EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2024
EMA/373005/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Rybrevant

International non-proprietary name: Amivantamab

Procedure No. EMEA/H/C/005454/II/0011

Marketing authorisation holder (MAH) Janssen-Cilag International N.V.

Note

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

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List of abbreviations

ACP	amivantamab, carboplatin-pemetrexed
ACP-L	amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin is completed)
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
B-R	benefit-risk
CCO	clinical cut off
CHMP	Committee for Medicinal Products for Human Use
CHO	chinese hamster ovary
CP	carboplatin/pemetrexed
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EGFRm NSCLC	locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations
EMA	European Medicines Agency
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
exon 19del	exon 19 deletion
exon 20ins	exon 20insertion
FDA	Food and Drug Administration
FIH	first in human
FOIA	Freedom of Information Act
HR	hazard ratio
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IgG	immunoglobulin G1
ILD	interstitial lung disease
IRR	infusion-related reaction
IV	intravenous
K-M	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
L858R	exon 21 L858R substitution
LACP	lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started C1D1)
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epidermal transition

N/A	not available
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	NCI Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NSCLC-SAQ	NSCLC Symptom Assessment Questionnaire
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
PFS2	PFS after subsequent therapy
PR	partial response
PRO	patient reported outcome
PROMIS-PF	Patient Reported Outcomes Measurement Information System – Physical Function
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2ChD	recommended Phase 2 chemotherapy combination dose
SAE	serious adverse event
SC	subcutaneous
SCP	summary of clinical pharmacology
SmPC	Summary of Product Characteristics
SOC	standard of care
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTF	time to treatment failure
TTSP	time to symptomatic progression
TTST	time to subsequent therapy
US	United States
USM	urgent safety measure
VTE	venous thromboembolic

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 23 November 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including a third-generation EGFR tyrosine kinase inhibitor (TKI) for RYBREVANT, based on the final results from study 61186372NSC3002 (MARIPOSA 2); this is a randomized, open label, multicenter Phase 3 study that compares efficacy and safety of amivantamab in combination with carboplatin and pemetrexed (ACP) with carboplatin and pemetrexed (CP). The primary objective of the MARIPOSA 2 study is to compare efficacy, as demonstrated by PFS, in participants treated with ACP versus CP alone. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.6 and 9 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the EU RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) is requesting an additional year of market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s)

P/0289/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. The request was withdrawn by the MAH

during the procedure as the one year market protection was already granted with procedure EMA/005454/II/10.

Scientific advice

The MAH received Scientific Advice from the CHMP on 20 May 2021 (EMA/SA/0000052936). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Johanna Lähteenvuo

Timetable	Actual dates
Submission date	23 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	16 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
PRAC Outcome	7 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	5 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
Opinion	25 July 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

State the claimed therapeutic indication

The following new indication was proposed to be added in the product information:

Rybrevant is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including a third-generation EGFR tyrosine kinase inhibitor (TKI).

Epidemiology

Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer worldwide (Globocan 2020). It is a major global health concern, with approximately 238,340 new diagnoses annually in the US (SEER 2023), 318,000 in the EU (ECIS 2021), and more than 1.3 million in Asia (Globocan 2020), with the highest reported incidence in Korea and China (Bray 2018, Pakzad 2015). NSCLC accounts for approximately 85% of lung cancers (Schabath 2019), with 5-year survival rates for NSCLC dependent upon on the stage at diagnosis and ranging from 65% for localized cancer to 9% for cancer that has spread to distant locations (ASCO 2023).

Biologic features

Over the past decade, there has been significant advancement in the understanding of the underlying biology of NSCLC, including the identification of multiple 'driver' mutations that can result in a constitutive activation of pro-growth signaling pathways. In patients with metastatic disease, driver mutations are observed in approximately 60% of adenocarcinomas (Herbst 2018).

In patients with NSCLC adenocarcinoma, among the most prevalent of these driver mutations are those that result in the activation of EGFR, which are identified in approximately 15% of these patients in Western populations (Pao 2011), and in up to 40% to 50% of these patients in Asian populations (Jänne 2006). The most frequently identified EGFR mutations, exon 19del and exon 21 L858R substitution mutations, are seen in approximately 85% of patients with NSCLC harbouring activating EGFR mutations (Gazdar 2009, Harrison 2020). Patients with EGFRm NSCLC tend to be younger and healthier than other patients with lung cancer, with a higher prevalence of EGFR mutation also seen in females and non-smokers (Zhang 2016).

Management

The current SOC for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations (EGFRm NSCLC) is a third-generation EGFR TKI, most commonly osimertinib. Despite improved initial disease control as first-line therapy, nearly all patients will develop resistance to third-generation EGFR TKIs and their disease will progress. There are currently no targeted therapies approved for patients with EGFRm NSCLC whose disease has

progressed on or after a third-generation EGFR TKI, although evidence indicates that the disease continues to be heavily dependent on signaling through the EGFR pathway (Remon 2016).

The NCCN and ESMO treatment guidelines for advanced or metastatic NSCLC recommend platinum-based combination chemotherapy regimens, including carboplatin/pemetrexed or cisplatin/pemetrexed for patients with EGFRm NSCLC whose disease has progressed on or after a third-generation EGFR TKI (Hendriks 2023; NCCN 2023; Planchard 2018). While the activity of cisplatin and carboplatin is largely considered to be similar with no associated difference in OS, carboplatin-based regimens, with their improved safety profile, are more often used in the metastatic NSCLC setting (Griesinger 2019, Abernethy 2017). Treatment with carboplatin and pemetrexed after first- or second-generation EGFR TKIs is associated with limited efficacy, with an ORR of approximately 30% and a median PFS of 4-5 months (Mok 2017, Soria 2015). Real world data looking at outcomes for patients with EGFRm NSCLC with disease progression on or after osimertinib, many of whom receive platinum doublet chemotherapy, show a median rwPFS of 3.4 months (Sabari 2022).

Therefore, treatment options for patients with EGFRm NSCLC are limited after treatment with a third-generation EGFR TKI, and there is a high unmet need for additional therapeutics that further control tumor growth.

Table 1: Recommended dosage of Rybrevant every 3 weeks

Body weight at baseline[a]	Rybrevant dose	Schedule	Number of vials
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	4
	1750 mg	Every 3 weeks starting at Week 7 onwards	5
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	5
	2100 mg	Every 3 weeks starting at Week 7 onwards	6

[a] Dose adjustments not required for subsequent body weight changes.

When used in combination with carboplatin and pemetrexed, Rybrevant should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then Rybrevant. See section 5.1 and the manufacturer's prescribing information for dosing instructions for carboplatin and pemetrexed.

2.1.2. About the product

Amivantamab is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumours with activating EGFR mutations such as Exon 19 deletions, L858R substitution, and Exon 20 insertion mutations. Amivantamab binds to the extracellular domains of EGFR and MET. Amivantamab disrupts EGFR and MET signalling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumour growth and progression. The presence of EGFR and MET on the surface of tumour cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

The indication as initially proposed was:

Rybrevant is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor

(EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including a third-generation EGFR tyrosine kinase inhibitor (TKI).

The indication as adopted by the CHMP is:

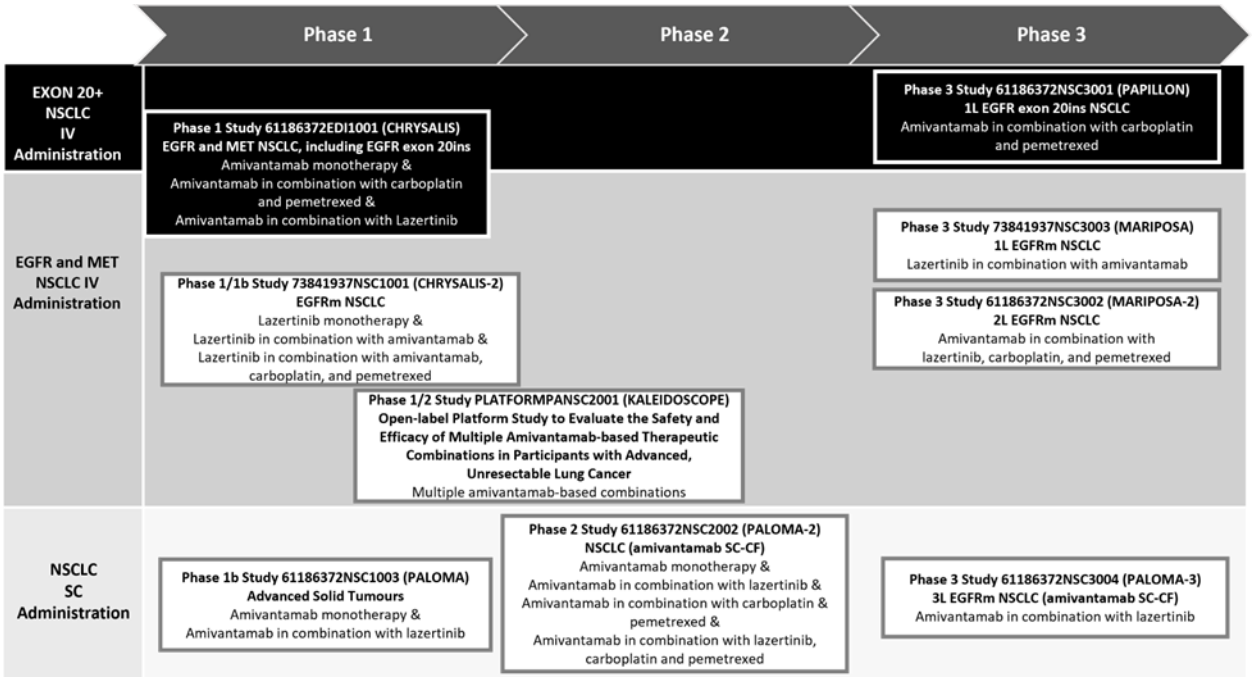
Rybrevant is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant's clinical development program for amivantamab (IV or SC) in NSCLC includes multiple studies in which amivantamab is administered as monotherapy and in combination therapy (see Figure 1). Amivantamab was the first approved targeted therapy for the treatment of EGFR exon 20ins NSCLC, for use after prior therapy with first-line, platinum-based chemotherapy. Based on data from the FIH Study 61186372EDI1001 (hereafter referred to as CHRYSALIS), amivantamab was granted accelerated approval as a monotherapy by the FDA on 21 May 2021 and conditional approval by EMA on 9 December 2021 for patients with EGFR exon 20ins mutations whose disease has progressed on or after platinum-based chemotherapy.

Key efficacy and safety data to support the current proposed product information update for ACP in EGFRm NSCLC are derived from the pivotal MARIPOSA-2 Study (130 participants who received ACP), the supportive Phase 3 Study 61186372NSC3001 (hereafter PAPILLON) (151 participants who received ACP; safety data only), and CHRYSALIS (20 participants who received ACP in the chemotherapy combination cohort).

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



All 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.

Compliance with Regulatory Guidance

A summary of relevant regulatory correspondence between the Applicant and the European Health Authorities, regarding the amivantamab development program is provided in Table 2.

Table 2: Regulatory Correspondence Relevant to Amivantamab in Combination with CP

Date	Regulatory Correspondence/Interaction
May 2021	The CHMP provided Scientific Advice on Study 61186372NSC3002 (MARIPOSA-2) and Janssen's development plans for lazertinib and amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC characterized by EGFR exon 19 deletions or exon 21 L858R substitution mutations whose prior therapy included a third-generation EGFR TKI.
October 2023	The Swedish Medicinal Products Agency pre-submission meeting prior to filing the MARIPOSA-2 study in support of the planned extension of indication submission for the treatment of adult patients with EGFRm NSCLC after failure of prior therapy including a third-generation EGFR TKI.

Phase 3 Scientific Advice

The Applicant sought scientific advice from the CHMP on the Phase 3 MARIPOSA-2 study in May 2021, regarding the development of lazertinib and amivantamab for the treatment of locally advanced or metastatic NSCLC with activating EGFR mutations, more specifically (1) the scientific rationale for development of the combination therapy with carboplatin/pemetrexed, (2) the design of the proposed Phase 3, open-label, randomized Study 61186372NSC3002, and (3) the overall clinical development plan in the proposed population.

The CHMP emphasized the importance of demonstrating the contribution of components from amivantamab and lazertinib. Based on this, a treatment arm evaluating ACP was added to the MARIPOSA-2 study with a randomization ratio of 2:2:1 for LACP, CP, and ACP, respectively. The CHMP also stated that the assessment of PFS according to BICR was supported, taking into account the open-label nature of the study and the proposed secondary endpoints, in general, were considered acceptable.

Rapporteur Pre-submission Meetings

A pre-submission meeting was held with the Rapporteur Agency (Sweden) on 20 October 2023. The main objective of this meeting was to present the topline results of the final analysis of theMARIPOSA-2 study and to seek input from the Rapporteur on the overall regulatory strategy supporting the planned extension of indication submission for amivantamab in the EU.

Overall, the meeting with the Rapporteur identified no barriers to proceed with the Type II variation. In general, the data presented were clear and would be suitable for assessment. Advice provided by the Rapporteur on specific aspects of the data package was taken into consideration and addressed appropriately in the current submission.

2.1.4. General comments on compliance with GLP, GCP

All 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.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application and no changes to the non-clinical information in the SmPC have been proposed.

2.2.1. Ecotoxicity/environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- **Tabular overview of clinical studies**

Table 3*:* Overview of Study Contributing Information to the Summary of Clinical Pharmacology

Study Number	Phase	Population	Amivantamab Dose	Number of Participants Dosed
61186372NSC3002 (MARIPOSA-2)	3	Participants with advanced or metastatic NSCLC with EGFR exon 19del or exon 21 (L858R) substitution mutations, after osimertinib failure	**Arm C: Amivantamab in combination with carboplatin and pemetrexed (ACP, RP2ChD Q3W)** Baseline body weight < 80 kg 1400 mg IV Cycle 1 Day 1/2 (Day 1 = 350 mg, Day 2 = 1050 mg), Day 8, Day 15, and Cycle 2 Day 1 (QW) 1750 mg IV Cycle 3 + Day 1 (Q3W) Baseline body weight ≥ 80 kg 1750 mg IV Cycle 1 Day 1/2 (Day 1 = 350 mg, Day 2 = 1400 mg), Day 8, Day 15, and Cycle 2 Day 1 (QW) 2100 mg IV Cycle 3 + Day 1 (Q3W)	130

2.3.2. Pharmacokinetics

The general absorption, distribution, metabolism, and excretion characteristics, dose proportionality and time dependency of amivantamab administered as monotherapy have been described in procedure number EMEA/H/C/005454/0000.

The clinical pharmacology data, relevant for the current application, originates from a single arm (Arm C) in an ongoing study (MARIPOSA-2) evaluating amivantamab in combination with standard of care

carboplatin and pemetrexed (CP) in participants with exon 19del or exon 21sub NSCLC. The PK data cut-off date for the pivotal MARIPOSA-2 study was 31 May 2023.

Bioanalytical methods

A validated ECLIA on the MSD platform was used to determine amivantamab PK concentrations in human serum samples with a lower limit of quantification of 0.32 µg/mL at a 1/40 dilution.

A validated sensitive, drug and target tolerant ECLIA method on the MSD platform was used to assess ADAs to amivantamab in human serum samples.

Pharmacokinetic data analyses

Methods

The PK data analyses were based on serum amivantamab concentrations of samples obtained from participants treated with ACP in Arm C of the MARIPOSA-2 study.

In the MARIPOSA-2 study, for Arm C, serum samples were collected on Day 1 of Cycle 1 at predose and EOI, Day 2 of Cycle 1 at predose, EOI, and Day 1 of Cycles 2, 3, 5, 7, 10, 13 and 17, at predose and EOI; and at end-of-treatment.

The population PK analysis was performed using a previously developed nonlinear mixed effects model, hereafter referred to as the *PAPILLON popPK model*, using standard methodology and adherence to regulatory guidelines for population PK analyses (see EMEA/H/C/005454/II/0010).

