Amsterdam, 11 December 2025
EMADOC-1700519818-2846450
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rybrevant

International non-proprietary name: amivantamab

Procedure No. EMA/X/0000268898

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

ADA	Anti-drug antibody
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
NAb	Neutralising antibody
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamics
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
SmPC	Summary of product characteristics
TKI	Tyrosine kinase inhibitor

1. Executive Summary

On 11 December 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the extension of the marketing authorisation for the medicinal product Rybrevant.

The CHMP recommended the approval of two new strengths of Rybrevant (2400 mg solution for injection and 3520 mg solution for injection) for subcutaneous route of administration for use in adults in all approved indications.

The indication for Rybrevant will be as follows:

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.

-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.

Rybrevant should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

2. Administrative/regulatory information and recommendations on the procedure

2.1. Submission of the dossier

On 02 May 2025 Janssen-Cilag International N.V submitted a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

The MAH applied for an addition of two new strengths of 2400 mg and 3520 mg solution for injection for subcutaneous use in all approved indications.

In addition, the MAH proposed:

C.I.4 (Type II): To include the Q3W dose regimen and to include the corresponding combination of amivantamab with carboplatin and pemetrexed indications which are currently approved for amivantamab IV (based on the PAPILLON and MARIPOSA-2 studies).

C.I.4 (Type II): To include a new Q4W dosing regimen for amivantamab SC for the monotherapy indication (treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy) and for the combination with Lazertinib indication (first-line treatment of adult patients with advanced non-small cell lung cancer with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations).

B.I.a.1.e (Type II): To register Samsung Biologics Co, Ltd. Plant 4A, 300, Songdo bio-daero, Yeonsu-gu, Incheon, Republic of Korea as an additional site for the manufacture and quality control testing of the parental anti-EGFR and anti-cMET parental monoclonal antibody intermediates (Stages 1 to 5) and the active substance (Stages 6 to 14).

B.I.a.3.c (Type II): To scale up the manufacturing process of the active substance (Stages 6 to 14).

B.II.c.4.c (Type II): To register Avid Bioservices Inc., 14191 Myford Road, Tustin, CA 92780, USA for manufacture and quality control testing of the excipient recombinant hyaluronidase (rHuPH20).

B.I.b.2.e (Type IB): To register PCR mycoplasma test as an alternative method for mycoplasma detection in the parental anti-EGFR and anti-cMET monoclonal antibody intermediates.

B.II.e.7.b (Type IA): To register Nuova Ompi as an alternative supplier for the 25R vials for the finished product.

2.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of extension of marketing authorisation and variations

2.3. Scientific advice and protocol assistance

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
22/04/2022	Quality, Clinical	EMA/SA/0000080094 Kristian Wennmalm and João Manuel Lopes de Oliveira	• The clinical dose selection strategy; • The overall design of a phase 3 non-inferiority/bioequivalence study 61186372NSC3004 and specifically the proposed patient population, choice of therapy, endpoints, statistical assumptions and analyses; • The design of a multiple cohort, Phase 2 bridging study 61186372NSC2002 to support approval of the SC formulation across all amivantamab IV indications.

An additional key regulatory correspondence/interaction between the Applicant and the European regulatory authorities relevant to the amivantamab Q3W and Q4W SC development was a pre-submission meeting held with the Rapporteur on 19 November 2024. The main objective of this meeting was to seek input from the Rapporteur on the overall regulatory strategy supporting the line extension submission for amivantamab Q3W and Q4W SC in the EU. Overall, the meeting with the Rapporteur identified no barriers to proceed with the line extension submission.

2.4. Information on paediatrics

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.

2.5. Information on orphan market exclusivity

2.5.1. Similarity with authorised orphan medicinal products

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.

2.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Filip Josephson
Co-Rapporteur:	NA

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur:	Gabriele Maurer

The application was received by the EMA on	2 May 2025
The procedure started on	22 May 2025
The CHMP Rapporteur's first Assessment Report was received on	11 August 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	13 August 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	19 August 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	18 September 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	10 October 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rybrevant on	11 December 2025

2.7. Final CHMP outcome

2.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 2.4. of this report.

2.7.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 2.5. of this report.

2.7.3. Final opinion

Based on the CHMP review of data on quality, clinical pharmacology, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rybrevant 2400 mg solution for injection and 3520 mg solution for injection is favourable in 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.

-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 CHMP therefore recommends the extension(s) of the marketing authorisation for Rybrevant, subject to the conditions described in the following sections.

In addition, the CHMP does recommend the variation to the terms of the marketing authorisation concerning the following changes:

Variation(s) adopted		Type	Annexes affected
B.II.c.4.c	B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient - B.II.c.4.c The excipient is a biological/immunological substance	Variation type II	NA
B.II.e.7.b	B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier) - B.II.e.7.b Replacement or addition of a supplier	Variation type IA	NA
B.I.b.2.e	B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - B.I.b.2.e Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	Variation type IB	NA
B.I.a.3.c	B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance - B.I.a.3.c The change requires assessment of the comparability of a biological/immunological active substance	Variation type II	NA
B.I.a.1.e	B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier - B.I.a.1.e The change relates to a biological active substance or a starting material/reagent/intermediate used	Variation type II	NA

Variation(s) adopted		Type	Annexes affected
	in the manufacture of a biological/immunological product		
C.I.4	C.I HUMAN AND VETERINARY MEDICINAL PRODUCTS - C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II	I and III
C.I.4	C.I HUMAN AND VETERINARY MEDICINAL PRODUCTS - C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II	I and III

2.7.4. Conditions or restrictions regarding supply and use

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

2.7.5. Other conditions and requirements of the marketing authorisation

2.7.5.1. 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.

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

2.7.6.1. 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.

3. Introduction

Therapeutic Context

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.*

Amivantamab IV is currently approved for all indications listed above.

Amivantamab SC is currently approved for the monotherapy indication (treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy) and when combined with lazertinib for first-line treatment of NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.

In the current line extension, the added further strengths for amivantamab SC intend to support administration under a Q3W (in combination with carboplatin and pemetrexed) or Q4W (in combination with lazertinib or as monotherapy) dosing schedule.
The rationale for the subcutaneous injection for amivantamab is to improve both patient and healthcare provider experience with amivantamab with a decrease in the rate ofinfusion related reactions (IRRs), decreased healthcare resource utilization, and lower incidence of any potential access-related complications, all while maintaining efficacy.

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 in the 13th -19th months range (Belaroussi 2023). 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).

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).

3.1. Aspects of development

The amivantamab SC formulation is already approved for Q2W dosing (see procedure EMEA/H/C/005454/X/0014). The current line extension introduces two new strengths (2400 mg and 3520 mg solution for injection).

The development programme is based on the same clinical studies which were submitted in procedure EMEA/H/C/005454/X/0014. New data from two of these studies – PALOMA and PALOMA-2 – have been provided, as described briefly below (for additional details on the previously submitted data, see procedure EMEA/H/C/005454/X/0014).

PALOMA and PALOMA-2 include data for SC Q3W and Q4W dosing.

PALOMA (61186372NSC1003) is An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Amivantamab, a Human Bispecific EGFR and cMET Antibody for the Treatment of Advanced Solid Malignancies. Compared to the previous PopPK model, new data for amivantamab SC (PK cutoff: 11 July 2024) includes Cohort 6a (n=19 patients) with a maintenance dose of 3 200 mg (4320 mg for participants ≥80 kg) Q4W. The previous PopPK model included data from Cohort 5a (n=25 patients) with a maintenance dose of 2560 mg (3360 mg if WT ≥80 kg) Q3W.

PALOMA-2 (61186372NSC2002) is a Phase 2, Open-Label, Parallel Cohort Study of SC Amivantamab in Multiple Regimens in Patients with Advanced or Metastatic Solid Tumors Including EGFR Mutated NSCLC. Compared to the previous PopPK model, new data for amivantamab SC (PK cutoff: 13 August 2024) includes Cohort 5 (n=77 patients) with a maintenance dose of 3520 mg (or 4640 mg for participants ≥80 kg) Q4W and Cohorts 2+3+3b (n=66+70+77 patients) with a maintenance dose of 2400 mg (or 3360 mg for participants ≥80 kg) Q3W.

3.2. Description of 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 depolymerises hyaluronan under physiologic conditions and acts as a spreading factor in vivo.

The proposed dosing regimens are as follows:

Q4W regimen

Rybrevant subcutaneous formulation in combination with lazertinib or as monotherapy

Body weight at baseline*	**Recommended dose**	**Dosing schedule**
Less than 80 kg	1600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4
	3520 mg	• Every 4 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
	4640 mg	• Every 4 weeks starting at Week 5 onwards

Q3W regimen

Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed

Body weight at baseline*	**Recommended dose**	**Dosing schedule**
Less than 80 kg	1600 mg	First dose at Week 1 Day 1
	2400 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards
Greater than or equal to 80 kg	2240 mg	First dose at Week 1 Day 1
	3360 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards

4. Quality aspects

4.1. 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 by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

This line extension application introduces two new strengths to the existing subcutaneous (SC) presentations (solution for injection in vial, 1600 mg and 2240 mg):

- 2400 mg in 15 mL vial (160 mg/mL concentration);

- 3520 mg in 22 mL vial (160 mg/mL concentration).

The qualitative formulation in excipient for the proposed new strengths remains unchanged compared to the current SC strengths: recombinant human hyaluronidase (rHuPH20), EDTA disodium salt dihydrate, glacial acetic acid, L-methionine, polysorbate 80, sodium acetate trihydrate, sucrose and water for injections.

4.2. Active substance

4.2.1. General information

No modifications have been made to the text in Module 3.2.S.1.

4.2.2. Manufacture, characterisation, and process controls

Description of manufacturing process and process controls

Manufacturing process

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

With this application, Samsung Biologics Co, Ltd. (SBL), 300, Songdo bio-daero, Yeonsu-gu, Incheon, Republic of Korea is registered as an additional site for the manufacture and quality control testing of the parental antibodies intermediates JNJ-55986736 (anti-EGFR) and JNJ-55944083 (anti-cMET) (Stages 1 to 5) and the active substance (Stages 6 to 14).

Both parental antibodies are manufactured in separate 5-stage processes at SBL Plant 2 and Plant 4A. The 2 parental antibodies are combined in a single 9-stage bispecific antibody manufacturing process which is performed at the currently authorised site Janssen Sciences Ireland UC, Co. Cork, Ireland (JSI) and at SBL Plant 4A.

The process in SBL is acceptably described. For this submission, no changes have been introduced in the overview process description. The batch numbering system for SBL Plant 4A is acceptably described.

For Stage 1-5, no changes have been introduced in the detailed process descriptions, except when referencing to plant specific validation documentation, and that the concentration during Stage 5 is not performed in cycles in the new SBL Plant 4A.

For Stage 6-14, the active substance stages are scaled up, i.e. a larger amount of material is used for Stage 6 (Thaw and Pool), in which parenteral antibodies are mixed for further processing. This results in a batch size increase for the active substance.

Otherwise, only minor changes have been introduced at SBL Plant 4A, in equipment-specific process parameters (i.e. centrifugation procedures, agitation rates & agitation times), a small increase in the concentration during diafiltration in Stage 13. Also, the material in the tank for preparation of the active substance before filtration in Stage 14 has been changed. The changes are assessed to be acceptable and not to be influencing the process performance.

Control of materials

No changes have been performed in the raw material related documentation for this submission, with the exception of the documents on end-of-production cells.

Extended end of production cell banks (EEPCB) were created at SBL from cells sampled from the Plant 4A bioreactor, during the process validation campaign. It is acknowledged that the analytical results, for adventitious and endogenous virus, demonstrate the ability to maintain integrity of the cell culture manufacturing process up to the limit of in vitro cell age intended for commercial production, also in the new plant.

Replenishment working cell banks (WCB), for each parental antibody, was used during the active substance process validation campaign at SBL Plant 4A. The WCBs were manufactured and tested according to the descriptions in 3.2.S.2.3 Control of Materials. The approach and results are assessed to be acceptable.

Control of critical steps and intermediates

The release and stability specifications for the concentrated Protein A eluates (Stage 4) 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, also for this submission.

Definitions of in-process control (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.

A new analytical method for mycoplasma detection at the end of the cultivations at SBL Plant 4A has been introduced in this submission. The method has been satisfactorily described. It is acknowledged that the polymerase chain reaction (PCR) Mycoplasma assay is validated as per Ph. Eur. 2.6.7. In addition, a generic comparability study was performed using the same challenge organisms, in accordance with Ph. Eur. 2.6.7, which demonstrated that the PCR mycoplasma assay is comparable to the earlier used compendial Mycoplasma assay. This is assessed as correct.

Process validation

For this submission, subsequent process validation activities were executed at SBL Plant 4A for the parental antibody intermediates and for the active substance. In general, the conclusions drawn from the initial process validation documents are assessed to be applicable also for this submission. Additions and potential exceptions are described below, with assessment of new data.

For process validation, five consecutive commercial-scale batches were manufactured and released for the anti-EGFR parental antibody and four consecutive commercial-scale batches for the anti-cMET parental antibody. Five consecutive commercial-scale active substance batches were then manufactured and released.

The manufacturing process stages were evaluated according to predetermined acceptance criteria. The results of process validation are presented and demonstrate that the process exhibited consistent process performance and met all process validation acceptance criteria for the IPCs and process parameters, except for the deviations listed. It is assessed that impact assessments for these deviations, that concluded that there was no impact on product quality, process performance, or the validity of the study due to these exceptions, are acceptable. Based upon the results, it is assessed that the manufacturing processes are validated.

Impurity Clearance

The results are presented and it is acknowledged that the impurities were demonstrated to be reduced to acceptable levels.

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, performed for SBL Plat 2/JSI, are applicable also for SBL Plant 4A, and assessed to be 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. The approach is considered acceptable also for SBL Plant 4A.

Reprocessing

Reduced-scale process validation data supporting reprocessing is provided. It is acknowledged that these validation studies demonstrate that product quality is not impacted. 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 also for SBL Plant 4A.

Process Intermediate Hold Times

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. It is acknowledged that the SBL Plant 2/JSI studies in general were assessed to be applicable, with some additional data points for SBL Plant 4A specific vessels.

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. A SBL Plant 4A specific study of the microbial hold time and vessel integrity is presented (3.2.S.2.5 Process Validation and/or Evaluation, Microbial Hold Times) and considered acceptable.

Proven acceptable ranges (PAR) for hold times associated with each process intermediate are acceptably justified; they are the minimum times 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. The shipping qualification is correctly extended with a new section for the transport of active substance from SBL in Korea to the finished product manufacturing site Cilag AG in Switzerland, due to the new active substance manufacturing location.

The manufacturing process is considered adequately validated.

Manufacturing process development

General

In general, the conclusions drawn from initial process development documents (for SBL Plant 2/JSI) are assessed to be applicable also for this submission, for SBL Plant 4A (e.g. for critical process parameter (CPP) assessments and PAR justifications). When applicable, corresponding documentation have been acceptably presented for SBL Plant 4A.

Process Development History

The active substance manufacturing process performed at SBL Plant 2/JSI has been transferred to SBL Plant 4A. A comparison of the active substance manufacturing process at SBL Plant 2/JSI and SBL Plant 4A is provided. At SBL Plant 4A, the Stages 6-14 of the manufacturing process were scaled up. A replenishment WCB for each parental antibody was also introduced during the process validation campaign at SBL Plant 4A.

The process changes are assessed to be minor and are well described, including changes related to plant specific equipment, e.g. for agitation rates and centrifugation procedures. The process changes are assessed to be acceptable and not to be critically influencing the process performance.

Process Comparability

It is acknowledged that the post-change IPC data all met the acceptance criteria, and that the release data for the intermediates, active substance and finished product were highly similar for pre- and post-change batches.

Pre-change and post-change active substance and finished product batches were also highly similar at release. All results for these attributes were within the historical ranges. This is assessed to be correct.

In general, results that were outside the min-max ranges but within the statistical ranges were assessed and considered to have a minimal, if any, potential impact on product stability, PK, safety, and activity because they showed only small differences that were not considered scientifically meaningful. This is acceptable.

The available stability data for the post-change active substance and finished product batches also met the stability criteria. In the head-to-head degradation rates study, the post-change active substance showed the same degradation pathways, and the degradation rates under heat-stress storage conditions were either highly similar or showed differences that were not scientifically meaningful. This is acknowledged.

Based on the totality of data for IPC and comparison of release, characterisation and stability data, it is assessed that pre- and post-change active substance and finished product are considered comparable.

Characterisation

No modifications have been made to the text in Module 3.2.S.3 (Characterisation) for the submission.

4.2.3. Specification

Specification

The active substance specification is unchanged with this submission, except for the addition of alternative analytical method numbers for bioburden and endotoxin. Hence, the text in Section S.4.1 is assessed to be acceptable.

No modifications have been made to the text in Module 3.2.S.4.5 (Justification of Specification) for the submission. Hence, the text in Section S.4.5 is assessed to be acceptable.2

Analytical procedures

Revised analytical procedures for bioburden and endotoxins in conformance with Ph. Eur. 2.6.12 and 2.6.14, respectively. Both methods have been verified as suitable for their intended use.

The information in Sections S.4.2 and S.4.3 is assessed to be acceptable.

Batch analysis

It is acknowledged that batch analyses results for the clinical and process validation batches (both SBL Plant 2/JSI and SBL Plant 4A) of the 160 mg/mL amivantamab active substance are correctly included in this section. Moreover, the results for the post-PV batches of the 160 mg/mL amivantamab active substance manufactured SBL Plant 4A are also included. This is assessed to be acceptable.

Reference standards or materials

No modifications have been made to the text in Module 3.2.S.5 (Reference standards or materials) for the submission.

Container closure

No modifications have been made to the text in Module 3.2.S.6 (Container closure system) for the submission, other than additions of new reference for detailed descriptions of the extractable and leachable studies. It is assessed that the conclusions initially reached does not change.

4.2.4. Stability

The shelf-life of the active substance manufactured at SBL Plant 4A is the same as the shelf-life approved for the active substance manufactured at JSI, when stored at the recommended storage condition. This is based on the comparability conclusions discussed in 3.2.S.2.6. This is acceptable.

4.3. Finished medicinal product

The components of the finished product are identical to the approved finished products of Rybrevant SC 1600 mg and 2240 mg (Table 2 and Table 3).

No novel excipients are used in the formulation.

The proposed 2400 mg and 3520 mg SC finished products are presented in a vial, 15 mL and 22 mL respectively, like the 1600 mg and 2240 mg SC presentations. With this submission, another supplier is introduced for the 25R vial.

Table 2: Composition of Amivantamab SC Finished Product, 2400 mg

Component	Grade	Function	Nominal Amount per Vial[a] (mg)	Concentration (mg/mL)
Amivantamab	Company Standard	Active	2400	160
rHuPH20	Company Standard	Permeation enhancer	30,000 U	2000 U/mL
Sodium acetate trihydrate[b]	USP-NF/Ph. Eur./JP	Buffer	54.9	3.66
Glacial acetic acid[b]	USP-NF/Ph. Eur./JP	Buffer	2.8	0.19
Sucrose	USP-NF/Ph. Eur./JP	Stabilizer/Tonicifier	1065	71[c]
Polysorbate 80[d]	USP-NF/Ph. Eur./JP	Surfactant	9.0	0.6
L-Methionine	USP-NF/Ph. Eur./JP	Stabilizer	15.0	1.0
EDTA disodium salt dihydrate	USP-NF/Ph. Eur./JP	Stabilizer/Chelating agent	0.30	0.02
Water for Injection[e]	USP-NF/Ph. Eur./JP	Solvent	q.s. to 15.0 mL	NA

[a] The nominal fill volume is 15.0 mL
[b] Combination of listed amounts of sodium acetate and glacial acetic acid produces a buffer at target pH of 5.7 and buffer strength of 30 mM.
[c] Reported values are described in 3.2.P.3.5 Process Validation and/or Evaluation.
[d] The concentration of 0.6 mg/mL polysorbate 80 is equivalent to 0.06% (w/v) polysorbate 80.
[e] Corresponding name in Ph. Eur. monograph is Water for Injections.

rHuPH20 = Recombinant human hyaluronidase
EDTA = Ethylenediaminetetraacetic acid
q.s. = *quantum satis* (as much as may suffice)
NA = Not applicable

Table 3: Composition of Amivantamab SC Finished Product, 3520 mg

Component	Grade	Function	Nominal Amount per Vial[a] (mg)	Concentration (mg/mL)
Amivantamab	Company Standard	Active	3520	160
rHuPH20	Company Standard	Permeation enhancer	44000 U	2000 U/mL
Sodium acetate trihydrate[b]	USP-NF/Ph. Eur./JP	Buffer	80.6	3.66
Glacial acetic acid[b]	USP-NF/Ph. Eur./JP	Buffer	4.1	0.19
Sucrose	USP-NF/Ph. Eur./JP	Stabilizer/Tonicifier	1562	71[c]
Polysorbate 80[d]	USP-NF/Ph. Eur./JP	Surfactant	13.2	0.6
L-Methionine	USP-NF/Ph. Eur./JP	Stabilizer	22.0	1.0
EDTA disodium salt dihydrate	USP-NF/Ph. Eur./JP	Stabilizer/Chelating agent	0.44	0.02
Water for Injection[e]	USP-NF/Ph. Eur./JP	Solvent	q.s. to 22.0 mL	NA

[a] The nominal fill volume is 22.0 mL
[b] Combination of listed amounts of sodium acetate and glacial acetic acid produces a buffer at target pH of 5.7 and buffer strength of 30 mM.
[c] Reported values are described in 3.2.P.3.5 Process Validation and/or Evaluation.
[d] The concentration of 0.6 mg/mL polysorbate 80 is equivalent to 0.06% (w/v) polysorbate 80.
[e] Corresponding name in Ph. Eur. monograph is Water for Injections.

rHuPH20 = Recombinant human hyaluronidase
EDTA = Ethylenediaminetetraacetic acid
q.s. = *quantum satis* (as much as may suffice)
NA = Not applicable

4.3.1. Pharmaceutical development

As indicated above, the qualitative composition in excipients for the proposed 2400 mg and 3520 mg SC presentations remains unchanged. The concentration in excipients also remain unchanged compared to the currently authorised SC presentations. No additional formulation development has been performed.

Compatibility and forced degradation studies of finished product including rHuPH20 excipient have already been addressed in the previous application with the 1600 and 2240 mg finished product presentations. This is found acceptable.

Process changes related to the introduction of the two new 2400 mg and 3520 mg presentations include:

- SBL Plant 4A as new plant for manufacturing of active substance;

- Nuova Ompi as an alternative source of 25R vials;

- Avid Bioservices (Avid) as additional secondary site for manufacture and quality control testing of rHuPH20.

In-process control
An additional in-process control was introduced regarding in-line weighing system for fill weight. The obtained fill weight range for the validation batches has been adequately reported.

The finished product manufacturing process was updated with relevant CPP for the new presentations including a PAR for target weight of rHuPH20 influencing the CQA activity. PARs were also defined for aseptic sterilisation pressure and time, fill weight and crimp quality. This is found acceptable.

Comparability
Comparability to evaluate the active substance site and scale changes and 2 new finished product presentations are described.

Comparability exercises have been performed with two batches of each presentation (2400 mg and 3520 mg) in commercial scale manufactured at the new SBL Plant 4A active substance site – with one of the batches of each presentation filled with vials from the new supplier of vials. The batches were further used for process validation and put on stability. Batch analysis of these batches is provided.

The new supplier of rHuPH20 (Avid) was introduced in a manufacturing campaign at SBL Plant 4A active substance with three batches each of the already approved presentations 1600 mg and 2240 mg in commercial scale with finished product manufacturing at Cilag AG (LPF2). Batch analysis of these batches is provided. These batches were placed in a stability monitoring program and 3 months of stability data are provided. This is found acceptable.

Compatibility
In-use stability studies (including microbial challenge studies) were conducted to investigate the stability and compatibility of the finished product with ancillaries composed of polypropylene, polyethylene, acrylic, silicone rubber, and stainless steel. This is considered acceptable.

4.3.2. Manufacture of the product and process controls

Manufacture

The finished product is manufactured at Cilag AG, Hochstrasse 201, 8200 Schaffhausen, Switzerland. Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands is responsible for EU release. All sites involved in manufacture and control of the finished product operate in accordance with EU GMP.

The finished product vials stored at 5 ± 3 °C.

Target composition and theoretical vial output for the minimum and maximum batch sizes including the two new presentations 2400 mg and 3520 mg are provided. This is found acceptable.

Associated PARs in finished product manufacturing process for are described for the applied new presentations 2400 mg and 3520 mg.

Summary of CPPs is adequately described.

1*Process validation and or evaluation*
Additional process validation (3 consecutive batches) was performed at Cilag AG to introduce the new finished product presentations (2400 and 3520 mg).

Hold time studies have been performed to support the new finished product presentations (2400mg/15 mL and 3520 mg/22 mL).

The manufacturing process is considered adequately validated.

Control of non-compendial biological excipients – rHuPH20, recombinant human hyaluronidase PH20
Section 3.2.P.4.1 and 3.2.P.4.4 were re-introduced with cross-references to Section 3.2.A.3 Excipients for the full report from the second manufacturer of rHuPH20, that will align with the Q&A recommendation (Questions and answers for biological medicinal products | European Medicines Agency (EMA), Non-novel excipients manufactured using recombinant technology).

Avid Bioservices was introduced to complement the current rHuPH20 manufacturer Catalent Indiana, LLC. The rHuPH20 specification in section 3.2.P.4.1 has not been changed since the approval of the previous presentations and that is found acceptable.

A process validation campaign consisting of five successful consecutive process validation batches was executed at full commercial scale for therHuPH20 bulk enzyme manufacturing process at Avid Bioservices. These batches met the current acceptance criteria for all attributes according to specification. Three of those, together with an engineering batch, were put on stability. For additional shelf-life extensions, the Applicant committed to provide data from three batches for each time point according to the protocol. This is found acceptable.

Comparability of rHuPH20

The originally approved supplier of rHuPH20 is Catalent and an alternative supplier i.e. Avid Bioservices is now proposed. It has been shown that both substances are derived from identical manufacturing processes and the analytical comparability of rHuPH20 from the approved and the new supplier has been shown adequately.

4.3.3. Product specification

Specifications

The specifications and limits are the same as for the approved strengths 1600 mg and 2240 mg, with the inclusion of extractable volume for the new strengths 2400 and 5320 mg. This is found acceptable.3

Analytical Procedures

Container closure integrity test and corresponding validation of analytical procedures have been updated to cover the new presentations.

Batch analysis

The clinical and (post-)process validation batch information and reference to the batch analyses data reports are provided for the 1600 mg and 2240 strengths. The process validation batches are representative of the commercial manufacturing process.

Batch information and reference to the batch analyses data reports for 2400 and 3520 mg process validation batches (n=6) manufactured using SBL Plant 4A active substance are also provided.

Reference standards or materials

See Active substance section.

Characterisation of impurities

The product-related impurities for amivantamab SC finished product are the same as those present in the active substance.

An exposure of finished product to mechanical stress (transportation study) exercise was performed for the finished product covering the range 1600 mg to 3728 mg. Process-related impurities for the finished product include the same impurities characterised for the active substance. No additional process-related impurities derived from the finished product manufacturing process were identified in the finished product.

A nitrosamine risk evaluation report for Amivantamab SC is provided concluding a remote risk of presence of nitrosamines.

Container closure

The alternative supplier of 25R glass vial is added to section P.7.

For the two new presentations, a specific colour label is described for the aluminium seal flip-off cap: silver for the 2400 mg presentation and dark red for the 3520 mg presentation. This is found acceptable.

4.3.4. Stability of the product

The proposed shelf-life of the two additional amivantamab SC finished product presentations, 2400 and 3520 mg is 24 months when stored at the recommended storage condition of 5 ± 3 °C and protected from light. These two additional finished product presentations contain the same formulation and packaging configuration as the 1600 mg and 2240 mg presentations with only differences in fill volume.

The stability program is based on ICH guidelines and the shelf-life claim is based on demonstrated comparability and poolability between data from finished product batches and an ongoing stability program for clinical finished product batches, as well as process validation finished product batches.

As per ICH Q1E, the objective of poolability is to determine whether data from different batches can be combined for an overall estimate of a single retest period or shelf life. The performed poolability showed no statistically significant change in intercept nor slope for any quality attribute when testing up to 18 months at recommended (5 °C) storage condition. Additionally, comparability has been demonstrated between active substance sourced from SBL/JSI and SBL Plant 4A to leverage the same shelf life for finished product presentations filled with comparable active substance materials.

