relevance of anticoagulation prophylaxis was noted in both PALOMA-2 and -3 studies, where the incidence of VTE events was reduced in participants who received full and partial anticoagulation, respectively, as compared to participants who received no anticoagulation.

The incidence of bleeding events was as anticipated and acceptable acceptable (see section 4.4 of the SmPC).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 48: Effects Table for Amivantamab SC (PALOMA-3 data cut-off: 03 January 2024).

Effect	Short DeSCription	Unit	Treatment Amivantamab SC+lazertinib	Control Amivantamab IV+lazertinib	Uncertainties/ Strength of evidence	References
Favourable Effects						
Ctrough C2D1	Predose concentration on C2D1	µg/mL	335	293	Non-inferiority demonstrated	PALOMA-3
	Geometric Mean Ratio (90% CI)	-	1.145 (1.040-1.261)			
Cycle 2 AUC D1-D15	Area under the concentration/time curve in cycle 2	µg·h/mL	135861	131704	Non-inferiority demonstrated	PALOMA-3
	Geometric Mean Ratio (90% CI)	-	1.032 (0.976-1.090)			
ORR	% CR+PR, per RECIST V1.1		30%	32.5%		
Unfavourable Effects						
SAEs		%	28.6	30.5		
TEAEs leading to death		%	3.4	4.8		
IRR/ARR		%	13	65.7		
VTE		%	9.2	14.3		

Abbreviations: AUCD1-D15=area under the concentration-time curve from Day 1 to 15; BW=body weight; CI=confidence interval; Ctrough=trough concentration; IV=intravenous; N=number of observations; PK=pharmacokinetic; PO=orally; Q2W=every 2 weeks; QD=daily; QW=every week; SC=subcutaneous.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This line extension is based on PALOMA-3 as pivotal trial. The primary objective was to show "non-inferiority" (=functional pharmacokinetic equivalence) of amivantamab SC over amivantamab IV from a PK perspective. The study also compared the efficacy and safety of the IV and SC formulations. Pharmacokinetic equivalence has been shown. Moreover, the activity of SC amivantamab was similar to that of the IV regimen. The safety profiles of the SC and IV regimens appears largely comparable with no new safety signals observed.

3.7.2. Balance of benefits and risks

A PK bridge for all Q2W administration regimens, for current and future indications, has been established between SC and IV amivantamab. Moreover, the efficacy and safety of SC and IV amivantamab are considered comparable.

3.8. Conclusions

The overall benefit/risk balance of Rybrevant SC is positive.

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, Rybrevant new strength (1600mg and 2240mg) and new pharmaceutical form (solution for injection) is favourable in the following indication(s):

Rybrevant subcutaneous formulation is indicated:

- in combination with lazertinib 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.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

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

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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