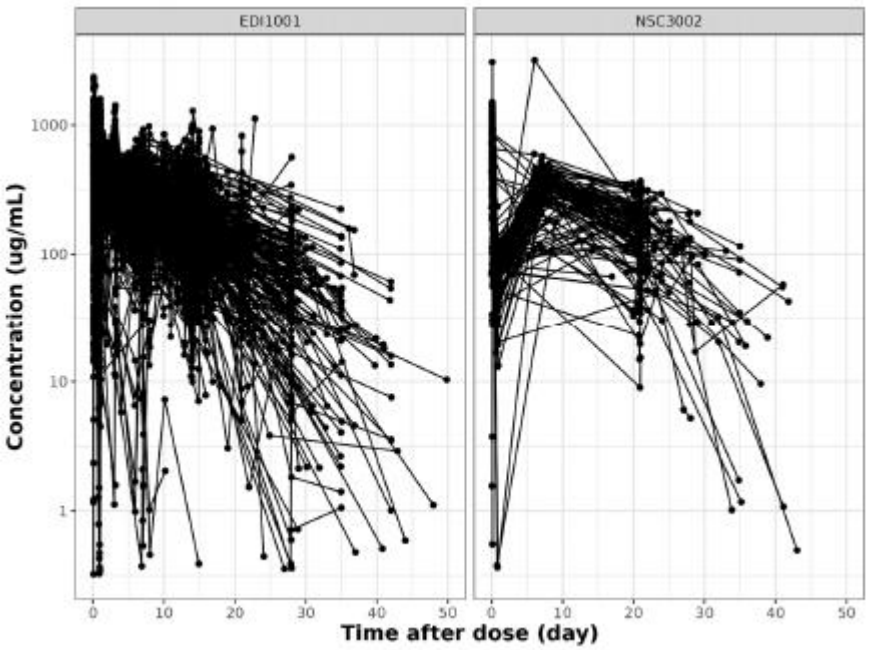
Population pharmacokinetic analysis

A population PK analysis was performed using the nonlinear mixed effect modelling software NONMEM (version 7.4.3). The PAPILLON popPK model was used to describe PK data from the MARIPOSA-2 study. An empirical Bayesian estimation approach (FOCE INTERACTION MAXEVAL=0) was used to predict individual PK profiles and individual PK parameters for the MARIPOSA-2 subjects. This approach was validated through conventional numerical and graphical model diagnostics.

Data

The MARIPOSA-2 PK dataset included 1106 amivantamab PK concentrations from 123 participants with EGFR mutated NSCLC. Individual amivantamab serum concentrations versus time after the previous dose, stratified by study (together with phase 1 study CHRYSALIS), are shown in **Figure *2*** below. Since the percentage of posttreatment samples below the limit of quantification (BLQ) was low (0.9%), the BLQ samples were omitted from the analysis.

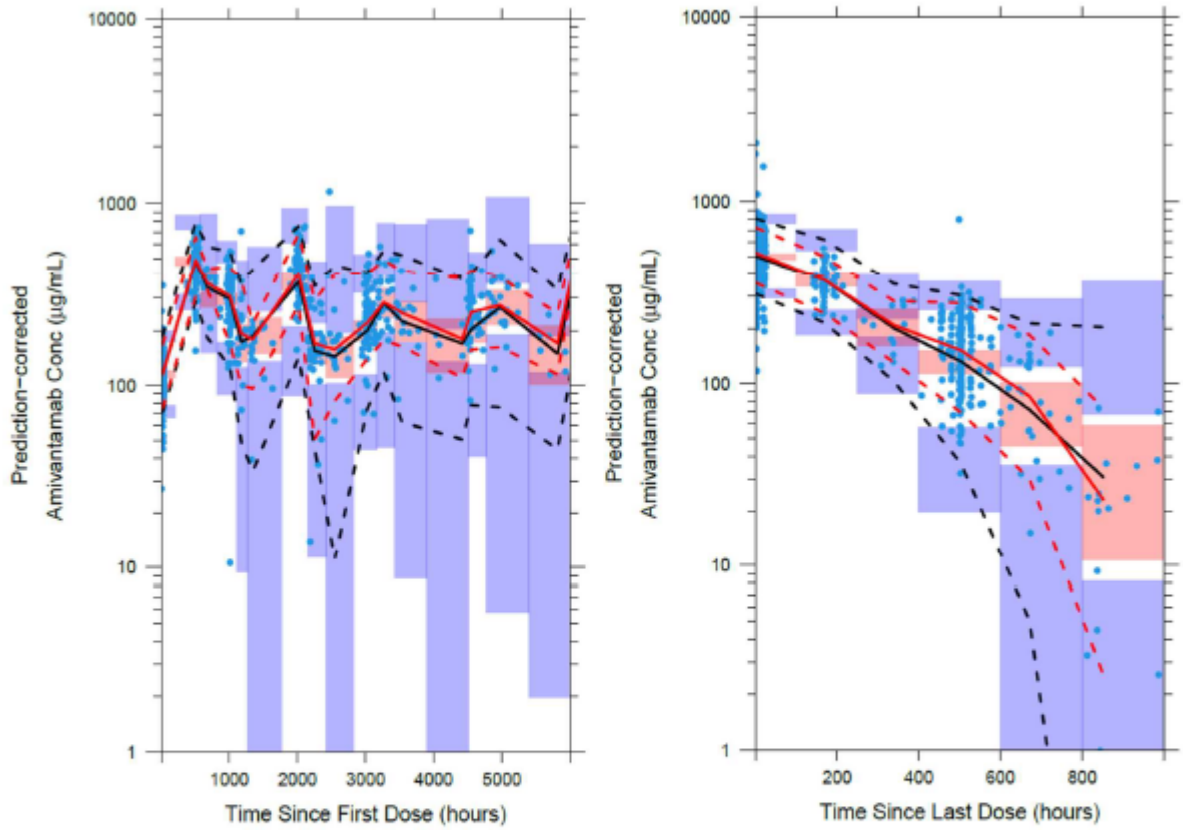
Figure 2: Scatter plot of amivantamab serum concentration versus time after previous dose stratified by study (EDI1001 = CHRYSALIS; NSC3002 = MARIPOSA-2).



Model

The PAPILLON popPK model of amivantamab has been described in procedure number EMEA/H/C/005454/II/0010. In short, it is a two-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination. The model is parameterized in terms of linear CL, V_1, Q, V_2, V_{max}, and K_m. The final model included body weight, sex, age, and albumin as covariates on CL, body weight and sex as covariates on V_1, and body weight as a covariate on V_2 (shared scaling exponent for V_1 and V_2). No population parameter estimates were reassessed in this application. Prediction corrected visual predictive checks (pcVPCs) for the MARIPOSA-2 data are presented in Figure 3. Summary statistics of individual (secondary) PK parameters, derived based on post hoc parameter estimates of participants in MARIPOSA-2, are presented in Table 4.

Figure 3: Prediction corrected visual predictive checks for the MARIPOSA-2 predictions from the PAPILLON population PK model.



CI=confidence interval; Conc=concentration; PK=pharmacokinetics; popPK=population pharmacokinetics.
Points are prediction-corrected observed concentrations; solid red lines represent the median and dashed red lines represent 5th and 95th percentiles of the prediction-corrected observed values; solid black lines represent the median and dashed black lines represent 5th and 95th percentiles of the prediction-corrected simulated values. Orange and blue shaded areas represent the 95% CI of the median and 5th and 95th percentiles of the prediction-corrected simulated concentrations based on 1,000 population PK simulations, respectively.

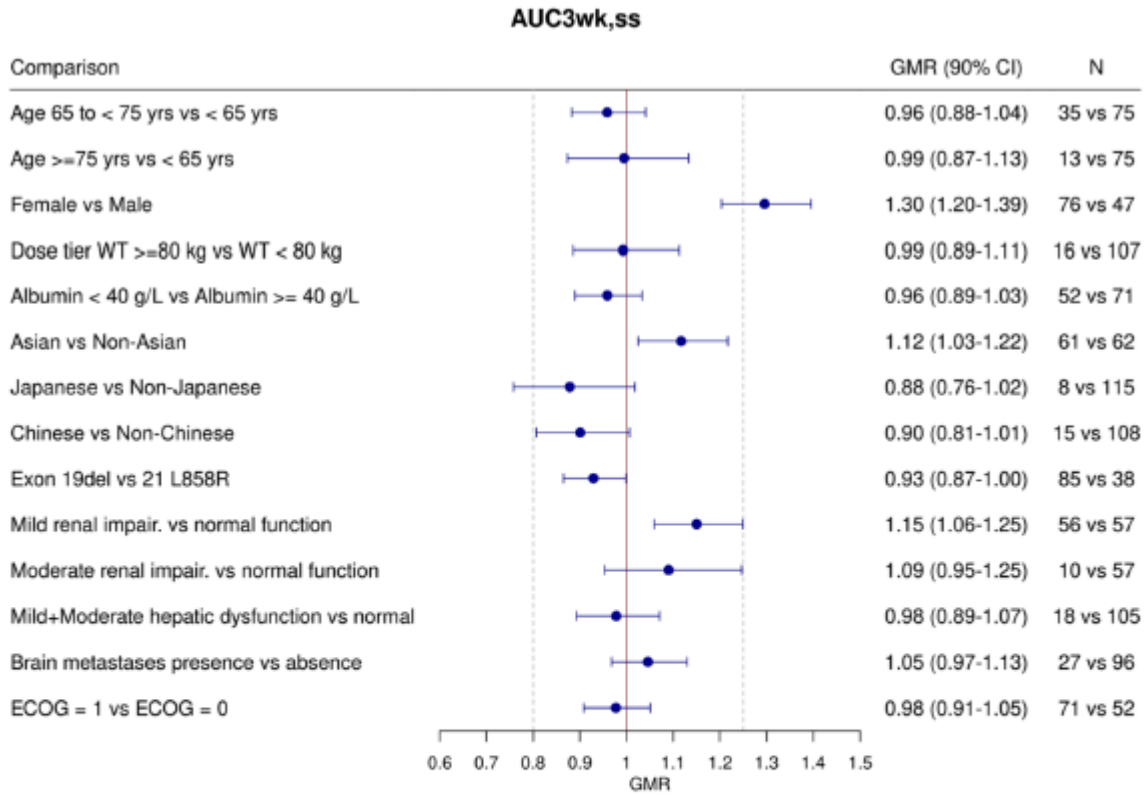
Table 4: Summary of (secondary) PK parameters derived based on post hoc parameter estimates of participants in MARIPOSA-2.

	MARIPOSA-2 (N=123)
T½ (day)	
Mean (SD)	14.7 (3.6)
Median [Min, Max]	14.6 [7.9, 24.2]
Geometric mean (Geometric CV%)	14.3 (24.8)
Total V (L)	
Mean (SD)	5.24 (1.17)
Median [Min, Max]	5.19 [2.70, 8.54]
Geometric mean (Geometric CV%)	5.12 (22.2)
CL (L/day)	
Mean (SD)	0.264 (0.0819)
Median [Min, Max]	0.243 [0.138, 0.578]
Geometric mean (Geometric CV%)	0.253 (29.0)

CL=linear clearance; CV=coefficient of variation; Max=maximum; Min=minimum; PK=pharmacokinetic(s); Q=intercompartment clearance; SD=standard deviation; T½=terminal half-life, the beta half-life of a 2-compartment model calculated using CL, Q, V1 and V2; V=total volume of distribution (V1+V2); V1=volume of distribution in the central compartment; V2=volume of distribution in the peripheral compartment.

A comparison of amivantamab steady-state exposure parameters ($AUC_{3weeks,ss}$ and $C_{eoi,ss}$) was conducted in specific subgroups using forest plots, i.e., by presenting the estimated GMR and its 90% CI for the exposure metrics for a given covariate stratum relative to the reference stratum. The simulation was done using the individual post hoc PK parameters for the PK population of the MARIPOSA-2 study, assuming all participants received the scheduled doses of the recommended Phase 2 chemotherapy combination dose (RP2ChD) regimen. Subgroups were considered to have comparable exposure if the estimated GMR and 90% CI limits were not entirely outside the 80%–125% range. To accommodate the correlation among the covariates, the GMR was adjusted with other covariates, where the effect of each covariate was estimated simultaneously using a multivariate regression model. The forest plot of $AUC_{3weeks,ss}$ with adjusted GMR is presented in Figure 4. The trend for $C_{eoi,ss}$ was similar to that of $AUC_{3weeks,ss}$.

Figure 4: Multivariate Forest Plot of $AUC_{3weeks,ss}$ (Top) and $C_{eoi,ss}$(Bottom) Based on the RP2ChD Q3W regimen (MARIPOSA-2 PK Population)



$AUC_{3weeks,ss}$=area under the concentration-time curve during the 3-week dosing interval at steady-state; BSA=body surface area; CI=confidence interval; CKD-EPI eGFR=Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; ECOG=Eastern Cooperative Oncology Group performance status; GFR=glomerular filtration rate; GMR=geometric mean ratio; PK=pharmacokinetic(s); N=number of participants; Q3W=every 3 weeks; RP2ChD=recommended Phase 2 chemotherapy combination dose; vs=versus; WT=weight; yrs=years.

Renal function is evaluated by absolute GFR (CKD-EPI eGFR corrected by ×BSA/1.73; normal: ≥90 mL/min, mild: 60 to <90 mL/min, moderate: 30 to <60 mL/min); hepatic function is evaluated by National Cancer Institute Organ Dysfunction Working Group criteria.

Filled circles and lines represent GMR and 90% CI; vertical dashed lines represent 80% (left) and 125% (right). Post hoc PK parameters of the MARIPOSA-2 PK population were used in the simulations (N=123).

Immunogenicity data analysis

Method

The possible generation of anti-amivantamab antibodies was assessed in participants, from the MARIPOSA-2 study, treated with ACP. The assessment of immunogenicity for amivantamab utilized a tiered assay approach, comprising screening, specificity (confirmatory), and titer assays to detect binding antibodies to amivantamab.

In the MARIPOSA-2 study, serum samples were collected prior to the administration of amivantamab on Day 1 of Cycles 1, 2, 3, 5, 7, 10, 13, and 17, and at the end of treatment visit.

Participants with at least 1 positive sample at any timepoint after exposure to amivantamab were classified as positive for ADA. If a participant had detectable ADAs in a baseline (predose) sample, the participant was considered ADA-positive only if the peak titer of the post-treatment samples was ≥2-fold higher than the titer of the baseline sample.

Participants were designated as negative when there was no positive sample at any timepoint evaluated after exposure to amivantamab. If a participant had detectable ADA in a baseline (predose) sample, the participant was considered ADA-negative if no post-treatment samples represented a ≥ 2-fold increase in the titer relative to the baseline sample.

Due to the low risk for immunogenicity and the low incidence of samples positive for antibodies to amivantamab, neutralizing antibodies were not evaluated.

Results

The immunogenicity analysis population in the MARIPOSA-2 study consisted of 119 participants who had appropriate samples. All subjects in the MARIPOSA-2 study tested negative for treatment-emergent antibodies to amivantamab (Table 5).

Table 5: Summary of the incidence of immunogenicity to amivantamab in participants in the MARIPOSA-2 study.

Study number	Amivantamab doses tested	Participants with appropriate samples[a]	Participants *positive* for treatment-emergent antibodies to amivantamab[b]	Participants *negative* for treatment-emergent antibodies to amivantamab[c]
61186372NSC3002 (MARIPOSA-2)	**Arm C: Amivantamab in combination with carboplatin and pemetrexed (ACP, RP2ChD Q3W)** Baseline body weight < 80 kg 1400 mg IV Cycle 1 Day 1/2 (Day 1 = 350 mg, Day 2 = 1050 mg), Day 8, Day 15, and Cycle 2 Day 1 (QW) 1750 mg IV Cycle 3 + Day 1 (Q3W) Baseline body weight ≥ 80 kg 1750 mg IV Cycle 1 Day 1/2 (Day 1 = 350 mg, Day 2 = 1400 mg), Day 8, Day 15, and Cycle 2 Day 1 (QW) 2100 mg IV Cycle 3 + Day 1 (Q3W)	119[d]	0 (0.0%)	119 (100.0%)

[a] Subjects with appropriate samples had 1 or more samples obtained after their first amivantamab administration.
[b] Subjects positive for treatment-emergent antibodies to amivantamab includes all subjects who were positive (treatment-boosted or treatment-induced) at any time after their first amivantamab administration. Subjects with baseline positive samples and without 2-fold increased titer after treatment are not considered treatment-boosted.
[c] Includes all subjects with negative samples at all times and excludes subjects who were treatment-emergent positive at any time.
[d] For two subjects, all ADA samples contained drug concentrations greater than the assay drug tolerance limit (> 400 µg/mL) and were excluded.

Pharmacokinetic interaction studies

No formal clinical drug-drug interaction studies were performed, and no interactions with concomitant medications are expected.

2.3.3. Pharmacodynamics

Details on the pharmacodynamics (PD) of amivantamab monotherapy are included in procedure number EMEA/H/C/005454/0000. No new PD data are available.

2.3.4. PK/PD modelling

Exposure-response (E-R) analyses were conducted for the efficacy and safety results from MARIPOSA-2. The E-R population included 123 participants who received amivantamab in combination with chemotherapy (ACP) with available efficacy/safety results and individual exposures, derived using each participant's actual dose records, covariates, and post hoc PK parameters (from the population PK analysis).