The stability data presented includes up to 24 months of stability data at 5 ± 3 °C for all batches included in the stability program.

A photostability study was conducted and the results from the study demonstrate the commercial secondary package will provide finished product with adequate protection from the effects of the light conditions specified in ICH Q1B. This is found acceptable.

The proposed finished product shelf life (unopened vial) of 2 years when stored at 2°C to 8°C protected from light is acceptable.

Chemical and physical in use stability has been demonstrated up to 24 hours at 2°C to 8°C followed by up to 24 hours at 15°C 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.

4. 3.5. Adventitious agents

There were no process changes in Stages 4, 9, 10, and 12 between the commercial active substance manufacturing process at JSI and SBL Plant 4A. Therefore, the results of the viral clearance studies that were performed as part of the JSI process validation apply to the active substance manufacturing process at SBL Plant 4A.

A report called Adventitious Agents Safety Evaluation – rHuPH20 (Avid) is provided in 3.2.A.2 for Viral Reduction Studies. This report is acknowledged, and satisfactory precautions have been taken for viral safety of the biological excipient rHuPH20 (Avid).

The log reduction values for the rHuPH20 bulk enzyme from Avid have been compared to the material manufactured at Catalent, and the values obtained are considered similar.

Adventitious agents safety is considered sufficiently assured.

4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Module 3 provided in support of the line extension for Rybrevant is in considered adequate. Relevant information is included into the specific sections.

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the active substance and finished product.

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

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

4.5. Recommendation(s) for future quality development

None.

5. Non-clinical aspects

No new non-clinical data have been submitted in this application.

5.1.1. Ecotoxicity/environmental risk assessment

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

5.2. Overall discussion and conclusions on non-clinical aspects

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

6. Clinical aspects

Introduction

6.1.1. 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.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

6.1.2. Tabular overview of clinical trials

Table 4: Tabular overview of main clinical studies

PALOMA-2 Amivantamab SC Study Cohorts	Matching Amivantamab IV Studies	Dosing Schedule	Treatment	Population
PALOMA-2 Cohort 5	MARIPOSA	Q4W*	amivantamab + lazertinib	Treatment-naïve participants with EGFR exon 19del or exon 21 L858R mutations (first-line)
PALOMA-2 Cohort 2	PAPILLON	Q3W	amivantamab + CP	Treatment-naïve participants with EGFR exon 20ins mutations (first-line)
PALOMA-2 Cohort 3b	MARIPOSA-2	Q3W	amivantamab + CP	Participants with EGFR exon 19del or exon 21 L858R mutations, post-osimertinib (second-line)

**PK modeling and simulation, supported by PALOMA-2 Cohort 5 clinical data, bridge the gap between the IV Q2W dose regimen in MARIPOSA and the SC Q4W dose regimen.*

General note: due to inherent differences in study designs, sample sizes, and follow-up time, caution should be exercised when comparing results across studies.

Type of Study	Study ID/Participant Population	Dose Regimen	Number of PK Samples	PK Sampling Scheme

Phase 2	Study 61186372NSC 2002 (PALOMA-2) in participants with EGFRm NSCLC (exon20ins mutation [Cohort 2] or EGFR exon19del or exon 21 L858R mutation [Cohorts 1, 3, 3b, 5, and 6]) after progression on osimertinib	*Q2W Regimen*
		Cohorts 1 and 6 (28-day cycles):
		• 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
		Cohort 6:
		• Prophylactic-dose anticoagulation per local guidelines
		
		Q3W Regimen
			Q2W Regimen
			Cohort 1:
			Amivantamab: 17 planned samples per participant
			Lazertinib: 8 planned samples per participant
			Cohort 6:
			Amivantamab: 21 planned samples per participant
			Lazertinib: 8 planned samples per participant
			
			Q3W Regimen
				Cohorts 1 and 6:
				Amivantamab:
				• C1D1 predose and 48 h postdose
				• Predose of C1D8, C1D15, and C1D22
				• C2D1 predose and 48 h postdose
				• Predose of C2D15, C3D1, C3D15, and C4D1
				• C4D1 at 8, 48, 96, and 168 h postdose (Cohort 6 only for ~25 participants)
				• Predose of C4D15, C5D1, C7D1, C9D1, and C11D1
				• EOT
				Lazertinib:
				• Predose of C1D1, C1D15, C2D1, and C3D1
				• C1D1, C1D15, and C2D1 at 2 h postdose

Type of Study	Study ID/Participant Population	Dose Regimen	Number of PK Samples	PK Sampling Scheme

	(Cohorts 3 and 3b).	<u>Cohorts 2, 3, and 3b (21-day cycles):</u>
		• Amivantamab SC
		  • Cycle 1: 1600 mg (2240 mg if BW ≥80 kg) on Day 1 and 2400 mg (or 3360 mg if BW ≥80 kg) on Days 8 and 15
		  • Cycles 2+: 2400 mg (or 3360 mg if BW ≥80 kg) on Day 1
		<u>Cohorts 2 and 3b:</u>
		• Pemetrexed 500 mg/m^2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance until disease progression
		• Carboplatin 5 mg/mL per minute to a maximum of 750 mg on Day 1 for up to 4 cycles
		<u>Cohort 3:</u>
		• Lazertinib 240 mg orally once daily starting Cycle 5 Day 1, or sooner if carboplatin was discontinued earlier than Cycle 4
		
		Q4W Regimen
		<u>Cohort 5 (28-day cycles):</u>
		• Amivantamab SC
		  • Cycle 1: 1600 mg (2240 mg if BW ≥80 kg) on Day 1, 8, 15, 22
		  • Cycles 2+: 3520 mg (or 4640 mg if BW ≥80 kg) on Day 1
		• Lazertinib 240 mg orally once daily
			<u>Cohorts 2, 3, and 3b:</u>
			Amivantamab: 13 planned samples per participant
			Lazertinib (Cohort 3 only): 6 planned samples per participant
			
			Q4W Regimen
			<u>Cohort 5:</u>
			Amivantamab: 17 planned samples per participant
			Lazertinib: 8 planned samples per participant
				• EOT
				
				<u>Cohorts 2, 3, and 3b:</u>
				Amivantamab:
				• C1D1 predose and 48 h postdose
				• Predose of C1D8 and C1D15
				• C2D1 predose and 48 h postdose
				• Predose of C3D1, C4D1, C5D1, C7D1, C9D1, and C11D1
				• EOT
				<u>Cohort 3:</u>
				Lazertinib:
				• Predose of C5D1, C6D1, and C7D1
				• C5D1 and C6D1 at 2 h postdose
				• EOT
				<u>Cohort 5:</u>
				Amivantamab:
				• C1D1 predose and 48 h postdose
				• Predose of C1D8, C1D15, and C1D22
				• C2D1 predose, 48 and 336 h postdose
				• Predose of C3D1, C4D1, C5D1, C7D1, C9D1, and C11D1
				• C3D1 and C4D1 336 h postdose
				• EOT
				
				<u>Cohort 5:</u>
				Lazertinib:
				• Predose and 2 h postdose of C1D1, C1D15, and C2D1
				• Predose on C3D1
				• EOT

Type of Study	Study ID/Participant Population	Dose Regimen	Number of PK Samples	PK Sampling Scheme
Phase 1b	Study 61186372NSC1003 (PALOMA) in participants with advanced solid malignancies	Cohort 4a (28-day cycles)[a]: Amivantamab SC (HC-CF) • 1600 mg (2240 mg if BW ≥80 kg); once weekly in Cycle 1 and Q2W schedule in subsequent cycles from C2D1 onwards Cohort 6a (28-day cycles): • Cycle 1: 1600 mg (2240 mg if BW ≥80 kg) weekly • Cycles 2+: 3200 mg (4320 mg if BW ≥80 kg) Q4W	Cohort 4a: 23 planned samples per participant Cohort 6a: 18 planned samples per participant	Cohort 4a: • C1D1 predose • C1D2 predose, 24, 48, and 72 h postdose • Predose of C1D8, C1D15, and C1D22 • C2D1 predose, 24, 48, and 72 h postdose • Predose of C2D15, C3D1, C3D15, C4D1, C4D15, C6D1, C6D15, C8D1, and C8D15 • 4 and 8 weeks after last dose Cohort 6a: • C1D1 predose • C1D2 predose, 24, 48, and 72 h postdose • Predose of C1D8, C1D15, and C1D22 • C2D1 predose, 24, 48, and 72 h postdose • Predose of C3D1, C4D1, C6D1, and C8D1 • 4 and 8 weeks after last dose

6.2. Clinical pharmacology

6.2.1. Methods

A validated and cross validated MSD ECLIA method was used to determine amivantamab PK concentrations in human serum samples. Antibodies to amivantamab and rHuPH20 were analysed using validated MSD ECLIA methods.

6.2.2. Pharmacokinetics

6.2.2.1. Introduction

The primary focus of this application is to support amivantamab SC Q3W dosage indications and expansion to Q4W dosage of the approved SC Q2W indications (amivantamab IV is approved for Q2W and Q3W administration). A population PK model was used to demonstrate PK similarity of amivantamab SC Q3W to IV Q3W and SC Q4W to IV Q2W dose regimens. This is the pivotal data in this application which is supported by comparisons of observed PK-data as well as some efficacy and safety data.

Proposed dosing regimens for SC Q3W and SC Q4W administration are presented, together with the recommended dosing regimens for IV Q3W, IV Q2W, and SC Q2W administration, in Table 7 and Table 8 for patients weighing <80 kg and ≥80 kg, respectively.

Table 5: Proposed and currently recommended dosing regimens for patients weighing <80 kg.

	SC Cycle 1	SC Cycle 2+	IV Cycle 1	IV Cycle 2+	Comment
Q2W	1600 mg QW	1600 mg Q2W	1050 mg QW	1050 mg Q2W	28-days cycles. Approved SC dosing regimen based on PK non-inferiority study PALOMA-3
Q3W	1600 mg Day 1 2400 mg Day 8 2400 mg Day 15	2400 mg Q3W	1400 mg QW	1750 mg Q3W	21-days cycles. For the IV regimen, the listed Cycle 1 dose is administered also Cycle 2 Day 1, whereas the listed Cycle 2 dose is administered from Cycle 3 and onwards.
Q4W	1600 mg QW	3520 mg Q4W	-	-	28-days cycles. The SC Q4W administration should be compared to the IV Q2W administration.

Table 6: Proposed and currently recommended dosing regimens for patients weighing ≥80 kg.

	SC Cycle 1	SC Cycle 2+	IV Cycle 1	IV Cycle 2+	Comment
Q2W	2240 mg QW	2240 mg Q2W	1400 mg QW	1400 mg Q2W	28-days cycles. Approved SC dosing regimen based on PK non-inferiority study PALOMA-3
Q3W	2240 mg Day 1 3360 mg Day 8 3360 mg Day 15	3360 mg Q3W	1750 mg QW	2100 mg Q3W	21-days cycles. For the IV regimen, the listed Cycle 1 dose is administered also Cycle 2 Day 1, whereas the listed Cycle 2 dose is administered from Cycle 3 and onwards.
Q4W	2240 mg QW	4640 mg Q4W	-	-	28-days cycles. The SC Q4W administration should be compared to the

					IV Q2W administration.

The SC Q2W dose regimen was approved based on data from the Phase 3 study PALOMA-3, a PK non-inferiority study ensuring adequate exposure following SC Q2W administration compared to IV Q2W administration.

6.2.2.2. Evaluation and qualification of models

6.2.2.2.1. Population Pharmacokinetics

A population PK analysis was provided in a modelling report. The population PK model was used to demonstrate PK similarity of amivantamab SC Q3W to IV Q3W and SC Q4W to IV Q2W dosing regimens.

The model used in the analysis was a previously developed population PK model, based on clinical data from CHRYSALIS, PALOMA, PALOMA-2, and PALOMA-3 (see Procedure EMEA/H/C/005454/X/0014). The model was externally validated on new data (3,814 measurable serum amivantamab concentrations from 463 participants) collected in the on-going PALOMA and PALOMA-2 studies. The new data included PK data following administration of the proposed SC Q3W and SC Q4W dosing regimens, as well as additional data on the already approved SC Q2W dosing regimen. For the proposed SC Q4W regimen, 851 measurable amivantamab serum concentrations were available from 77 participants (an additional 239 concentrations from 19 participants were also available from a slightly lower SC Q4W dosing regimen). For the proposed SC Q3W regimen, 2084 measurable amivantamab serum concentrations were available from 238 participants.

A summary of baseline characteristics and laboratory values for the subjects who received SC Q3W or IV Q3W administration is provided in Table 9, and a summary of baseline characteristics and laboratory values for the subjects who received SC Q4W or IV Q2W administration is provided in Table 10.

Table 7: Summary of baseline characteristics and laboratory values for the subjects who received SC Q3W or IV Q3W administration

	SC Q3W[1] **(N=238)**	**IV Q3W**[2] **(N=330)**
Gender		
Male	99 (41.6%)	137 (41.5%)
Female	139 (58.4%)	193 (58.5%)
Age (years)		
Median [Min, Max]	63.0 [31.0, 84.0]	62.0 [27.0, 86.0]
Age Group (years)		
<65	134 (56.3%)	203 (61.5%)
≥65 to <75	81 (34.0%)	99 (30.0%)
≥75	23 (9.7%)	28 (8.5%)
Weight (kg)		
Median [Min, Max]	60.9 [37.4, 115]	63.5 [38.5, 127]
Weight Category		
WT < 80	210 (88.2%)	289 (87.6%)
WT >=80	28 (11.8%)	41 (12.4%)
Body surface area (m^2)		
Median [Min, Max]	1.66 [1.25, 2.44]	1.70 [1.27, 2.63]
Body mass index[3] **(kg/m^2)**		
Median [Min, Max]	23.0 [14.8, 36.7]	23.6 [15.9, 50.0]
Race		
White	109 (45.8%)	118 (35.8%)

	SC Q3W[1] (N=238)	IV Q3W[2] (N=330)
Black or African American	5 (2.1%)	5 (1.5%)
Asian	122 (51.3%)	198 (60.0%)
Other	2 (0.8%)	9 (2.7%)
Japanese origin		
Not Japanese (including not reported, unknown)	224 (94.1%)	294 (89.1%)
Japanese	14 (5.9%)	36 (10.9%)
Chinese origin		
Not Chinese (including not reported, unknown)	206 (86.6%)	255 (77.3%)
Chinese	32 (13.4%)	75 (22.7%)
Albumin (g/L)		
Median [Min, Max]	41.0 [22.0, 53.0]	40.9 [23.0, 52.8]
Renal Function		
Normal	76 (31.9%)	149 (45.2%)
Mild	115 (48.3%)	143 (43.3%)
Moderate	47 (19.7%)	37 (11.2%)
Severe	0 (0%)	0 (0%)
Missing	0 (0%)	1 (0.3%)
Hepatic function[4]		
Normal	212 (89.1%)	275 (83.3%)
Mild dysfunction	26 (10.9%)	54 (16.4%)
Moderate dysfunction	0 (0%)	1 (0.3%)
ECOG Category		
0	87 (36.6%)	123 (37.3%)
≥1	151 (63.4%)	207 (62.7%)
History of brain metastasis		
No	147 (61.8%)	252 (76.4%)
Yes	91 (38.2%)	78 (23.6%)
Initial diagnosis cancer stage		
Grade 0-III	33 (13.9%)	41 (12.4%)
grade IV	204 (85.7%)	289 (87.6%)
Not reported	1 (0.4%)	0 (0%)
Use of anti-coagulant as a preventative measure for VTE		
No	44 (18.5%)	0 (0%)
Yes	51 (21.4%)	0 (0%)
Not reported	143 (60.1%)	330 (100%)
EGFR Primary mutations		
exon 19del	88 (37.0%)	292 (88.5%)
exon 21 L858R	60 (25.2%)	38 (11.5%)
Other or not reported	90 (37.8%)	0 (0%)
Health status		
NSCLC	238 (100%)	330 (100%)
Other cancer	0 (0%)	0 (0%)

[1] Including data from PALOMA Cohort 5a (n=25) and PALOMA-2 cohorts 2, 3, and 3b (n=213).
[2] Including data from PAPILLON arm A and B (monotherapy crossover) (n=207) and MARIPOSA-2 arm C (n=123).
[3] Equation for BMI: weight/height^2
[4] Hepatic function was based on the NCI-ODWG criteria: Normal=TB and AST ≤ULN, Mild dysfunction=TB ≤ULN and AST >ULN or ULN <TB ≤1.5*ULN, Moderate dysfunction=1.5*ULN <TB ≤3.0*ULN.

AST=aspartate aminotransferase; BQL=below quantifiable limit; BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; Max=maximum; Min=minimum; N=number of participants; NCI-ODWG=National Cancer Institute Organ Dysfunction Working Group; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; TB=total bilirubin; ULN=upper limit of normal; VTE=venous thromboembolic event; WT=body weight.

Table 8: Summary of baseline characteristics and laboratory values for the subjects who received SC Q4W or IV Q2W administration

	SC Q4W[1] (N=96)	IV Q2W[2] (N=820)
Gender		
Male	34 (35.4%)	301 (36.7%)

	SC Q4W[1] (N=96)	IV Q2W[2] (N=820)
Female	62 (64.6%)	519 (63.3%)
Age (years)		
Median [Min, Max]	63.0 [31.0, 84.0]	63.0 [25.0, 88.0]
Age Group (years)		
<65	51 (53.1%)	468 (57.1%)
≥65 to <75	37 (38.5%)	258 (31.5%)
≥75	8 (8.3%)	94 (11.5%)
Weight (kg)		
Median [Min, Max]	61.5 [36.1, 123]	61.0 [31.6, 140]
Weight Category		
WT < 80	88 (91.7%)	721 (87.9%)
WT >=80	8 (8.3%)	99 (12.1%)
Body surface area (m^2)		
Median [Min, Max]	1.67 [1.22, 2.53]	1.66 [1.12, 2.69]
Missing	0 (0%)	1 (0.1%)
Body mass index[3] (kg/m^2)		
Median [Min, Max]	23.6 [15.8, 37.5]	23.5 [13.7, 45.7]
Missing	0 (0%)	1 (0.1%)
Race		
White	33 (34.4%)	279 (34.0%)
Black or African American	1 (1.0%)	14 (1.7%)
Asian	61 (63.5%)	490 (59.8%)
Other	1 (1.0%)	37 (4.5%)
Japanese origin		
Not Japanese (including not reported, unknown)	86 (89.6%)	755 (92.1%)
Japanese	10 (10.4%)	65 (7.9%)
Chinese origin		
Not Chinese (including not reported, unknown)	73 (76.0%)	739 (90.1%)
Chinese	23 (24.0%)	81 (9.9%)
Albumin (g/L)		
Median [Min, Max]	41.0 [26.0, 49.0]	40.0 [23.0, 53.8]
Renal Function		
Normal	35 (36.5%)	271 (33.0%)
Mild	46 (47.9%)	371 (45.2%)
Moderate	15 (15.6%)	176 (21.5%)
Severe	0 (0%)	2 (0.2%)
Hepatic function[4]		
Normal	81 (84.4%)	738 (90.0%)
Mild dysfunction	15 (15.6%)	82 (10.0%)
Moderate dysfunction	0 (0%)	0 (0%)
ECOG Category		
0	28 (29.2%)	244 (29.8%)
≥1	68 (70.8%)	576 (70.2%)
History of brain metastasis		
No	54 (56.3%)	506 (61.7%)
Yes	42 (43.8%)	314 (38.3%)
Initial diagnosis cancer stage		
Grade 0-III	14 (14.6%)	133 (16.2%)
grade IV	79 (82.3%)	687 (83.8%)
Not reported	3 (3.1%)	0 (0%)
Use of anti-coagulant as a preventative measure for VTE[5]		
No	29 (30.2%)	820 (100%)
Yes	67 (69.8%)	0 (0%)
Not reported	0 (0%)	0 (0%)
EGFR Primary mutations		
exon 19del	46 (47.9%)	365 (44.5%)
exon 21 L858R	31 (32.3%)	238 (29.0%)
Other or not reported	19 (19.8%)	217 (26.5%)
Health status		
NSCLC	94 (97.9%)	820 (100%)
Other cancer	2 (2.1%)	0 (0%)

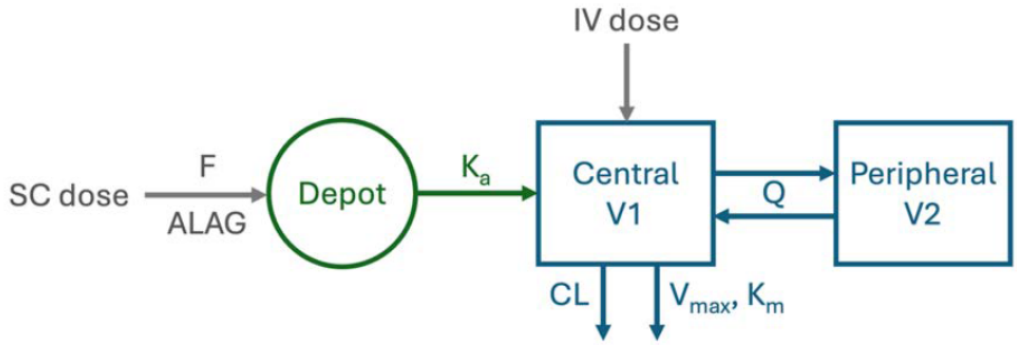
[1] Including data from PALOMA Cohort 6a (n=19) and PALOMA-2 Cohort 5 (n=77).
[2] Including data from CHRYSALIS monotherapy (n=413) and MARIPOSA (n=407). One participant from MARIPOSA was excluded for only having a single measurable amivantamab concentration at an unscheduled visit.
[3] Equation for BMI: weight/height^2
[4] Hepatic function was based on the NCI-ODWG criteria: Normal=TB and AST ≤ULN, Mild dysfunction=TB ≤ULN and AST >ULN or ULN <TB ≤1.5*ULN, Moderate dysfunction=1.5*ULN <TB ≤3.0*ULN.
[5] The use of anti-coagulant as a preventative measure for VTE was reported as "No" in CHRYSALIS, and was not available in MARIPOSA.

	SC Q4W[1] (N=96)	IV Q2W[2] (N=820)

AST=aspartate aminotransferase; BQL=below quantifiable limit; BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; Max=maximum; Min=minimum; N=number of participants; NCI-ODWG=National Cancer Institute Organ Dysfunction Working Group; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; TB=total bilirubin; ULN=upper limit of normal; VTE=venous thromboembolic event; WT=body weight.

A structural overview of the previously developed amivantamab population PK model is provided in Figure and associated parameter estimates are provided in Table 11.

Figure 2: Structural Overview of the Previously Developed Amivantamab PopPK Model.



ALAG=subcutaneous absorption delay time; CL=linear clearance; F=subcutaneous bioavailability; IV=intravenous; K_a=first-order subcutaneous absorption rate constant; K_m=Michaelis-Menten constant (amivantamab concentration at half maximum velocity of the nonlinear clearance); popPK=population pharmacokinetics; Q=intercompartmental clearance; SC=subcutaneous; 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.

Table 9: Parameter Estimates of the Previously Developed PopPK Model

Parameter	Estimate (RSE%[i])	Shrinkage (%)[j]
Fixed effect		
F	0.683 (1.6)	
BMI on LF[a]	-0.0363 (21.7)	
Ka (h^{-1})	0.0172 (4.1)	
Age on Ka[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)	
V1 (L)	2.63 (1.3)	
Weight on V1 and V2[d,e]	0.421 (8.3)	
Sex=Male on V1[d]	0.121 (17.9)	
V2 (L)	2.41 (2.2)	
Q (L/h)	0.0373 (2.3)	
Vmax (mg/h)	0.751 (4.1)	
Km (µg/mL)	18.4 (21.5)	
IIV		
F (SD)[f]	0.109 (7.4)	20.8
Ka (CV%)[g]	25.4 (31.5)	12.8
CL (CV%)[g]	25.4 (3)	10.7
V1 (CV%)[g]	19.6 (2.2)	18.9
V2 (CV%)[g]	47.4 (3.1)	21.7

Correlation F ~Ka	0.895 (0.0401)
Correlation F ~V1	-0.229 (0.0324)
Correlation V1 ~Ka	-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; Ka=first-order subcutaneous absorption rate constant; Km=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; SD=standard deviation; TV=typical value; V1=volume of distribution in the central compartment; V2=volume of distribution in the peripheral compartment; Vmax=maximum velocity of the nonlinear clearance; WT=weight.

[a]BMI effect on the typical value of F was modeled as follows:
TVF= $\frac{1}{1+e^{-\left(LF+(BMI-24)\times\theta_{\mathrm{bmi,f}}\right)}}$, where TV stands for "typical value," LF is the logit transformation of θF in a typical participant with baseline BMI of 24 kg/m2, and θbmi,f is the BMI coefficient for SC bioavailability. BMI was calculated as weight/(height2).

[b]Age effect on the typical value of Ka was modeled as follows:
$TVKa=\theta_{Ka}\times(AGE/63)^{\theta age,Ka}$, where θKa is the absorption rate constant in a typical participant with baseline age of 63 years, θage,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, ALB, 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 V1 was modeled as follows:
$TVV1=\theta V1\times(WT/60)\theta wt,V\times(1+\theta sex,V1\times sex)$, where θV1 is the central volume of distribution value in a typical female participant with baseline weight of 60 kg, and θwt,V is the weight coefficient for V1 and V2, sex is an indicator variable for female (sex=0; reference category) or male (sex=1) participants, and θsex,V1 is the multiplicative term for male sex effect on central volume of distribution.

[e]Weight effect on the typical value of V2 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 θwt,V is the weight coefficient for V1 and V2.

[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 θF was the SC bioavailability in a typical participant with baseline BMI of 24 kg/m2.

[g]IIV was estimated in relative percentage scale, calculated as (evar-1)1/2×100%, where var represents the variance estimate for log-normally distributed random effects as returned by NONMEM.

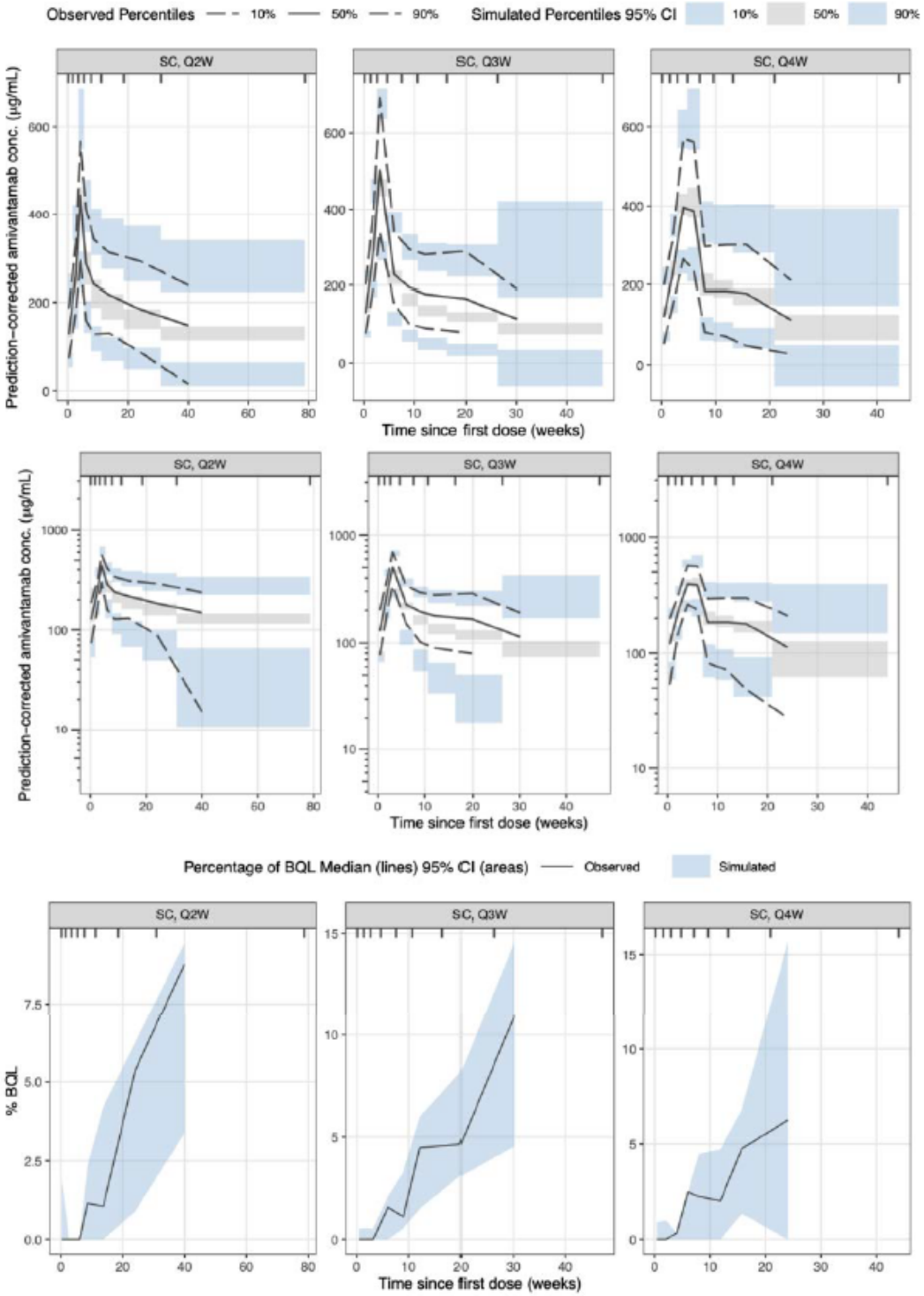
[h]Residual variability was estimated as THETAs in standard deviation.