The E-R analysis for efficacy focused on the primary endpoint PFS evaluated by BICR (hereafter referred to as PFS). The E-R analysis for safety included selected common (incidence ≥ 10%) treatment-emergent adverse events (TEAEs) related to amivantamab administration. Analyses were performed with R (version ≥ 3.6.2).

Efficacy

The E-R relationships for PFS (time-to-event endpoint) were evaluated with Kaplan-Meier plots stratified by exposure tertiles using the log-rank test. Covariates were explored further graphically or using Cox-PH modelling if exploratory analyses indicated a trend with exposure or if covariates were imbalanced across exposure groups.

No apparent E-R trend for PFS was observed across exposure tertiles, using the log-rank test and univariate Cox-PH. EGFR mutation type (exon 21 L858R vs exon 19 del) appeared to correlate with PFS. Although females appeared to have ~30% higher PK exposures than males, PFS was similar among males and females.

A multivariate Cox-PH analysis was performed aiming to adjust the covariate effects of EGFR mutation type. After accounting for the covariate effect of EGFR mutation type, the PK metrics still did not correlate with PFS.

Safety

The E-R relationships for all safety endpoints (binary endpoints) were evaluated using bar plots, stratified by exposure quartiles.

Participants with higher $C_{eoi,1st}$ appeared to have lower rate of IRR (any grade). This could be explained by dose interruptions in participants with IRR leading to lower concentrations at the EOI.

Incidence of hypoalbuminemia increased slightly with the increase of amivantamab exposure. This adverse event is consistent with the known safety profile of amivantamab monotherapy.

2.3.5. Discussion on clinical pharmacology

PK

In the current application, the pharmacokinetic (PK) analysis is descriptive, with population PK modelling applied to characterize the PK of amivantamab when administered in combination with carboplatin and pemetrexed (CP) in subjects with either exon 19del or exon 21sub non-small cell lung cancer (NSCLC).

The previously developed popPK-model for amivantamab, with the same dosing regimen as in the current application, has been assessed in EMEA/H/C/005454/II/0010. The new indication in the current application is not expected to have any impact on the pharmacokinetic behaviour of amivantamab, compared to the indication for which the popPK model was originally developed.

The bioanalytical and immunogenicity methods were assessed during procedure EMEA/H/C/005454/0000 and were found acceptable. Both the bioanalytical and immunogenicity methods have since been transferred to another site where the methods were acceptably re-validated and the bioanalytical method also cross-validated to the previous site (EMEA/H/C/005454/II/0010).

The PAPILLON popPK model (assessed in EMEA/H/C/005454/II/0010), developed on pooled monotherapy and combination therapy data from the CHRYSALIS (Phase 1) and PAPILLON (Phase 3) studies, was used together with the MARIPOSA-2 PK data to predict individual PK profiles and individual PK parameters for the MARIPOSA-2 subjects. The model is a two-compartment model with parallel linear and Michaelis-Menten nonlinear elimination pathways, parameterized in terms of linear CL, V_1, Q, V_2, V_{max}, and K_m. The model includes body weight, sex, age, and albumin as covariates on CL, body weight and sex as covariates on V_1, and body weight as a covariate on V_2 (shared scaling exponent for V_1 and V_2). No population parameters were re-estimated in this application. Model diagnostics, as well as summary statistics of individual (post hoc) parameter estimates, confirmed that the PAPILLON popPK model described the PK data from MARIPOSA-2 adequately. This was expected since the new indication was not anticipated to have a significant impact on PK. The same applies to the forest plot, which overall is similar to the forest plot presented for subjects in PAPILLON. The forest plot shows that females had an approximately 30% higher exposure than males, consistent with previous findings of amivantamab PK. None of the observed differences in exposure, across subpopulations, are considered clinically relevant.

The incidence of anti-drug antibodies (ADAs) was low. The small number of participants who were confirmed positive for antibodies to amivantamab precludes drawing conclusions regarding the impact of antibodies on PK, efficacy, and safety.

PD

Details on the pharmacodynamics (PD) of amivantamab monotherapy can be found in procedure number EMEA/H/C/005454/0000. No new PD data are available. This is acceptable. Conclusions on clinical pharmacology

The information on clinical pharmacology is based on data from the ongoing MARIPOSA-2 study. Population PK modelling has been applied to characterise the PK of amivantamab when administered in combination with carboplatin and pemetrexed in subjects with advanced non-small cell lung cancer with exon 19del or exon 21sub mutations.

Overall, the clinical pharmacology data submitted support this extension of indication.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The detailed clinical pharmacology information for amivantamab is described in previous submissions (EMEA/H/C/005454/0000 and EMEA/H/C/005454/II/0010). ACP was first evaluated in the Part 1 chemotherapy combination cohort in the Phase 1 CHRYSALIS study where the RP2ChD was established based on PK, pharmacodynamic, safety, and efficacy data. Subsequently, the RP2ChD dosing regimen, as confirmed in the CHRYSALIS chemotherapy combination cohort was used in the Phase 3 pivotal MARIPOSA 2 study.

The proposed regimen (RP2ChD Q3W) was selected to accommodate the chemotherapy Q3W dosing schedule and to achieve Ctrough at the end of the once weekly dosing period and at steady state that

are comparable to the approved Q2W dosing regimen. The regimen for ACP in MARIPOSA-2 is identical to the one approved for PAPILLON.

2.4.2. Main study(ies)

A tabular overview of the studies supporting the evaluation of efficacy of ACP is provided below.

Table 6: Overview of the Clinical Studies Included in the SCE

Study number/name[a] Cohort (if applicable) Status SCE data cutoff	**Study Design**	**Treatment regimen**	**Study Population/Sample Size (Actual)**
61186372NSC3002 MARIPOSA-2 ongoing 10 July 2023	A Phase 3, randomized, open-label study. The SCE focuses on two arms: [b] Arm C: treatment with ACP. Arm B: treatment with CP.	Arm C (ACP): Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) by IV infusion on Cycle 1 Days 1/2,[c] 8, and 15, and Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3. Pemetrexed 500 mg/m^2 (with folic acid and vitamin B12 vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression. Carboplatin AUC 5, up to 750 mg, on Day 1 of each 21-day cycle, for up to 4 cycles. Arm B (CP): Pemetrexed 500 mg/m^2 (with folic acid and vitamin B12 supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression. Carboplatin AUC 5, up to 750 mg, on Day 1 of each 21-day cycle, for up to 4 cycles	**Study Population:** Participants at least 18 years of age with locally-advanced or metastatic NSCLC characterized by either EGFR exon 19del or exon 21 L858R mutations whose disease progressed on or after osimertinib monotherapy. **Sample Size:** Arm C (ACP): N=131 Arm B (CP): N=263
61186372EDI1001[d, e] CHRYSALIS **Chemotherapy Combination Cohort** Ongoing 15 November 2022	A Phase 1, FIH, open-label, dose escalation study in subjects with advanced NSCLC. After confirmation of the safety of the regimen, a total of 20 participants with	**ACP:** Participants with body weight <80 kg: amivantamab 1,400 mg by IV infusion once weekly up through Cycle 2 Day 1, then 1,750 mg on Day 1 of	**Study Population:** At least 18 years of age. Histologically or cytologically confirmed NSCLC that was metastatic or unresectable. No specific driver mutation was required.

Table 6: Overview of the Clinical Studies Included in the SCE

Study number/name[a] Cohort (if applicable) Status SCE data cutoff	Study Design	Treatment regimen	Study Population/Sample Size (Actual)
	advanced NSCLC (no specific driver mutation required) were enrolled in this cohort and treated with ACP in a 21-day cycle.	each 21-day cycle, starting with Cycle 3. Participants with body weight ≥80 kg: amivantamab 1,750 mg by IV infusion once weekly up through Cycle 2 Day 1, then 2,100 mg on Day 1 of each 21-day cycle, starting with Cycle 3. Carboplatin and pemetrexed were administered in accordance with local guidelines and labeling.	**Sample Size** Chemotherapy combination cohort: N=20 participants[f]

AUC=area under the curve; AUC 5=area under the concentration-time curve 5 mg/mL per minute; ACP=amivantamab combined with standard of care carboplatin-pemetrexed; CP=standard of care carboplatin-pemetrexed; EGFR=epidermal growth factor receptor; exon 19del=exon 19 deletion; FIH=first-in-human; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed; NSCLC=non-small cell lung cancer.
[a] All 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.
[b] The MARIPOSA-2 study included 3 treatment arms. In addition to ACP (Arm C) and CP (Arm B), the study also evaluated the addition of lazertinib to the ACP treatment regimen (Arm A). As the present regulatory submission is focused on the ACP combination, only information regarding the ACP and CP arms is included in this table and SCE..
[c] The first dose was split across Days 1 and 2, with 350 mg administered on Day 1 and 1,050 mg (<80 kg) or 1,400 mg (≥80 kg) administered on Day 2.
[d] This study consists of different cohorts in which participants either receive amivantamab and lazertinib combination therapy or amivantamab and carboplatin/pemetrexed combination therapy (Part 1 chemotherapy combination cohort). Only information regarding the chemotherapy combination cohort is included in this table and the SCE.[e].
[f] Nineteen of the 20 participants had baseline RECIST measurable disease.

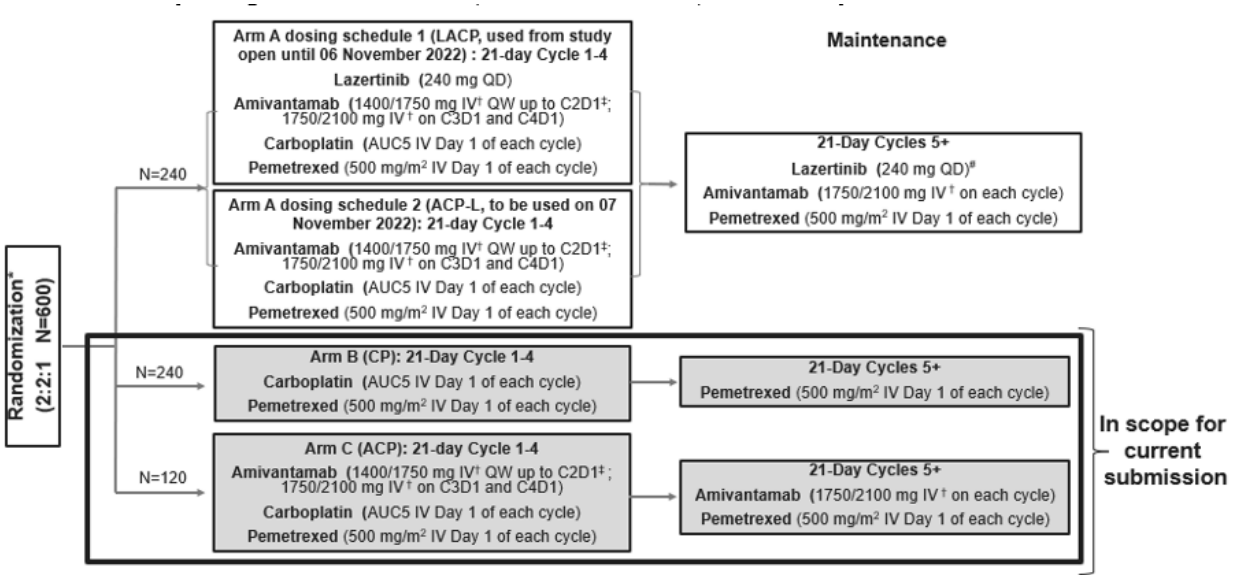
MARIPOSA-2 (Pivotal study)

The pivotal study for the current application for extension of indication is MARIPOSA-2, an ongoing, randomized, open-label, multicentre Phase 3 study that compares the efficacy and safety of ACP (Arm C) versus CP (Arm B) in participants with EGFRm NSCLC whose disease has progressed on or after treatment with osimertinib.

The study was initiated on 17 November 2021 (ie, the date that the first participant was screened) and is currently ongoing. This clinical study report describes data through a clinical cutoff date (CCO) of 03 May 2023 (ie, the date of the last observation recorded as part of the database for the final analysis of the primary endpoint).

A schematic representation of the MARIPOSA-2 study design is shown in Figure below:

Figure 5 : Study design: Mariposa-2 (Main study)



ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin treatment is completed); AUC=area under the concentration-time curve; C#D#=Cycle # Day #; IV=intravenously; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started C1D1); QD=once daily; QW=once weekly.

Arm A Dosing schedule 2 (ACP-L) started on 7 November 2022.

Note: the treatment arms in scope for the SCE are presented in the grey shaded boxes.

* Stratification factors: osimertinib line of therapy (first-line versus second-line), history of brain metastases (yes versus no), Asian race (yes versus no)

† Doses shown by body weight (<80 kg/≥80 kg)

‡ Cycle 1: Days 1/2 (split dose), 8, and 15; Cycle 2: Day 1

\# Lazertinib for participants receiving dosing schedule 2 in Arm A may start sooner if carboplatin discontinued earlier than Cycle 4.

Study design

In the original design of MARIPOSA-2 proposed to health authorities, the primary objective was to compare the combination of lazertinib, amivantamab, carboplatin and pemetrexed (all beginning Cycle 1 Day 1, LACP dosing, Arm A) versus CP (Arm B). This combination had been previously evaluated in the ongoing Phase 1/1b 73841937NSC1001 (hereafter CHRYSALIS-2) study (Marmarelis 2022).

At the time of the initial meetings with health authorities (May 2021), the importance of demonstrating the contribution of components from amivantamab and lazertinib was emphasized. Based on this feedback, a treatment arm evaluating ACP (Arm C) was added to MARIPOSA-2 with a randomization ratio of 2:2:1 for LACP, CP, and ACP, respectively (n=500).

The initial protocol for MARIPOSA-2 study (9 July 2021) had besides the hypothesis testing of LACP versus CP, also a provision for hypothesis testing for treatment effect within a biomarker-driven subgroup. The same biomarker assessed in the CHRYSALIS-2 study was not confirmed to support this analysis; therefore, the plan for this testing was removed. As a result of the removal of the biomarker analysis, as well as emerging data from the CHRYSALIS study that demonstrated meaningful efficacy for the ACP regimen, the decision was made to amend MARIPOSA-2 to repurpose the alpha allocated for the biomarker subgroup analysis to implement a dual primary hypothesis to independently evaluate the efficacy of both the LACP/ACP-L (ACPL is described below) and ACP treatment arms versus CP.

To provide sufficient power for these dual primary hypotheses testing, the Applicant increased the total study enrolment number from 500 to 600 while retaining the 2:2:1 randomization scheme. To support the formal statistical comparison of ACP versus CP (in addition to LACP/ACP-L versus CP), the Applicant planned a graphical testing strategy between these two hypotheses to control an overall familywise Type I error rate of 0.05 (2sided); the primary endpoint of PFS was initially tested at a two-sided alpha of 0.03 for ACP vs CP and at a two-sided alpha of 0.02 for LACP/ACP-L vs CP.

The decision to amend the protocol was made on 19 May 2022, and was implemented in Protocol Amendment 3 (finalized on 27 June 2022); the change was based purely on factors external to MARIPOSA-2. As of 19 May 2022, approximately 59 participants across the study had completed a disease evaluation, and the Applicant had only received blinded data from the BICR vendor on 12 of these participants. The applicant states that it is standard process to not review aggregated data by treatment arm while the study is ongoing, even in open-label studies such as MARIPOSA2.

During the 04 November 2022 IDMC meeting review of safety data, the Applicant was notified of an imbalance observed in SAE, related SAE, and Grade 4 AE incidence for participants receiving LACP compared with CP. The majority of these AEs were toxicities typically associated with the use of chemotherapy, i.e., haematologic toxicities (e.g., neutropenia, thrombocytopenia, and opportunistic infections due to immunosuppression from chemotherapy) and gastrointestinal toxicities (e.g., nausea and stomatitis).

Based on these findings, a USM was implemented to delay lazertinib administration until Cycle 5 Day 1, or earlier if carboplatin was discontinued prior to Cycle 4. This new dosing schedule for Arm A (ACP-L dosing) was formalized in Amendment 5 of the protocol (finalized on 25 November 2022). In Arm A, 166 participants were treated based on the LACP dosing schedule and 97 participants were treated based on the ACP-L dosing schedule.

No changes were made regarding the randomization ratio, nor were any changes made to the ACP or CP arms of the trial.

In addition, an extension cohort was added to the study in Protocol Amendment 6 (finalized 22 December 2022) to further characterize the safety and efficacy of the ACP-L dosing schedule; the extension cohort includes approximately 90 additional participants randomized between ACP L and ACP treatment arms (2:1 randomization, approximately 60 and 30 participants in each arm, respectively). Participants enrolled in the extension cohort were not included in the primary analysis for the main study and will be analyzed separately. Follow-up for the extension cohort is ongoing and the primary analysis for this cohort has not been conducted. No changes to the design or statistical analysis plan were made at this time.

Due to the USM and dosing schedule change implemented in Arm A, participants receiving ACP-L in the main study and the extension cohort have limited follow-up at the time of CCO. As a result, data from Arm A (LACP/ACP-L) are not in scope for the current Type II variation. The Applicant will evaluate available data on ACP-L once mature and plans to submit these data in a future application if warranted.

Methods

This is an ongoing, randomized, open-label, multicentre Phase 3 study to compare the efficacy and safety of ACP (Arm C) versus CP (Arm B) and LACP/ACP-L (Arm A) versus CP (Arm B) in participants with EGFR-mutated locally advanced or metastatic non-squamous NSCLC who have disease progression on or after treatment with osimertinib.

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

After screening and enrolment, eligible participants were randomly assigned to study treatment in a 2:2:1
ratio (Arms A:B:C). Randomization was stratified by osimertinib line of therapy (first-line vs second-line),
history of brain metastases (yes vs no), and Asian race (yes vs no).

The Treatment Phase for each participant started at Cycle 1 Day 1 and continued in 21-day cycles until the End of Treatment visit (approximately 30 days after the last dose of study treatment). Participants were to discontinue upon documented disease progression (using RECIST v1.1) confirmed by BICR, or if they met another criterion for discontinuation of study treatment. Participants who discontinued assigned study treatment for any reason were followed for subsequent anticancer therapy, disease status, survival, and symptomatic progression in the Follow-up phase.

An IDMC was commissioned for this study to periodically review safety and tolerability data.
It should be noted that the treatment schedule in Arm A was modified during the study. At the IDMC meeting on 04 November 2022, the IDMC noted an imbalance in SAE, related SAE, and Grade 4 AE incidence affecting patients in Arm A treated with the combination of lazertinib, amivantamab, carboplatin
and pemetrexed all beginning on cycle 1 day 1 (LACP dosing) more than patients in the CP arm (Arm B).

Based on these findings, a USM was implemented to delay lazertinib administration until Cycle 5 Day 1, or earlier if carboplatin was discontinued prior to Cycle 4. Any patient receiving LACP during the first 4 cycles of treatment as of 07 November 2022 was advised to hold lazertinib immediately, with a plan to restart Cycle 5 Day 1, or earlier if carboplatin was discontinued prior to Cycle 4. This new dosing schedule for Arm A (ACP-L) was formalized in Amendment 5 of the protocol. An open-label randomized extension cohort was added to the study in Protocol Amendment 6 to further characterize the safety and efficacy of the ACP-L dosing schedule versus ACP. Data from Arm A (LACP/ACP-L) were pooled for all analyses presented in the current CSR.

Study participants

Key inclusion criteria were as follows:

Participants must have:

-histologically or cytologically confirmed, locally advanced or metastatic, non-squamous NSCLC, characterized at or after the time of locally advanced or metastatic disease
diagnosis by either an EGFR exon 19 deletion or an EGFR exon 21 L858R substitution mutation
-measurable disease according to RECIST v1.1
-ECOG performance status 0 or 1
-adequate organ and bone marrow function
-Participants must have had disease progression on or after osimertinib monotherapy as the most recent line of treatment, 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 with a history of brain metastases must have had all lesions treated as clinically indicated (i.e., no current indication for further definitive local therapy)

Key exclusion criteria were as follows:

-Participants were to be excluded if they received prior systemic anticancer treatment in the locally advanced or metastatic setting, or in the adjuvant setting, for the same non-squamous NSCLC intended for treatment in the study aside from those treatments allowed above. Participants who received either neoadjuvant and/or adjuvant treatment were eligible if progression to locally advanced or metastatic disease occurred at least 12 months after the last dose of such therapy with disease progression on or after osimertinib in the locally advanced or metastatic setting.

Treatments

Study treatment was administered open-label, without blinding, in 21-day cycles until disease progression or until the participant met another criterion for discontinuation of study treatment. Continuation of study treatment after BICR-confirmed disease progression by RECIST v1.1 was allowed after approval from the Medical Monitor, if the investigator believed the participant was deriving clinical benefit.

Relevant study treatment for the current application:

Arm B (CP):

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

• Pemetrexed 500 mg/m2 (with folic acid and vitamin B12 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

Arms C (ACP):

• Amivantamab by IV infusion in 21-day cycles:

– 1,400 mg (1,750 mg if body weight ≥80 kg) on Cycle 1 Days 1/2 (ie, the first dose was split across Days 1 and 2, as described above), 8, and 15, and Cycle 2 Day 1

– 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3

• Carboplatin and pemetrexed as in Arm B

Objectives/endpoints

Primary Objective/Endpoint

The primary efficacy endpoint for the MARIPOSA-2 study in scope for this submission was the assessment of PFS (by BICR using RECIST v1.1) in participants treated with ACP versus CP, where PFS was defined as the time from randomization until the date of objective disease progression or death, whichever came first. Investigator-assessed PFS was evaluated as a sensitivity analysis.

The dual primary hypotheses tested in participants with osimertinib-relapsed EGFR-mutated locally advanced or metastatic NSCLC were initially that:
• ACP would demonstrate superior progression-free survival (PFS) compared with CP
• LACP/ACP-L would demonstrate superior progression-free survival (PFS) compared with CP

Secondary Objectives/Endpoints

Secondary objectives of the MARIPOSA-2 study were:

To further assess the clinical benefit of ACP versus CP as measured by the following endpoints:

ORR (by BICR); DOR (by BICR); OS; Intracranial PFS (by BICR); Intracranial ORR (by BICR); Intracranial DOR (by BICR); Time to intracranial disease progression (by BICR); TTST; PFS2 (by investigator assessment); TTSP.

To assess health-related quality of life and disease-related symptoms in participants treated with ACP versus CP:

NSCLC-SAQ assesses symptoms of advanced NSCLC; EORTC-QLQ-C30 measures cancer patients' functioning for all cancer types; PROMIS-PF assesses physical function, including upper, central, and lower extremity functions and instrumental activities of daily living.

Table 7: Overview of Primary and Secondary Endpoint Analyses

Primary Endpoint	**Definition**	**Analysis and presentation of results**
Progression Free Survival (PFS)	The time from randomization until the date of objective disease progression or death, whichever comes first, based on BICR using RECIST v1.1. Participants who have not progressed or have not died at the time of analysis will be censored at their last evaluable RECIST v1.1 assessment date.	• Analyzed using a log-rank test, stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no). • The HR for PFS was calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test. The Kaplan- Meier method was used to estimate the distribution of PFS by treatment group.
Secondary Endpoint		
Objective Response Rate (ORR) (by BICR)	The proportion of participants who achieve either a CR or PR, as defined by BICR using RECIST v1.1.	• Analyzed using a logistic regression model stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes vs no), and Asian race (yes vs no). • Results presented in terms of an odds ratio together with its associated 95% CI and corresponding p-value.
Duration of Response (DOR) (by BICR)	The time from the date of first documented response (CR or PR) until the date of documented progression, as assessed by BICR, or death, whichever comes first.	• A Kaplan-Meier plot and median DOR with 95% confidence interval (calculated from the Kaplan-Meier estimate) were presented by treatment arm.
Overall Survival (OS)	The time from the date of randomization until the date of death due to any cause.	• Analyzed using the same methodology and model as for the analysis of PFS. • 3 analyses of OS are planned: at the time of the primary analysis of PFS (included in this report), and when approximately 300 and 400 deaths are observed (will be included in subsequent report[s]).
Time to Subsequent Therapy (TTST)	The time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation, or death, whichever comes first.	• Analyzed using the same method as the analysis of PFS.

Table 7: Overview of Primary and Secondary Endpoint Analyses

Progression-free Survival After First Subsequent Therapy (PFS2)	The time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first.	• Analyzed using the same method as the analysis of PFS.
Time to Symptomatic Progression (TTSP)	The time from randomization to documentation in the eCRF of any of the following (whichever occurs earlier): • onset of new symptoms OR • symptom worsening that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms, or death.	• Analyzed using the same method as the analysis of PFS.
Intracranial PFS (by BICR)	The time from randomization until the date of objective intracranial disease progression or death, whichever comes first, based on BICR using RECIST v1.1	• Analyzed using the same method as the analysis of PFS.
Intracranial Objective Response Rate (ORR) (by BICR)	The proportion of participants who achieve either an intracranial CR or PR,[a] as defined by BICR using RECIST v1.1	• Analyzed using the same method as the analysis of ORR for participants with baseline intracranial disease identified by BICR
Intracranial Duration of Response (DOR) (by BICR)	The time from the date of first documented intracranial response (PR[a] or CR) until the date of documented intracranial progression, as assessed by BICR, or death, whichever comes first	• Analyzed using the same method as the analysis of DOR for participants with intracranial response identified by BICR
Time to Intracranial Disease Progression (by BICR)	The time from randomization until the date of objective intracranial disease progression, as assessed by BICR using RECIST v1.1	• Analyzed using the same method as the analysis of PFS.
PRO NSCLC-SAQ	NSCLC-SAQ assesses symptoms of advanced NSCLC.	• The change of scores from baseline over time was assessed using MMRM analysis based on REML.
PRO EORTC-QLQ-C30	EORTC-QLQ C30 measures cancer patients' functioning for all cancer types.	• The change of scores from baseline over time was assessed using MMRM analysis based on REML. • Time to deterioration was analyzed using the same method as the primary analysis of PFS
PRO PROMIS-PF	PROMIS-PF assesses physical function, including upper, central, and lower extremity functions and instrumental activities of daily living.	• The change of scores from baseline over time was assessed using MMRM analysis based on REML.

Exploratory Objectives/Endpoints

Exploratory objectives of the MARIPOSA-2 study included:

To further assess the clinical benefit of ACP versus CP as measured by the following endpoints:

Disease control rate (by BICR);

Time to treatment discontinuation

Time to response (by BICR)

To further assess health-related quality of life in participants treated with ACP versus CP:

EQ-5D-5L and PRO CTCAE

Sample size

Initially, the primary objective of the study was to assess the efficacy of LACP versus CP. The primary hypothesis was that LACP was to demonstrate superior progression-free survival (PFS) compared with CP.

Subjects in a third treatment arm was to receive ACP to describe the contribution of lazertinib to the activity of LACP using summary statistics and nominal p-values.

The total sample size needed was then approximately 400 participants, 200 each in the LACP arm and CP arm. Additionally, approximately 100 participants were to be enrolled in the ACP arm for the secondary objective of describing the contribution of lazertinib to the activity of LACP.

Within protocol amendment 3 (27 June 2022) hypothesis testing for the analysis of ACP vs CP was added. To provide sufficient power for hypothesis testing for both LACP versus CP and ACP versus CP the sample size was increased from 500 to 600. The sample size calculation text was updated accordingly. The assumption initially made regarding the difference between treatments was not changed.

The median PFS for CP was estimated to be 5.5 months (Mok 2017, Soria 2015). Assuming a median PFS of 8.5 months for LACP and ACP, respectively, with an approximate 16-month accrual period and an additional 3-month follow-up, a total of 350 PFS events in all three arms combined were to provide approximately 93% power for LACP over CP, and 83% power for ACP over CP to detect a 35% reduction in the risk of either progression or death, (HR of 0.65 for LACP vs CP and ACP vs CP, respectively) with a log-rank test, assuming an overall family-wise Type I error rate at two-sided significance level of 5%.

As per amendment 6 an extension cohort was added with the aim to collect more data on the efficacy and safety for the add-on of both L and A to C and P. With this followed the notation "main study".

The total sample size for the extension cohort was approximately 90 subjects: 60 in the ACP-L arm (arm A2) and 30 in the ACP arm (arm C2).

Randomisation

This study used central randomisation. In the study (or, after amendment 6, the main study), participants were randomly assigned to 1 of 3 study treatment groups in a 2:2:1 ratio based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.

In the main study, the randomisation was to be balanced using randomly permuted blocks and was stratified by osimertinib line of therapy (first-line vs second line), history of brain metastases (yes vs no), and Asian race (yes vs no).

Baseline disease assessments including brain MRI should have been performed no more than 28 days prior to randomisation.

An interactive web response system (IWRS) was to assign a unique treatment code, which was to dictate the treatment assignment and matching study treatment kit for the participant. The requestor had to use his or her own user identification and personal identification number when contacting the IWRS and was then to give the relevant participant details to uniquely identify the participant.

In the extension cohort (added within CSP amendment 6), eligible participants were to be randomly assigned to receive ACP-L or ACP in a 2:1 ratio (Arms A2:C2) based on a computer-generated randomisation schedule prepared before the extension cohort by or under the supervision of the sponsor. Randomisation was to be stratified using the same stratification factors as used in the main study.

Enrolment of participants into the extension cohort could begin after enrolment into the main study was complete and when the Sponsor opened the extension cohort for enrolment.

Blinding (masking)

This is an open-label study.

Tumour response was assessed by blinded independent central review (BICR) according to RECIST v1.1.

Statistical methods

Study Period

The study initiation date was 17 November 2021 (date of first participant screened). As of 12 April 2023, enrolment of the main study was complete, with 657 participants randomised. The study is ongoing; results presented describe data through a CCO date of 10 July 2023.

Statistical analysis plan (SAP)

Below is the SAP version history. Amendment 1 describes the most important changes to the analysis plan affecting the comparison that is the subject for the current application. The submitted SAP version is amendment 3, dated 19 May 2023.

Table 8: SAP version history

SAP Version	Approval Date	Change	Rationale
Original SAP	16 February 2022	Not Applicable	Initial release
Amendment 1	23 June 2022	1. Add hypothesis tests of amivantamab, carboplatin, and pemetrexed (ACP) vs carboplatin and pemetrexed (CP) for PFS, ORR and OS endpoints, and associated analyses. 2. Increase sample size from 500 to 600 while retaining 2:2:1 randomization ratio. 3. Remove hypothesis testing and analysis for biomarker-defined subgroup. 4. Update multiplicity control strategy using a graphical approach. 5. Add additional analyses for patient report outcomes (PROs).	To add hypothesis testing for ACP versus CP as a dual primary and secondary hypotheses with an increased study sample size to provide sufficient power. To remove biomarker-defined subgroup analyses. To control family-wise type I error rate under dual primary hypothesis testing upon the removal of biomarker-defined subgroup testing. To have a comprehensive assessment of PRO measures.
Amendment 2		1. Add analysis by dosing schedule. 2. Remove NSCLC subtype at screening from baseline characteristic. 3. Add analysis for the extension cohort 4. Add venous thromboembolic (VTE) events to analysis of AESI	To add analysis for lazertinib dosing schedule change per IDMC recommendation. NSCLC subtype at screening was not collected in the study. To further describe the safety and efficacy of the ACP-L dosing schedule versus ACP with additional data. In protocol amendment 4, VTE was included into AESI.
Amendment 3		1. Update definition of time to symptomatic progression (TTSP) 2. Add additional intracranial endpoints (ORR, dor, time to intracranial disease progression) 3. Remove improvement rate and time to first improvement from PRO EORTC QLQ C30 analysis 4. Item-wise descriptive summary of PROMIS-PF data for each timepoint is dropped. Add Time to Symptom	Provides additional clarification regarding the definition of time to symptomatic progression to include both symptomatic progression and death as events. To further evaluate the intracranial efficacy. EORTC QLQ C30 is not expected to be improved for majority of patients.

General considerations

The hypothesis testing was to be based on the data from the main study only. The data from the extension cohort was not to be included.

Hypothesis testing of the primary efficacy endpoints and key secondary efficacy endpoints were to be performed for LACP/ACP-L (Arm A) versus CP (Arm B) and ACP (Arm C) versus CP (Arm B), respectively.

Comparison of LACP/ACP-L (Arm A) with ACP (Arm C) was to be performed to describe the contribution of lazertinib based on intracranial PFS, ORR, DoR, and PFS, using summary statistics and nominal p-values; there will be no formal hypothesis testing for this comparison.

Additional analysis based on the open-label randomised extension cohort will be performed to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP, but no formal hypothesis testing has been planned.

The efficacy analysis set

Unless otherwise specified, all efficacy analyses were to be performed using the Full Analysis Set, which was to include all randomised subjects, classified according to their assigned treatment arm regardless of the actual treatment received.

The primary estimand for PFS

The primary estimand for PFS was defined by the following components:

- Study treatment:
    - Experimental: LACP/ACP-L and ACP
    - Control: CP
- Population: participants with osimertinib-relapsed EGFR-mutated locally advanced or metastatic NSCLC
- Variable: time to event, PFS
- Population-level summary: hazard ratio for LACP/ACP-L vs CP and ACP vs CP
- Intercurrent events and their corresponding strategies

Intercurrent events	**Strategy for addressing intercurrent events**
Study treatment discontinuation due to any reason	Treatment policy strategy: use time to disease progression or death regardless of whether or not study treatment discontinuation had occurred
Study treatment switching to other anticancer therapy	Treatment policy strategy: use time to disease progression or death regardless of whether or not the subject started subsequent anticancer therapies
Death	Composite variable strategy: death being a component of the variable

Analysis of the primary endpoint (PFS)

Progression-free survival (PFS) was defined as the time from randomisation until the date of objective disease progression or death, whichever came first, based on BICR using RECIST v1.1.