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

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

The previously developed population PK model's ability to predict the new amivantamab serum concentrations, following the SC Q2W, SC Q3W, and SC Q4W regimens, is visualised in the prediction-corrected VPCs (pcVPC) in Figure 3 and Figure 4.

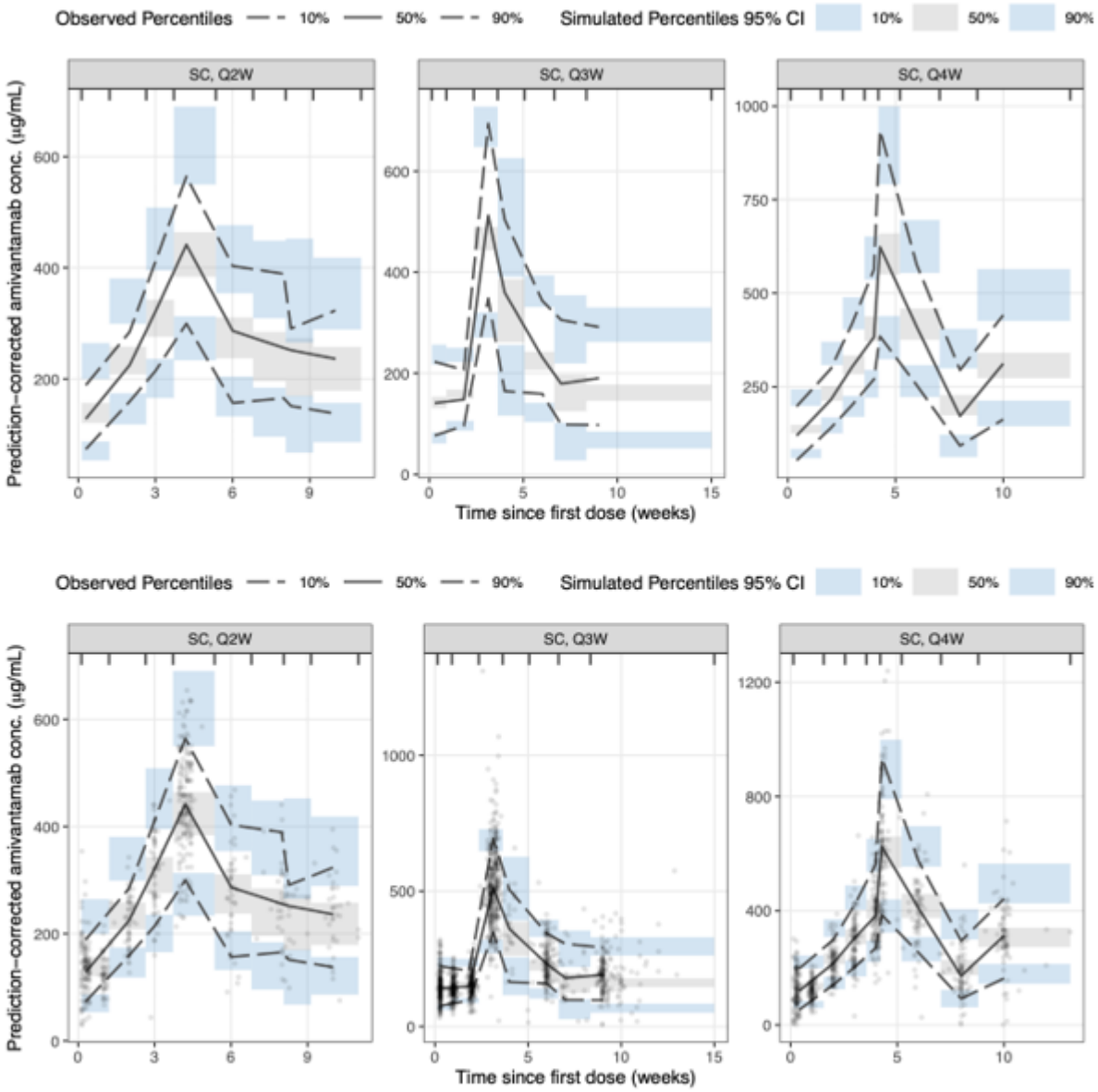
Figure 3: Prediction-Corrected Visual Predictive Checks Used in the External Validation of the Amivantamab Population PK model on the New PALOMA and PALOMA-2 Data



BQL=below quantification limit; CI=confidence interval; conc.=concentration; n=number of observations; popPK=population pharmacokinetics; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; SC=subcutaneous.

Within each panel, the median (bold line) and 10th and 90th percentiles (dashed lines) of the observed data are compared with the 95% CIs (shaded areas) for the median (gray area) and 10th and 90th percentiles (light areas) of the simulated data (n=1,000). A lower limit of quantification of 0.32 µg/mL was used to censor observations prior to the prediction correction. Individual observations are not shown for clarity.

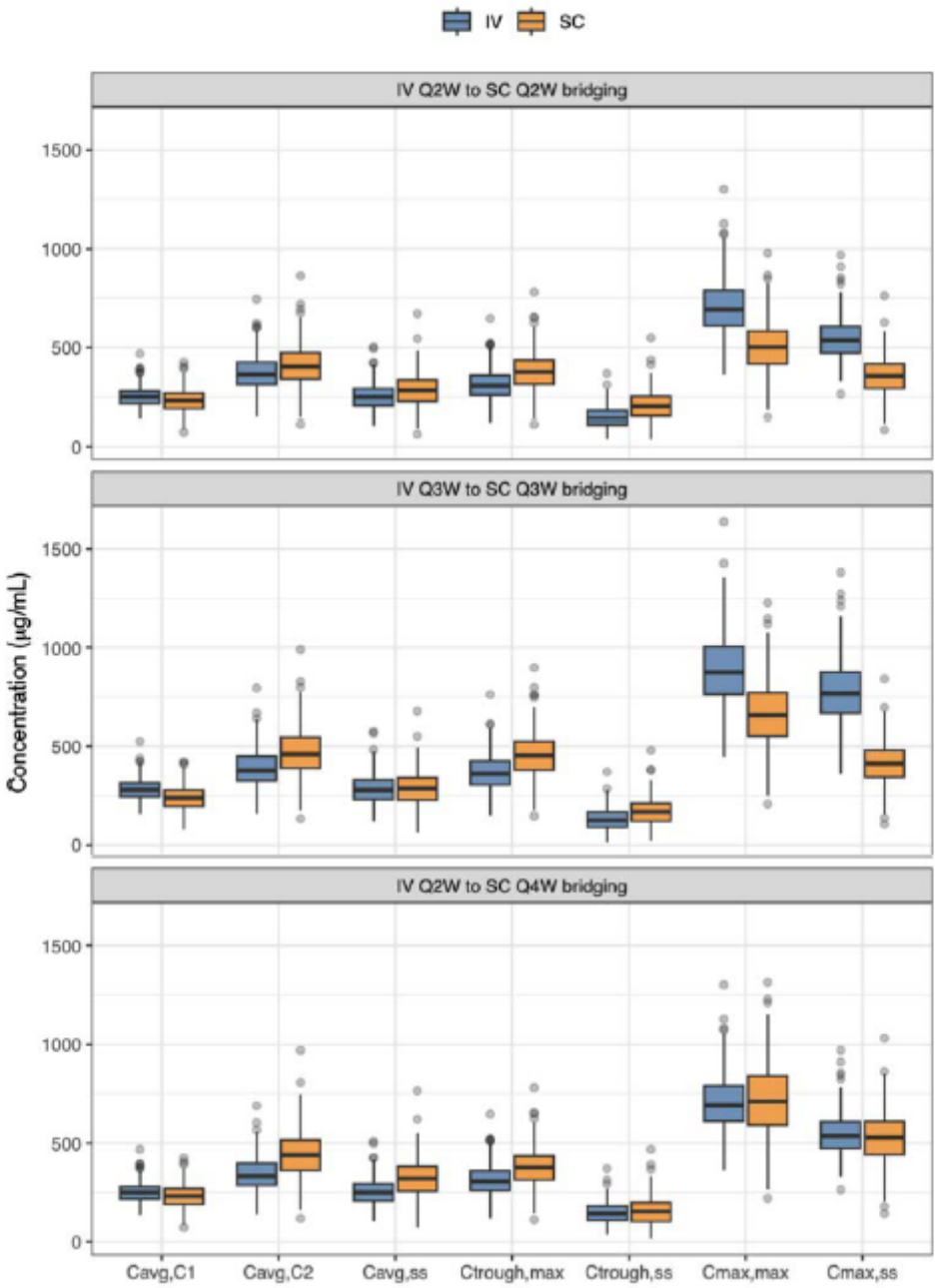
Figure 4: Prediction-Corrected Visual Predictive Checks Used in the External Validation of the Amivantamab Population PK model on the New PALOMA and PALOMA-2 Data, With Focus on the First 3 Treatment Cycles for SC Q2W and SC Q4W, and the First 4 Treatment Cycles for SC Q3W



CI=confidence interval; conc.=concentration; n=number of observations; popPK=population pharmacokinetics; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; SC=subcutaneous.
Within each panel, the median (bold line) and 10th and 90th percentiles (dashed lines) of the observed data are compared with the 95% CIs (shaded areas) for the median (gray area) and 10th and 90th percentiles (light areas) of the simulated data (n=1,000). A lower limit of quantification of 0.32 µg/mL was used to censor observations prior to the prediction-correction.

The externally validated population PK model and information on individual participants from the PALOMA-3 study (i.e. individual post-hoc parameters and covariates) were used to derive exposure metrics for assessment of PK similarity. The original 2-arm parallel design of PALOMA-3 was used for the reference (IV) and test (SC) arms, respectively. Nominal dosing according to the recommended doses for IV (Q3W and Q2W) administration, and the proposed doses for SC (Q3W and Q4W) administration, was assumed. Individual amivantamab PK profiles were predicted up to the end of Cycle 5 (i.e. steady state). From the individual profiles, individual amivantamab trough (C_{trough}), peak (C_{max}), and average (C_{avg}) concentrations at Cycle 2 and at steady state were derived (Figure).

Figure 5: Predicted Amivantamab Exposure Metrics for IV and SC Regimens at All Dose Regimens (Q2W, Q3W, and Q4W)



$C_{avg,C1}$=average concentration in Cycle 1; $C_{avg,C2}$=average concentration in Cycle 2; $C_{avg,ss}$=average concentration at steady state; $C_{max,max}$=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); IQR=interquartile range; IV=intravenous; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; SC=subcutaneous.

Within each panel are represented the median (thick line) and the IQR (distance between the 25th and 75th percentiles [colored box]). The lower and upper whiskers extend to the smallest and largest value, respectively, but no further than 1.5*IQR. Data beyond the end of the whiskers are called "outlying" points and are plotted individually.

The reference time frame was different for the IV Q2W in the Q2W and Q4W regimen bridging to accommodate for the difference in dose regimen.

The geometric mean ratios (GMR), for the exposure following SC administration relative the exposure following IV administration, were calculated, and the model predicted exposures were compared to the corresponding observed exposures. The SC Q3W administration of amivantamab is predicted to result in a 21% higher $C_{avg,C2}$, a comparable $C_{avg,ss}$, a higher $C_{trough,max}$ and $C_{trough,ss}$, and a lower $C_{max,max}$ and $C_{max,ss}$, compared to the approved IV Q3W administration (Table 12). The SC Q4W administration of amivantamab is predicted to result in a 30% higher $C_{avg,C2}$, a 26% higher $C_{avg,ss}$, a higher $C_{trough,max}$ but comparable $C_{trough,ss}$, and a comparable $C_{max,max}$ and $C_{max,ss}$, compared to the approved IV Q2W administration (Table 13).

Table 10: Summary of model-predicted and observed amivantamab exposure metrics for the proposed SC Q3W regimen compared to the recommended IV Q3W regimen.

	Model predictions			Observed data[a]		
	Geometric mean [% geometric CV]			Geometric mean		
Exposure metric (µg/mL)	**SC Q3W (N=204)**	**IV Q3W (N=207)**	**SC/IV GMR [90% CI]**	**SC Q3W**	**IV Q3W**	**SC/IV GMR [90% CI]**
$C_{avg,C2}$	456 [28%]	378 [27%]	1.21 [1.15, 1.26]	-	-	-
$C_{trough,max}$	443 [27%]	359 [26%]	1.23 [1.18, 1.29]	438 [N=83]	355 [N=215]	1.23 [1.16, 1.31]
$C_{max,max}$[b]	637 [28%]	877 [20%]	0.73 [0.70, 0.76]	663 [N=186]	871 [N=74]	0.761 [0.714, 0.811]
$C_{avg,ss}$	277 [32%]	275 [28%]	1.01 [0.96, 1.06]	-	-	-
$C_{trough,ss}$	158 [46%]	120 [49%]	1.32 [1.23, 1.42]	208 [N=72]	142 [N=154]	1.46 [1.29, 1.66]
$C_{max,ss}$	398 [30%]	767 [20%]	0.52 [0.50, 0.54]	-	-	-

[a] Cross-study comparison of PALOMA-2 Cohorts 2 and 3b (SC Q3W) versus PAPILLON Arm A and MARIPOSA-2 Arm C (IV Q3W).

[b] Observed C_{max} is EOI for IV and 48h post dose for SC.

$C_{avg,C2}$=predicted average concentration in Cycle 2 Day 1 to Day 21; $C_{avg,ss}$=predicted average concentration at steady state from Day 1 to Day 21; $C_{max,max}$=predicted maximum peak concentration after Cycle 2 Day 1 dose; $C_{max,ss}$=predicted peak concentration at steady state; $C_{trough,max}$=predicted maximum trough concentration (ie, Cycle 2 Day 1 predose); $C_{trough,ss}$=predicted trough concentration at steady state; CV=coefficient of variation; GMR=geometric mean ratio; IV=intravenous; N=number of participants; SC=subcutaneous; Q3W=every 3 weeks.

Table 11: Summary of model-predicted and observed amivantamab exposure metrics for the proposed SC Q4W regimen compared to the recommended IV Q2W regimen.

	Model predictions			Observed data[a]		
	Geometric mean [% geometric CV]			Geometric mean		
Exposure metric (µg/mL)	SC Q4W (N=204)	IV Q2W (N=207)	SC/IV GMR [90% CI]	SC Q4W	IV Q2W	SC/IV GMR [90% CI]
$C_{avg,C2}$	432 [29%]	333 [26%]	1.30 [1.24, 1.35]	-	-	-
$C_{trough,max}$	367 [28%]	305 [27%]	1.20 [1.15, 1.26]	350 [N=56]	303 [N=284]	1.16 [1.07, 1.25]
$C_{max,max}$[b]	689 [28%]	696 [20%]	0.99 [0.95, 1.03]	634 [N=51]	714 [N=212]	0.889 [0.824, 0.958]
$C_{avg,ss}$	311 [32%]	246 [27%]	1.26 [1.20, 1.32]	-	-	-
$C_{trough,ss}$	140 [56%]	139 [40%]	1.01 [0.93, 1.09]	131 [N=39]	142 [N=180]	0.92 [0.80, 1.07]
$C_{max,ss}$	506 [29%]	534 [20%]	0.95 [0.91, 0.99]	-	-	-

[a] Cross-study comparison of PALOMA-2 Cohort 5 (SC Q4W) versus MARIPOSA Arm A (IV Q2W).
[b] Observed C_{max} is EOI for IV and 48h post dose for SC.

$C_{avg,C2}$=predicted average concentration in Cycle 2 Day 1 to Day 21; $C_{avg,ss}$=predicted average concentration at steady state from Day 1 to Day 21; $C_{max,max}$=predicted maximum peak concentration after Cycle 2 Day 1 dose; $C_{max,ss}$=predicted peak concentration at steady state; $C_{trough,max}$=predicted maximum trough concentration (ie, Cycle 2 Day 1 predose); $C_{trough,ss}$=predicted trough concentration at steady state; CV=coefficient of variation; GMR=geometric mean ratio; IV=intravenous; N=number of participants; SC=subcutaneous; Q2W=every 2 weeks; Q4W=every 4 weeks.

6.2.2.3. Observed data

Amivantamab SC Q3W and Q4W were evaluated in 2 studies to support the current submission:

Phase 2 Study PALOMA-2 in participants with various stages of NSCLC

Phase 1b Study PALOMA in participants with various advanced solid malignancies

Only data from cohorts relevant to the current submission are assessed in this report.

PALOMA-2

Cohorts 1 and 6 (Q2W Regimen) was mainly assessed in procedure EMA/H/C/005454/X-14 but has been updated with new data. Data is now available for 68 participants in Cohort 1 and 67 participants in Cohort 6.

Cohorts 2 (n=66) and 3b (n=77) assessed amivantamab SC (Q3W) in combination with CP.

Cohort 5 (n=77) assessed amivantamab SC (Q4W) in combination with lazertinib.

PALOMA

Cohorts 4a and 6a are within the scope of this SCP. In both cohorts, most participants were diagnosed with NSCLC (48 of 56 participants in Cohort 4a; 17 of 19 participants in Cohort 6a).

Cohort 4a assessed (Q2W schedule)

Cohort 6a assessed Q4W schedule using a lower maintenance dose than the one proposed in this application (3200 mg or 4320 mg for ≥80 kg BW). Observed data from this Cohort is for this reason not included in the table comparing exposure cross-studies (Table 14).

Table 12: Summary of Descriptive Statistics of Amivantamab, Cycle 2 Day 1 and Cycle 5 Day 1 – Cross-study Comparison (Studies PALOMA 2, PAPILLON, MARIPOSA 2, and MARIPOSA)

Summary of C_{trough} of Amivantamab (µg/mL)	PAPILLON Arm A, Arm B Combination IV (Q3W)	PALOMA-2 Cohort 2 SC (Q3W)	MARIPOSA-2 Arm A1, Arm A2, Arm C, Combination IV (Q3W)	PALOMA-2 Cohort 3b SC (Q3W)	MARIPOSA Arm A IV (Q2W)	PALOMA-2 Cohort 5 SC (Q4W)	PAPILLON Arm A, Arm B, and MARIPOSA-2 Arm A1, Arm A2, Arm C Combination IV (Q3W)	PALOMA-2 Cohort 2 and Cohort 3b Combination SC (Q3W)
Cycle 2 Day 1								
n	140	41	193	42	285	56	333	83
Mean	365	439	359	469	317	366	362	455
Mean %CV	30.2	26.7	30.2	26.4	32.0	30.5	30.2	26.6
Geometric Mean	350	423	344	453	-	350	346	438
Geometric Mean %CV	30.2	29.2	30.3	27.9	-	31.4	30.2	28.6
Cycle 5 Day 1								
n	100	32	153	40	181	39	253	72
Mean	173	211	157	231	156	153	163	222
Mean %CV	85.2	34.9	67.8	36.0	47.1	55.9	76.1	35.6
Geometric Mean	138	199	-	216	-	131	-	208
Geometric Mean %CV	75.1	35.6	-	39.7	-	72.1	-	37.9

Note that data from a currently unapproved combination treatment used in PALOMA-2 Cohort 3 and MARIPOSA-2 Arms A1 and A2 are included in this table.

Table 13: Cross-study comparison of different dosing regimens

Exposure Metric (µg/mL)	Median [min, max]		Geometric Mean [% Geometric CV]	
	SC Q4W	**IV Q2W**	**SC Q4W**	**IV Q2W**
$C_{trough,max}$	336 [142, 653]	300 [BQL, 686]	350 [31%]	303 [NC]
$C_{trough,ss}$	133 [7, 443]	145 [BQL, 484]	131 [72%]	142 [NC]
$C_{max,max}$[b]	642 [329, 1086]	718 [257, 1926]	634 [30%]	714 [30%]
	SC Q3W	**IV Q3W**	**SC Q3W**	**IV Q3W**
$C_{trough,max}$	462 [171, 867]	369 [149, 799]	438 [29%]	355 [29%]
$C_{trough,ss}$	208 [83, 402]	154 [18, 967]	208 [38%]	142 [67%]
$C_{max,max}$[b]	687 [316, 1140]	903 [186, 1591]	663 [28%]	871 [29%]

[b] Observed C_{max} is EOI for IV and 48h post dose for SC. BQL: Below quantification limit (< 0.32 µg/ml)
IV Q3W: PAPILLON Arm A, Arm B & MARIPOSA-2 Arm C
SC Q3W: PALOMA-2 Cohorts 2 and 3B
IV Q2W: MARIPOSA Arm A
SC Q4W: PALOMA-2 Cohort 5

6.2.3. Pharmacodynamics

6.2.3.1. Mechanism of action

No new information has been provided. Amivantamab is an EGFR and MET receptor bispecific antibody. Three potential mechanisms of action for amivantamab to inhibit tumours with aberrant EGFR and MET signalling are proposed: 1) inhibition of ligand-dependent signalling, 2) downregulation of EGFR and MET levels from cell surface, and 3) initiation of ADCC and/or ADCT.

6.2.3.2. Primary and secondary pharmacology

No new information has been provided.

6.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

No new information has been provided.

6.2.3.4. Genetic differences in PD response

No new information has been provided.

6.2.3.5. Immunological events

Anti-amivantamab antibodies

Overall, 729 participants who received amivantamab SC had appropriate samples (Table 16).

Table 14: Summary of the Incidence of Antibodies to Amivantamab in SC studies

Study Number	Amivantamab Doses Tested	Participants With Appropriate Samples[a]	Participants Positive for Treatment-emergent Antibodies to Amivantamab[b,c]	Participants Negative for Treatment-emergent Antibodies to Amivantamab[b,d]
61186372NSC1003 (PALOMA)				
Cohort 1a	1050 mg (if BW	8	0	8 (100)
Cohort 1b	<80 kg)/1400 mg (if	8	0	8 (100)
Cohort 2a	BW ≥80 kg)	9	0	9 (100)
Cohort 2b		8	0	8 (100)
Cohort 3a	1600 mg (if BW	21	0	21 (100)
Cohort 4a	<80 kg)/2240 mg (if BW ≥80 kg)	53	0	53 (100)
Cohort 5a	2560 mg (if BW <80 kg)/3360 mg (if BW ≥80 kg)	22	0	22 (100)
Cohort 6a	3200 mg (if BW <80 kg)/4320 mg (if BW ≥80 kg)	18	0	18 (100)
Total	NA	147	0	147 (100)
61186372NSC2002 (PALOMA-2)				
Cohort 1[e]	1600 mg SC-CF (if BW <80 kg) or 2240 mg (if BW ≥80 kg)	66	0	66 (100)
Cohort 2[f]	C1 D1: 1600 mg SC-CF	62	1 (1.6)	61 (98.4)
Cohort 3[e]	(or 2240 mg if BW is	68	0	68 (100)
Cohort 3b[g]	≥80 kg); C1 D8 and D15, and C2+: 2400 mg (or 3360 mg if BW ≥80 kg)	72	0	72 (100)
Cohort 5	C1: 1600 mg SC-CF (if BW <80 kg) or 2240 mg (if BW ≥80 kg) C2+: 3520 mg SC-CF (if BW <80 kg) or 4640 mg (if BW is ≥80 kg)	77	0	77 (100)
Cohort 6[f]	1600 mg SC-CF (if BW <80 kg) or 2240 mg (if BW ≥80 kg)	62	1 (1.6)	61 (98.4)
Total[h]	NA	407	2 (0.5)	405 (99.5)
61186372NSC3004 (PALOMA-3)				
amivantamab SC + lazertinib arm	1600 mg SC-CF (if BW <80 kg), 2240 mg SC-CF (if BW ≥80 kg)	175	1 (0.6)	174 (99.4)

Anti-rHuPH20 Antibodies

Across PALOMA, PALOMA-2 and PALOMA-3, a total of 741 participants received amivantamab SC co-formulated with rHuPH20 and were rHuPH20 immunogenicity-evaluable (Table 17).

Table 15: 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[b,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	53	1 (1.9)	52 (98.1)
Cohort 5a	22	3 (13.6)	19 (86.4)
Cohort 6a	18	1 (5.6)	17 (94.4)
Total	131	10 (7.6)	121 (92.4)
61186372NSC2002 (PALOMA-2)			
Cohort 1	66	9 (13.6)	57 (86.4)
Cohort 2	64	9 (14.1)	55 (85.9)
Cohort 3	69	8 (11.6)	61 (88.4)
Cohort 3b	75	7 (9.3)	68 (90.7)
Cohort 5	77	2 (2.6)	75 (97.4)
Cohort 6	66	6 (9.1)	60 (90.9)
Total	417	41 (9.8)	376 (90.2)
61186372NSC3004 (PALOMA-3)			
amivantamab SC + lazertinib arm	193	15 (7.8)	178 (92.2)

6.2.4. Dose selection and therapeutic window

By achieving similar amivantamab PK exposure (C_{trough}, C_{max}, and AUC_T), at Cycle 2 and steady state, to the approved IV Q3W and Q2W regimens, amivantamab SC Q3W and Q4W dose regimens are expected to maintain the established safety and efficacy profiles observed with amivantamab IV.

6.2.5. Overall discussion and conclusions on clinical pharmacology

6.2.5.1. Discussion

New PK data from Studies PALOMA and PALOMA-2, including PK data collected following administration of the SC Q3W and SC Q4W regimens, were submitted. The benefit-risk assessments for the proposed regimens are based on a PK-bridging strategy with the IV Q3W and IV Q2W regimens as respective reference treatment. Thus, PK is pivotal for the current submission.

The recommended SC Q2W doses are 52-60% higher than the recommended IV Q2W doses. It is noted that the Applicant has not used the same conversion factor across regimens (and body weight categories). However, although not the same, the conversion factors are overall similar.

A limitation with PALOMA and PALOMA-2 is that neither study included a reference arm where patients received the reference treatment (IV Q3W or IV Q2W, respectively). Thus, within-study exposure comparisons of observed PK data between the proposed SC regimens and the reference IV treatments are impossible. The Applicant provided cross-study comparisons of observed PK data, as well as model-based exposure comparisons, comparing the proposed SC regimens to the recommended IV regimens. In this procedure, PK simulation-based exposure comparisons, supported by comparisons of observed data, are considered pivotal for assessing the benefit-risk of the proposed regimens.

Bioanalysis

The ECLIA for amivantamab was previously fully validated and cross-validated. It had adequate performance of the pre-study and within study validation, including ISR and long-term stability.

The applied ADA methods were assessed during procedure number EMEA/H/C/005454/X/0014 and were found acceptable.

Pharmacokinetics

Overall, the amount of data available for the SC Q3W and SC Q4W regimens are considered sufficient to allow characterisation of the PK profiles for these regimens using a population PK approach. The PALOMA study included PK sampling at several pre-dose time-points and post-dose samples at 24, 48, and 72 hours during Cycle 2 for the SC Q3W and SC Q4W regimens. The PALOMA-2 study included PK sampling at several pre-dose time-points and post-dose samples at 48 hours for the SC Q3W and SC Q4W regimens. Further post-dose samples at Cycle 2 Day 15 were collected for the SC Q4W regimen during Cycle 2.

The Applicant has submitted a PK dataset including 2084 measurable amivantamab serum concentrations from 238 participants on the proposed SC Q3W regimen. The majority of the available PK data following SC Q3W were from PALOMA-2 (66 patients with treatment-naïve locally advanced or metastatic NSCLC harbouring an EGFR Exon20ins mutation co-treated with carboplatin and pemetrexed [CP] in Cohort 2, 70 patients with locally advanced or metastatic NSCLC harbouring an EGFR Exon19del or Exon 21 L858R mutation who have experienced disease progression on or after treatment with a third-generation EGFR TKI co-treated with CP and lazertinib in Cohort 3, and 77 patients with locally advanced or metastatic NSCLC harbouring an EGFR Exon19del or Exon 21 L858R mutation who have experienced disease progression on or after treatment with a third-generation EGFR TKI co-treated with CP in Cohort 3b). Furthermore, data from 25 patients with advanced solid malignancies were available from Cohort 5a from PALOMA.