Participants who had not progressed or had not died at the time of analysis were to be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.

Key censoring rules for PFS are summarized below.

Situation	**Date of censoring**
No evaluable baseline or postbaseline disease assessment	Censored at the date of randomisation
Lost to follow-up or withdraw from study	Censored at the date of last evaluable disease assessment

No documented disease progression or death	Censored at the date of last evaluable disease assessment
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visits

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

The primary analysis was to be performed after approximately 350 events from all three arms combined had occurred.

PFS was first to be analysed using a log-rank test stratified by the stratification factors used at randomisation: osimertinib line of therapy (first-line vs second line), history of brain metastases (yes vs no), and Asian race (yes vs no). The p-values (LACP/ACP-L vs CP, ACP vs CP) generated from the stratified log-rank test were to be used for the primary hypotheses testing.

The hazard ratio (HR) for PFS was to be calculated, along with its 95% CI, based on a stratified Cox model using the same stratification factors as for the log-rank test.

The median PFS with 95% CI was to be estimated using the Kaplan-Meier method. The Kaplan-Meier PFS curve was to be plotted by treatment group.

The number and percentage of participants who had a PFS event or were censored was to be reported, and reasons for PFS event and censoring was to be summarized.

Sensitivity analyses of PFS

An analysis using unstratified log-rank test.

The proportional hazards assumption was to be examined.

Supplementary analyses of PFS

-Censored for death/PD after start of subsequent anticancer therapy

A supplementary analysis was to be performed using progression or death prior to the start of the subsequent anticancer therapy as events. Subjects who had not progressed or had not died before the initiation of subsequent therapy were to be censored at the date of the last evaluable disease assessment prior to the start of subsequent therapy.

-Not censored for missing more than one disease evaluation

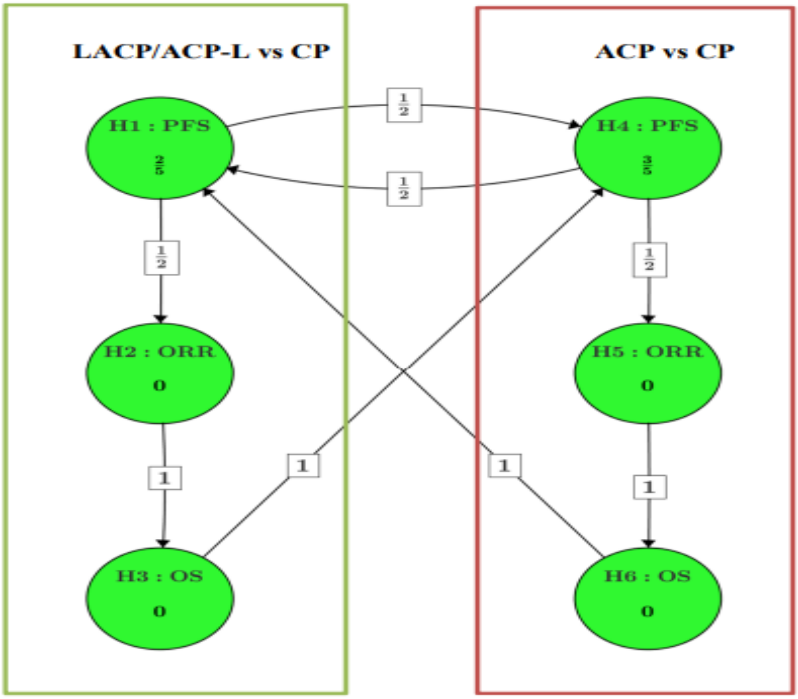
A supplementary analysis was to be performed using all progression or death, whichever occurred first, as event regardless missed/unevaluable disease assessment for 2 or more consecutive visits.

Multiplicity

Multiplicity due to multiple hypotheses of interest and multiple analyses was to be addressed using a graphical approach applied in a group sequential design setting (SAP amendment 1, 23 June 2022) as described by Maurer and Bretz (2013).

A primary analysis for PFS and key secondary endpoints (i.e., ORR and OS) was planned in the study. In addition, OS was to be analysed at 2 additional timepoints, at 75% information fraction of OS and final OS analysis.

The proposed graphical testing strategy (added) used to control the overall family-wise Type I error rate at a two-sided significance level of 0.05 was as follows.



The six elementary hypotheses were grouped into the 2 families of F1 = {H1: PFS, H2: ORR, H3: OS} and F2 = {H4: PFS, H5: ORR, H6: OS} for the comparison of LACP/ACP-L vs CP and ACP vs CP, respectively. A sequential (hierarchical) testing approach was to be utilized within each family starting with PFS, followed by ORR, and OS.

The figure above shows the distribution of initial amount of alpha (local significance level) allocated to the 6 hypotheses; the local significance levels are represented as numerical values within the circular nodes corresponding to each hypothesis of interest. Particularly H1 and H4 had the initial assigned local alpha of 2/5 α and 3/5 α, respectively.

The local significance levels were to be re-allocated after each hypothesis was rejected per the algorithm described (Maurer and Bretz 2013) according to the directed edges with the associated weights, and the weights are represented as numerical values within the squares.

If all the hypotheses were rejected in one family, the total level was to be allocated to the other family.

The O'Brien Fleming alpha spending function as implemented by the Lan-DeMets method was to be used to determine the statistical boundary for each of the interim analyses of OS.

Analysis of type I-error adjusted secondary endpoints

ORR: Objective response rate was defined as the proportion of participants who achieved either a complete response (CR) or partial response (PR), as defined by BICR using RECIST v1.1.

Data obtained up until progression or last evaluable disease assessment in the absence of progression was to be included in the assessment of ORR. However, any CR or PR, which occurred after a subsequent anticancer therapy was received, was not to be included in the numerator for the ORR calculation.

Subjects who did not have a tumour response assessment for any reason were to be considered non-responders and were to be included in the denominator when calculating the response rate.

Objective response was to be analysed using a logistic regression model stratified by the stratification factors used at randomisation. The results of the analysis were to be presented in terms of an odds ratio together with its associated 95% confidence interval and corresponding p-value.

OS: Overall survival was defined as the time from the date of randomization until the date of death due to any cause. Any participant not known to have died at the time of analysis was to be censored based on the last recorded date on which the participant was known to be alive.

The comparison between LACP/ACP-L and ACP over CP in OS was to be performed using the similar methodology and model as for the primary analysis of PFS in the Full Analysis Set.

Interim Analyses

There was no interim analysis planned for PFS.

For both ACP versus CP and LACP/ACP-L versus CP, two interim analyses were planned for OS.

The first interim analysis for OS was to be performed at the time of the primary analysis for PFS, when approximately 170 deaths (all 3 arms combined, approximately 43% of the total planned OS events) were expected.

The second interim analysis for OS will be performed approximately 32 months after the first participant is randomised, when approximately 300 deaths (all 3 arms combined, approximately 75% of the total planned OS events) are expected.

The significance level at the interim analyses for OS was to be determined based on the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method.

The final analysis for OS will be conducted at approximately 48 months after the first participant is randomized, when 400 deaths (all 3 arms combined) are anticipated.

The final analysis of OS will be conducted at the end of study. If the testing of both PFS and ORR shows statistical significance in either of the families of comparison (LACP/ACP-L vs CP and ACP vs CP), the analysis of OS will be carried out in the same family using a total 2-sided alpha reallocated after previous hypotheses rejection per the algorithm (above).

Analysis of intracranial Progression-free Survival

This secondary endpoint was not included in the multiple testing procedure.

Intracranial PFS was defined as the time from randomisation until the date of objective intracranial disease progression or death, whichever came first, based on BICR using RECIST v1.1.

Specifically, intracranial disease progression was defined as having progression of brain metastasis or occurrence of new brain lesion. Subjects who had not progressed intracranially or died were to be censored at their last evaluable intracranial disease assessment date.

Intracranial PFS was to be analysed using the similar methods as for the primary analysis of PFS. A similar analysis was to be repeated in the subgroup of randomised participants who had history of brain metastasis at screening. The corresponding Cox model was to be stratified by osimertinib line of therapy and race.

Subgroup analyses

The following pre-specified subgroup analyses were to be performed for the efficacy and/or safety endpoints. Additional subgroup analyses might be planned if deemed necessary.

Definition of Subgroups

Subgroup	Definition
Age Group	<65 years, ≥65 years; <75 years, ≥75 years
Sex	Male, Female
Race	Asian, Non-Asian
Weight	<80 kg, ≥80 kg
History of brain metastasis	Yes, No
Osimertinib line of therapy	First-line, Second-line
ECOG performance status score	0, 1
History of smoking	Yes, No

Analysis by Arm A Dosing Schedule

Following the 04 November 2022 safety data review for MARIPOSA-2, the IDMC recommended modification of Arm A to withhold lazertinib during administration of carboplatin due to an apparent imbalance in AEs affecting Arm A. The lazertinib dosing schedule for participants randomized to Arm A was thus modified in Amendment 5 of the protocol, such that new participants randomized to Arm A began treatment with amivantamab, carboplatin, and pemetrexed, and only started lazertinib after treatment with carboplatin treatment was complete.

The primary analysis was to be based on safety and full analysis set irrespective of Arm A dosing schedule change. To show that the two dosing schedules had no clinically relevant impact on key efficacy endpoints, supplemental descriptive analyses were to be performed for subgroup of subjects randomised prior to 07 November 2022 (S1) and subgroup of subjects randomised from 07 November 2022 onward (S2).

Subjects in arm A from S1 (A-S1) were intended to receive LACP, and subjects in arm A from S2 were intended to receive ACP-L. Subjects from arm B from both subgroups (B-S1 and B-S2) were to receive CP, and subjects from arm C from both subgroups (C-S1 and C-S2) were to receive ACP as treatment.

Results

Table 9: Study Disposition; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP	LACP/ACP-L	Total
Analysis set: Full	263	131	263	657
Subjects randomized but not treated	20 (7.6%)	1 (0.8%)	0	21 (3.2%)
Subjects treated	243 (92.4%)	130 (99.2%)	263 (100.0%)	636 (96.8%)
Subjects still on the study	169 (64.3%)	99 (75.6%)	186 (70.7%)	454 (69.1%)
Completed study participation[a]	65 (24.7%)	26 (19.8%)	67 (25.5%)	158 (24.0%)
Subjects discontinued the study	29 (11.0%)	6 (4.6%)	10 (3.8%)	45 (6.8%)
Reason for termination				

	CP	ACP	LACP/ACP-L	Total
Withdrawal by Subject	29 (11.0%)	6 (4.6%)	9 (3.4%)	44 (6.7%)
Lost to Follow-Up	0	0	1 (0.4%)	1 (0.2%)

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

Recruitment

Study Period: The study initiation date was 17 November 2021 (date of first participant screened).

The study is ongoing; results presented in this report describe data through a CCO date of 10 July 2023.

This study was conducted at 235 centres in 29 countries/territories.

The efficacy analyses were performed on the Full Analysis Set, if not otherwise indicated. At the time of CCO (10 July 2023), 263 participants were randomized to the CP arm, and 131 to the ACP arm. Twenty-one of the randomized participants (20 in the CP arm and 1 in the ACP arm) did not receive any dose of study treatment, primarily due to withdrawal of consent prior to the first dose. The higher proportion of participants who were randomized and not treated in the CP arm is driven by participants being reluctant to participate in a clinical study after they were randomized to receive standard of care chemotherapy. A total of 243 participants in the CP arm and 130 participants in the ACP arm received at least 1 dose of study treatment.

At the time of the CCO (10 July 2023), 67 participants (51.5%) in the ACP arm and 55 participants (22.6%) in the CP arm remained on treatment (Table 10). The most common reason for discontinuation of study treatment was progressive disease, with a higher proportion of discontinuation due to progressive disease seen in the CP arm (31.5% in the ACP versus 62.6% in the CP arm).

Table 10: Treatment Disposition - CP/ACP; Safety Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP	Total
Analysis set: Safety	243	130	373
Subjects ongoing	55 (22.6%)	67 (51.5%)	122 (32.7%)
Discontinued all study agents[a]	188 (77.4%)	63 (48.5%)	251 (67.3%)
Reason for discontinuation of last study agent			
Progressive Disease	152 (62.6%)	41 (31.5%)	193 (51.7%)

	CP	ACP	Total
Adverse Event	10 (4.1%)	14 (10.8%)	24 (6.4%)
Adverse event --COVID-19 related	0	1 (0.8%)	1 (0.3%)
Subject Refused Further Study Treatment	21 (8.6%)	3 (2.3%)	24 (6.4%)
Physician Decision	5 (2.1%)	5 (3.8%)	10 (2.7%)

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

Conduct of the study

Protocol deviations

An overview of major protocol deviations is provided in Table 10. At the time of CCO, 43 major protocol deviations were identified in 39 participants overall (5.9%): 12 participants (4.6%) in the CP arm, 6 (4.6%) in the ACP arm, and 21 (8.0%) in the LACP/ACP-L arm. While most participants (37 of the 39) each had 1 major protocol deviation, 2 participants in the LACP/ACP-L arm had >1 major protocol deviation (1 participant had 4 and the other participant had 2) (Appendix 14 [LSIDEV01]).

Table 11: Summary of Subjects with Major Protocol Deviations; Full Analysis Set (Study JNJ- 61186372NSC3002

	CP	ACP	LACP/ACP-L	Total
Analysis set: Full	263	131	263	657
Subjects with major protocol deviations	12 (4.6%)	6 (4.6%)	21 (8.0%)	39 (5.9%)
Entered but did not satisfy criteria	9 (3.4%)	5 (3.8%)	11 (4.2%)	25 (3.8%)
Received wrong treatment or incorrect dose	0	0	4 (1.5%)	4 (0.6%)
Received a disallowed concomitant treatment	0	0	1 (0.4%)	1 (0.2%)
Other	3 (1.1%)	1 (0.8%)	7 (2.7%)	11 (1.7%)

Note: Subjects may appear in more than one category.

Protocol amendments

Table 12: Summary of protocol amendments

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	22 December 2022
Amendment 5	25 November 2022
Amendment 4	23 August 2022
Amendment 3	27 June 2022
Amendment 2	24 March 2022
Amendment 1	06 August 2021
Original Protocol	09 July 2021

As of the CCO of 10 July 2023, there were 6 amendments to the original protocol dated 09 July 2021, as well as several country/territory-specific amendments to address minor HA requests.

Two important changes were made to the protocol during the study: (1) addition of a dual primary hypothesis (described in Section 3.1.2 and formalized in Amendment 3) and (2) modification of the dosing schedule in Arm A, which resulted from a USM (described in Section 3.1 and formalized in Amendment 5).

Details of each global amendment are included in the protocol (Appendix 1), with key changes implemented by each global amendment summarized in Table 13 and a timeline of key updates in Figure 6.