The Applicant has submitted a PK dataset including 1090 measurable amivantamab serum concentrations from 96 participants on SC Q4W regimens (851 concentrations from 77 participants on the proposed SC Q4W regimen). The majority of the available PK data following SC Q4W were from patients with treatment-naïve locally advanced or metastatic NSCLC harbouring an EGFR Exon19del or Exon 21 L858R mutation co-treated with lazertinib in Cohort 5 in PALOMA-2. Furthermore, data from 19 patients with advanced solid malignancies were available from Cohort 6a in PALOMA (17 of these were NSCLC patients).

Taken together, the observed data for the SC Q3W and Q4W regimens appear sufficiently representative and allows characterisation of patients across all the proposed indications in SmPC 4.1 (that is, type of disease and co-treatments). However, it should be noted that Cohort 3 in PALOMA-2 assessed amivantamab SC (Q3W) in combination with CP and lazertinib. This is corresponding to the IV study MARIPOSA-2 arms A1 and A2, which have not yet been submitted and approved. Thus, data from Cohort 3 and comparisons with MARIPOSA-2 arms A1 and A2 will not be evaluated in this report as PK, efficacy and safety are not established for this combination posology. However, results from these unapproved combination treatments are presented in Table 14, as this table is still considered of interest as it contains other data presented in a relevant manner. It is not expected that PK will be different in the not yet approved combination treatment, as so far neither target population nor combination treatment has affected the pharmacokinetics of amivantamab.

The baseline covariates/demographics were confirmed to be comparable between the SC dosing regimens and respective IV reference regimen, which enables a direct comparison of observed exposures following the different dosing regimens.

The new PK data were analysed using a previously developed population PK model for amivantamab (see procedure EMEA/H/C/005454/X/0014), developed on data following SC and IV administration of amivantamab. The model was externally validated on new data from PALOMA and PALOMA-2. The Applicant provided model diagnostic plots, including VPCs stratified by SC dose regimen, which indicate that the previous model provides an acceptable description of the observed PK data for the SC Q2W and SC Q4W dosing regimens. The model underpredicted the data at later time-points for the SC Q3W regimen, but this is acceptable given that observed exposures at later treatment cycles may be affected by time-varying factors, such as decreasing target levels and/or non-random drop-out, that are not accounted for in the model. Furthermore, the observations at later time-points included mainly pre-dose samples (based on the PALOMA and PALOMA-2 protocols), and an underprediction of the pre-dose concentrations would imply that the simulations are conservative from an efficacy perspective. When focusing on the first 12 weeks after start of treatment (i.e. the first 3 treatment cycles for the Q2W and Q4W regimens, and the first 4 treatment cycles for the Q3W regimen), the model provides an adequate description of the data following SC Q2W, SC Q3W, and SC Q4W administration.

The Applicant provided virtual studies where the SC Q3W and SC Q4W regimens were compared against the corresponding reference treatment (IV Q3W and IV Q2W, respectively). Apart from the dosing regimen, the study design mimicked the PALOMA-3 study, where both the observed baseline covariates and the individual PK parameters for participants in PALOMA-3 were used to derive PK exposure metrics for the comparison. The exposure comparisons included C_{avg}, C_{max}, and C_{trough} at Cycle 2 as well as at steady state. Although non-inferiority normally is assessed at steady state, the exposure in Cycle 2 is, in this case, considered a relevant measure for both safety and efficacy. Due to the weekly administration of amivantamab during Cycle 1, followed by Q2W, Q3W, or Q4W administration in subsequent cycles, the highest exposure is achieved in Cycle 2, followed by a decrease in exposure until steady state is reached after approximately 12 weeks of treatment. Based on previous applications for different indications (EMEA/H/C/005454/0000, EMEA/H/C/005454/II/10-11-13), it is known that the efficacy response of amivantamab is rather immediate and correlates with early exposure metrics, while the identified safety issues are mainly on-target effects. To ensure a comparable efficacy response over an extended period of time, it is considered important that C_{trough} at steady state is not substantially lower for the proposed SC regimens as for the corresponding recommended IV regimen. The exposure comparisons included graphical comparisons (boxplots) and tabular comparisons, which allowed comparisons of both the central tendency and the variability. These comparisons indicate that, overall, the exposures for the proposed SC regimens are comparable to the exposures following the corresponding reference IV regimens, as described below.

For the SC Q3W regimen, the predicted geometric mean $C_{avg,C2}$ was 21% higher than the exposure for the IV Q3W reference treatment, whereas $C_{avg,ss}$ was comparable to the exposure for the IV reference treatment. A 21% higher $C_{avg,C2}$ is not considered clinically relevant given available information on variability and PK/PD for this antibody. The predicted geometric mean $C_{max,max}$ and $C_{max,ss}$ were lower for the proposed SC regimen than for the IV reference treatment, which may be beneficial from a safety perspective and should not affect the efficacy. The predicted $C_{trough,max}$ and $C_{trough,ss}$ were higher for the proposed SC regimen than for the IV reference treatment.

The graphical comparisons with boxplots indicate that, overall, the variability in the predicted exposure metrics was comparable for the SC and IV Q3W administrations. This is somewhat

surprising, given that the between-subject variabilities in absorption and subcutaneous bioavailability are expected to increase the variability in exposure.

The predicted geometric mean $C_{trough,max}$ and $C_{max,max}$ were comparable to the observed geometric mean $C_{trough,max}$ and $C_{max,max}$, respectively, both for the SC Q3W and the reference IV Q3W regimens. At steady state, the model underpredicted C_{trough} for the SC Q3W regimen by 24%, while C_{trough} for the IV Q3W regimen was underpredicted by 15%. The underprediction may be due to time-varying factors not accounted for in the model. Since the underprediction was greater for the SC Q3W regimen than for the IV reference regimen, the predictions are conservative in terms of efficacy.

For the SC Q4W regimen, the predicted geometric means of $C_{avg,C2}$ and $C_{avg,ss}$ were 30% and 26% higher, respectively, than the exposure for the IV Q2W reference treatment. These differences are not considered clinically relevant for an antibody. The predicted geometric mean $C_{max,max}$ was comparable to the exposure for the IV reference treatment, whereas the predicted geometric mean $C_{max,ss}$ was slightly lower than the exposure for the IV reference treatment. The predicted geometric mean $C_{trough,max}$ was higher than the exposure for the IV reference treatment, whereas the predicted geometric mean $C_{trough,ss}$ was comparable to the exposure for the IV reference treatment. These PK properties are not expected to affect efficacy or safety. It should be noted that the dosing in Cycle 1 is identical between the proposed SC Q4W regimen and the already approved SC Q2W regimen, the higher exposure in Cycle 2 compared with the SC Q2W regimen is hence expected.

The graphical comparisons with boxplots indicate that the variability in the predicted exposure metrics is slightly larger for the SC Q4W administration than for the IV Q2W administration, which is expected given the longer dosing interval. However, an even bigger difference was expected, given that the between-subject variabilities in absorption and subcutaneous bioavailability are expected to increase the variability in exposure.

The predicted geometric mean $C_{trough,max}$ was comparable to the observed geometric mean $C_{trough,max}$, both for the SC Q4W and the reference IV Q2W regimens. The predicted geometric mean $C_{max,max}$ was comparable to the observed geometric mean $C_{max,max}$ for the reference IV Q2W regimen but was slightly overpredicted (9%) for the SC Q4W regimen. At steady state, the predicted geometric mean C_{trough} was comparable to the observed geometric mean C_{trough} for the reference IV Q2W regimen but was slightly overpredicted (7%) for the SC Q4W regimen. The overprediction of $C_{max,max}$ is likely caused by differences in T_{max} following SC administration, and the fact that PK samples were only collected 48 hours after dose, while concentration predictions were generated hourly. In PALOMA-3 (rich PK-profile) the observed C_{max} was approximately 72 hours post dose, but with a rather flat profile between 48-96 hours. The observed 48 h post dose data from PALOMA-2 is hence considered a decent proxy for C_{max}. The overprediction of C_{trough} at steady state is minor and may be due to the limited number of observations at steady state for the SC Q4W regimen (N=39).

Overall, the model-based exposure comparisons suggest that the proposed SC dosing regimens could be acceptable. However, a comparison of model predictions may be sensitive to the observed baseline covariates/demographics and individual PK parameters in PALOMA-3. Thus, further exposure comparisons were requested to confirm the appropriateness of the proposed posologies.

Multiple comparisons, and summaries of both simulated, predicted, and observed data, were provided (not shown). Overall, the comparison of simulated exposures gave similar results as the comparison of predicted exposures. However, differences were observed at steady state, where the simulated exposures were lower than the predicted exposures for the SC dosing regimens. This was expected for the SC Q3W regimen, given the underprediction observed at steady state. However, an underprediction at steady state is not evident for the SC Q4W regimen.

When comparing the SC Q3W regimen to the IV Q3W regimen, both predicted and simulated exposures, in Cycle 2 and at steady state, support an extrapolation of efficacy and safety from the recommended IV Q3W and the corresponding indication in combination with carboplatin and permetrexed regimen to the proposed SC Q3W regimen.

When comparing the SC Q4W regimen to the IV Q2W regimen, both predicted and simulated exposures in Cycle 2 support an extrapolation of efficacy and safety from the recommended IV Q2W regimen to the proposed SC Q4W regimen. However, at steady state, the predicted C_{trough} indicate similar exposure, whereas the simulated C_{trough} indicate a slightly lower exposure (the geometric mean is 18% lower when comparing simulated C_{trough} at steady state).

Table 15 show cross-study comparisons without the data from study-arms using not approved treatments. As pointed out there are indications from the simulations that C_{trough} at steady state for SC Q4W could be lower than from IV Q2W. The observed median [range] was 133 µg/mL [7, 443] for SC 4QW and 145 µg/mL [BQL, 484] for IV 2QW. The corresponding geometric mean values [%CV] were 131 µg/mL [72%] and 142 µg/mL [NC] respectively. There are only limited data available on the steady state exposure following SC Q4W administration, but the data available do not indicate a clinically relevant difference in $C_{trough,ss}$ between SC Q4W and IV Q2W administration. This, in combination with the provided predicted and simulated exposure comparisons of SC Q4W to IV Q2W regimen, support an extrapolation of efficacy and safety from the recommended IV Q2W regimen to the proposed SC Q4W regimen.

The Applicant provided subgroup analyses which supported that there are no clinically relevant differences in exposure between various subgroups. Note that this included subgroup analysis of body weight, which supported that there are no clinically relevant differences between patients ≥80kg, who are recommended higher doses, compared to patients <80kg.

Immunogenicity

The applicant submitted bioanalytical report for NAb assay for rHuPH20. The applicant also submitted NAb results for PALOMA and PALOMA-2. However, these have not been assessed as the results are not considered reliable due to low sensitivity in the NAb assay (9.877 µg/ml in LabCorp US and 22.5 µg/ml in LabCorp Shanghai).

No discussion regarding lacking NAb assay for amivantamab was submitted. This is however acceptable given the overall low incidence of anti-amivantamab antibodies.

The incidence of anti-amivantamab antibodies and anti-rHuPH20 antibodies are comparable to previously approved Rybrevant indications.

6.2.5.2. Conclusions

The provided exposure comparisons show that the proposed SC dosing regimens result in comparable exposure as the corresponding recommended IV dosing regimens. Hence, extrapolation of efficacy and safety from the recommended IV Q3W regimen to the proposed SC Q3W regimen, and from the recommended IV Q2W regimen to the proposed SC Q4W regimen, is supported.

6.3. Clinical efficacy

6.3.1. Dose response study(ies)

For the dose justification please refer to 6.2.5 section.

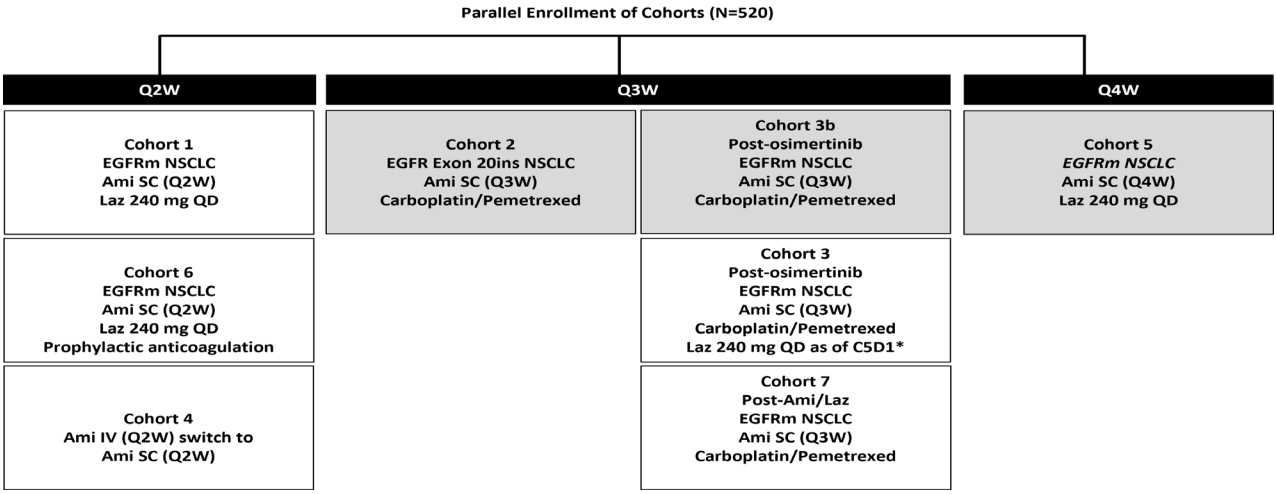
6.3.2. Main study(ies)

6.3.2.1.1. 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.

6.3.2.1.2. Study design

Figure 6: Study schema



Primary analysis efficacy data (CCO of 24 October 2024) in support of the amivantamab SC Q4W dose regimen in combination with lazertinib are provided from PALOMA-2 **Cohort 5** in treatment-naïve EGFRm NSCLC participants (reflective of the MARIPOSA [Study 73841937NSC3003] study population).

Primary analysis efficacy data (CCO of 24 October 2024) in support of amivantamab SC Q3W in combination with CP are provided from:

PALOMA-2 **Cohort 2** in treatment-naïve NSCLC participants with EGFR exon 20ins mutations (reflective of the PAPILLON [61186372NSC3001] study population)

PALOMA-2 **Cohort 3b** in participants with EGFRm NSCLC who have progressed on or after the third-generation EGFR TKI osimertinib (reflective of the MARIPOSA-2 [61186372NSC3002] study population).

The clinical data from these cohorts are intended to complement the modeling and simulation approach to support extending the dosing interval from Q2W to Q3W and Q4W, respectively for the amivantamab SC in the relevant indications.

6.3.2.1.2.1. Treatment

Cohort 5 (Q4W) participants were treated as follows:

Amivantamab SC 1,600 mg (or 2,240 mg if BW ≥80 kg) on Cycle 1 Days 1, 8, 15, and 22, and 3,520 mg (4,640 mg if BW ≥80 kg) Q4W thereafter (on Day 1 of each subsequent 28-day cycle, starting with Cycle 2)

Lazertinib (240 mg orally QD)

Prophylactic anticoagulation was recommended

Cohort 2 and 3b (Q3W) participants were treated as follows:

Amivantamab SC 1,600 mg (or 2,240 mg if BW ≥80 kg) on Cycle 1 Day 1, and 2,400 mg (or 3,360 mg if BW ≥80 kg) on Cycle 1 Days 8 and 15, and Q3W thereafter (on Day 1 of each subsequent 21-day cycle, starting with Cycle 2)

Pemetrexed 500 mg/m2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance until disease progression

Carboplatin AUC 5 maximum 750 mg on Day 1 of each 21-day cycle, for up to 4 cycles

The Treatment phase for each participant started at Cycle 1 Day 1 and continued in 28-day cycles for the Q4W dose regimen and in 21-day cycles for the Q3W dose regimen until the EOT visit, approximately 30 days after the last dose of study treatment. Participants who discontinued study treatment for any reason were followed for survival and symptomatic progression in the Follow-up phase. The Follow-up phase starts after the EOT visit and continues until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first.

Concomitant and rescue therapies

Required pre-injection medications consisting of 1 each of an antihistamine and antipyretic were allowed on all infusion days, as well as a glucocorticoid on Cycle 1 Day 1.

Optional post-injection medications with anihistamines, glucocorticoids, antipyretic, opiates or antiemetics could be prescribed and continued for up to 48 hours after any infusion if clinically indicated, at the discretion of the investigator.

Permitted prophylactic medications for pemetrexed-carboplatin include the following:

• Appropriate prophylactic antiemetic regimens for high risk of emesis associated with carboplatin (eg, ondansetron, aprepitant, dexamethasone), in accordance with institutional practice or current NCCN and/or ESMO guidelines.

6.3.2.1.2.2. Randomisation and blinding

Randomisation is not applicable. As this is an open-label study, blinding procedures are not applicable.

6.3.2.1.2.3. Patient population

The key eligibility criteria for inclusion in Cohorts 1, 2, 3, 3b, 5, and 6 were as follows:
Participants had to be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study took place).

Participants had to have:

- histologically or cytologically confirmed, locally advanced or metastatic, NSCLC that is not amenable to curative therapy including surgical resection or chemoradiation and has an EGFR exon 19del or exon 21 L858R mutation (Cohorts 1, 3, 3b, 5, and 6) or EGFR exon20ins mutation (Cohort 2). Squamous NSCLC was excluded for Cohorts 2, 3, and 3b.
- measurable disease according to RECIST v1.1.
- ECOG performance status 0 or 1.
- adequate organ and bone marrow function.

The key exclusion criteria were:

Prior therapy restriction or requirements were as follows:

- Cohorts 1, 5, and 6: participant should not have received any prior systemic therapy for locally advanced or metastatic NSCLC.
- Cohort 2: participant should not have received any prior systemic therapy for locally advanced or metastatic NSCLC, with exceptions of:
  - prior adjuvant or neo-adjuvant platinum-based doublet chemotherapy was allowed, if completed at least 12 months prior to signing the study ICF
  - prior monotherapy with an approved EGFR TKI targeting common EGFR mutations as first-line therapy for the treatment of locally advanced or metastatic disease was allowed, if: 1) treatment duration did not exceed 8 weeks; 2) lack of disease response was documented radiographically 3) associated toxicities have resolved to baseline; and 4) the EGFR TKI was discontinued at least 2 weeks or 4 half-lives prior to treatment initiation at C1D1, whichever is longer. Prior therapy with EGFR TKI agents targeting exon20ins mutations (eg, TAK788/mobocertinib or poziotinib), was not allowed.
- Cohorts 3 and 3b: Participant must have progressed on or after osimertinib monotherapy as the most recent line of treatment. Osimertinib must have been administered as either the first-line treatment for locally advanced or metastatic disease or in the second-line setting after prior treatment with first- or second-generation EGFR TKI as a monotherapy. Participants who received either neo-adjuvant and/or adjuvant treatment of any type were eligible if progression to locally advanced or metastatic disease occurred at least 12 months after the last dose of such therapy and then the participant progressed on or after osimertinib in the locally advanced or metastatic setting.

Participants with symptomatic brain metastases, an uncontrolled illness, medical history of ILD, a history of clinically significant cardiovascular disease, or uncontrolled tumour-related pain were excluded from participation in the study.

6.3.2.1.3. Objectives and estimands

Table 16: Overview of Primary and Secondary Efficacy Endpoint Analyses for PALOMA-2

Endpoint[a,b]	Definition	Analysis and Presentation of Results
Primary Endpoint		
ORR (INV)	The proportion of participants who achieve either a CR or PR as best response, based on RECIST v1.1, as confirmed by INV.	• Observed ORR along with 2-sided 95% exact confidence interval will be calculated for each cohort for the FAS.
Secondary Endpoints		
ORR (ICR)	The proportion of participants who achieve a CR or PR, based on RECIST v1.1, as confirmed by ICR.	• Observed ORR along with 2-sided 95% exact confidence interval will be calculated for each cohort for the FAS.
DOR (INV)	The time from the date of first documented response (PR or CR) until the date of documented progression or death, whichever comes first, for participants who have PR or CR, as confirmed by INV.	• DOR analysis will be conducted at prespecified landmarks (eg, at 6 months, 12 months, 18 months, etc) for the FAS and the REAS. • Median DOR and 95% CI will be estimated using the KM method for each cohort. A KM plot for DOR and median DOR with 95% CI (calculated from the KM estimate) will be presented by cohort, as well as a tabulation of the KM estimates for each cohort.
TTR (INV)	The time from the first dose of study treatment to the date of first documentation of a response (PR or CR) prior to any disease progression and subsequent anticancer therapy, as defined by RECIST v1.1., for participants who have PR or CR as their best response, as determined by INV.	• Descriptive statistics will be provided to summarize TTR for the FAS and the REAS.
CBR (INV)	The percentage of participants achieving CR or PR, or durable stable disease (defined as a duration of at least 11 weeks) as defined by RECIST v1.1 and as determined by INV.	• The CBR and its 95% 2-sided exact confidence interval will be presented for each cohort.
PFS	The time between the date of first dose until the date of objective disease progression or death due to any cause, whichever occurs first, based on RECIST v1.1.	• PFS analysis will be conducted at prespecified landmarks (eg, at 6 months, 12 months, 18 months, etc) for the FAS and REAS. • The median PFS and 95% CI will be estimated using the KM method for each cohort. A KM plot for PFS and median PFS with 95% CI (calculated from the KM estimate) will be presented by cohort, as well as a tabulation of the KM estimates for each cohort.
OS	The time between the date of the first dose and the date of death due to any cause.	• OS analysis will be conducted at prespecified landmarks (eg, at 6 months, 12 months, 18 months, etc) for the FAS and REAS. • Median OS and 95% CI will be estimated using the KM method for each cohort. A KM plot for OS and median OS with 95% CI (calculated from the KM estimate) will be presented by cohort, as well as a tabulation of the KM estimates for each cohort.

6.3.2.1.3.1. Primary objective

The study primary objective was to assess the anti-tumour activity of amivantamab SC in combination treatment. ORR (INV) was the primary endpoint.

6.3.2.1.4. Estimands for the primary objective

The primary scientific question of interest was:

What is the observed ORR assessed by investigator in the population of each cohort?

The primary estimand for ORR by INV is defined by the components provided in the table below.

Table 17: Estimands for primary objective

Population	**Cohort 5, 1, and 6: participants with treatment-naïve locally advanced or metastatic EGFRmNSCLC** **Cohort 2: participants with treatment-naïve locally advanced or metastatic EGFR exon20insNSCLC** **Cohort 3 and 3b: participants with locally advanced or metastatic EGFRm NSCLC after progression on Osimertinib.**
Treatment condition<s>	Assignment to the treatment, regardless of discontinuation as follows: Cohort 5: the combination of amivantamab SC Q4W and lazertinib Cohort 1: the combination of amivantamab SC Q2W and lazertinib Cohort 6: The combination of amivantamab SC Q2W and lazertinib plus mandatory prophylactic anticoagulants Cohort 2 and 3b: the combination of amivantamab SC Q3W with carboplatin and pemetrexed
Endpoint (variable)	Overall response by investigator assessment based on RECIST v1.1.
Population-level summary	For each cohort, the proportion of participants who achieve either a CR or PR as best response.
Intercurrent events and strategy to handle them	
Intercurrent event and corresponding strategy	Start of new anticancer therapy. While on treatment strategy: the disease assessment data collected before the occurrence of the intercurrent event will be used

6.3.2.1.5. Secondary objectives

To assess additional measures of anti-tumor activity of amivantamab SC the following secondary endpoints were used:

- ORR (ICR)
- DOR (INV)
- TTR (INV)
- CBR (INV)

- PFS
- OS

To characterize the VTE risk of amivantamab SC and lazertinib by frequency and severity of VTE among AEs defined by the NCI-CTCAE Criteria Version 5.0.

6.3.2.1.6. Exploratory objectives

To assess the relationship between PK or immunogenicity and selected endpoints including but not limited to efficacy and safety by:

- Serum amivantamab concentrations and serum anti-amivantamab antibodies
- Plasma lazertinib concentrations (Cohorts 1, 3, 5 and 6)
- To assess the immunogenicity to amivantamab and rHuPH20 in participants treated with
- amivantamab SC
- The presence or absence of anti-amivantamab and anti-rHuPH20 antibodies

6.3.2.2. Statistical methods for estimation and sensitivity analysis

6.3.2.2.1. Planned analyses

All efficacy analyses were performed on the Full Analysis set, with each cohort analysed separately. The primary analysis for PALOMA-2 Cohorts 2, 3b, and 5 was performed after all participants had completed at least 3 disease assessments (unless they withdrew consent or died prior). The final analysis of the primary and secondary endpoints will be performed after the last participant in that cohort will have completed the Follow-up phase.

Hypothesis in Cohort 5 (Q4W Dosing)

Cohort 5: the combination of amivantamab SC (Q4W) and lazertinib in participants with treatment-naïve locally advanced or metastatic NSCLC harboring an EGFR exon19del or exon 21 L858R mutation will result in an ORR (INV) >50%.

Hypotheses in Cohorts 2 and 3b (Q3W Dosing)

Cohort 2: the combination of amivantamab SC Q3W with CP in participants with treatment-naïve locally advanced or metastatic NSCLC harboring an EGFR exon20ins mutation will result in an ORR (INV) >25%.

Cohort 3b: the combination of amivantamab SC Q3W with CP in participants with locally advanced or metastatic NSCLC harboring an EGFR exon19del or exon 21 L858R mutation who have experienced disease progression on or after treatment with a third-generation EGFR TKI will result in an ORR (INV) >25%.

6.3.2.2.2. Planned subgroup analyses

According to the statistical analysis plan, the following subgroups were specified for the efficacy and/or safety endpoints: age, sex, race, ECOG performance status, history of smoking, prior line of therapy Osimertinib, prior line of therapy first or second generation EGFR TKIs, mutation type.

6.3.2.2.3. Sample size determination

Number of Participants (Planned and Analyzed):

The planned total sample size across all cohorts is approximately 520 participants; approximately 65 participants were to be enrolled per cohort. The sample size of 65 participants would have at least 90% power to test the null hypothesis (according to the table below) with a 2-sided alpha of 0.05.

The following null hypothesis were used for the sample size calculation:

Table 18: Hypothesis and Power Table

Cohort	N	H0	H1	Power
1, 5, and 6	65	ORR ≤50%	ORR ≥70%	>90%
2	65	ORR ≤25%	ORR ≥45%	>90%
3, 3b, and 7	65	ORR ≤25%	ORR ≥45%	>90%

H_0 = null hypothesis; H_1 = alternative hypothesis; ORR = objective response rate.

The actual numbers of participants in the Full Analysis Set and Safety Analysis Set are presented in the table below.

Table 19: Number of subjects in each analysis set

Cohorts	Full Analysis Set	Safety Analysis Set
Cohort 5	77	77
Cohort 1	68	68
Cohort 6	67	67
Total (Cohorts 1 and 6)	135	135
Cohort 2	66	66
Cohort 3b	77	77
Cohort 3	70	70

Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Full analysis set	All participants who were assigned to the study treatment.
Pharmacokinetic analysis set[a]	All participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline concentration measurement. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK.
Safety analysis set	All participants who receive at least 1 dose of study drug.
Immunogenicity analysis set	All participants who receive at least 1 dose of study drug and provide at least 1 postdose immunogenicity sample.

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

6.3.2.2.4. Error probabilities, adjustment for multiplicity and interim analyses

The statistical significance was set to a 2-sided α-level of 0.05. Where appropriate, 95% confidence intervals were provided.

Interim analyses of the primary and secondary endpoints could be conducted for each cohort during the conduct of the study to generate supportive data for regulatory submissions.

No hypothesis testing was performed at the time of these analyses. There was no adjustment for multiplicity due to potential interim analyses.

6.3.2.2.5. Changes from protocol-specified analyses

The listing of protocol deviations was presented for all the concerned cohorts.

6.3.2.3. Data quality assurance

Steps to ensure the accuracy and reliability of data included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions were provided for collection, handling, storage, and shipment of samples.

The investigator was responsible for all data entered into the CRFs and documented their review and approval of the data, verifying the validity and completeness of the data. The investigator was responsible for appropriate retention of essential study documents.

Case report form data were captured via data entry by study center personnel in a sponsor database system or a database system owned by a CRO. Data quality checks were applied using manual and/or electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained.

Study centers were monitored by the sponsor. Centers were visited at regular intervals and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study-specific CRFs.

Local laboratories were used to analyze blood samples for clinical assessment. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors. An audit(s) of this study was included as part of the independent sponsor quality assessment performed by the Sponsor Quality Assurance Auditing. The audit certificate for this study is provided in Appendix 8 Audit Certificates.

The data quality assurance measures put in place are considered adequate. No concerns indicating the need for GCP inspection were identified.

6.3.2.4. Results

6.3.2.4.1. Changes in the planned conduct of the study

As of the CCO of 24 October 2024, there were 4 amendments to the original protocol dated 24 June 2022, as well as several country/territory specific amendments to study conduct to address minor HA requests. The key changes implemented by each global amendment are summarized in the below table.

Table 20: Key Changes Implemented with Global Protocol Amendments to 61186372NSC2002

Amendment Number (Date)	Key Changes
Amendment 1 (23 August 2022)	• To include VTE events in the list of AESIs. • To provide clarity on the Schedule of Assessments and visits, timing of PK sampling.
Amendment 2 (31 January 2023)	• To add 2 new cohorts (Cohort 5 and Cohort 6) evaluating amivantamab and lazertinib in participants with treatment-naïve EGFRm NSCLC: o Cohort 5 evaluates amivantamab administration Q4W to improve patient and provider convenience. o Cohort 6 evaluates whether mandatory prophylactic anticoagulants in the first 4 months of study treatment with amivantamab and lazertinib mitigates the risk of VTE events. • For Cohort 3, to incorporate changes of lazertinib dosing schedule from LACP (lazertinib and amivantamab in combination with chemotherapy, carboplatin and pemetrexed all started on Cycle 1 Day 1) to ACP-L (amivantamab in combination with carboplatin and pemetrexed, followed by initiation of lazertinib once treatment with carboplatin is complete) in order to align with the changes to Protocol 61186372NSC3002 (MARIPOSA-2) that were made in response to the USM. • To add a new secondary objective, "VTE risk of amivantamab SC and lazertinib (all cohorts except Cohort 4)". • To add language clarifying study procedures at the end of study. • To update several inclusion criteria to clarify the target population. • To update prohibited medications and therapies to align with the latest concomitant medication guidance for the combination of amivantamab and lazertinib. • To add a new bullet point to study treatment discontinuation criteria concerning Grade 4 rash, severe bullous, blistering, or exfoliating skin conditions including TEN.
Amendment 3 (08 May 2023)	• To update the Cohort 2 and Cohort 3 amivantamab SC Q3W dose based on emerging clinical and PK data reviewed at the Study 61186372NSC1003 (PALOMA) SET meeting on 30 March 2023. • For Cohorts 1, 4, 5, and 6 (chemotherapy-free regimens), to update the cutoff for the creatinine clearance eligibility criteria to ensure equitable trial access. • To add language about interim analyses of the primary and secondary endpoints that may be conducted to generate supportive data for regulatory submissions. • To add language to comply with EU CTR guidelines.
Amendment 4 (17 October 2023)	• To add a new Cohort 3b evaluating the ACP regimen in participants with locally advanced or metastatic NSCLC harboring an EGFR exon 19del or exon 21 L858R mutation whose disease has progressed on or after treatment with osimertinib. • To add a new Cohort 7 evaluating the ACP regimen in participants with locally advanced or metastatic NSCLC harboring an EGFR exon 19del or exon 21 L858R mutation whose disease has progressed on or after the first-line treatment with the combination of amivantamab and lazertinib as the most recent therapy. • To update Cohort 5 amivantamab SC Q4W dose to 3,520 mg (or 4,640 mg if BW ≥80 kg). • To update the protocol to further comply with EU CTR guidelines. • To allow optional collection of tumor tissue.

Table 21: Protocol amendment summary of changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	17 October 2023
Amendment 3/ESP-1	19 July 2023
Amendment 3	08 May 2023
Amendment 2/ESP-1	08 February 2023
Amendment 2	31 January 2023
Amendment 1	23 August 2022
Original Protocol	24 June 2022

Global protocol amendment 4 (17 October 2023)

Overall Rationale for the Amendment:

The overall purpose of this amendment is as follows:

1) Add a new Cohort 3b evaluating the ACP regimen in participants with locally advanced or metastatic NSCLC harbouring an EGFR Exon19del or Exon 21 L858R mutation who have experienced disease progression on or after treatment with a third-generation EGFR TKI (osimertinib). Cohort 3b will enrol 65 participants.

2) Add a new Cohort 7 evaluating the ACP regimen in participants with locally advanced or metastatic NSCLC harbouring an EGFR Exon19del or Exon 21 L858R mutation who have experienced disease progression on or after the first-line treatment with the combination of amivantamab and lazertinib as the most recent therapy.

3) Update Cohort 5 amivantamab SC-CF Q4W dose to 3,520 mg (or 4,640 mg if BW ≥80 kg). The new dosing regimen is based on population pharmacokinetic modelling and simulation to ensure that the predicted steady state Cmax of SC Q4W does not exceed 125% above the Cmax of the approved IV Q2W dose.

4) To update the protocol to comply with EU-CTR guidelines.

6.3.2.4.2. Methods

For Cohorts 1, 2, 3, 3b, 5, and 6, this study was conducted at 86 centers that enrolled participants in the USA, Japan, China, South Korea, Malaysia, Brazil, Spain, Germany, United Kingdom, Italy, France, and Israel.

Study Period: 11 November 2022 to 24 October 2024

6.3.2.4.3. Participant flow and numbers analysed

A total of 77 participants were enrolled in **Cohort 5** and were included in the FAS.

A total of 66 participants were enrolled in **Cohort 2** and included in the FAS. A total of 77 participants were enrolled in **Cohort 3b** and were included in the FAS.

Disposition

At the time of the CCO, 67 participants (87.0%) in **Cohort 5** remained on treatment. The reasons for treatment discontinuation were adverse event (7 participants [9.1%]), progressive disease (2 participants [2.6%]), and physician's decision in 1 participant [1.3%]. As required by the protocol, 3 participants (3.9%) discontinued study treatment due to pneumonitis.

At the time of the CCO, 37 participants (56.1%) in **Cohort 2** remained on treatment. The most frequently reported reasons for treatment discontinuation were progressive disease (19.7%) and adverse event (18.2%). No TEAEs leading to any study treatment discontinuation occurred at a frequency ≥5%.

At the time of the CCO, 48 participants (62.3%) in **Cohort 3b** remained on treatment. The most frequently reported reasons for treatment discontinuation were progressive disease (28.6%) and adverse event (7.8%). No TEAEs leading to any study treatment discontinuation occurred at a frequency ≥5%.

Exposure

The median follow-up in **Cohort 5** was 6.5 months and the median (range) duration of treatment with amivantamab and lazertinib was 6.7 months (0.13; 9.30). In **Cohort 2**, the median follow-up was 10.5 months and the median (range) duration of treatment was 9.4 months (0.23; 15.44) for amivantamab, 2.1 months [0.03; 3.48] for carboplatin, and 8.5 months (0.03; 14.26) for pemetrexed.

In **Cohort 3b**, the median follow-up was 7.0 months and the median duration of treatment was 6.2 months for amivantamab, 2.1 months for carboplatin, and 5.9 months for pemetrexed.

6.3.2.4.4. Baseline data

PALOMA-2 Cohort 5 (Amivantamab SC Q4W + Lazertinib)

The target population for the proposed amivantamab SC Q4W indication from PALOMA-2 **Cohort 5**, was intended to match patient population in PALOMA-2 Cohorts 1 and 6 (amivantamab SC Q2W) and MARIPOSA (amivantamab IV Q2W). Hence, a side-by side presentation of selected demographic and baseline disease characteristics is presented below.

Table 22: Demographic and Baseline Characteristics of Q4W Population (PALOMA-2 Cohort 5) and Historical Data of Q2W Populations (PALOMA-2 Cohorts 1 and 6 and MARIPOSA)

Population	**Treatment-naive EGFRm NSCLC**		
Dose Regimen	**Q4W**	**Q2W***	
Treatment	**Amivantamab SC + lazertinib**	**Amivantamab SC + lazertinib**	**Amivantamab IV + lazertinib**
Study Cohort or Arm	**PALOMA-2 Cohort 5**	**PALOMA-2 Cohorts 1+6**	**MARIPOSA Arm A**
Analysis (CCO)	**Primary Analysis** (24 October 2024)	**Primary Analysis for Cohort 1 Interim Analysis for Cohort 6** (06 January 2024)	**Primary Analysis** (11 August 2023)
Median Follow-up (Months)	**6.5**	**8.6**	**22.2**
Analysis set: FAS	**77**	**126**	**429**
Demographics			
Age, years			
Median	63.0	59.0	64.0
Range	(31; 80)	(28; 85)	(25; 88)
≥65	37 (48.1%)	41 (32.5%)	194 (45.2%)
Sex			
Female	52 (67.5%)	76 (60.3%)	275 (64.1%)
Male	25 (32.5%)	50 (39.7%)	154 (35.9%)
Race			
Asian	48 (62.3%)	85 (67.5%)	250 (58.3%)
Black or African American	1 (1.3%)	5 (4.0%)	4 (0.9%)
White	27 (35.1%)	35 (27.8%)	164 (38.2%)
Baseline ECOG score[a]			
0	25 (32.5%)	34 (27.2%)	141 (32.9%)
1	52 (67.5%)	91 (72.8%)	288 (67.1%)
Weight, kg			
<80	72 (93.5%)	104 (83.2%)	376 (87.6%)
≥80	5 (6.5%)	21 (16.8%)	53 (12.4%)
History of smoking			

Table 22: Demographic and Baseline Characteristics of Q4W Population (PALOMA-2 Cohort 5) and Historical Data of Q2W Populations (PALOMA-2 Cohorts 1 and 6 and MARIPOSA)

Population	**Treatment-naive EGFRm NSCLC**		
Dose Regimen	**Q4W**	**Q2W***	
Treatment	**Amivantamab SC + lazertinib**	**Amivantamab SC + lazertinib**	**Amivantamab IV + lazertinib**
Study Cohort or Arm	**PALOMA-2 Cohort 5**	**PALOMA-2 Cohorts 1+6**	**MARIPOSA Arm A**
Analysis (CCO)	**Primary Analysis** (24 October 2024)	**Primary Analysis for Cohort 1 Interim Analysis for Cohort 6** (06 January 2024)	**Primary Analysis** (11 August 2023)
Median Follow-up (Months)	**6.5**	**8.6**	**22.2**
Analysis set: FAS	**77**	**126**	**429**
Yes	25 (32.5%)	33 (26.2%)	130 (30.3%)
No	52 (67.5%)	93 (73.8%)	299 (69.7%)
Baseline Disease Characteristics			
Initial diagnosis NSCLC subtype			
Adenocarcinoma (Malignant)	77 (100.0%)	122 (96.8%)	417 (97.2%)
Cancer stage at screening			
IV	72 (93.5%)	122 (96.8%)	414 (96.5%)[b]
Location of metastasis at screening[a]			
Adrenal Gland	4 (5.2%)	9 (7.1%)	41 (9.7%)
Bone	35 (45.5%)	58 (46.0%)	206 (48.9%)
Brain	33 (42.9%)	38 (30.2%)	178 (42.3%)
Liver	18 (23.4%)	20 (15.9%)	64 (15.2%)
Lung	59 (76.6%)	90 (71.4%)	257 (61.0%)
Lymph Node	62 (80.5%)	96 (76.2%)	282 (67.0%)
History of brain metastasis			
Yes	33 (42.9%)	38 (30.2%)	178 (41.5%)
No	44 (57.1%)	88 (69.8%)	251 (58.5%)
Time since metastatic disease diagnosis (months)			
Median	1.31	1.28	1.31
Range	(0.1; 5.6)	(0.3; 3.6)	(0.16; 24.08)

Key: NSCLC=non-small cell lung cancer. mEGFR= exon 19del or exon 21 L858R mutation
Note: for age, weight, initial diagnosis NSCLC subtype, cancer stage at screening, location of metastasis at screening, and time since metastatic disease diagnosis, only the categories with the highest frequencies, or more relevant for the discussion, are reported.

* Due to differences in study designs, sample sizes, and follow-up time, caution should be exercised when comparing results across studies and cohorts.

a. Participants can be counted in more than one category.
b. IVA + IVB
Sources: PALOMA-2 Cohort 5: Mod5.3.5.2/61186372NSC2002/CSR Primary & Updated Analysis 24Oct2024/Tab8, Tab9, and AttTSIFU01Q4; PALOMA-2 Cohorts 1+6: Appendix 1 Attachment 1, Attachment 2, and Attachment 3; MARIPOSA: Appendix 2 Attachment 8, Attachment 9, and Attachment 10.

Primary Analysis: PALOMA-2 Cohorts 2 and 3b (Amivantamab SC Q3W + CP)

Overall, participants in PALOMA-2 Cohorts 2 and 3b is to match the target populations of the proposed indications for amivantamab SC Q3W in combination with CP (reflecting the PAPILLON and MARIPOSA-2 populations, respectively). Hence, a side-by side presentation of selected demographic and baseline disease characteristics is presented below.

Table 23: Demographic and Baseline Characteristics of Amivantamab SC Q3W + CP Population (PALOMA-2 Cohorts 2 and 3b) and Historical Data of Amivantamab IV Q3W + CP Populations (PAPILLON and MARIPOSA-2)

Population	**Treatment-naive EGFR exon20 ins NSCLC**		**Post-osimertinib EGFRm NSCLC**	
Dose Regimen	**Q3W**	**Q3W**	**Q3W**	**Q3W**
Treatment	**Amivantamab SC + CP**	**Amivantamab IV + CP**	**Amivantamab SC + CP**	**Amivantamab IV + CP**
Study Cohort or Arm	**PALOMA-2 Cohort 2**	**PAPILLON Arm A**	**PALOMA-2 Cohort 3b**	**MARIPOSA-2 Arm C**
Median Follow-up (Months)	**10.5**	**14.6**	**7.0**	9.0
Analysis set: FAS	66	153	77	131

Population	Treatment-naive EGFR exon20 ins NSCLC		Post-osimertinib EGFRm NSCLC	
Dose Regimen	**Q3W**	**Q3W**	**Q3W**	**Q3W**
Treatment	**Amivantamab SC + CP**	**Amivantamab IV + CP**	**Amivantamab SC + CP**	**Amivantamab IV + CP**
Study Cohort or Arm	**PALOMA-2 Cohort 2**	**PAPILLON Arm A**	**PALOMA-2 Cohort 3b**	**MARIPOSA-2 Arm C**
Demographics				
Age, years				
Median	62.5	61.0	63.0	62.0
Range	(31; 80)	(27; 86)	(41; 77)	(36; 84)
≥65	30 (45.5%)	56 (36.6%)	36 (46.8%)	52 (39.7%)
Sex				
Female	32 (48.5%)	85 (55.6%)	44 (57.1%)	81 (61.8%)
Male	34 (51.5%)	68 (44.4%)	33 (42.9%)	50 (38.2%)
Race				
Asian	37 (56.1%)	97 (64.2%)	38 (49.4%)	63 (48.1%)
Black or African American	1 (1.5%)	2 (1.3%)	2 (2.6%)	3 (2.3%
White	27 (40.9%)	49 (32.5%)	37 (48.1%)	60 (45.8%)
Baseline ECOG score[a]				
0	24 (36.4%)	54 (35.3%)	32 (41.6%)	55 (42.0%)
1	42 (63.6%)	99 (64.7%)	45 (58.4%)	76 (58.0%)
Weight, kg				
<80	58 (87.9%)	132 (86.3%)	65 (84.4%)	113 (86.3%)
≥80 kg	8 (12.1%)	21 (13.7%)	12 (15.6%)	18 (13.7%)
History of smoking				
Yes	24 (36.4%)	65 (42.5%)	27 (35.1%)	41 (31.3%)
No	42 (63.6%)	88 (57.5%)	50 (64.9%)	90 (68.7%)
Baseline Disease Characteristics				
Initial diagnosis NSCLC subtype				
Adenocarcinoma (Malignant)	64 (97.0%)	151 (98.7%)	77 (100.0%)	130 (99.2%)
Cancer stage at screening				
IV	63 (95.5%)	149 (97.4%)[b]	77 (100.0%)	131 (100%)[b]
Location of metastasis at screening[a]				
Adrenal Gland	7 (10.8%)	10 (6.6%)	9 (11.7%)	22 (16.8%)
Bone	37 (56.9%)	71 (47.0%)	44 (57.1%)	69 (52.7%)
Brain	24 (36.9%)	35 (23.2%)	27 (35.1%)	54 (41.2%)
Liver	15 (23.1%)	18 (11.9%)	15 (19.5%)	31 (23.7%)
Lung	48 (73.8%)	113 (74.8%)	57 (74.0%)	88 (67.2%)
Lymph Node	49 (75.4%)	102 (67.5%)	45 (58.4%)	85 (64.9%)
History of brain metastasis				
Yes	24 (36.4%)	35 (22.9%)	27 (35.1%)	58 (44.3%)
No	42 (63.6%)	118 (77.1%)	50 (64.9%)	73 (55.7%)
Time since metastatic disease diagnosis (months)				
Median	1.64	1.51	23.06	22.998
Range	(0.7; 48.1)	(0.2; 40.0)	(1.2; 97.1)	(0.23; 115.29)

Key: NSCLC=non-small cell lung cancer. mEGFR= exon 19del or exon 21 L858R mutation
Note: for age, weight, race, initial diagnosis NSCLC subtype, cancer stage at screening, location of metastasis at screening, and time since metastatic disease diagnosis, only the categories with the highest frequencies, or more relevant for the discussion, are reported.
a. Participants can be counted in more than one category.
b. IVA + IVB
Sources: PALOMA-2 Cohorts 2 and 3b: Mod5.3.5.3/ISE/TSIFU01Q3EU, TSIDEM01Q3EU, and TSIDEM04Q3EU; PAPILLON; Appendix 2 Attachment 15, Attachment 16, and Attachment 17; MARIPOSA-2: Appendix 2 Attachment 24, Attachment 25, and Attachment 26.

6.3.2.4.5. Outcomes and estimation

Primary Endpoint - Objective Response Rate by Investigator

PALOMA-2 Cohort 5 (Amivantamab SC Q4W + Lazertinib)

Table 24: Summary of Objective Response Rate Based on RECIST v1.1 Criteria - Investigator - Cohort 5; Full Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Full	77
Best overall responses	
Complete response (CR)	0
Partial response (PR)	61 (79.2%)
Stable disease (SD)	14 (18.2%)
Progressive disease (PD)	0
Not evaluable/unknown	2 (2.6%)
Objective response rate (confirmed CR + confirmed PR)	61 (79.2%)
95% CI	(68.5%, 87.6%)
Clinical Benefit Rate[a] (confirmed CR + confirmed PR + SD)	75 (97.4%)
95% CI	(90.9%, 99.7%)

Key: CI = confidence interval
[a]Clinical benefit rate (CBR) is defined as the percentage of subjects achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks).

Secondary Endpoints

- **Objective Response Rate by Independent Central Review**

Table 25: Summary of Objective Response Rate Based on RECIST v1.1 Criteria - ICR - Cohort 5; Full Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Full	77
Best overall responses	
Complete response (CR)	0
Partial response (PR)	64 (83.1%)
Stable disease (SD)	11 (14.3%)
Progressive disease (PD)	1 (1.3%)
Not evaluable/unknown	1 (1.3%)
Objective response rate (confirmed CR + confirmed PR)	64 (83.1%)
95% CI	(72.9%, 90.7%)
Clinical Benefit Rate[a] (confirmed CR + confirmed PR + SD)	74 (96.1%)
95% CI	(89.0%, 99.2%)

Key: CI = confidence interval
[a]Clinical benefit rate (CBR) is defined as the percentage of subjects achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks).

- **Duration of Response as Assessed by Investigator**

Given the short follow-up time in Cohort 5, the median DOR was not estimable. Among the 61 confirmed responders, 4 (6.6%) had disease progression or died.

- **Time to Response as Assessed by Investigator**

The median TTR as assessed by investigator was 1.87 (range: 1.6, 3.8) months in Cohort 5).

- **Clinical Benefit Rate as Assessed by Investigator**

The CBR by investigator assessment was 97.4% (95% CI: 90.9%, 99.7%) in Cohort 5 (75 of 77 participants had confirmed PR or stable disease.

- **Progression-free Survival**

Given the short follow-up time, the median PFS was not estimable for Cohort 5 The 6-month event-free rate was 0.88 (95% CI: 0.72, 0.95).

- **Overall Survival**

Given the short follow-up time, the median OS was not estimable for Cohort 5. The 6-month event-free rate was 0.97 (95% CI: 0.90, 0.99).

Side-by-side Presentation of Amivantamab SC Q4W Results and Historical Amivantamab Q2W Data

Table 26: Overview of Key Efficacy Results (ORR) for Amivantamab SC Q4W Dosing (PALOMA-2 Cohort 5) and Historical Data of Amivantamab SC Q2W (PALOMA-2 Cohorts 1 and 6) and IV Q2W Dosing (MARIPOSA Arm A)

Population	**Treatment-naive EGFRm NSCLC**		
Dose Regimen	**Q4W Dosing**	**Q2W Dosing******	
Treatment	**Amivantamab SC + lazertinib**	**Amivantamab SC+ lazertinib**	**Amivantamab IV + lazertinib**
Study Cohort or Arm	**PALOMA-2 Cohort 5**	**PALOMA-2 Cohorts 1+6**	**MARIPOSA Arm A**
Analysis (CCO)	**Primary Analysis** (24 October 2024)	**Primary Analysis Cohort 1 Interim Analysis Cohort 6** (06 January 2024)	**Primary Analysis** (11 August 2023)
N (FAS)	77	113	429
Follow-up (months)	6.5	8.6	22.2
ORR (INV) Confirmed responses* (95% CI)	**79.2%** (68.5, 87.6)	**66.4%** (56.9, 75.0)	**72.3%** (67.8, 76.4)
Complete Response (CR)	0	0	0.5%
Partial Response (PR)	79.2%	66.4%	71.8%
Stable Disease (SD)	18.2%	30.1%	19.3%
ORR (INV) Confirmed + Unconfirmed responses** (95% CI)	**81.8%** (71.4, 89.7)	**77.0%** (68.1, 84.4)	**78.1%** (73.9, 81.9)
Complete Response (CR)	0	1.8%	0.5%
Partial Response (PR)	81.8%	75.2%	77.6%
Stable Disease (SD)	15.6%	19.5%	13.5%
ORR ([B]ICR)*** Confirmed responses* (95% CI)	**83.1%** (72.9, 90.7)	**72.6%** (63.4, 80.5)	**79.8%** (75.7, 83.5)
Complete Response (CR)	0	1.8%	5.5%
Partial Response (PR)	83.1%	70.8%	74.3%
Stable Disease (SD)	14.3%	23.9%	13.3%
ORR ([B]ICR)*** Confirmed + Unconfirmed responses** (95% CI)	**87.0%** (77.4, 93.6)	**78.8%** (70.1, 85.9)	**86.2%** (82.6, 89.4)
Complete Response (CR)	3.9%	2.7%	6.9%
Partial Response (PR)	83.1%	76.1%	79.3%
Stable Disease (SD)	10.4%	17.7%	7.1%

(B)ICR: (blinded) independent central review; INV: investigator; IV: intravenous; ORR: overall response rate; SC: subcutaneous
* Confirmed CR + confirmed PR.
** CR and PR do not have to be confirmed.
*** ICR applies to PALOMA-2; BICR applies to MARIPOSA.
**** Due to differences in study designs, sample sizes, and follow-up time, caution should be exercised when comparing results across studies and cohorts.

Amivantamab SC in Combination with CP: PALOMA-2 Cohorts 2 and 3b

- **Primary Endpoint - Objective Response Rate by Investigator**

Table 27: Summary of Objective Response Rate Based on RECIST v1.1 Criteria - Investigator - Cohort 2 and Cohort 3b; Full Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Full	66	77
Best overall responses		
Complete response (CR)	0	0
Partial response (PR)	47 (71.2%)	31 (40.3%)
Stable disease (SD)	15 (22.7%)	41 (53.2%)
Progressive disease (PD)	1 (1.5%)	3 (3.9%)
Not evaluable/unknown	3 (4.5%)	2 (2.6%)
Objective response rate (confirmed CR + confirmed PR)	47 (71.2%)	31 (40.3%)
95% CI	(58.7%, 81.7%)	(29.2%, 52.1%)
Clinical Benefit Rate[a] (confirmed CR + confirmed PR + SD)	62 (93.9%)	65 (84.4%)
95% CI	(85.2%, 98.3%)	(74.4%, 91.7%)

Key: CI = confidence interval
[a]Clinical benefit rate (CBR) is defined as the percentage of subjects achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks).

Secondary Endpoints

- **Objective Response Rate by Independent Central Review**

Table 28: Summary of Objective Response Rate Based on RECIST v1.1 Criteria - ICR - Cohort 2 and Cohort 3b; Full Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Full	66	77
Best overall responses		
Complete response (CR)	3 (4.5%)	3 (3.9%)
Partial response (PR)	41 (62.1%)	37 (48.1%)
Stable disease (SD)[b]	17 (25.8%)	30 (39.0%)
Progressive disease (PD)	2 (3.0%)	4 (5.2%)
Not evaluable/unknown	3 (4.5%)	3 (3.9%)
Objective response rate (confirmed CR + confirmed PR)	44 (66.7%)	40 (51.9%)
95% CI	(54.0%, 77.8%)	(40.3%, 63.5%)
Clinical Benefit Rate[a] (confirmed CR + confirmed PR + SD)	59 (89.4%)	64 (83.1%)
95% CI	(79.4%, 95.6%)	(72.9%, 90.7%)

Key: CI = confidence interval
[a]Clinical benefit rate (CBR) is defined as the percentage of subjects achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks).
[b]Includes non-CR/non-PD in subjects with non-target lesions at baseline.

- **Duration of Response as Assessed by Investigator**

With a median follow-up time of 10.5 months in **Cohort 2**, the median DOR was 10.6 months (95% CI: 8.31, NE)

With a median follow-up time of 7.0 months in **Cohort 3b**, the median DOR was 6.3 months (95% CI: 5.49, NE)

- **Time to Response as Assessed by Investigator**

The median TTR as assessed by investigator was 1.48 (range: 0.8, 5.0) months for **Cohort 2** and 1.51 (range: 1.2, 4.1) months in **Cohort 3b**.

- **Clinical Benefit Rate as Assessed by Investigator**

The CBR by investigator assessment was 93.9% (95% CI: 85.2%, 98.3%) in **Cohort 2** (62 of 66 participants had confirmed PR or stable disease) 84.4% (95% CI: 74.4%, 91.7%) in **Cohort 3b** (65 of 77 participants had confirmed PR or stable disease)

- **Progression-free Survival**

With a median follow-up time of 10.5 months in **Cohort 2**, the median PFS was 12.22 (95% CI: 8.38, NE) months. The 6-month event-free rate was 0.83 (95% CI: 0.71, 0.90).

With a median follow-up time of 7.0 months in **Cohort 3b**, the median PFS was 7.92 (95% CI: 6.77, NE) months. The 6-month event-free rate was 0.67 (95% CI: 0.55, 0.77).

- **Overall Survival**

Given the short median follow-up time (10.5 months in **Cohort 2** and 7.0 months in **Cohort 3b**), the median OS was not estimable for **Cohort 2** and **Cohort 3b**.