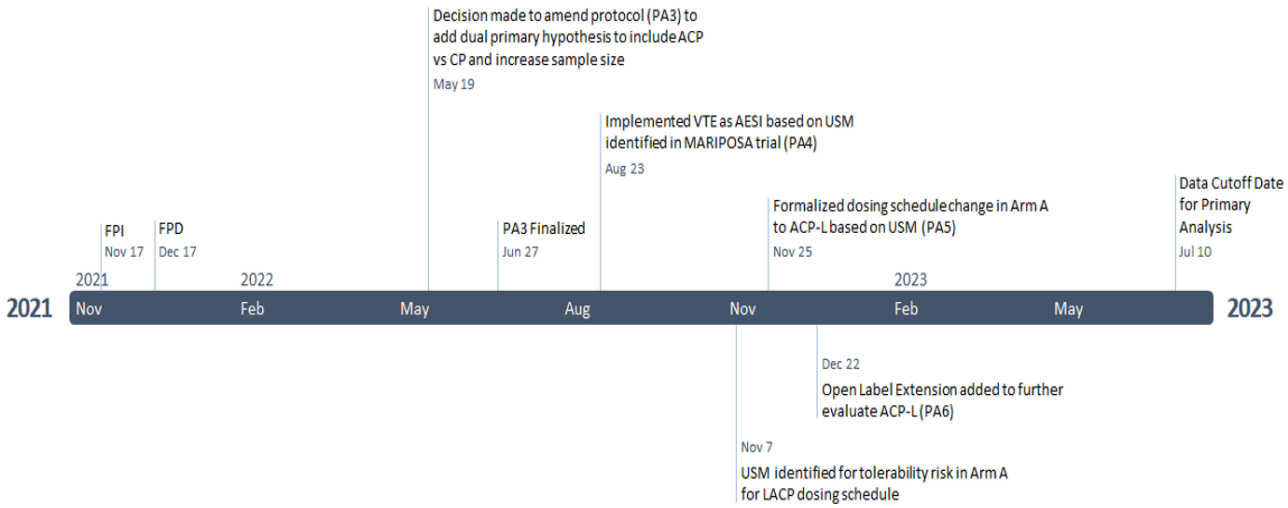
Table 13: Key Changes Implemented with Global Protocol Amendments to 61186372NSC3002

Amendment Number (Date)	Key Changes
Amendment 1 (06 August 2021)	• Removed the requirement to review clinical benefit with the Medical Monitor at each assessment when a participant is treated beyond BICR-confirmed disease progression • Added pregnancy testing within 72 hours before Day 1 of each cycle
Amendment 2 (24 March 2022)	• Updated the timeframe for conduct of the primary analysis for PFS • Clarified inclusion criteria related to brain metastases • Provided additional and clarified guidance to investigators for the management of toxicities • Modified prohibited and restricted medications based on the availability of new information
Amendment 3 (27 June 2022)	• Added hypothesis testing for ACP versus CP as dual primary and secondary hypotheses with an increased study population to provide sufficient power

Amendment Number (Date)	Key Changes
	• Removed biomarker-defined subgroup analysis based on emerging data from other trials
Amendment 4 (23 August 2022)	• Implemented the AESI of VTE events, as well as associated measures for monitoring and prophylaxis of these events as a result of the USM identified in the MARIPOSA trial. • Updated guidance on the dose modification for the participants who had clinically significant CTCAE Grade 3 AEs
Amendment 5 (25 November 2022)	• Formalized the study changes required by the USM identified in the MARIPOSA-2 trial (tolerability risk for participants treated in Arm A with LACP dosing schedule) released on 07 November 2022, ie, to change the lazertinib dosing schedule in Arm A. • Incorporated additional changes that were recommended by health authorities in response to the USM identified in the MARIPOSA trial (VTE risk with combination of amivantamab and lazertinib) released on 22 July 2022
Amendment 6 (22 December 2022)	• Added an open-label randomized extension cohort to provide additional data to further describe the safety and efficacy of the ACP-L dosing schedule versus ACP

ACP=amivantamab, carboplatin, and pemetrexed; ACP-L=amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin is completed); AESI=adverse event of special interest; BICR=blinded independent
central review; CP=carboplatin and pemetrexed; CTCAE=common terminology criteria for adverse events; LACP=lazertinib, amivantamab, carboplatin, and pemetrexed; PFS=progression-free survival; USM = Urgent Safety Measure; VTE=venous thromboembolism

Figure 6: Timeline of Key Study Updates



FPD=first participant dosed; FPI=first participant in; PA#=protocol amendment number, eg, 3, 4, 5, 6; USM=Urgent Safety Measure

Note: As of 19 May 2022 (i.e., when the decision was made to amend the protocol to add the dual primary hypothesis), approximately 59 participants across the trial had completed a disease evaluation, and the Sponsor had only received blinded data.

Analysis Sets

The number of participants included in each analysis set is provided in Table 14.

All 657 participants randomised in the study were included in the Full Analysis Set, which was used for the demographics, baseline disease characteristics, and efficacy analyses. A total of 636 participants received at least 1 dose of study treatment and were therefore included in the Safety Analysis Set.

Table 14: Number of Subjects in Each Analysis Set; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP	LACP/ACP-L	Total
Analysis set: Full	263	131	263	657
Safety analysis set	243 (92.4%)	130 (99.2%)	263 (100.0%)	636 (96.8%)
Pharmacokinetics Analysis set	0[a]	130 (99.2%)	259 (98.5%)	389 (59.2%)

[tsidem03.rtf] [PROD/jnj-61186372/nsc3002/dbr_csr/re_csr1/tsidem03.sas] 24AUG2023, 19:09

[a] Because only amivantamab and lazertinib concentrations were evaluated (per protocol design), participants in this arm were not included in the PK analysis set.

Baseline data

Demographic and Other Baseline Characteristics

Table 15: Summary of Demographics and Baseline Characteristics - CP / ACP; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP	Total
Analysis set: Full	263	131	394
Age, years			
N	263	131	394
Mean (SD)	60.6 (10.13)	61.2 (10.06)	60.8 (10.10)
Median	62.0	62.0	62.0
Range	(31; 85)	(36; 84)	(31; 85)
<65	166 (63.1%)	79 (60.3%)	245 (62.2%)
>=65	97 (36.9%)	52 (39.7%)	149 (37.8%)
<75	244 (92.8%)	118 (90.1%)	362 (91.9%)
>=75	19 (7.2%)	13 (9.9%)	32 (8.1%)
Sex			
N	263	131	394
Female	157 (59.7%)	81 (61.8%)	238 (60.4%)
Male	106 (40.3%)	50 (38.2%)	156 (39.6%)
Undifferentiated	0	0	0
Unknown	0	0	0
Race			
N	263	131	394
American Indian or Alaska Native	3 (1.1%)	1 (0.8%)	4 (1.0%)
Asian	127 (48.3%)	63 (48.1%)	190 (48.2%)
Black or African American	1 (0.4%)	3 (2.3%)	4 (1.0%)
Native Hawaiian or other Pacific Islander	0	0	0

	CP	ACP	Total
White	123 (46.8%)	60 (45.8%)	183 (46.4%)
Multiple	2 (0.8%)	0	2 (0.5%)
Not Reported	6 (2.3%)	2 (1.5%)	8 (2.0%)
Unknown	1 (0.4%)	2 (1.5%)	3 (0.8%)
Asian	127 (48.3%)	63 (48.1%)	190 (48.2%)
Non-Asian	129 (49.0%)	64 (48.9%)	193 (49.0%)
Other	7 (2.7%)	4 (3.1%)	11 (2.8%)
Ethnicity			
N	263	131	394
Hispanic or Latino	23 (8.7%)	9 (6.9%)	32 (8.1%)
Not Hispanic or Latino	234 (89.0%)	118 (90.1%)	352 (89.3%)
Not Reported	3 (1.1%)	1 (0.8%)	4 (1.0%)
Unknown	3 (1.1%)	3 (2.3%)	6 (1.5%)
Weight, kg			
N	263	131	394
Mean (SD)	64.28 (13.892)	65.10 (14.077)	64.55 (13.941)
Median	63.00	63.00	63.00
Range	(37.2; 118.0)	(38.5; 111.9)	(37.2; 118.0)
<80 kg	226 (85.9%)	113 (86.3%)	339 (86.0%)
>=80 kg	37 (14.1%)	18 (13.7%)	55 (14.0%)
Height, cm			
N	263	131	394
Mean (SD)	164.19 (10.289)	164.79 (10.791)	164.39 (10.449)
Median	163.00	163.00	163.00
Range	(140.0; 195.0)	(128.0; 190.0)	(128.0; 195.0)
Body mass index, kg/m^2			
N	263	131	394
Mean (SD)	23.71 (3.926)	23.89 (4.254)	23.77 (4.034)
Median	23.63	23.53	23.60
Range	(15.9; 36.3)	(15.9; 50.0)	(15.9; 50.0)
IQ range	(20.57; 26.06)	(21.29; 25.78)	(20.82; 26.00)
Baseline ECOG score			
N	263	131	394
0	101 (38.4%)	55 (42.0%)	156 (39.6%)
1	162 (61.6%)	76 (58.0%)	238 (60.4%)
History of smoking			
N	263	131	394
Yes	95 (36.1%)	41 (31.3%)	136 (34.5%)
Current	4 (1.5%)	1 (0.8%)	5 (1.3%)
Former	91 (34.6%)	40 (30.5%)	131 (33.2%)
No	168 (63.9%)	90 (68.7%)	258 (65.5%)
Unknown	0	0	0

Key: ECOG = Eastern Cooperative Oncology Group
Note: N's for each parameter reflect non-missing values.

Table 16: Summary of Baseline Disease Characteristics - CP / ACP; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP	Total
Analysis set: Full	263	131	394
History of brain metastasis			
N	263	131	394
Yes	120 (45.6%)	58 (44.3%)	178 (45.2%)

	CP	ACP	Total
No	143 (54.4%)	73 (55.7%)	216 (54.8%)
Mutation Type			
N	262	131	393
Exon 19del	183 (69.8%)	89 (67.9%)	272 (69.2%)
Exon 21 L858R	79 (30.2%)	42 (32.1%)	121 (30.8%)
NSCLC subtype at initial diagnosis			
N	263	131	394
Adenocarcinoma	260 (98.9%)	130 (99.2%)	390 (99.0%)
Large cell carcinoma	0	1 (0.8%)	1 (0.3%)
Squamous cell carcinoma	1 (0.4%)	0	1 (0.3%)
Other	2 (0.8%)	0	2 (0.5%)
Histology grade at initial diagnosis			
N	263	131	394
Moderately differentiated	54 (20.5%)	30 (22.9%)	84 (21.3%)
Poorly differentiated	29 (11.0%)	14 (10.7%)	43 (10.9%)
Well differentiated	14 (5.3%)	16 (12.2%)	30 (7.6%)
Other	166 (63.1%)	71 (54.2%)	237 (60.2%)
Cancer stage at initial diagnosis			
N	262	131	393
0	0	0	0
IA	2 (0.8%)	1 (0.8%)	3 (0.8%)
IB	3 (1.1%)	5 (3.8%)	8 (2.0%)
IIA	1 (0.4%)	1 (0.8%)	2 (0.5%)
IIB	3 (1.1%)	0	3 (0.8%)
IIIA	3 (1.1%)	4 (3.1%)	7 (1.8%)
IIIB	4 (1.5%)	3 (2.3%)	7 (1.8%)
IIIC	2 (0.8%)	0	2 (0.5%)
IVA	97 (37.0%)	42 (32.1%)	139 (35.4%)
IVB	147 (56.1%)	75 (57.3%)	222 (56.5%)
Histology grade at screening			
N	263	131	394
Moderately differentiated	50 (19.0%)	27 (20.6%)	77 (19.5%)
Poorly differentiated	28 (10.6%)	14 (10.7%)	42 (10.7%)
Well differentiated	12 (4.6%)	15 (11.5%)	27 (6.9%)
Other	173 (65.8%)	75 (57.3%)	248 (62.9%)
Cancer stage at screening			
N	263	131	394
IIIA	0	0	0
IIIB	0	0	0
IIIC	1 (0.4%)	0	1 (0.3%)
IVA	51 (19.4%)	18 (13.7%)	69 (17.5%)
IVB	211 (80.2%)	113 (86.3%)	324 (82.2%)
Location of metastasis at screening [a,b]			
N	263	131	394
Bone	147 (55.9%)	69 (52.7%)	216 (54.8%)
Liver	62 (23.6%)	31 (23.7%)	93 (23.6%)
Brain	108 (41.1%)	54 (41.2%)	162 (41.1%)
Lymph Node	164 (62.4%)	85 (64.9%)	249 (63.2%)
Adrenal Gland	28 (10.6%)	22 (16.8%)	50 (12.7%)
Lung	154 (58.6%)	88 (67.2%)	242 (61.4%)
Other	121 (46.0%)	61 (46.6%)	182 (46.2%)
Time since initial lung cancer diagnosis (months)			
N	263	131	394
Mean (SD)	27.277 (18.6447)	28.622 (17.9225)	27.724 (18.3959)
Median	22.439	25.232	23.080
Range	(4.34; 123.40)	(4.11; 115.29)	(4.11; 123.40)
Time since metastatic disease diagnosis (months)			
N	263	131	394
Mean (SD)	25.706 (16.1094)	26.515 (16.3853)	25.975 (16.1853)

	CP	ACP	Total
Median	20.961	22.998	22.456
Range	(0.10; 99.12)	(0.23; 115.29)	(0.10; 115.29)

Key: NSCLC = non-small cell lung cancer
[a] Subjects can be counted in more than one category.
[b] Refers to a history of metastases in these organs.

Prior Therapies for Lung Cancer

All participants (100%) received prior lung cancer therapy (

Table 17). All participants (100%) received prior systemic therapy, 51.0% received prior radiotherapy, and 16.7% had prior cancer- related surgery. All participants received prior osimertinib as required by the protocol, which was given as first-line systemic therapy for 70.5% of participants and second-line therapy for 29.4% of participants.

Prior Systemic Therapies

The most common prior systemic therapies (other than osimertinib) were 1st and 2nd generation EGFR TKIs including gefitinib (66 participants [10.0%]), afatinib (58 participants [8.8%]), and erlotinib (39 participants [5.9%]).

Table 17: Prior Therapies for Lung Cancer; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP	LACP/ACP-L	Total
Analysis set: Full	263	131	263	657
Total number of subjects with any prior therapies for lung cancer	263 (100.0%)	131 (100.0%)	263 (100.0%)	657 (100.0%)
Prior systemic therapy	263 (100.0%)	131 (100.0%)	263 (100.0%)	657 (100.0%)
Prior radiotherapy	124 (47.1%)	69 (52.7%)	142 (54.0%)	335 (51.0%)
Prior cancer-related surgery	40 (15.2%)	19 (14.5%)	51 (19.4%)	110 (16.7%)
Number of prior lines of systemic therapy in the Locally Advanced or Metastatic setting				
1	181 (68.8%)	97 (74.0%)	185 (70.3%)	463 (70.5%)
2	82 (31.2%)	34 (26.0%)	77 (29.3%)	193 (29.4%)
>2	0	0	1 (0.4%)	1 (0.2%)
Prior line of Osimertinib line of therapy				
First-Line	181 (68.8%)	97 (74.0%)	185 (70.3%)	463 (70.5%)
Second-Line	82 (31.2%)	34 (26.0%)	77 (29.3%)	193 (29.4%)

	CP	ACP	LACP/ACP-L	Total
>2 Lines	0	0	1 (0.4%)	1 (0.2%)
Prior Systemic Therapy Setting				
N	263	131	263	657
Adjuvant	3 (1.1%)	3 (2.3%)	7 (2.7%)	13 (2.0%)
Neo-adjuvant	0	0	2 (0.8%)	2 (0.3%)
Curative/Palliative/Any other intent	263 (100.0%)	131 (100.0%)	263 (100.0%)	657 (100.0%)
Concurrent chemoradiation	0	0	0	0

Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Exposure

The median duration of treatment in the ACP arm was 6.31 months (range: 0.0 to 14.7). Participants received amivantamab for a median of 9 cycles, carboplatin for a median of 4 cycles, and pemetrexed for a median of 9 cycles. The median duration of treatment in the CP arm was 3.68 months (range: 0.0 to 15.9). Participants received carboplatin for a median of 4 cycles and pemetrexed for a median of 6 cycles.

Numbers analysed

Outcomes and estimation

At the time of CCO (10 July 2023), the median follow-up in the study was 8.97 months in the ACP arm and 8.34 months in the CP arm.

The efficacy analyses were performed on the Full Analysis Set, if not otherwise indicated.

2.4.2.1. Primary Endpoint: Progression-free Survival by BICR

As of the CCO of 10 July 2023, after a median follow-up of 8.74 months, a total of 371 BICR-assessed PFS events were observed across all 3 treatment arms, which met the requirement for the primary analysis of PFS as defined in the SAP.

Table 18: Summary of Progression-free Survival – Primary Analysis – Stratified Analysis – BICR; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP
Analysis set: Full	263	131
Event	171 (65.0%)	74 (56.5%)
Censored	92 (35.0%)	57 (43.5%)
Time to event (months)		
25th percentile (95% CI)	2.50 (1.51, 2.83)	4.37 (4.17, 5.39)
Median (95% CI)	4.17 (4.04, 4.44)	6.28 (5.55, 8.41)
75th percentile (95% CI)	6.93 (5.78, 8.31)	11.76 (9.72, NE)
Range	(0.0+, 14.0+)	(0.0+, 14.9)
6-month event-free rate (95% CI)	0.30 (0.23, 0.36)	0.51 (0.41, 0.60)
9-month event-free rate (95% CI)	0.16 (0.11, 0.23)	0.38 (0.28, 0.48)
12-month event-free rate (95% CI)	0.13 (0.08, 0.20)	0.22 (0.12, 0.34)
p-value [a] (ACP vs CP)		<0.0001
Hazard ratio (95% CI) [b] (ACP vs CP)		0.48 (0.36, 0.64)

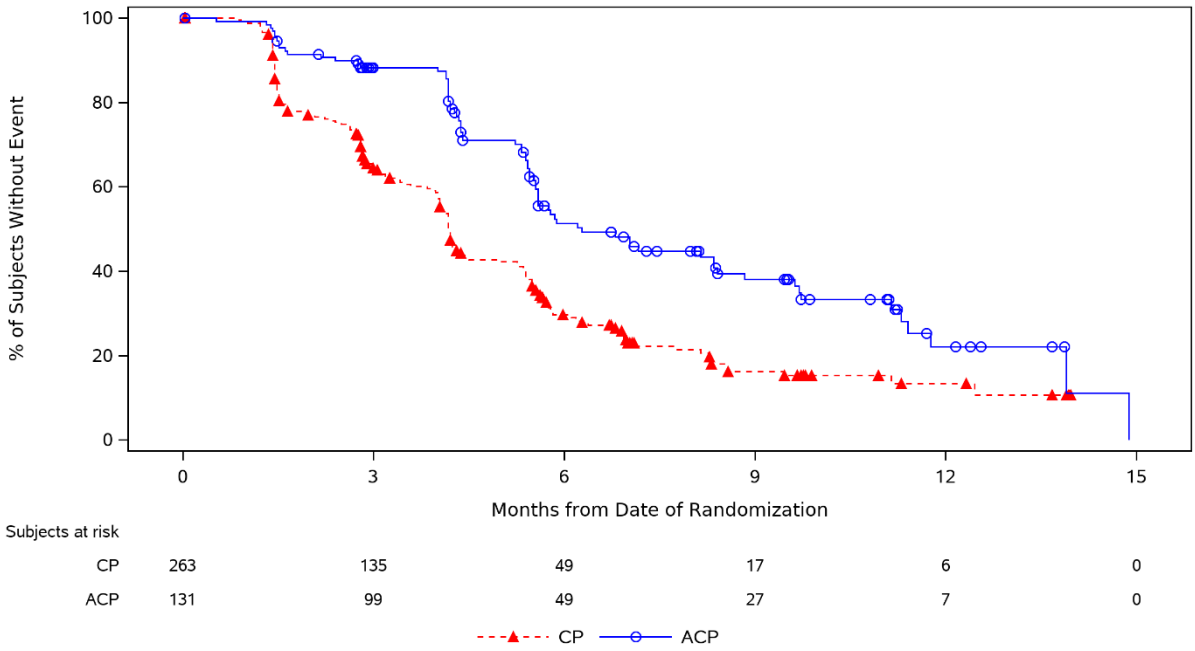
[a] p-value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors experimental treatment.
Note: + = censored observation; NE = not estimable

Table 19: Summary of reasons for censoring PFS

	CP	ACP
Analysis set: Full	263	131
Subjects with event	171 (65.0%)	74 (56.5%)
Progressive disease	161 (61.2%)	62 (47.3%)
Death without progressive disease	10 (3.8%)	12 (9.2%)
Subjects censored	92 (35.0%)	57 (43.5%)
Reason for censoring		
Study cut-off	55 (20.9%)	53 (40.5%)
Withdrawal of consent to study participation	27 (10.3%)	2 (1.5%)
No post-baseline disease assessment [a]	8 (3.0%)	1 (0.8%)
No PD or death prior to >= 2 consecutively missing or unevaluable assessments	2 (0.8%)	1 (0.8%)

[a] Includes subjects who were randomized but never treated.

Figure 7: Kaplan-Meier Plot of Progression-free Survival Primary Analysis – BICR – ACP vs CP; Full Analysis Set (Study JNJ-61186372NSC3002)



2.4.2.2. Secondary Endpoints

2.4.2.2.1. Objective Response Rate

BICR Assessment of Response

Based on BICR assessment, 130 participants in the ACP arm and 260 participants in the CP arm had measurable disease at baseline and were included in the analysis of ORR.

Table 20: Summary of Objective Response Rate Based on RECIST [Version 1.1] Criteria in Subjects With Measurable Disease at Baseline – BICR; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP
Analysis set: Full	263	131
Number of subjects with measurable disease at baseline	260	130
Objective response rate (CR+PR)	94 (36.2%)	83 (63.8%)
95% CI	(30.3%, 42.3%)	(55.0%, 72.1%)
p-value[a] (ACP vs CP)		<0.0001
Odds ratio (95% CI)[b] (ACP vs CP)		3.10 (2.00, 4.80)
Best Overall Response		
Complete Response (CR)	1 (0.4%)	2 (1.5%)
Partial Response (PR)	93 (35.8%)	81 (62.3%)
Stable Disease (SD)	82 (31.5%)	30 (23.1%)
Progressive Disease (PD)	52 (20.0%)	10 (7.7%)
Not Evaluable (NE)	32 (12.3%)	7 (5.4%)

[a] p-value is from a logistic regression stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).
[b] Odds ratio >1 favors experimental treatment.
Note: CR and PR do not have to be confirmed. Percent of Responder is based on the number of subjects with measurable disease at baseline.

2.4.2.2.2. Duration of Response in Confirmed Responders

BICR Assessment

Table 21: Summary of Duration of Response in Confirmed Responders Based on Subjects With Measurable Disease at Baseline – BICR; Full Analysis Set (Study JNJ-61186372NSC3002)

	CP	ACP
Analysis set: Full	263	131
Number of subjects with measurable disease at baseline	260	130
Responder (confirmed CR + confirmed PR)	75	69
Event	34 (45.3%)	29 (42.0%)
Censored	41 (54.7%)	40 (58.0%)
Time to event (months)[a]		
25th percentile (95% CI)	2.99 (2.79, 4.17)	4.17 (3.94, 5.59)
Median (95% CI)	5.55 (4.17, 9.56)	6.90 (5.52, NE)
75th percentile (95% CI)	11.10 (6.64, NE)	12.12 (9.69, NE)
Range	(1.0+, 12.4+)	(1.2+, 12.1)
Duration of response >=6 months	15 (20.0%)	22 (31.9%)
Duration of response >=12 months	1 (1.3%)	1 (1.4%)
Duration of response >=18 months	0	0

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

2.4.2.2.3. Overall Survival

The results of second interim analysis of OS were received during the procedure. The second interim OS analysis (CCO of 26 April 2024) was performed when a total of 208 OS events were observed across both arms, including 65 in the ACP arm and 143 in the CP arm. Based on this, OS was to be evaluated at a 2-sided alpha level of 0.0142 for ACP vs CP (O'Brien-Fleming alpha spending approach as implemented by the Lan-DeMets method). Updates to Section 5.1 of the SmPC were made accordingly.

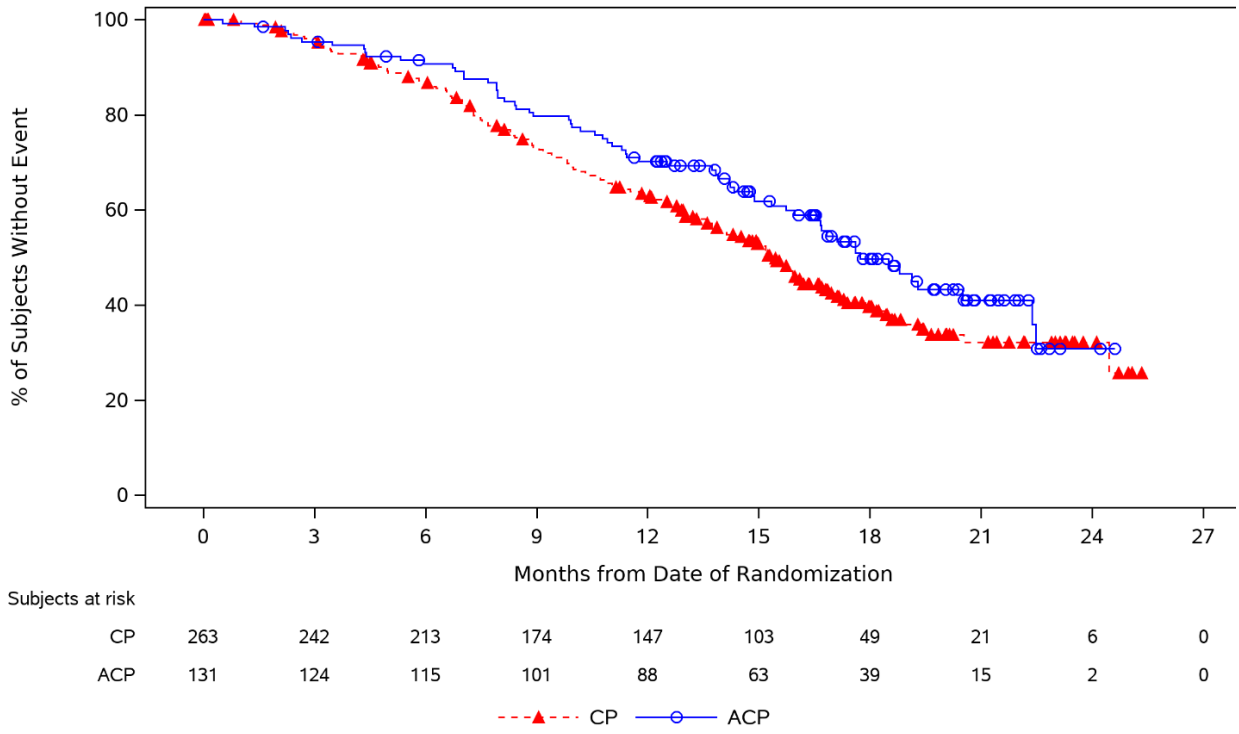
The results demonstrate a substantial improvement for OS for ACP over CP (HR = 0.73; 95% CI: 0.54, 0.99; p=0.0386). Given the alpha allocated to this interim analysis (a 2-sided alpha of 0.0142), the study will continue to the final analysis for OS, which is planned to be conducted when approximately 400 OS events have been observed in all 3 arms (approximately 250 OS events in ACP vs. CP arms combined). Results are anticipated by mid-year 2025.

Table 22: Summary of Overall Survival – Second Interim Analysis (MARIPOSA-2)

	CP (N=263)	ACP (N=131)
OS		
Number of events (%)	143 (54.4%)	65 (49.6%)
Median, months (95% CI)	**15.34 (13.73, 16.76)**	**17.74 (15.97, 22.37)**
HR (95% CI); p-value[a]	**0.73 (0.54, 0.99); 0.0386**	
6-month event-free rate (95% CI)	0.87 (0.82, 0.90)	0.91 (0.84, 0.95)
9-month event-free rate (95% CI)	0.73 (0.67, 0.78)	0.80 (0.72, 0.86)
12-month event-free rate (95% CI)	0.63 (0.57, 0.69)	0.70 (0.61, 0.77)
18-month event-free rate (95% CI)	0.40 (0.33, 0.46)	0.50 (0.40, 0.59)

[a] Statistical significance for OS at this interim analysis required p<0.0142

Figure 8: Kaplan-Meier Plot of Overall Survival - ACP vs CP; Full Analysis Set (Study JNJ-61186372NSC3002)



2.4.2.2.4. Intracranial PFS by BICR

Intracranial PFS (defined as the time from randomization until the date of objective intracranial disease progression or death) as assessed by BICR, is summarized in the table below.

Baseline disease characteristics showed that 120 participants (45.6%) in the CP arm and 58 participants (44.3%) in the ACP arm, had a history of brain metastasis. Notably, of the participants who had a history of brain metastasis, 61/120 (50.8%) in the CP arm and 24/58 (41.4%) in the ACP arm had not received prior radiotherapy for the brain metastasis.

Table 23: Summary of Intracranial Endpoints – Second Interim Analysis (MARIPOSA-2)

	CP (N=263)	ACP (N=131)
Intracranial PFS (BICR)		
Number of events (%)	174 (66.2%)	86 (65.6%)
Median, months (95% CI)	**8.90 (8.15, 11.07)**	**12.45 (10.58, 14.36)**
HR (95% CI); p-value	**0.65 (0.49, 0.84); 0.0012**	
6-month event-free rate (95% CI)	0.67 (0.61, 0.73)	0.82 (0.74, 0.88)
9-month event-free rate (95% CI)	0.50 (0.43, 0.56)	0.64 (0.54, 0.71)
12-month event-free rate (95% CI)	0.40 (0.33, 0.46)	0.50 (0.41, 0.59)
18-month event-free rate (95% CI)	0.17 (0.11, 0.23)	0.28 (0.19, 0.38)
Intracranial ORR[bc] (BICR)		
ORR, % (95% CI)	16.7% (8.3%, 28.5%)	23.3% (9.9%, 42.3%)
OR (95% CI); p-value	1.52 (0.51, 4.50); 0.4481	
Complete response	10 (16.7%)	7 (23.3%)
Partial response	0	0
Intracranial DOR[cd] (BICR)		
Median, months (95% CI)	2.23 (1.38, NE)	13.27 (1.41, NE)
Duration of response >=6 months	1 (10.0%)	5 (71.4%)
Duration of response >=9 months	0	5 (71.4%)
Duration of response >=12 months	0	2 (28.6%)
Duration of response >=18 months	0	0
Time to Intracranial Disease Progression[e] (BICR)		
Number of events (%)	82 (31.2%)	40 (30.5%)
Median, months (95% CI)	13.83 (11.24, 16.62)	16.76 (13.96, 21.88)
HR (95% CI); p-value	0.56 (0.38, 0.82); 0.0025	
6-month event-free rate (95% CI)	0.73 (0.66, 0.79)	0.88 (0.81, 0.93)
9-month event-free rate (95% CI)	0.61 (0.53, 0.68)	0.78 (0.68, 0.85)
12-month event-free rate (95% CI)	0.55 (0.46, 0.63)	0.69 (0.59, 0.78)
18-month event-free rate (95% CI)	0.39 (0.28, 0.49)	0.50 (0.36, 0.62)

[b] Among subjects with baseline intracranial disease by BICR
[c] Note that only intracranial CRs are considered in this analysis because, as per charter, brain lesions could not be selected as target lesions by BICR.
[d] Among subjects with intracranial response by BICR.
[e] Defined as time from randomization until the date of objective intracranial disease progression, as assessed by BICR

Subsequent systemic therapies

Subsequent systemic therapies were received by 29 participants (22.1%) in the ACP arm and 114 participants (43.3%) in the CP arm.

Chemotherapy/immuno-oncology therapy based regimens were most frequently prescribed (13.0% of participants in the ACP arm and 27.4% of participants in the CP arm), followed by TKI/TKI-based regimens (9.2% for the ACP arm and 20.2% for the CP arm). Only 4 (1.5%) of patients in the control arm received amivantamab after progression.

2.4.2.2.5. Secondary endpoints (Time to Subsequent Therapy/TTST, PFS After First Subsequent Therapy/PFS2, Time to Symptomatic Progression /TTSP)

A longer median time to initiation of subsequent anti-cancer therapy was observed in the ACP arm of 12.16 (10.71, 14.29) months compared with the CP arm 6.60 (6.11, 7.39) with a HR of 0.51 (0.39, 0.65); nominal P<0.0001. Of note, the TTST analysis reflects the persistence of treatment benefit independent of the RECIST criteria as, per protocol, participants were allowed to continue the assigned study treatment if they continued to demonstrate clinical benefit per investigator assessment after

determination of radiographic progressive disease; 34.5% in the ACP arm and 16.2% in the CP arm remained on study treatment for more than 28 days beyond radiographic disease progression.

For the secondary endpoints related to the subsequent systemic therapies (Time to Subsequent Therapy/TTST, PFS After First Subsequent Therapy/PFS2, Time to Symptomatic Progression /TTSP) please see the table below:

Table 24: Summary of secondary endpoints related the subsequent systemic therapies – Second Interim Analysis (MARIPOSA-2)

	CP (N=263)	ACP (N=131)
Secondary Endpoints		
TTST[f]		
Number of events (%)	207 (78.7%)	88 (67.2%)
Median, months (95% CI)	6.60 (6.11, 7.39)	12.16 (10.71, 14.29)
HR (95% CI); nominal p-value	0.51 (0.39, 0.65); <0.0001	
6-month event-free rate (95% CI)	0.58 (0.52, 0.64)	0.81 (0.73, 0.86)
9-month event-free rate (95% CI)	0.35 (0.29, 0.41)	0.67 (0.58, 0.75)
12-month event-free rate (95% CI)	0.24 (0.19, 0.30)	0.51 (0.42, 0.60)
18-month event-free rate (95% CI)	0.12 (0.08, 0.17)	0.31 (0.22, 0.40)
PFS2[g]		
Number of events (%)	150 (57.0%)	70 (53.4%)
Median, months (95% CI)	11.60 (10.05, 12.98)	16.03 (13.90, 17.61)
HR (95% CI); nominal p-value	0.64 (0.48, 0.85); 0.0020	
6-month event-free rate (95% CI)	0.82 (0.77, 0.87)	0.89 (0.82, 0.93)
9-month event-free rate (95% CI)	0.62 (0.55, 0.68)	0.76 (0.67, 0.82)
12-month event-free rate (95% CI)	0.48 (0.41, 0.55)	0.64 (0.55, 0.72)
18-month event-free rate (95% CI)	0.27 (0.21, 0.34)	0.39 (0.29, 0.48)
TTSP[h]		
Number of events	159 (60.5%)	72 (55.0%)
Median, months (95% CI)	11.76 (8.87, 13.60)	16.03 (12.71, 19.38)
HR (95% CI); nominal p-value	0.73 (0.55, 0.96); 0.0259	

[f] Defined as time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation, or death, whichever comes first.