Side-by-side Presentation of Amivantamab SC Q3W +CP Results and Historical Amivantamab IV Q3W + CP Data

Table 29: Overview of Key Efficacy Results for Amivantamab SC Q3W + CP (PALOMA-2 Cohorts 2 and 3b) and Historical Data of Amivantamab IV Q3W + CP (PAPILLON and MARIPOSA-2, respectively)

Population	**Treatment-naïve (EGFR exon 20ins NSCLC)**		**Post-osimertinib (EGFRm NSCLC)**	
Dose Regimen	**Q3W**		**Q3W**	
Treatment	**Amivantamab SC + CP**	**Amivantamab IV + CP**	**Amivantamab SC + CP**	**Amivantamab IV + CP**
Study Cohort or Arm	**PALOMA-2 Cohort 2**	**PAPILLON**** **Arm A**	**PALOMA-2 Cohort 3b**	**MARIPOSA-2**** **Arm C**
Analysis (CCO)	**Primary Analysis** (24 October 2024)	**Primary Analysis** (3 May 2023)	**Primary Analysis** (24 October 2024)	**Primary Analysis** (10 July 2023)
N (FAS)	66	153	77	131
Follow-up (months)	10.5	14.6	7.0	9.0
ORR (INV) Confirmed responses* (95% CI)	**71.2%** (58.7, 81.7)	**62.1%** (53.9, 69.8)	**40.3%** (29.2, 52.1)	**44.3%** (35.6, 53.2)
Complete Response (CR)	0	0.7%	0	0.8%
Partial Response (PR)	71.2%	61.4%	40.3%	43.5%

Table 29: Overview of Key Efficacy Results for Amivantamab SC Q3W + CP (PALOMA-2 Cohorts 2 and 3b) and Historical Data of Amivantamab IV Q3W + CP (PAPILLON and MARIPOSA-2, respectively)

Population	**Treatment-naïve (EGFR exon 20ins NSCLC)**		**Post-osimertinib (EGFRm NSCLC)**	
Dose Regimen	**Q3W**		**Q3W**	
Treatment	**Amivantamab SC + CP**	**Amivantamab IV + CP**	**Amivantamab SC + CP**	**Amivantamab IV + CP**
Study Cohort or Arm	**PALOMA-2 Cohort 2**	**PAPILLON**** **Arm A**	**PALOMA-2 Cohort 3b**	**MARIPOSA-2**** **Arm C**
Analysis (CCO)	**Primary Analysis** (24 October 2024)	**Primary Analysis** (3 May 2023)	**Primary Analysis** (24 October 2024)	**Primary Analysis** (10 July 2023)
Stable Disease (SD)	22.7%	29.4%	53.2%	42.0%
ORR (INV) Confirmed + Unconfirmed responses** (95% CI)	**75.8%** (63.6, 85.5)	**66.0%** (57.9, 73.5)	**46.8%** (35.3, 58.5)	**51.9%** (43.0, 60.7)
Complete Response (CR)	0	0.7%	0	0.8%
Partial Response (PR)	75.8%	65.4%	46.8%	51.1%
Stable Disease (SD)	18.2%	25.5%	46.8%	34.4%
ORR ([B]ICR)*** Confirmed responses* (95% CI)	**66.7%** (54.0, 77.8)	**67.1%** (59.0, 74.5)	**51.9%** (40.3, 63.5)	**53.1%** (44.1, 61.9)
Complete Response (CR)	4.5%	3.9%	3.9%	0.8%
Partial Response (PR)	62.1%	63.2%	48.1%	52.3%
Stable Disease (SD)	25.8%	25.0%	39.0%	33.8%
ORR ([B]ICR)*** Confirmed + Unconfirmed responses** (95% CI)	**77.3%** (65.3, 86.7)	**73.0%** (65.2, 79.9)	**53.2%** (41.5, 64.7)	**63.8%** (55.0, 72.1)
Complete Response (CR)	6.1%	3.9%	3.9%	1.5%
Partial Response (PR)	71.2%	69.1%	49.4%	62.3%
Stable Disease (SD)	15.2%	19.1%	35.1%	23.1%
DOR (INV) Median, months (95% CI)	**10.64** (8.31, NE)	**15.28** (10.87, NE)	**6.31** (5.49, NE)	**7.13** (5.55, NE)
PFS (INV) Number of events (%) Median, months (95% CI)	27 (40.9%) **12.22** (8.38, NE)	76 (49.7%) **12.91** (11.37, 16.66)	32 (41.6%) **7.92** (6.77, NE)	67 (51.1%) **8.18** (6.80, 10.94)

(B)ICR: (blinded) independent central review; DOR: duration of response; PFS: progression-free survival; INV: investigator; IV: intravenous; ORR: overall response rate; SC: subcutaneous
* Confirmed CR + confirmed PR.
** CR and PR do not have to be confirmed.
*** ICR applies to PALOMA-2; BICR applies to MARIPOSA.
**** Due to differences in study designs, sample sizes, and follow-up time, caution should be exercised when comparing results across studies and cohorts.

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

Please refer to the presentation of ORR across studies in section 6.3.2.4.5

6.3.4. GCP aspects

The studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

6.3.5. Overall discussion and conclusions on clinical efficacy

6.3.5.1. Discussion

The primary efficacy data to support the PK modelling and simulation approach proposed for amivantamab SC formulation with Q3W and Q4W administration are derived from the ongoing Phase 2 PALOMA-2 study.

PALOMA-2 study

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. Other inclusion and exclusion criteria are generally in line with the criteria applied in the amivantamab IV pivotal studies.

Objectives, endpoints and estimands

The primary objective was to assess anti-tumour activity of amivantamab SC Q3W+CP and amivantamab Q4W+lazertinib, to support the PopPK modelling bridging IV to SC concept. ORR by Investigator according to RECIST1.1 criteria was the primary endpoint. The proposed endpoint is considered appropriate considering the single arm design of the study (SAT) and the study primary objective. The estimand defining the primary endpoint ORR analysed in the ITT population separate per each cohort with while on treatment principle for handling the intercurrent events is considered adequate to serve the primary objective.

The cut off for primary analysis was 03 October 2024.

The secondary endpoints ORR (ICR), DoR, TTR and CBR were chosen to support the primary endpoint. PFS and OS analyses were also provided, however their relevance considering the short follow up and SAT design is limited.

Sample size

Approximately 65 participants were to be enrolled per cohort. However, a larger number of participants than planned was included per cohort: 77 participants in Cohort 5 and Cohort 3b respectively, and 66 participants in Cohort 2. The risk for data driven size increase in Cohort 5 and 3b, respectively, cannot theoretically be excluded. However, as the applicant's claims rely on PK bridging, ORR is considered descriptive.

Statistical plan

The null hypothesis and the success criteria proposed (null hypothesis 25% ORR) for the concerned cohorts are acceptable considering the ORR achieved for the amivantamab IV in the concerned pivotal studies. Notably, ORR has mostly a supporting function of the anti-tumoral activity of the amivantamab SC and not to support the indications in the studied populations. The statistical significance was set to a 2-sided α-level of 0.05 with no adjustment for multiplicity.

Totally there were 4 amendments to the original protocol dated 24 June 2022, the latest introduced 1 year before the CCO (24 October 2024) for the primary analysis. The reasons, details and timing for protocol amendments are adequately presented. Considering that the primary endpoint ORR was analysed per cohort, none of the amendments seems to affect the data integrity per cohort.

Demographics

The baseline patient and disease characteristics of the population from PALOMA-2 Cohort 5 (amivantamab SC Q4W), Cohort 2 and 3b (amivantamab SC Q3W) are generally similar with those in the patient population in MARIPOSA study (amivantamab IV Q2W) and PAPILLON (amivantamab IV Q3W first line) and MARIPOSA-2 (amivantamab IV Q3W second line), respectively.

Results

The primary endpoint ORR across Cohort 5 (ORR 79.2% 95 %CI: 68.5%, 87.6%), Cohort 2 (ORR 71.2 %, 95%CI 58.7%, 81.7%) and Cohort 3b (ORR 40% 95% CI 29.2%, 52.1%) met the prespecified success criteria of ORR (INV) >50% for Cohort 5 and ORR (INV) >25% for Cohort 2 and 3b, respectively, established on the ORR values reached in the pivotal studies, thus supporting the antitumoral activity of the amivantamab SC in the combination regimens.

The secondary endpoint ORR (ICR) is in line with the primary endpoint ORR by Inv.

TTR is consistent with the TTR from the amivantamab IV in the relevant pivotal studies.

For the Cohort 2 and 3b, the median DOR differs somewhat in comparison with amivantamab IV corresponding studies IV, however different treatment intervals and different median follow up between studies have impact on the mDOR metric and prevent a reliable comparison. Given the short follow-up time in Cohort 5, the median DOR was not estimable, while in MARIPOSA stud with amivantamab IV given with Lazertinib, the mDOR was 25.8 months with a median follow up of approximately 31 months.

Median PFS and OS are not reached. However, given that this is a PK bridging application based on non-comparative efficacy data, this is not an issue.

The efficacy results from PALOMA-2 study are not included in section 5.1 of the SmPC since they are not supporting a new indication.

6.3.5.2. Conclusions on the clinical efficacy

The primary and related secondary endpoints suggests that the antitumoral activity of the amivantamab SC Q3W and Q4W in the combination regimens is preserved and is generally in line with the amivantamab IV Q3W and Q2W respectively. Given the consistency of amivantamab PK across NSCLC patient populations is demonstrated and taking into account the absence of drug interaction between amivantamab and lazertinib, the efficacy of the Q3W and Q4W SC regimens (and the corresponding indications in combination with carboplatin and pemetrexed) may be bridged to the original efficacy demonstration for IV use.

6.4. Clinical safety

Safety data collection

Primary analysis safety data (CCO of 24 October 2024) in support of the amivantamab SC Q4W dose regimen in combination with lazertinib are provided from the safety population of PALOMA 2 Cohort 5 (N= 77) in treatment-naïve EGFRm NSCLC participants (reflective of the MARIPOSA [61186372NSC3003] study population).

Primary analysis safety data (CCO of 24 October 2024) in support of amivantamab SC Q3W in combination with CP are provided from the safety population of:

- PALOMA-2 Cohort 2 (N=66) in treatment-naïve NSCLC participants with EGFR exon 20ins mutations (reflective of the PAPILLON [61186372NSC3001] study population)

- PALOMA-2 Cohort 3b (N=77) in participants with EGFRm NSCLC who have progressed on or after the third-generation EGFR TKI osimertinib (reflective of the MARIPOSA-2 study population). Data are presented per cohort and pooled (Cohorts 2 and 3ba).

6.4.1. Patient exposure

PALOMA-2 Cohort 5 (Amivantamab SC Q4W + Lazertinib)

Table 30: Treatment Disposition - Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5 Amivantamab + Lazertinib
Analysis set: Safety	77
Subjects ongoing any study agent	67 (87.0%)
Discontinued all study agents	10 (13.0%)
Reason for discontinuation of last study agent	
Adverse event	7 (9.1%)
Progressive disease	2 (2.6%)
Physician decision	1 (1.3%)

Table 31: Summary of Exposure to Study Agent - Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5		
	Amivantamab + Lazertinib		
	Total	Amivantamab	Lazertinib
Analysis set: Safety	77		
Duration of study treatment (months)[a]			
N	7	77	77
Mean (SD)	6.443 (1.6189)	5.669 (1.9393)	6.427 (1.6234)
Median	6.735	6.242	6.735
Range	(0.13; 9.30)	(0.03; 9.23)	(0.13; 9.30)
Duration of study treatment (months)[a]			
<3	4 (5.2%)	9 (11.7%)	4 (5.2%)
3-<6	14 (18.2%)	27 (35.1%)	15 (19.5%)
6-<9	58 (75.3%)	40 (51.9%)	57 (74.0%)
>=9	1 (1.3%)	1 (1.3%)	1 (1.3%)
Duration of study treatment (months)[a]			
>=3	73 (94.8%)	68 (88.3%)	73 (94.8%)
>=6	59 (76.6%)	41 (53.2%)	58 (75.3%)
>=9	1 (1.3%)	1 (1.3%)	1 (1.3%)
Cumulative dose (mg)			
N		77	77
Mean (SD)		25476.6 (8735.03)	41334.0 (13539.53)
Median		27520.0	43920.0
Range		(1600; 50720)	(960; 62640)
Number of Amivantamab dose injections			

Table 31: Summary of Exposure to Study Agent - Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5		
	Amivantamab + Lazertinib		
	Total	Amivantamab	Lazertinib
N		77	
Mean (SD)		9.5 (2.44)	
Median		10.0	
Range		(1; 13)	
Total dose days of lazertinib			
N			77
Mean (SD)			183.3 (51.70)
Median			191.0
Range			(4; 261)

[a]Duration of treatment for subjects who received 'any' study drug in combination arm is the maximum duration of amivantamab + lazertinib received.

PALOMA-2 Cohort 2 and Cohort 3b (Amivantamab SC Q3W + CP)

Table 32: Treatment Disposition – Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Safety	66	77	143
Subjects ongoing any study agent	37 (56.1%)	48 (62.3%)	85 (59.4%)
Discontinued all study agents[a]	29 (43.9%)	29 (37.7%)	58 (40.6%)
Reason for discontinuation of last study agent			
Progressive disease	13 (19.7%)	22 (28.6%)	35 (24.5%)
Adverse event	12 (18.2%)	6 (7.8%)	18 (12.6%)
Subject refused further study treatment	3 (4.5%)	1 (1.3%)	4 (2.8%)
Physician decision	1 (1.5%)	0	1 (0.7%)

[a]Include subjects who completed 4 cycles of carboplatin or discontinued carboplatin prematurely before cycle 4.

Table 33: Summary of Exposure to Study Agent - Cohort 2 and Cohort 3b; Safety Analysis Set (Study - 61186372NSC2002)

	Cohort 2				Cohort 3b				Total			
	Amivantamab + Carboplatin + Pemetrexed				Amivantamab + Carboplatin + Pemetrexed				Amivantamab + Carboplatin + Pemetrexed			
	Total	Amivantamab	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed
Analysis set: Safety	66				77				143			

Table 33: Summary of Exposure to Study Agent - Cohort 2 and Cohort 3b; Safety Analysis Set (Study - 61186372NSC2002)

	Cohort 2				Cohort 3b				Total			
	Amivantamab + Carboplatin + Pemetrexed				Amivantamab + Carboplatin + Pemetrexed				Amivantamab + Carboplatin + Pemetrexed			
	Total	Amivantamab	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed
Duration of study treatment (months) [a]												
N	66	66	66	66	77	77	77	77	143	143	143	143
Mean (SD)	8.219 (3.6943)	8.117 (3.7563)	2.052 (0.5024)	7.696 (3.6237)	5.723 (2.0883)	5.651 (2.1000)	2.026 (0.5713)	5.248 (2.2325)	6.875 (3.1845)	6.789 (3.2158)	2.038 (0.5389)	6.378 (3.1904)
Median	9.347	9.347	2.103	8.542	6.242	6.242	2.136	5.848	6.932	6.899	2.103	6.472
Range	(0.23; 15.44)	(0.23; 15.44)	(0.03; 3.48)	(0.03; 14.26)	(0.03; 9.13)	(0.03; 9.13)	(0.03; 3.02)	(0.03; 9.13)	(0.03; 15.44)	(0.03; 15.44)	(0.03; 3.48)	(0.03; 14.26)
Duration of study treatment (months) [a]												
<3	8 (12.1%)	9 (13.6%)	65 (98.5%)	9 (13.6%)	11 (14.3%)	11 (14.3%)	76 (98.7%)	16 (20.8%)	19 (13.3%)	20 (14.0%)	141 (98.6%)	25 (17.5%)
3-<6	10 (15.2%)	10 (15.2%)	1 (1.5%)	11 (16.7%)	22 (28.6%)	25 (32.5%)	1 (1.3%)	23 (29.9%)	32 (22.4%)	35 (24.5%)	2 (1.4%)	34 (23.8%)
6-<9	12 (18.2%)	11 (16.7%)	0	15 (22.7%)	43 (55.8%)	40 (51.9%)	0	37 (48.1%)	55 (38.5%)	51 (35.7%)	0	52 (36.4%)
9-<12	30 (45.5%)	30 (45.5%)	0	27 (40.9%)	1 (1.3%)	1 (1.3%)	0	1 (1.3%)	31 (21.7%)	31 (21.7%)	0	28 (19.6%)
12-<15	5 (7.6%)	5 (7.6%)	0	4 (6.1%)	0	0	0	0	5 (3.5%)	5 (3.5%)	0	4 (2.8%)
>=15	1 (1.5%)	1 (1.5%)	0	0	0	0	0	0	1 (0.7%)	1 (0.7%)	0	0
Duration of study treatment (months) [a]												
>=3	58 (87.9%)	57 (86.4%)	1 (1.5%)	57 (86.4%)	66 (85.7%)	66 (85.7%)	1 (1.3%)	61 (79.2%)	124 (86.7%)	123 (86.0%)	2 (1.4%)	118 (82.5%)
>=6	48 (72.7%)	47 (71.2%)	0	46 (69.7%)	44 (57.1%)	41 (53.2%)	0	38 (49.4%)	92 (64.3%)	88 (61.5%)	0	84 (58.7%)
>=9	36 (54.5%)	36 (54.5%)	0	31 (47.0%)	1 (1.3%)	1 (1.3%)	0	1 (1.3%)	37 (25.9%)	37 (25.9%)	0	32 (22.4%)
>=12	6 (9.1%)	6 (9.1%)	0	4 (6.1%)	0	0	0	0	6 (4.2%)	6 (4.2%)	0	4 (2.8%)

Table 33: Summary of Exposure to Study Agent - Cohort 2 and Cohort 3b; Safety Analysis Set (Study - 61186372NSC2002)

	Cohort 2				Cohort 3b				Total			
	Amivantamab + Carboplatin + Pemetrexed				Amivantamab + Carboplatin + Pemetrexed				Amivantamab + Carboplatin + Pemetrexed			
	Total	Amivantamab	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed
>=15	1 (1.5%)	1 (1.5%)	0	0	0	0	0	0	1 (0.7%)	1 (0.7%)	0	0
Cumulative dose (mg)												
N		66	66	66		77	77	77		143	143	143
Mean (SD)		30227.9 (13625.57)	2078.9 (621.14)	9169.1 (4623.79)		22808.9 (8081.80)	1887.5 (563.87)	6420.5 (2821.71)		26233.1 (11563.57)	1975.8 (596.62)	7689.1 (3992.31)
Median		30960.0	2101.0	10132.5		23200.0	1914.0	6622.5		25760.0	2000.0	7652.3
Range		(4000; 62720)	(450; 3000)	(738; 17244)		(1600; 42560)	(489; 3000)	(730; 12258)		(1600; 62720)	(450; 3000)	(730; 17244)
Number of Amivantamab dose injections												
N		66				77				143		
Mean (SD)		13.4 (5.40)				9.9 (3.13)				11.5 (4.65)		
Median		15.0				11.0				11.0		
Range		(2; 23)				(1; 16)				(1; 23)		

[a]Duration of treatment for subjects who received 'any' study drug in combination arm is the maximum duration of study treatment.

6.4.2. Adverse events

PALOMA-2 Cohort 5 (Amivantamab SC Q4W + Lazertinib)

Table 34: Overall Summary of Treatment-emergent Adverse Events – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Safety	77
Subjects with 1 or more AEs	77 (100.0%)
Related AEs[a]	77 (100.0%)
Related to Amivantamab	77 (100.0%)
Related to Lazertinib	77 (100.0%)
Maximum toxicity grade	
Grade 1	2 (2.6%)
Grade 2	39 (50.6%)

Table 34: Overall Summary of Treatment-emergent Adverse Events – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Grade 3	32 (41.6%)
Grade 4	2 (2.6%)
Grade 5	2 (2.6%)
AEs leading to death[b]	2 (2.6%)
Related AEs leading to death	0
Related to Amivantamab	0
Related to Lazertinib	0
Serious AEs	21 (27.3%)
Related serious AEs	14 (18.2%)
Related to Amivantamab	14 (18.2%)
Related to Lazertinib	11 (14.3%)
AEs leading to dose discontinuation of any study agent	8 (10.4%)
Discontinuation of Amivantamab	8 (10.4%)
Discontinuation of Lazertinib	7 (9.1%)
AEs leading to dose reduction of any study agent	31 (40.3%)
Dose reduction of Amivantamab	21 (27.3%)
Dose reduction of Lazertinib	23 (29.9%)
AEs leading to dose interruption of any study agent	50 (64.9%)
Interruption of Amivantamab	43 (55.8%)
Interruption of Lazertinib	42 (54.5%)

Key: AE = adverse event
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.

Table 35: Number of Subjects With Toxicity Grade 3 or Higher Treatment-emergent Adverse Events Occurring in 2% or More Subjects by System Organ Class, Preferred Term – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Safety	77
Subjects with 1 or more toxicity grade 3 or higher AEs	36 (46.8%)
System organ class	
Preferred term	
Skin and subcutaneous tissue disorders	17 (22.1%)
Rash	9 (11.7%)
Dermatitis acneiform	6 (7.8%)
Infections and infestations	10 (13.0%)
Paronychia	4 (5.2%)
Pneumonia	2 (2.6%)

Table 35: Number of Subjects With Toxicity Grade 3 or Higher Treatment-emergent Adverse Events Occurring in 2% or More Subjects by System Organ Class, Preferred Term – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Metabolism and nutrition disorders	8 (10.4%)
Hypoalbuminaemia	4 (5.2%)
Hypokalaemia	2 (2.6%)
Gastrointestinal disorders	6 (7.8%)
Stomatitis	3 (3.9%)
Diarrhoea	2 (2.6%)
Blood and lymphatic system disorders	3 (3.9%)
Lymphopenia	2 (2.6%)
Investigations	3 (3.9%)
Alanine aminotransferase increased	3 (3.9%)

Key: AE = adverse event; 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.

PALOMA-2 Cohort 2 and Cohort 3b (Amivantamab SC Q3W + CP)

Table 36: Overall Summary of Treatment-emergent Adverse Events - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Safety	66	77	143
Subjects with 1 or more AEs	66 (100.0%)	77 (100.0%)	143 (100.0%)
Related AEs[a]	66 (100.0%)	75 (97.4%)	141 (98.6%)
Related to Amivantamab	66 (100.0%)	74 (96.1%)	140 (97.9%)
Related to Carboplatin	62 (93.9%)	75 (97.4%)	137 (95.8%)
Related to Pemetrexed	66 (100.0%)	74 (96.1%)	140 (97.9%)
Maximum toxicity grade			
Grade 1	0	2 (2.6%)	2 (1.4%)
Grade 2	19 (28.8%)	22 (28.6%)	41 (28.7%)
Grade 3	36 (54.5%)	37 (48.1%)	73 (51.0%)
Grade 4	8 (12.1%)	12 (15.6%)	20 (14.0%)
Grade 5	3 (4.5%)	4 (5.2%)	7 (4.9%)
AEs leading to death[b]	3 (4.5%)	4 (5.2%)	7 (4.9%)
Related AEs leading to death	0	1 (1.3%)	1 (0.7%)
Related to Amivantamab	0	0	0
Related to Carboplatin	0	1 (1.3%)	1 (0.7%)
Related to Pemetrexed	0	1 (1.3%)	1 (0.7%)
Serious AEs	28 (42.4%)	25 (32.5%)	53 (37.1%)
Related serious AEs	21 (31.8%)	20 (26.0%)	41 (28.7%)
Related to Amivantamab	15 (22.7%)	10 (13.0%)	25 (17.5%)
Related to Carboplatin	8 (12.1%)	15 (19.5%)	23 (16.1%)
Related to Pemetrexed	15 (22.7%)	17 (22.1%)	32 (22.4%)

Table 36: Overall Summary of Treatment-emergent Adverse Events - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
AEs leading to dose discontinuation of any study agent	18 (27.3%)	19 (24.7%)	37 (25.9%)
Discontinuation of Amivantamab	12 (18.2%)	7 (9.1%)	19 (13.3%)
Discontinuation of Carboplatin	7 (10.6%)	10 (13.0%)	17 (11.9%)
Discontinuation of Pemetrexed	15 (22.7%)	16 (20.8%)	31 (21.7%)
AEs leading to dose reduction of any study agent	39 (59.1%)	38 (49.4%)	77 (53.8%)
Dose reduction of Amivantamab	27 (40.9%)	24 (31.2%)	51 (35.7%)
Dose reduction of Carboplatin	17 (25.8%)	23 (29.9%)	40 (28.0%)
Dose reduction of Pemetrexed	25 (37.9%)	30 (39.0%)	55 (38.5%)
AEs leading to dose interruption of any study agent	49 (74.2%)	47 (61.0%)	96 (67.1%)
Interruption of Amivantamab	48 (72.7%)	46 (59.7%)	94 (65.7%)
Interruption of Carboplatin	23 (34.8%)	20 (26.0%)	43 (30.1%)
Interruption of Pemetrexed	35 (53.0%)	31 (40.3%)	66 (46.2%)

Key: AE = adverse event
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.

Table 37: 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, Preferred Term - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Safety	66	77	143
Subjects with 1 or more toxicity grade 3 or higher AEs	47 (71.2%)	53 (68.8%)	100 (69.9%)
System organ class Preferred term			
Blood and lymphatic system disorders	29 (43.9%)	31 (40.3%)	60 (42.0%)
Neutropenia	19 (28.8%)	26 (33.8%)	45 (31.5%)
Thrombocytopenia	9 (13.6%)	10 (13.0%)	19 (13.3%)
Leukopenia	4 (6.1%)	12 (15.6%)	16 (11.2%)
Anaemia	10 (15.2%)	5 (6.5%)	15 (10.5%)
Febrile neutropenia	2 (3.0%)	1 (1.3%)	3 (2.1%)
Lymphopenia	2 (3.0%)	1 (1.3%)	3 (2.1%)
Metabolism and nutrition disorders	21 (31.8%)	10 (13.0%)	31 (21.7%)
Hypoalbuminaemia	7 (10.6%)	5 (6.5%)	12 (8.4%)
Hypokalaemia	5 (7.6%)	4 (5.2%)	9 (6.3%)
Hypocalcaemia	4 (6.1%)	2 (2.6%)	6 (4.2%)
Hyponatraemia	4 (6.1%)	1 (1.3%)	5 (3.5%)
Hypomagnesaemia	3 (4.5%)	1 (1.3%)	4 (2.8%)
Hyperkalaemia	2 (3.0%)	0	2 (1.4%)
Infections and infestations	14 (21.2%)	10 (13.0%)	24 (16.8%)
Paronychia	3 (4.5%)	2 (2.6%)	5 (3.5%)
Sepsis	4 (6.1%)	0	4 (2.8%)

Table 37: 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, Preferred Term - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Cellulitis	2 (3.0%)	0	2 (1.4%)
Pneumonia	2 (3.0%)	0	2 (1.4%)
Gastrointestinal disorders	9 (13.6%)	13 (16.9%)	22 (15.4%)
Stomatitis	4 (6.1%)	3 (3.9%)	7 (4.9%)
Vomiting	1 (1.5%)	6 (7.8%)	7 (4.9%)
Diarrhoea	2 (3.0%)	2 (2.6%)	4 (2.8%)
Nausea	1 (1.5%)	2 (2.6%)	3 (2.1%)
Skin and subcutaneous tissue disorders	10 (15.2%)	8 (10.4%)	18 (12.6%)
Rash	6 (9.1%)	3 (3.9%)	9 (6.3%)
Dermatitis acneiform	3 (4.5%)	2 (2.6%)	5 (3.5%)
General disorders and administration site conditions	7 (10.6%)	7 (9.1%)	14 (9.8%)
Fatigue	3 (4.5%)	4 (5.2%)	7 (4.9%)
Asthenia	1 (1.5%)	2 (2.6%)	3 (2.1%)
Investigations	3 (4.5%)	8 (10.4%)	11 (7.7%)
Alanine aminotransferase increased	1 (1.5%)	4 (5.2%)	5 (3.5%)
Aspartate aminotransferase increased	1 (1.5%)	3 (3.9%)	4 (2.8%)
Gamma-glutamyltransferase increased	1 (1.5%)	2 (2.6%)	3 (2.1%)
Musculoskeletal and connective tissue disorders	1 (1.5%)	4 (5.2%)	5 (3.5%)
Muscular weakness	0	2 (2.6%)	2 (1.4%)
Nervous system disorders	2 (3.0%)	3 (3.9%)	5 (3.5%)
Syncope	1 (1.5%)	2 (2.6%)	3 (2.1%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.
Note: The event experienced by the subject with the worst toxicity is used.

6.4.3. Adverse drug reactions

Amivantamab+lazertinib combination

To support update of the ADR presentation in SmPC 4.8 section for amivantamab + lazertinib, data from PALOMA-2 Cohort 5 were pooled with safety data from PALOMA-2 Cohorts 1 and 6, MARIPOSA, and PALOMA-3 SC arm (Arm A). This pooled population (n=829) was used to determine frequency categories for each ADR term.

Table 38: Incidence of Treatment-emergent Adverse Drug Reactions (ADRs) for Amivantamab by System Organ Class, Preferred Term and Toxicity Grade (Study 73831937NSC3003, 61186372NSC2002 - Cohort 1, 5 and 6 and 61186372NSC3004)

			Amivantamab SC (Q4W) + Lazertinib (N=77)		Pooled SC and IV (Amivantamab + Lazertinib) (N=829)	
System Organ Class (SOC)	Adverse Drug Reaction	Frequency (all grades)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Subjects with any treatment-emergent adverse drug reaction			76 (98.7%)	27 (35.1%)	823 (99.3%)	397 (47.9%)
Skin and subcutaneous tissue disorders	Rash[a]	Very common	70 (90.9%)	15 (19.5%)	724 (87.3%)	185 (22.3%)
	Nail toxicity[a]	Very common	58 (75.3%)	4 (5.2%)	562 (67.8%)	64 (7.7%)
	Dry skin[a]	Very common	24 (31.2%)	1 (1.3%)	208 (25.1%)	6 (0.7%)
	Pruritus	Very common	26 (33.8%)	1 (1.3%)	195 (23.5%)	3 (0.4%)
	Palmar-plantar erythrodysaesthesia syndrome	Common	0	0	29 (3.5%)	1 (0.1%)
	Urticaria	Common	1 (1.3%)	0	13 (1.6%)	0
Injury, poisoning and procedural complications	Infusion-/Administration-related reactions					
	Amivantamab intravenous[b,d]	Very common	-	-	265 (62.9%)	27 (6.4%)
	Amivantamab subcutaneous[c,e]	Very common	9 (11.7%)	1 (1.3%)	55 (13.5%)	2 (0.5%)
Metabolism and nutrition disorders	Hypoalbuminaemia[a]	Very common	49 (63.6%)	4 (5.2%)	409 (49.3%)	38 (4.6%)
	Decreased appetite	Very common	12 (15.6%)	0	191 (23.0%)	6 (0.7%)
	Hypocalcaemia	Very common	10 (13.0%)	0	150 (18.1%)	9 (1.1%)
	Hypokalaemia	Very common	5 (6.5%)	2 (2.6%)	101 (12.2%)	22 (2.7%)
	Hypomagnesaemia	Common	4 (5.2%)	0	50 (6.0%)	0
Gastrointestinal disorders	Stomatitis[a]	Very common	38 (49.4%)	3 (3.9%)	360 (43.4%)	18 (2.2%)
	Diarrhoea	Very common	22 (28.6%)	2 (2.6%)	216 (26.1%)	15 (1.8%)
	Constipation	Very common	10 (13.0%)	0	207 (25.0%)	0
	Nausea	Very common	15 (19.5%)	0	197 (23.8%)	6 (0.7%)
	Vomiting	Very common	12 (15.6%)	0	125 (15.1%)	4 (0.5%)
	Abdominal pain[a]	Common	6 (7.8%)	0	78 (9.4%)	1 (0.1%)
	Haemorrhoids	Common	4 (5.2%)	0	67 (8.1%)	1 (0.1%)
Hepatobiliary disorders	Hepatotoxicity[a]	Very common	31 (40.3%)	4 (5.2%)	358 (43.2%)	55 (6.6%)
General disorders and administration site conditions	Oedema[a]	Very common	34 (44.2%)	0	348 (42.0%)	20 (2.4%)
	Fatigue[a]	Very common	18 (23.4%)	2 (2.6%)	283 (34.1%)	28 (3.4%)
	Pyrexia	Very common	5 (6.5%)	0	91 (11.0%)	0
	Injection site reactions[a,c,f]	Common	0	0	26 (6.4%)	0
Vascular disorders	Venous thromboembolism					

Table 38: Incidence of Treatment-emergent Adverse Drug Reactions (ADRs) for Amivantamab by System Organ Class, Preferred Term and Toxicity Grade (Study 73831937NSC3003, 61186372NSC2002 - Cohort 1, 5 and 6 and 61186372NSC3004)

			Amivantamab SC (Q4W) + Lazertinib (N=77)		Pooled SC and IV (Amivantamab + Lazertinib) (N=829)	
System Organ Class (SOC)	Adverse Drug Reaction	Frequency (all grades)	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
	Amivantamab intravenous[a,b]	Very common	-	-	157 (37.3%)	45 (10.7%)
	Amivantamab subcutaneous[a,c]	Very common	10 (13.0%)	0	45 (11.0%)	3 (0.7%)
Nervous system disorders	Paraesthesia[a]	Very common	22 (28.6%)	0	243 (29.3%)	10 (1.2%)
	Dizziness[a]	Very common	3 (3.9%)	0	96 (11.6%)	0
Eye disorders	Other eye disorders[a]	Very common	12 (15.6%)	0	155 (18.7%)	4 (0.5%)
	Visual impairment[a]	Common	3 (3.9%)	0	30 (3.6%)	0
	Keratitis	Common	3 (3.9%)	0	16 (1.9%)	2 (0.2%)
	Growth of eyelashes[a]	Common	2 (2.6%)	0	15 (1.8%)	0
Musculoskeletal and connective tissue disorders	Myalgia	Very common	12 (15.6%)	0	127 (15.3%)	4 (0.5%)
	Muscle spasms	Very common	8 (10.4%)	0	107 (12.9%)	3 (0.4%)
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[a]	Common	3 (3.9%)	1 (1.3%)	30 (3.6%)	14 (1.7%)

[a] Preferred terms are displayed as adverse drug reaction groupings.
[b] Frequency based on amivantamab intravenous studies only (MARIPOSA [N=421]).
[c] Frequency based on amivantamab subcutaneous studies only (PALOMA-2 cohorts 1 and 6 [N=125], cohort 5 [N=77] and PALOMA-3 subcutaneous arm [N=206]).
[d] Infusion related reactions are systemic signs and symptoms associated with infusion of amivantamab intravenous.
[e] Administration related reactions are systemic signs and symptoms associated with administration of amivantamab subcutaneous
[f] Injection site reactions are local signs and symptoms associated with subcutaneous mode of administration.
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.

Based on ADR update with data from Cohort 5, 5 new PTs were identified and added to the pre-existing amivantamab ADR grouped terms:

Stomatitis (grouped term) had 1 new PT added (angular cheilitis)

Dry skin (grouped term) had 1 new PT added (eczema asteatotic)

Nail toxicity (grouped term) had 1 new PT added (nail dystrophy)

Other eye disorders (grouped term) had 1 new PT added (episcleritis)

VTE (grouped term) had 1 new PT added (superficial vein thrombosis) for the amivantamab + lazertinib combination only

Amivantamab+CP combinations

To support update of the ADR presentation in SmPC 4.8 section for amivantamab + lazertinib, data from PALOMA-2 Cohort 2 and 3b were pooled with safety data from the amivantamab IV with CP arms in PAPILLON, MARIPOSA-2, and CHRYSALIS. This pooled population (n=444) was used to determine frequency categories for each ADR term.

Table 39: Incidence of Treatment-emergent Adverse Drug Reactions (ADRs) for Amivantamab by System Organ Class, Preferred Term and Toxicity Grade (Study 61186372EDI1001, 61186372NSC3001, 61186372NSC3002, 61186372NSC2002 - Cohort 2 and 3b)

			Pooled SC and IV [Amivantamab + Chemotherapy (ACP)] (N=444)	
System Organ Class (SOC)	Adverse Drug Reaction	Frequency (all grades)	All Grades (%)	Grade 3-4 (%)
Subjects with any treatment-emergent adverse drug reaction			441 (99.3%)	282 (63.5%)
Skin and subcutaneous tissue disorders	Rash[a]	Very common	369 (83.1%)	60 (13.5%)
	Nail toxicity[a]	Very common	251 (56.5%)	19 (4.3%)
	Dry skin[a]	Very common	63 (14.2%)	1 (0.2%)
	Pruritus	Very common	51 (11.5%)	0
Blood and lymphatic system disorders	Neutropenia	Very common	248 (55.9%)	161 (36.3%)
	Thrombocytopenia	Very common	179 (40.3%)	56 (12.6%)
Injury, poisoning and procedural complications	Infusion-/Administration-related reactions			
	Amivantamab intravenous[b,d]	Very common	152 (50.5%)	9 (3.0%)
	Amivantamab subcutaneous[c,e]	Common	10 (7.0%)	0
General disorders and administration site conditions	Fatigue[a]	Very common	205 (46.2%)	26 (5.9%)
	Oedema[a]	Very common	182 (41.0%)	6 (1.4%)
	Pyrexia	Very common	56 (12.6%)	1 (0.2%)
	Injection site reactions[a,c,f]	Common	5 (3.5%)	0
Gastrointestinal disorders	Nausea	Very common	195 (43.9%)	6 (1.4%)
	Stomatitis[a]	Very common	186 (41.9%)	19 (4.3%)
	Constipation	Very common	175 (39.4%)	1 (0.2%)
	Vomiting	Very common	102 (23.0%)	13 (2.9%)
	Diarrhoea	Very common	83 (18.7%)	11 (2.5%)
	Abdominal pain[a]	Very common	54 (12.2%)	2 (0.5%)
	Haemorrhoids	Common	37 (8.3%)	2 (0.5%)
Metabolism and nutrition disorders	Hypoalbuminaemia[a]	Very common	159 (35.8%)	23 (5.2%)
	Decreased appetite	Very common	141 (31.8%)	5 (1.1%)
	Hypokalaemia	Very common	86 (19.4%)	29 (6.5%)
	Hypocalcaemia	Very common	60 (13.5%)	9 (2.0%)
	Hypomagnesaemia	Very common	49 (11.0%)	8 (1.8%)
Investigations	Alanine aminotransferase increased	Very common	124 (27.9%)	18 (4.1%)
	Aspartate aminotransferase increased	Very common	107 (24.1%)	6 (1.4%)
	Blood alkaline phosphatase increased	Common	34 (7.7%)	1 (0.2%)
Vascular disorders	Venous thromboembolism			
	Amivantamab subcutaneous[a,c]	Very common	25 (17.5%)	4 (2.8%)
	Amivantamab intravenous[a,b]	Very common	42 (14.0%)	9 (3.0%)
Eye disorders	Other eye disorders[a]	Very common	66 (14.9%)	0
	Visual impairment[a]	Common	13 (2.9%)	0
	Growth of eyelashes	Uncommon	3 (0.7%)	0
	Keratitis	Uncommon	1 (0.2%)	0
	Uveitis	Uncommon	1 (0.2%)	0
Nervous system disorders	Dizziness[a]	Very common	45 (10.1%)	2 (0.5%)

Table 39: Incidence of Treatment-emergent Adverse Drug Reactions (ADRs) for Amivantamab by System Organ Class, Preferred Term and Toxicity Grade (Study 61186372EDI1001, 61186372NSC3001, 61186372NSC3002, 61186372NSC2002 - Cohort 2 and 3b)

			Pooled SC and IV [Amivantamab + Chemotherapy (ACP)] (N=444)	
System Organ Class (SOC)	Adverse Drug Reaction	Frequency (all grades)	All Grades (%)	Grade 3-4 (%)
Musculoskeletal and connective tissue disorders	Myalgia	Common	27 (6.1%)	2 (0.5%)
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[a]	Common	11 (2.5%)	6 (1.4%)

[a] Preferred terms are displayed as adverse drug reaction groupings.
[b] Frequency based on amivantamab intravenous studies only (CHRYSALIS [N=20], PAPILLON [N=151], MARIPOSA-2 [N=130]).
[c] Frequency based on amivantamab subcutaneous studies only (PALOMA-2 cohorts 2 and 3B [N=143]).
[d] Infusion related reactions are systemic signs and symptoms associated with infusion of amivantamab intravenous.
[e] Administration related reactions are systemic signs and symptoms associated with administration of amivantamab subcutaneous
[f] Injection site reactions are local signs and symptoms associated with subcutaneous mode of administration.
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.

6.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Deaths

Cohort 5

Table 40: Summary of Death and Cause of Death – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Safety	77
Deaths during study	3 (3.9%)
Adverse Event	2 (2.6%)
Other	1 (1.3%)
Deaths within 30 days of last dose[a]	2 (2.6%)
Adverse Event	2 (2.6%)

[a] Subjects who died within 30 days will be counted in both categories.

Cohort 2+3b

Table 41: Number of Subjects With Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Safety	66	77	143
Subjects with 1 or more AEs leading to death	3 (4.5%)	4 (5.2%)	7 (4.9%)
System organ class Preferred term			
Infections and infestations	2 (3.0%)	1 (1.3%)	3 (2.1%)
Pneumonia	1 (1.5%)	0	1 (0.7%)
Respiratory tract infection	1 (1.5%)	0	1 (0.7%)
Neutropenic sepsis	0	1 (1.3%)	1 (0.7%)
Vascular disorders	1 (1.5%)	0	1 (0.7%)
Thrombophlebitis migrans	1 (1.5%)	0	1 (0.7%)
Gastrointestinal disorders	0	1 (1.3%)	1 (0.7%)
Intestinal ischaemia	0	1 (1.3%)	1 (0.7%)
General disorders and administration site conditions	0	1 (1.3%)	1 (0.7%)
Sudden death	0	1 (1.3%)	1 (0.7%)
Injury, poisoning and procedural complications	0	1 (1.3%)	1 (0.7%)
Traumatic intracranial haemorrhage	0	1 (1.3%)	1 (0.7%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.
Note: AEs leading to death are based on AE outcome of Fatal.

SAEs

Cohort 5

Table 42: Number of Subjects With Treatment-emergent Serious Adverse Events Occurring in 2% or More Subjects by System Organ Class and Preferred Term – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Safety	77
Subjects with 1 or more SAEs	21 (27.3%)
System organ class Preferred term	

Table 42: Number of Subjects With Treatment-emergent Serious Adverse Events Occurring in 2% or More Subjects by System Organ Class and Preferred Term – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Infections and infestations	9 (11.7%)
Paronychia	2 (2.6%)
Pneumonia	2 (2.6%)
Respiratory, thoracic and mediastinal disorders	4 (5.2%)
Pneumonitis	3 (3.9%)

Key: AE = adverse event; 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.

Cohort 2+3b

Table 43: 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 - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Safety	66	77	143
Subjects with 1 or more SAEs	28 (42.4%)	25 (32.5%)	53 (37.1%)
System organ class Preferred term			
Infections and infestations	11 (16.7%)	6 (7.8%)	17 (11.9%)
Pneumonia	3 (4.5%)	1 (1.3%)	4 (2.8%)
Sepsis	4 (6.1%)	0	4 (2.8%)
Cellulitis	2 (3.0%)	0	2 (1.4%)
Gastrointestinal disorders	3 (4.5%)	10 (13.0%)	13 (9.1%)
Vomiting	1 (1.5%)	3 (3.9%)	4 (2.8%)
Nausea	0	3 (3.9%)	3 (2.1%)
Blood and lymphatic system disorders	4 (6.1%)	4 (5.2%)	8 (5.6%)
Neutropenia	1 (1.5%)	2 (2.6%)	3 (2.1%)
Febrile neutropenia	2 (3.0%)	0	2 (1.4%)
Respiratory, thoracic and mediastinal disorders	6 (9.1%)	0	6 (4.2%)
Pneumonitis	3 (4.5%)	0	3 (2.1%)

Key: SAE = serious adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

[tsfae03p2q3eu.rtf] [jnj-61186372/nsc2002/dbr_pa_ia_c1to6/re_scs/tafae03p2q3eu.sas] 05FEB2025, 10:49

Adverse Events of Special Interest

Cohort 5-AESI

Table 44: Number of Subjects With Treatment-emergent Adverse Events of Special Interest by Special Interest Category and Preferred Term – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Safety	77
Subjects with 1 or more AEs of special interest	72 (93.5%)
Special interest category Preferred term	
Rash	70 (90.9%)
Rash	45 (58.4%)
Dermatitis acneiform	31 (40.3%)
Rash pustular	3 (3.9%)
Acne	1 (1.3%)
Dermatitis	1 (1.3%)
Erythema	1 (1.3%)
Rash maculo-papular	1 (1.3%)
Skin lesion	1 (1.3%)
Venous Thromboembolic Event	10 (13.0%)
Embolism venous	4 (5.2%)
Pulmonary embolism	3 (3.9%)
Deep vein thrombosis	2 (2.6%)
Superficial vein thrombosis	1 (1.3%)
Administration Related Reaction	9 (11.7%)
Administration related reaction	9 (11.7%)
Pneumonitis / Interstitial Lung Disease	3 (3.9%)
Pneumonitis	3 (3.9%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

ARR

The incidence of ARR with amivantamab SC Q4W was 11.7%. Most ARRs were Grade 1 or 2. One participant (1.3%) had a serious Grade 3 ARR (with symptoms of hypotension and atrial fibrillation) on Day 114 (Cycle 5 Day 1) for which the participant was hospitalized for treatment and monitoring. There were several other concurrent AEs prior to and ongoing at the onset of the Grade 3 ARR (including Grade 3 hyponatremia and Grade 2 hypophosphatemia) which could also have been contributing factors. Importantly, the Grade 3 ARR was noted to be resolved the same day. None of the ARRs led to study treatment discontinuation.

VTE

Due to the increased risk of VTE events for study participants receiving amivantamab in combination with lazertinib during the first 4 months of treatment in the MARIPOSA study, the PALOMA-2 study protocol was amended to recommend prophylactic-dose anticoagulants as per local guidelines for the first 4 months of therapy.

Table 45: Overall Summary of Treatment-emergent Adverse Events Venous Thromboembolic Event – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5
	Amivantamab + Lazertinib
Analysis set: Safety	77
Subjects with 1 or more VTE AEs	10 (13.0%)
Related AEs[a]	9 (11.7%)
Related to Amivantamab	9 (11.7%)
Related to Lazertinib	9 (11.7%)
Maximum toxicity grade	
Grade 1	1 (1.3%)
Grade 2	9 (11.7%)
Grade 3	0
Grade 4	0
Grade 5	0
AEs leading to death[b]	0
Related AEs leading to death	0
Related to Amivantamab	0
Related to Lazertinib	0
Serious AEs	0
Related serious AEs	0
Related to Amivantamab	0
Related to Lazertinib	0
AEs leading to dose discontinuation of any study agent	0
Discontinuation of Amivantamab	0
Discontinuation of Lazertinib	0
AEs leading to dose reduction of any study agent	0
Dose reduction of Amivantamab	0
Dose reduction of Lazertinib	0
AEs leading to dose interruption of any study agent	2 (2.6%)
Interruption of Amivantamab	2 (2.6%)
Interruption of Lazertinib	2 (2.6%)

Key: AE = adverse event; VTE = Venous Thromboembolic Event
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
Note: VTE adverse event terms are identified by the standardized MedDRA query for "EMBOLIC AND THROMBOTIC EVENTS, VENOUS (SMQ)" and Preferred Term is "THROMBOSIS", "EMBOLISM".

Table 46: Overall Summary of Treatment-emergent Adverse Events Venous Thromboembolic Event by Use of Anticoagulants – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5	
	Amivantamab + Lazertinib	
	With Prophylactic Anticoagulants	No Prophylactic Anticoagulants
Analysis set: Safety	67	10

Table 46: Overall Summary of Treatment-emergent Adverse Events Venous Thromboembolic Event by Use of Anticoagulants – Cohort 5; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 5	
	Amivantamab + Lazertinib	
	With Prophylactic Anticoagulants	No Prophylactic Anticoagulants
% of VTE[a] events, all grades	7 (10.4%)	3 (30.0%)
Gr3+	0	0
Gr5	0	0
% of VTE SAE	0	0
% of VTE TEAEs leading to discontinuation	0	0

Key: VTE = Venous Thromboembolic Event, SAE = Serious Adverse Event and TEAE = Treatment Emergent Adverse Event.
[a]VTE adverse event terms are identified by the standardized MedDRA query for "EMBOLIC AND THROMBOTIC EVENTS, VENOUS (SMQ)" and Preferred Term is "THROMBOSIS", "EMBOLISM".
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.
With Prophylactic Anticoagulation: Any subject who had anticoagulation prior or at C1D1 plus 3 days window until progression, death, withdrawn from the study, occurrence of VTE or C5D1.
No Prophylactic Anticoagulation: Subjects who never took prophylactic anticoagulation during first 4 months of amivantamab and lazertinib combination treatment.

Table 47: Overview of Treatment-emergent VTEs by Anticoagulants Use for Amivantamab SC Q4W (PALOMA-2 Study [Cohort 5]), Amivantamab SC Q2W (PALOMA-2 Study [Cohorts 1 and 6]), and Amivantamab SC Q2W (PALOMA-3 Study)

Study	**PALOMA-2 Cohort 5**		**PALOMA-2 Cohorts 1 and 6**		**PALOMA-3 Arm A**	
	Amivantamab SC Q4W + Lazertinib		**Amivantamab SC Q2W + Lazertinib**		**Amivantamab SC Q2W+ Lazertinib**	
CCO	**24 October 2024**		**06 January 2024**		**03 January 2024**	
Median follow-up (months)	**6.54**		**8.64**		**7.26**	
	With Prophylactic Anticoagulants	**No Prophylactic Anticoagulants**	**With Prophylactic Anticoagulants**	**No Prophylactic Anticoagulants**	**With Prophylactic Anticoagulants**	**No Prophylactic Anticoagulants**
Analysis set: Safety	67	10	105	20	164	42
% of VTE[a] events, all grades	7 (10.4%)	3 (30.0%)	12 (11.4%)	4 (20.0%)	12 (7.3%)	7 (16.7%)
Gr3+	0	0	0	1 (5.0%)	2 (1.2%)	0
Gr5	0	0	0	0	0	0
% of VTE SAE	0	0	3 (2.9%)	2 (10.0%)	2 (1.2%)	2 (4.8%)
% of VTE TEAEs leading to discontinuation	0	0	0	0	0	0

Table 47: Overview of Treatment-emergent VTEs by Anticoagulants Use for Amivantamab SC Q4W (PALOMA-2 Study [Cohort 5]), Amivantamab SC Q2W (PALOMA-2 Study [Cohorts 1 and 6]), and Amivantamab SC Q2W (PALOMA-3 Study)

Study	PALOMA-2 Cohort 5		PALOMA-2 Cohorts 1 and 6		PALOMA-3 Arm A	
	Amivantamab SC Q4W + Lazertinib		Amivantamab SC Q2W + Lazertinib		Amivantamab SC Q2W+ Lazertinib	
CCO	24 October 2024		06 January 2024		03 January 2024	
Median follow-up (months)	6.54		8.64		7.26	
	With Prophylactic Anticoagulants	No Prophylactic Anticoagulants	With Prophylactic Anticoagulants	No Prophylactic Anticoagulants	With Prophylactic Anticoagulants	No Prophylactic Anticoagulants

Key: VTE = Venous Thromboembolic Event, SAE = Serious Adverse Event and TEAE = Treatment Emergent Adverse Event.
[a]VTE adverse event terms are identified by the standardized MedDRA query for "EMBOLIC AND THROMBOTIC EVENTS, VENOUS (SMQ)" and Preferred Term is "THROMBOSIS", "EMBOLISM".
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.
With Prophylactic Anticoagulation: Any subject who had anticoagulation prior or at C1D1 plus 3 days window until progression, death, withdrawn from the study, occurrence of VTE or C5D1.
No Prophylactic Anticoagulation: Subjects who never took prophylactic anticoagulation during first 4 months of amivantamab and lazertinib combination treatment.

Rash

The incidence of rash in Cohort 5 was 90.9%. Most rash events were Grade 1 or 2. No Grade 4 or 5 rash was reported. Grade 3 rash was reported for 19.5% of participants and serious rash was reported for 1 participant. Rash did not lead to study treatment discontinuation.

Pneumonitis/ILD

The incidence of pneumonitis/ILD in Cohort 5 was low (pneumonitis in 3 participants [3.9%]). Two out of the 3 participants with pneumonitis/ILD also had clinical presentation of infection with fever, increased white blood cells and elevated C-reactive protein at the onset of pneumonitis/ILD, suggesting a multifactorial etiology with possibility of underlying pulmonary infection. For all 3 participants, the events were considered serious (as required by the protocol), related to study treatment, and led to study treatment discontinuation (as required by the protocol). Two participants had Grade 2 events and 1 participant had a Grade 3 event.

Cohort 2+3b-AESI

Table 48: Number of Subjects With Selected Treatment-emergent Adverse Events of Special Interest by Special Interest Category and Preferred Term - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Analysis set: Safety	66	77	143
Subjects with 1 or more AEs of special interest	62 (93.9%)	61 (79.2%)	123 (86.0%)

Table 48: Number of Subjects With Selected Treatment-emergent Adverse Events of Special Interest by Special Interest Category and Preferred Term - Cohort 2 and Cohort 3b; Safety Analysis Set (Study JnJ-61186372NSC2002)

	Cohort 2	Cohort 3b	Total
	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed	Amivantamab + Carboplatin + Pemetrexed
Special interest category Preferred term			
Rash	58 (87.9%)	59 (76.6%)	117 (81.8%)
Rash	30 (45.5%)	39 (50.6%)	69 (48.3%)
Dermatitis acneiform	26 (39.4%)	16 (20.8%)	42 (29.4%)
Rash maculo-papular	7 (10.6%)	5 (6.5%)	12 (8.4%)
Folliculitis	6 (9.1%)	4 (5.2%)	10 (7.0%)
Acne	2 (3.0%)	0	2 (1.4%)
Dermatitis	2 (3.0%)	3 (3.9%)	5 (3.5%)
Skin exfoliation	2 (3.0%)	2 (2.6%)	4 (2.8%)
Dermatitis infected	1 (1.5%)	0	1 (0.7%)
Erythema	1 (1.5%)	2 (2.6%)	3 (2.1%)
Papule	1 (1.5%)	0	1 (0.7%)
Rash pruritic	1 (1.5%)	0	1 (0.7%)
Rash pustular	1 (1.5%)	3 (3.9%)	4 (2.8%)
Skin lesion	1 (1.5%)	2 (2.6%)	3 (2.1%)
Rash erythematous	0	1 (1.3%)	1 (0.7%)
Rash papular	0	3 (3.9%)	3 (2.1%)
Venous Thromboembolic Event	13 (19.7%)	12 (15.6%)	25 (17.5%)
Deep vein thrombosis	6 (9.1%)	3 (3.9%)	9 (6.3%)
Embolism venous	3 (4.5%)	0	3 (2.1%)
Pulmonary embolism	3 (4.5%)	5 (6.5%)	8 (5.6%)
Superficial vein thrombosis	1 (1.5%)	0	1 (0.7%)
Thrombophlebitis migrans	1 (1.5%)	0	1 (0.7%)
Venous thrombosis limb	1 (1.5%)	2 (2.6%)	3 (2.1%)
Thrombophlebitis	0	2 (2.6%)	2 (1.4%)
Venous thrombosis	0	1 (1.3%)	1 (0.7%)
Administration Related Reaction	4 (6.1%)	6 (7.8%)	10 (7.0%)
Administration related reaction	4 (6.1%)	6 (7.8%)	10 (7.0%)
Pneumonitis / Interstitial Lung Disease	4 (6.1%)	0	4 (2.8%)
Pneumonitis	3 (4.5%)	0	3 (2.1%)
Interstitial lung disease	1 (1.5%)	0	1 (0.7%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

ARR

The incidence of ARR with amivantamab SC Q3W with CP was 6.1% in Cohort 2 and 7.8% in Cohort 3b. All ARRs were Grade 1 or 2. The median time to onset of first administrationrelated reactions was 2.1 hours (range: 0.7 to 3.1 hours). None of the ARRs were serious or led to study treatment discontinuation.

VTE

VTE is an ADR only for the combination of amivantamab with lazertinib and was therefore not considered an AESI for Cohorts 2 and 3b.

In Cohort 2, VTE events were reported in 13 participants (19.7%). Most participants (10/13) had Grade 1 or 2 VTE events. Two participants had Grade 3 VTE (pulmonary embolism and DVT) and 1 participant had Grade 5 VTE (thrombophlebitis migrans). The VTE leading to death was not considered to be related to study treatment. One participant had VTE that led to study treatment discontinuation

Rash

Consistent with the on-target activity of amivantamab against the EGFR pathway, most participants in Cohorts 2 and 3b had rash.

The incidence of rash was 87.9% in Cohort 2 and 76.6% in Cohort 3b. Most of these events were Grade 1 or 2. No Grade 4 or 5 rash or serious rash was reported. Rash led to study treatment discontinuation in 1 participant in Cohort 2 and 2 participants in Cohort 3b.

Pneumonitis/ILD

The incidence of pneumonitis/ILD was 6.1% in Cohort 2 and 0 in Cohort 3b. Three participants had Grade 2 events and 1 participant had a Grade 4 event of pneumonitis. All events were considered serious and led to study treatment discontinuation (as required by the protocol). Among these 4 participants with pneumonitis/ILD, 2 participants had comorbidities of lung infections.

6.4.5. Discontinuation due to adverse events

Cohort 5

The incidence of TEAEs leading to study treatment dose reduction was 40.3% (27.3% for amivantamab and 29.9% for lazertinib). Frequently reported (in ≥5% of participants) TEAEs leading to dose reduction were rash, dermatitis acneiform, and paronychia, which are cutaneous toxicities that can be associated with EGFR inhibition.

The incidence of TEAEs leading to interruption of any study treatment was 64.9% (55.8% for amivantamab and 54.5% for lazertinib). Frequently reported (in ≥5% of participants) TEAEs leading to study treatment interruption were rash, dermatitis acneiform, paronychia, and hypoalbuminemia, which are known to be associated with EGFR and MET inhibition.

The incidence of TEAEs leading to discontinuation of any study treatment was 10.4% (10.4% for amivantamab and 9.1% for lazertinib) and the incidence of TEAEs that led to discontinuation of all study treatment was 9.1%. As required by the protocol, 3 participants (3.9%) discontinued study treatment due to pneumonitis. Otherwise, there was no overarching reason for study treatment discontinuation, and no other TEAEs led to study treatment discontinuation in >1 participant.

Cohort 2+3b

In Cohort 2, the incidence of TEAEs leading to study treatment dose reduction was 59.1%. Frequently reported (in ≥5% of participants) TEAEs leading to dose reduction of any study treatment were rash (12.1%), paronychia, neutropenia, fatigue (9.1% each), and thrombocytopenia (7.6%). In Cohort 3b, the incidence of TEAEs leading to study treatment dose reduction was 49.4%. Frequently reported (in ≥5% of participants) TEAEs leading to dose reduction of any study treatment were neutropenia (16.9%), rash (9.1%), thrombocytopenia (7.8%), fatigue (6.5%), paronychia, stomatitis, and vomiting (5.2% each).

In Cohort 2, the incidence of TEAEs leading to interruption of any study treatment was 74.2%. Frequently reported (in ≥5% of participants) TEAEs leading to drug interruption were neutropenia (22.7%), rash (16.7%), thrombocytopenia (9.1%), paronychia and hypoalbuminemia (7.6% each) anemia, and leukopenia, dermatitis acneiform (6.1%). In Cohort 3b, the incidence of TEAEs leading to interruption of any study treatment was 61.0%. Frequently reported (in ≥5% of participants) TEAEs leading to drug interruption were neutropenia (23.4%), leukopenia (9.1%), paronychia (7.8%), rash and thrombocytopenia (6.5%), anemia and hypoalbuminemia (5.2% each).

The incidence of TEAEs leading to discontinuation of any study treatment was 27.3% in Cohort 2 (18.2% for amivantamab) and 24.7% in Cohort 3b (9.1% for amivantamab). No TEAEs leading to any study treatment discontinuation occurred in ≥5% of participants in any cohort.

6.4.6. Safety in special populations

For Cohort 5 (n=77) and Cohorts 2 (n=66) and 3b (n=77), no subgroup analysis for safety was performed due to the small number of participants in these cohorts.

6.4.7. Immunological events

Based on the results obtained from the amivantamab SC studies PALOMA (Cohorts 1 through 6), PALOMA-2 (Cohorts 1, 2, 3, 3b, 5, and 6), and PALOMA-3, the overall incidence of participants with treatment-emergent antibodies to amivantamab following SC administration was low with low titers. The majority of participants were negative for treatment-emergent ADA (726 of 729 participants, 99.6% ADA negativity.

The small number of participants who were positive for antibodies to amivantamab precludes drawing a definitive conclusion regarding the impact of ADA on the serum concentrations, efficacy, or safety of amivantamab.

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

No new information is available on drug interactions with amivantamab SC.

6.4.9. Vital signs and laboratory findings

Cohort 5 (Amivantamab SC Q4W + Lazertinib)

- **Hematology**

In PALOMA-2 Cohort 5, changes in hematology values by worst grouped NCI-CTCAE toxicity grade during the Treatment phase were generally consistent with the established safety profile for amivantamab IV Q2W with lazertinib (in MARIPOSA), and no clinically meaningful deleterious effects on hematology were observed during the treatment period.

- **Chemistry**

In PALOMA-2 Cohort 5, changes in clinical chemistry by worst grouped NCI-CTCAE toxicity grade during the Treatment phase were generally consistent with the established safety profile for amivantamab IV Q2W with lazertinib (in MARIPOSA), and no clinically meaningful deleterious effects were observed during the treatment period.

Cohort 2 and Cohort 3b (Amivantamab SC Q3W + CP)

- **Hematology**

In PALOMA-2 Cohorts 2 and 3b, changes in hematology values by worst grouped NCI-CTCAE toxicity grade during the Treatment phase were generally consistent with the established safety profile of the individual components (in PAPILLON and MARIPOSA-2).

- **Chemistry**

In PALOMA-2 Cohorts 2 and 3b, changes in clinical chemistry by worst grouped NCI-CTCAE toxicity grade during the Treatment phase were generally consistent with the established safety profile of the individual components (in PAPILLON and MARIPOSA-2).

6.4.10. Post marketing experience

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

6.4.11. Overall discussion and conclusions on clinical safety

6.4.11.1. Discussion

6.4.11.1.1. Overall assessment of available safety data

The overall safety data for the amivantamab SC in the Q4W dose regimen in combination with lazertinib and of amivantamab SC Q3W in combination with carboplatin and pemetrexed (CP) for the treatment of patients with EGFR-mutated NSCLC, based on the primary analysis of PALOMA-2 Cohort 5 (Q4W) and Cohorts 2 and 3b (Q3W).

Exposure

At the time of the CCO (24 October 2024), the median follow-up of safety in patients included in Cohort 5 was 6.54 months. For Cohort 2 and 3b the median follow-up was 10.5 months and 7.0 months respectively. The median follow-up covers the median duration of treatment, allowing detection on AEs while on treatment. This is considered sufficient taking into account the supporting function of the safety data from this study for the extrapolation to the new SC regimens and the well-known safety profile of the amivantamab in combination with lazertinib, or with CP.

The volume required for administered dose of Rybrevant SC Q4W from week 4 and onwards although higher than in the previously approved Q2W is considered feasible for administration in split volumes while following the recommendation from section 4.2 of the SmPC (see section 4.4.2 of this report).

Cohort 5 (Amivantamab SC Q4W + Lazertinib)

All participants (100.0%) were reported to have at least 1 TEAE. Most of these events were Grade 1 or 2 and non-serious with few discontinuations of study treatment. The majority of TEAEs were known

on-target due to EGFR and/or MET inhibition. The most frequently reported EGFR-associated TEAEs were paronychia, rash, dermatitis acneiform, stomatitis, and diarrhea; the MET-associated TEAEs were hypoalbuminemia and peripheral edema.

Grade ≥3 TEAEs were reported for 46.8% of participants.

SAEs were observed in 27.3% of participants. Frequently reported (in ≥2% of participants) SAEs included pneumonitis (3.9%), pneumonia (2.6%), and paronychia (2.6%).

TEAEs leading to death were observed in 3 participants (3.9%), however, considered not related to study treatment.

TEAEs leading to dose reduction, interruption, and discontinuation of any study treatment occurred in 40.3%, 64.9%, and 10.4% of participants, respectively. Pneumonitis was the most frequent cause for discontinuation and was reported in 3 participants (3.9%). No other TEAEs led to study treatment discontinuation in more than 1 participant.

AESI

The AESI observed in Cohort 5 were pneumonitis/ILD reported in three participants (3.9%), ARR in nine participants (11.7%), rash in majority of the participants (90.9%) and VTE in ten participants (13.0%) that received recommended prophylactic anticoagulants and in 3 of 10 participants who did not receive prophylactic anticoagulants.

All the VTEs were Grade 1 or Grade 2 and no participants had serious VTEs. Two participants (2.6%) had a VTE that led to study treatment interruption with no treatment discontinuation or dose reduction due to VTEs.

Cohort 2 and Cohort 3b (Amivantamab SC Q3W + CP)

All participants (100.0%) were reported to have at least 1 or more TEAE of any grade. TEAEs associated with the on-target activity of amivantamab against the EGFR pathway, the MET pathway, hematologic TEAEs, and other frequently reported TEAEs are qualitatively in line with the TEAEs known for the amivantamab IV+CP. Most of these events were Grade 1 or 2, non-serious, and rarely led to study treatment discontinuation

In Cohort 2, Grade ≥3 TEAEs were observed in 71.2% of participants. Grade ≥3 TEAEs reported in ≥10% of participants were neutropenia (28.8%), anemia (15.2%), thrombocytopenia (13.6%), and hypoalbuminemia (10.6%). In Cohort 3b, Grade ≥3 TEAEs were observed in 66.8% of participants. Grade ≥3 TEAEs reported in ≥10% of participants were neutropenia (33.8%), leukopenia (15.6%), and thrombocytopenia (13.0%).

In Cohort 2, SAEs were observed in 42.4% of participants. SAEs reported for ≥2% of participants included sepsis (6.1%), pneumonia and pneumonitis (4.5% each), cellulitis and febrile neutropenia (3.0% each). In Cohort 3b, SAEs were observed in 32.5% of participants. SAEs reported for ≥2% of participants included vomiting and nausea (3.9% each), and neutropenia (2.6%).

TEAEs leading to death were observed in 3 participants (4.5%) in Cohort 2 and 4 participants (5.2%) in Cohort 3b. TEAEs leading to death were reported in 3 participants (4.5%) in Cohort 2 (pneumonia, respiratory tract infection, and thrombophlebitis migrans). TEAEs leading to death were reported in 4 participants (5.2%) in Cohort 3b (neutropenic sepsis, intestinal ischemia, sudden death, and traumatic intracranial hemorrhage). The only TEAE that was related to study treatment was neutropenic sepsis in Cohort 3b.

TEAEs leading to any study treatment discontinuation occurred in 27.3% of participants in Cohort 2 and 24.7% of participants in Cohort 3b. In Cohort 2, the incidence of TEAEs leading to study treatment dose reduction was 59.1%. In Cohort 3b, the incidence of TEAEs leading to study treatment dose reduction was 49.4%. In Cohort 3b, the incidence of TEAEs leading to interruption of any study treatment was 61.0%.

AESI

The AESI observed were pneumonitis/ILD reported in 6.1% of the participants in Cohort 2 and none in Cohort 3b, ARR in 6.1% of participants in Cohort 2 and 7.8% in Cohort 3b, rash in 87.9% of participants in Cohort 2 and 76.6% in Cohort 3b, and VTE in 13 participants (19.7%) in Cohort 2 and in 12 participants (15.6%) in Cohort 3b.

All AESI are recognized ADRs for Rybrevant SC and IV in combination with chemotherapy (CP).

Adverse drug reactions in the SmPC

Amivantamab + lazertinib

Safety data from PALOMA-2 Cohort 5 informed the update of the SmPC section 4.8 with the ADRs with amivantamab SC in terms of incidence and description. As per SmPC guideline the update was based on the pooled analysis of the ADRs from the studies with amivantamab SC and amivantamab IV in combination with Lazertinib (n=829). Hence, 5 new PTs were identified and added to the existing amivantamab ADR grouped terms of stomatitis, dry skin, nail toxicity, other eye disorders and VTE (1 PT of superficial vein thrombosis) with no new ADR in terms of grouped terms identified. No significant changes besides the change in incidence of the grouped terms were introduced to the ADR table in section 4.8 of the SmPC.

Amivantamab + CP

The incidence data from PALOMA-2 Cohorts 2 and 3b for the combination of amivantamab SC with CP were pooled with incidence data from the amivantamab IV with CP arms in PAPILLON, MARIPOSA-2, and CHRYSALIS. This pooled population (n=444) was used to inform the PI section 4.8 with the frequencies of ADRs and to characterize the selected ADRs.

8 new PTs were identified and added to the pre-existing amivantamab ADR grouped terms with no new ADR in terms of grouped terms identified. No significant changes besides the change in incidence of the grouped terms were introduced to the ADR table in section 4.8 of the SmPC.

6.4.11.2. Conclusions on clinical safety

The safety profile for the amivantamab SC Q3W +CP and amivantamab SC Q4W +lazertinib is generally in line with the safety profile of amivantamab IV in the corresponding studies. No new adverse reactions were identified.

7. Risk management plan

7.1. Safety specification

The MAH did not propose an update to the summary of safety concerns in the RMP.

Table 49: Summary of safety concerns in the proposed RMP

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.*

7.1.1. Discussion on proposed safety specification

The MAH did not propose amendments to the summary of safety concerns in the RMP, which is considered acceptable. No new safety concerns are identified following the review of safety data in the current procedure.

Venous thromboembolic (VTE) events remain an important identified risk for the combination of amivantamab and lazertinib, Hepatotoxicity and Impaired fertility and embryofetal toxicity remain important potential risks; there is no missing information.

Considering the data in the safety specification, the safety concerns listed above are appropriate.

7.2. Pharmacovigilance plan

7.2.1. Pharmacovigilance plan

Table 50: Ongoing and planned additional pharmacovigilance activities

Study and status	Summary of objectives	Safety concern(s) addressed	Milestones	Due dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2: Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3: Required additional pharmacovigilance activities				
Not applicable				

7.2.2. Discussion on the Pharmacovigilance Plan

7.2.2.1. Routine pharmacovigilance activities

The MAH did not propose any routine pharmacovigilance activities beyond adverse reaction reporting and signal detection. This is considered acceptable.

7.2.2.2. Additional pharmacovigilance activities

The MAH did not propose any additional pharmacovigilance activities. There are no additional pharmacovigilance activities ongoing and planned. This is considered acceptable.

7.3. Risk minimisation measures

7.3.1. Risk minimisation measures

Table 51: Routine risk minimisation measures

Venous thromboembolic (VTE) events*
Routine risk communication SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** 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. **Other routine risk minimization measures beyond the Product Information** Legal status
Hepatotoxicity

Routine risk communication SmPC Section 4.8 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** Legal status
Impaired fertility and embryofetal toxicity
Routine risk communication: •SmPC Section 4.6 •SmPC Section 5.3 •PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** •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. **Other routine risk minimization measures beyond the Product Information:** •Legal status

* Applies only to the combination of amivantamab and lazertinib.

7.3.2. Discussion on the risk minimisation measures

7.3.2.1. Routine risk minimisation measures

There are no changes proposed by the MAH to the routine risk minimisation measures.

The routine risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indication(s).

7.3.2.2. Additional risk minimisation measures

There are no additional risk minimization measures proposed by the MAH. Routine risk minimisation activities are sufficient to manage the safety concerns of RYBREVANT.

7.4. Overall conclusion on the Risk Management Plan

The updated risk management plan version 7.1 is acceptable.

8. Pharmacovigilance

Pharmacovigilance system

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

8.1. 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.

9. Product information

9.1. Summary of Product Characteristics (SmPC)

The SmPC of the subcutaneous presentations has been updated to reflect the addition of the 2 new strengths (2400 mg and 3520 mg solution for injection). The main changes are in section 4.2 where the QW3 dose regimen and QW4 dose regimen have been added. As a result of the newly added QW3 dose regimen, sections 4.1 and 5.1 of the SmPC has been updated to reflect the indications in combination with carboplatin and pemetrexed (already included in the IV presentations) linked to the QW3 dose regimen.

See edited product information.

9.2. Package leaflet

See edited product information.

9.3. 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 the previous made user tests for Rybrevant (initial application EMEA/H/C/005454/0000 and extension EMEA/H/C/005454/X/0014). The bridging report submitted by the MAH has been found acceptable since user tests have already been performed and the layout will remain the same.

9.4. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Lack of space to accommodate all information; consistency with already approved presentations; the fact that vial must be stored inside the box with full information until the point of administration.

The particulars to be omitted as per the QRD Group decision described above will, however, be included in the Annexes published with the EPAR on EMA website and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

9.5. Additional monitoring

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

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

10. Benefit-risk assessment

Therapeutic context

10.1.1. 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).

In the current line extension, the added further strengths for amivantamab SC intend to support administration under a Q3W dosing schedule which corresponds to the currently approved indications of amivantamab IV:

• 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.

Moreover, a Q4W (as an alternative to Q2W) s.c. dosing regimen for the previously approved indications in combination with lazertinib or as monotherapy is also proposed.

10.1.2. Available therapies and unmet medical need

A subcutaneous formulation and SC posologies for already approved Q2W and Q3W intravenous indications is applied for. No new clinical indication was sought.

The claimed benefits that amivantamab Q3W SC regimen (amivantamab in combination with carboplatin-pemetrexed) 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.

The claimed benefit that amivantamab Q4W SC regimen (in combination with lazertinib or as monotherapy) would address is to further reduce the burden with amivantamab therapy by spacing out the administration every 2 weeks in case of IV formulation to every 4 weeks with SC formulation of amivantamab.

Notably, the amivantamab SC Q2W has been approved already in the previous procedure Rybrevant-14 (see Procedure EMEA/H/C/005454/X/0014) based on the bridging study Phase 3 PALOMA-3 comparing amivantamab SC Q2W to amivantamab IV Q2W, both in combination with lazertinib. Importantly, in this study amivantamab SC regimen was related with reduced rates and grades of IRR/ARR, reduced incidence of VTE, as well as reduction in administration time.

10.2. Main clinical studies

This application is mainly based on PK results from new data from clinical studies PALOMA and PALOMA-2.

PALOMA (61186372NSC1003) is An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Amivantamab, a Human Bispecific EGFR and cMET Antibody for the Treatment of Advanced Solid Malignancies. Compared to the previous population PK analysis, new data for amivantamab SC (PK cutoff: 11 July 2024) includes Cohort 6a (n=19 patients) with a maintenance dose of 3200 mg (4320 mg for participants ≥80 kg) Q4W. The previous population PK analysis included data from Cohort 5a (n=25 patients) with a maintenance dose of 2560 mg (3360 mg if WT ≥80 kg) Q3W.

PALOMA-2 (61186372NSC2002) is a Phase 2, Open-Label, Parallel Cohort Study of SC Amivantamab in Multiple Regimens in Patients with Advanced or Metastatic Solid Tumors Including EGFR Mutated NSCLC. Compared to the previous population PK analysis, new data for amivantamab SC (PK cutoff: 13 August 2024) includes Cohort 5 (n=77 patients) with a maintenance dose of 3520 mg (or 4640 mg for participants ≥80 kg) Q4W and Cohorts 2+3+3b (n=66+70+77 patients) with a maintenance dose of 2400 mg (or 3360 mg for participants ≥80 kg) Q3W.

Model-based analyses have also been submitted which also includes PK data from Studies PALOMA-3 and CHRYSALIS, which have been submitted in a previous Rybrevant line extension for the SC Q2W regimen (see Procedure EMEA/H/C/005454/X/0014).

Efficacy and safety assumptions for the proposed SC Q3W and SC Q4W regimens are based on extrapolation from the IV Q3W and IV Q2W regimens via PK bridging.

In addition, to support the bridging strategy, supportive efficacy and safety data relevant for the current application and relevant indications were provided from PALOMA-2 study, specifically from Cohort 5 (amivantamab SC Q4W with lazertinib) and Cohorts 2 and 3b (amivantamab SC Q3W with CP).

10.3. Favourable effects

The population PK model was used to predict the outcome of exposure-comparisons where the proposed SC Q3W and SC Q4W regimens were compared against the corresponding reference treatment (IV Q3W and IV Q2W, respectively). For an antibody, the most relevant exposure metrics from an efficacy perspective are C_{trough} and C_{avg}. The efficacy profile is maintained if C_{trough} and C_{avg} are at least as high for the SC regimen as for the corresponding IV regimen. Comparisons of these exposure metrics, in Cycle 2 ($C_{trough,max}$ and $C_{avg,C2}$) and at steady state ($C_{trough,ss}$ and $C_{avg,ss}$), were provided:

The SC Q3W regimen of amivantamab is predicted to result in a 21% higher $C_{avg,C2}$, a comparable $C_{avg,ss}$, and a higher $C_{trough,max}$ and $C_{trough,ss}$ (23% and 32% higher, respectively), compared to the approved IV Q3W regimen. The SC Q4W regimen of amivantamab is predicted to result in a 30% higher $C_{avg,C2}$, a 26% higher $C_{avg,ss}$, a higher $C_{trough,max}$ (20% higher) but comparable $C_{trough,ss}$, compared to the approved IV Q2W regimen.

The observed $C_{trough,ss}$ median [range] was 208 µg/mL [83, 402] for SC Q3W and 154 µg/mL [18, 967] for IV Q3W. The corresponding geometric mean values [%CV] were 208 µg/mL [38%] and 142 µg/mL [67%] respectively.

The observed $C_{trough,ss}$ median [range] was 133 µg/mL [7, 443] for SC Q4W and 145 µg/mL [BQL, 484] for IV Q2W. The corresponding geometric mean values [%CV] were 131 µg/mL [72%] and 142 µg/mL [NC] respectively.

The most relevant exposure metrics from a safety perspective are C_{max} and C_{avg}. The safety profile is maintained if C_{max} and C_{avg} are at most as high for the SC regimen as for the corresponding IV regimen. Comparisons of these exposure metrics, in Cycle 2 ($C_{max,max}$) and at steady state ($C_{max,ss}$), were provided (for C_{avg}, see above):

The SC Q3W regimen of amivantamab is predicted to result in a lower $C_{max,max}$ and $C_{max,ss}$ (27% and 48% lower, respectively), compared to the approved IV Q3W regimen. The SC Q4W regimen of amivantamab is predicted to result in a comparable $C_{max,max}$ and $C_{max,ss}$, compared to the approved IV Q2W regimen.

In PALOMA-2 study, the primary endpoint ORR across Cohort 5 (ORR 79.2% 95 %CI: 68.5%, 87.6%), Cohort 2 (ORR 71.2 %, 95%CI 58.7%, 81.7%) and Cohort 3b (ORR 40% 95% CI 29.2%, 52.1%) met the prespecified success criteria supporting the antitumoral activity of the amivantamab SC across the combination regimens amivantamab SC Q4W with lazertinib in Cohort 5 and amivantamab SC Q3W with CP in Cohorts 2 and 3b.

10.3.1. Uncertainties and limitations about favourable effects

A limitation with PALOMA and PALOMA-2 is that neither study included a reference arm where patients received the reference treatment (IV Q3W or IV Q2W, respectively). Thus, only cross-study comparisons of observed PK data are available. Model-based exposure comparisons provided help in overcoming this limitation.

In terms of model-based analyses, the Applicant provided comparisons of model predictions and model simulations, where the SC Q3W and SC Q4W regimens were compared against the corresponding reference treatment (IV Q3W and IV Q2W, respectively). As further support, the Applicant also provided comparisons of observed exposures. Separately, each of these comparisons comes with uncertainties; however, taken together they support extrapolation of efficacy and safety from the recommended IV Q3W regimen to the proposed SC Q3W regimen, and from the recommended IV Q2W regimen to the proposed SC Q4W regimen.

10.4. Unfavourable effects

The overall safety data for the amivantamab SC to support the PK bridging and the sought indications originated from the primary analysis of PALOMA-2 Cohort 5 (Q4W) and Cohorts 2 and 3b (Q3W), respectively. For the amivantamab SC Q3W safety data was pooled for Cohort 2 and 3b.

In terms of **TEAEs** all participants (100.0%) across Cohort 5 (Amivantamab SC Q4W + Lazertinib) and Cohort 2 and Cohort 3b (Amivantamab SC Q3W + CP) were reported to have at least 1 TEAE. Most of these events were Grade 1 or 2 and non-serious with few discontinuations of study treatment. The majority of TEAEs were known on-target due to EGFR and/or MET inhibition. The most frequently reported EGFR-associated TEAEs were paronychia, rash, dermatitis acneiform, stomatitis, and diarrhoea; the MET-associated TEAEs were hypoalbuminemia and peripheral oedema.

Grade ≥3 TEAEs were reported for 46.8% of participants in Cohort 5, for 71.2% of participants in Cohort 2 and in 66.8% of participants I Cohort 3b. Overall, Grade ≥3 TEAEs reported in ≥10% of participants were neutropenia, leukopenia, anaemia, thrombocytopenia and hypoalbuminemia.

SAEs were observed in 27.3% of participants in Cohort 5, in 42.4% of participants in Cohort 2 and in 32.5% of participants in Cohort 3b. Overall, SAEs reported for ≥2% of participants included sepsis, pneumonia and pneumonitis, cellulitis and febrile neutropenia, vomiting and nausea.

TEAEs leading to death were observed in 3 participants (3.9%) in Cohort 5, in 3 participants (4.5%) in Cohort 2 and 4 participants (5.2%) in Cohort 3b. The only TEAE considered related to study treatment was neutropenic sepsis in Cohort 3b.

TEAEs leading to dose reduction, interruption, and discontinuation of any study treatment occurred in 40.3%, 64.9%, and 10.4% of participants, respectively in Cohort 5. Pneumonitis was the most frequent cause for discontinuation (3.9%). TEAEs leading to any study treatment discontinuation occurred in 27.3% of participants in Cohort 2 and 24.7% of participants in Cohort 3b. In Cohort 2, the incidence of TEAEs leading to study treatment dose reduction was 59.1%. In Cohort 3b, the incidence of TEAEs leading to study treatment dose reduction was 49.4%, while the incidence of TEAEs leading to interruption of any study treatment was 61.0%.

The **AESI** relevant for the claims related to the new amivantamab SC Q3W and Q4W regimens are:

ARR: ARR events were reported across all three cohorts. All ARRs were Grade 1 or 2. None of the ARRs were serious or led to study treatment discontinuation. In Cohort 5 nine participants (11.7%) had ARR with serious Grade 3 ARR in one participant (1.3%). Most ARRs (9.1%) occurred after the first injection. The incidence of ARR with amivantamab SC Q3W with CP was 6.1% in Cohort 2 and 7.8% in Cohort 3b.

VTE: Prophylactic anticoagulation was recommended for the first 4 months of therapy in Cohort 5 due to the increased risk of VTE events for study participants receiving amivantamab in combination with lazertinib during the first 4 months of treatment observed in the MARIPOSA study.

However prophylactic anticoagulation was not required for cohort 2 and 3b.

In Cohort 5, 87.0% of participants (67 of 77) received recommended prophylactic anticoagulants with VTEs in ten participants (13.0%). The incidence of VTEs for participants who did not receive prophylactic anticoagulants was 3-fold higher, 30.0% (3 participants of 10). All the VTEs were Grade 1 or Grade 2 and no participants had serious VTEs. Two participants (2.6%) had a VTE that led to study treatment interruption. No treatment discontinuation or dose reduction due to VTEs were reported in this study.

In Cohort 2, VTE events were reported in 13 participants (19.7%)), mostly (10/13) Grade 1 or 2 VTE events. Two participants had Grade 3 VTE (pulmonary embolism and DVT) and 1 participant had Grade 5 VTE (thrombophlebitis migrans), not considered to be related to study treatment. In Cohort 3b, VTE events were reported in 12 participants (15.6%), most of them (10/12) with Grade 1 or 2 VTE events. Two participants had Grade 3 VTE (pulmonary embolism and venous thrombosis).

ADRs

No significant changes besides the change in incidence of some of the grouped terms included already in the ADR tables of the SmPC were introduced.

10.4.1. Uncertainties and limitations about unfavourable effects

Not applicable.

10.5. Benefit-risk assessment and discussion

10.5.1. Importance of favourable and unfavourable effects

This application is based on a PK-bridge. A model-based exposure comparison, based on a previously developed population PK model, is pivotal evidence to support the benefit-risk of the SC Q3W and SC Q4W regimens.

Comparisons of predicted, simulated, and observed PK data support extrapolation of efficacy and safety from the recommended IV Q3W regimen to the proposed SC Q3W regimen, and from the recommended IV Q2W regimen to the proposed SC Q4W regimen.

In terms of efficacy and safety data, the study PALOMA-2 was designed only to provide supportive efficacy and safety data for the bridging strategy based on population PK modelling and simulation.

The primary objective of the study was to quantify the antitumoral activity of amivantamab SC for the Q3W and Q4W regimens. The study also gave insight over the safety profile of these new amivantamab SC regimen. Acknowledging the drawbacks of the inter-study comparison and lack of comparator arm in PALOMA-2, the data on the activity of SC amivantamab Q3W and Q4W (in combinations with CP and lazertinib, respectively) are in the range of antitumoral activity (ORR and mDOR) observed in the corresponding pivotal studies for the IV regimens. The safety profiles of the SC and IV regimens appear largely comparable with no new safety signals observed.

10.5.2. Balance of benefits and risks

The provided PK comparisons support extrapolation of efficacy and safety from the recommended IV Q3W regimen to the proposed SC Q3W regimen, and from the recommended IV Q2W regimen to the proposed SC Q4W regimen. Hence, the balance of benefits and risks for the proposed posologies is considered positive.

10.6. Benefit-risk conclusions

10.6.1. CHMP conclusions

The overall benefit/risk balance of Rybrevant strengths 2400 mg and 3520 mg solution for injection supporting SC Q3W and SC Q4W administration is considered positive.