[g] Defined as time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first.

[h] Time to symptomatic progression-Defined as time from randomization to the onset of new or worsening lung cancer symptoms requiring a change in anticancer therapy or intervention, or to death, whichever comes first.

2.4.2.2.6. Patient-reported Outcomes

PRO measures in this study included the EORTC-QLQ-C30, PROMIS PF, and NSCLC-SAQ. In both the ACP and CP arms, participants reported low symptom burden at baseline that was maintained on treatment.

Time to Response

Time to response (ie, time to first response) was defined as the time from randomization to the first documentation of a response (PR or CR) prior to any disease progression or subsequent anticancer therapy, as defined by BICR using RECIST v1.1.

As of the CCO, 83 participants (63.4%) in the ACP arm and 94 participants (35.7%) in the CP arm had a documented first response of PR or CR. The median time to first response was 1.58 months in both treatment arms.

Ancillary analyses

Sensitivity Analyses

Sensitivity Analysis: Investigator-assessed PFS

As of the CCO, investigator assessed PFS events occurred for 67 participants (51.1%) in the ACP arm and 183 participants (69.6%) in the CP arm. The outcome of the investigator assessed PFS analysis was HR=0.41 [95% CI: 0.30, 0.54] (nominal p<0.0001) with a median PFS of 8.18 months (95% CI: 6.80, 10.94) in the ACP arm compared with 4.21 months (95% CI: 4.04, 4.47) in the CP arm.

The investigator and BICR agreed on PFS event status for 87.0% of participants in the ACP arm and 89.4% of participants in the CP arm. A Kaplan-Meier plot of PFS by investigator assessment showed an early and maintained separation of the treatment arms, favoring treatment with ACP.

Sensitivity Analysis: PFS by BICR Assuming Untreated CP Arm Participants Were Event-free at CCO

To address the potential bias due to censoring of participants who were randomized and not treated in the CP arm, a sensitivity analysis for the PFS by BICR was performed by assuming these 20 participants were event-free until the CCO. According to the Applicant, the demographic and baseline disease characteristics were similar between these 20 participants and the 243 participants in the CP arm who were treated.

For ACP versus CP, the results from the sensitivity analysis remained statistically significant: (HR=0.65 [95% CI: 0.49, 0.85]; nominal p=0.0017).

Supplementary Analysis of PFS by BICR

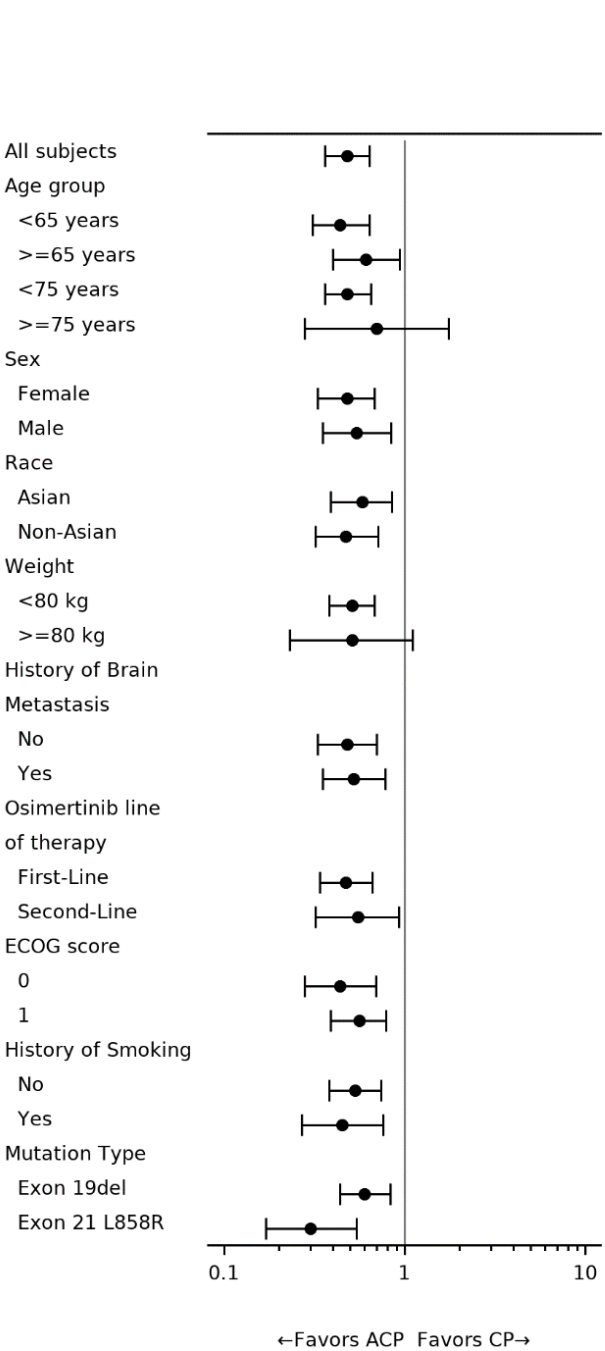
The results of the analysis of PFS by BICR censoring death/progressive disease after the start of subsequent anticancer therapy were similar to those observed in the primary analysis: for the comparison of ACP versus CP, the HR was 0.48 (95% CI: 0.36, 0.64; nominal p<0.0001).

The results from the analysis of PFS by BICR not censoring for missing more than 1 disease assessments were similar to those observed in the primary analysis: for the comparison of ACP versus CP, the HR was 0.48 (95% CI: 0.36, 0.63; nominal p<0.0001).

Subgroup Analysis of PFS by BICR

Analyses of PFS by BICR for subgroups defined by baseline clinical disease characteristics (age group, sex, race, weight, history of brain metastasis, osimertinib line of therapy, ECOG performance status score, EGFR mutation type, and history of smoking) are shown below in a forest plot.

Figure 9: Forest Plot of Progression-free Survival for Subgroups Defined by Baseline Clinical Disease Characteristics – BICR – for ACP vs CP; Full Analysis Set (Study JNJ-61186372NSC3002)



	HR (95% CI)	Median (months) CP	Median (months) ACP	Events/N CP	Events/N ACP
All subjects	0.48 (0.36, 0.64)	4.17	6.28	171/263	74/131
Age group					
<65 years	0.44 (0.31, 0.64)	4.24	7.16	106/166	40/79
>=65 years	0.61 (0.40, 0.94)	4.14	5.55	65/97	34/52
<75 years	0.48 (0.36, 0.65)	4.21	7.03	160/244	65/118
>=75 years	0.70 (0.28, 1.75)	3.42	5.42	11/19	9/13
Sex					
Female	0.48 (0.33, 0.68)	4.24	7.03	103/157	45/81
Male	0.54 (0.35, 0.84)	4.14	5.88	68/106	29/50
Race					
Asian	0.58 (0.39, 0.85)	4.24	6.8	82/127	39/63
Non-Asian	0.47 (0.32, 0.71)	4.17	5.59	84/129	34/64
Weight					
<80 kg	0.51 (0.38, 0.68)	4.21	6.28	148/226	64/113
>=80 kg	0.51 (0.23, 1.11)	4.01	5.45	23/37	10/18
History of Brain Metastasis					
No	0.48 (0.33, 0.70)	4.24	8.34	92/143	40/73
Yes	0.52 (0.35, 0.78)	4.04	5.59	79/120	34/58
Osimertinib line of therapy					
First-Line	0.47 (0.34, 0.66)	4.07	6.28	117/181	54/97
Second-Line	0.55 (0.32, 0.93)	5.26	6.21	54/82	20/34
ECOG score					
0	0.44 (0.28, 0.69)	4.24	7.16	65/101	30/55
1	0.56 (0.39, 0.79)	4.07	5.85	106/162	44/76
History of Smoking					
No	0.53 (0.38, 0.74)	4.21	6.21	110/168	55/90
Yes	0.45 (0.27, 0.76)	4.17	6.8	61/95	19/41
Mutation Type					
Exon 19del	0.60 (0.44, 0.83)	4.21	5.59	118/183	58/89
Exon 21 L858R	0.30 (0.17, 0.54)	4.07	9.69	53/79	16/42

Key: ECOG = Eastern Cooperative Oncology Group
Note: Hazard ratio for the analysis of all subjects is from a proportional hazards model stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).
Note: Hazard ratio for the analysis of subgroups is from an unstratified proportional hazards model.

Summary of main study(ies)

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

Table 25: Summary of Efficacy Results (MARIPOSA-2)

	CP (N=263)	ACP (N=131)
Primary Endpoint		
PFS (BICR)		
Number of events (%)	171 (65.0%)	74 (56.5%)
Median, months (95% CI)	**4.17 (4.04, 4.44)**	**6.28 (5.55, 8.41)**
HR (95% CI); p-value	**0.48 (0.36, 0.64); P<0.0001**	
6-month event-free rate (95% CI)	0.30 (0.23, 0.36)	0.51 (0.41, 0.60)
9-month event-free rate (95% CI)	0.16 (0.11, 0.23)	0.38 (0.28, 0.48)
12-month event-free rate (95% CI)	0.13 (0.08, 0.20)	0.22 (0.12, 0.34)
Secondary Endpoints		
ORR (BICR)[a,b]		
ORR, % (95% CI)	36.2% (30.3%, 42.3%)	63.8% (55.0%, 72.1%)
OR (95% CI); p-value	**3.10 (2.00, 4.80); P<0.0001**	
Complete response	0.4%	1.5%
Partial response	35.8%	62.3%
DOR for confirmed responders[a] (BICR)		
Median, months (95% CI)	**5.55 (4.17, 9.56)**	**6.90 (5.52, NE)**
Participants with DOR ⩾6 months	15 (20.0%)	22 (31.9%)
Duration of response ⩾12 months	1 (1.3%)	1 (1.4%)
OS		
Number of events (%)	143 (54.4%)	65 (49.6%)
Median, months (95% CI)	**15.34 (13.73, 16.76)**	**17.74 (15.97, 22.37)**
HR (95% CI); p-value	**0.73 (0.54, 0.99); 0.0386**	
6-month event-free rate (95% CI)	0.87 (0.82, 0.90)	0.91 (0.84, 0.95)
9-month event-free rate (95% CI)	0.73 (0.67, 0.78)	0.80 (0.72, 0.86)
12-month event-free rate (95% CI)	0.63 (0.57, 0.69)	0.70 (0.61, 0.77)
18-month event-free rate (95% CI)	0.40 (0.33, 0.46)	0.50 (0.40, 0.59)
Intracranial PFS (BICR)		
Number of events (%)	174 (66.2%)	86 (65.6%)
Median, months (95% CI)	**8.90 (8.15, 11.07)**	**12.45 (10.58, 14.36)**
HR (95% CI); nominal p-value	**0.65 (0.49, 0.84); 0.0012**	
6-month event-free rate (95% CI)	0.67 (0.61, 0.73)	0.82 (0.74, 0.88)
9-month event-free rate (95% CI)	0.50 (0.43, 0.56)	0.64 (0.54, 0.71)
12-month event-free rate (95% CI)	0.40 (0.33, 0.46)	0.50 (0.41, 0.59)
18-month event-free rate (95% CI)	0.17 (0.11, 0.23)	0.28 (0.19, 0.38)
Intracranial ORR[cd] (BICR)		
ORR, % (95% CI)	16.7% (8.3%, 28.5%)	23.3% (9.9%, 42.3%)
OR (95% CI); nominal p-value	1.52 (0.51, 4.50); 0.4481	
Complete response	10 (16.7%)	7 (23.3%)
Partial response	0	0
Intracranial DOR[de] (BICR)		
Median, months (95% CI)	2.23 (1.38, NE)	13.27 (1.41, NE)
Duration of response ≥6 months	1 (10.0%)	5 (71.4%)

	CP (N=263)	ACP (N=131)
Duration of response >=9 months	0	5 (71.4%)
Duration of response >=12 months	0	2 (28.6%)
Time to Intracranial Disease Progression[f] (BICR)		
Number of events (%)	82 (31.2%)	40 (30.5%)
Median, months (95% CI)	13.83 (11.24, 16.62)	16.76 (13.96, 21.88)
HR (95% CI); nominal p-value	0.56 (0.38, 0.82); 0.0025	
6-month event-free rate (95% CI)	0.73 (0.66, 0.79)	0.88 (0.81, 0.93)
9-month event-free rate (95% CI)	0.61 (0.53, 0.68)	0.78 (0.68, 0.85)
12-month event-free rate (95% CI)	0.55 (0.46, 0.63)	0.69 (0.59, 0.78)
18-month event-free rate (95% CI)	0.39 (0.28, 0.49)	0.50 (0.36, 0.62)
TTST[g]		
Number of events (%)	207 (78.7%)	88 (67.2%)
Median, months (95% CI)	6.60 (6.11, 7.39)	12.16 (10.71, 14.29)
HR (95% CI); nominal p-value	0.51 (0.39, 0.65); <0.0001	
6-month event-free rate (95% CI)	0.58 (0.52, 0.64)	0.81 (0.73, 0.86)
9-month event-free rate (95% CI)	0.35 (0.29, 0.41)	0.67 (0.58, 0.75)
12-month event-free rate (95% CI)	0.24 (0.19, 0.30)	0.51 (0.42, 0.60)
18-month event-free rate (95% CI)	0.12 (0.08, 0.17)	0.31 (0.22, 0.40)
PFS2[h]		
Number of events (%)	150 (57.0%)	70 (53.4%)
Median, months (95% CI)	11.60 (10.05, 12.98)	16.03 (13.90, 17.61)
HR (95% CI); nominal p-value	0.64 (0.48, 0.85); 0.0020	
6-month event-free rate (95% CI)	0.82 (0.77, 0.87)	0.89 (0.82, 0.93)
9-month event-free rate (95% CI)	0.62 (0.55, 0.68)	0.76 (0.67, 0.82)
12-month event-free rate (95% CI)	0.48 (0.41, 0.55)	0.64 (0.55, 0.72)
18-month event-free rate (95% CI)	0.27 (0.21, 0.34)	0.39 (0.29, 0.48)
TTSP[i]		
Number of events	159 (60.5%)	72 (55.0%)
Median, months (95% CI)	11.76 (8.87, 13.60)	16.03 (12.71, 19.38)
HR (95% CI); nominal p-value	0.73 (0.55, 0.96); 0.0259	

PFS, ORR and DOR results are from data cut-off 10 July 2023 when hypothesis testing and final analysis for these endpoints was performed. OS and all other secondary endpoint results are from data cut-off 26 April 2024 from the second interim OS analysis.

[a] Based on subjects with measurable disease at baseline by BICR.

[b] Based on Kaplan-Meier estimate.

[c] Among subjects with baseline intracranial disease by BICR

[d] Note that only intracranial CRs are considered in this analysis because, as per charter, brain lesions could not be selected as target lesions by BICR.

[e] Among subjects with intracranial response by BICR.

[f] Defined as time from randomization until the date of objective intracranial disease progression, as assessed by BICR

[g] Defined as time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation, or death, whichever comes first.

[h] Defined as time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first.

[i] Time to symptomatic progression-Defined as time from randomization to the onset of new or worsening lung cancer symptoms requiring a change in anticancer therapy or intervention, or to death, whichever comes first.

Supportive study(ies)

CHRYSALIS Chemotherapy Cohort: Supportive Efficacy

Study Population and Exposure

A total of 20 participants with NSCLC were enrolled in the chemotherapy combination cohort; participants were enrolled in this cohort to evaluate safety. Notably, participants were not required to have a specific molecular phenotype to enroll in the chemotherapy combination cohort; 11 participants had EGFRm NSCLC, 8 patients had NSCLC with less common EGFR mutations and 1 participant had NSCLC with a KRAS mutation. As a result, comparison of aggregate efficacy data for this cohort to more uniform populations such as that seen in MARIPOSA-2 must be done with caution.

Overall, participants had a median age of 62 years, with 35.0% being ≥65 years of age. An equal number of male and female participants (10 each) were enrolled in the chemotherapy combination cohort. Most participants were white (45.0%) or Asian (40.0%), and 3 participants (15.0%) were black or African American.

All participants (100.0%) were diagnosed with adenocarcinoma and most participants had stage IV disease (85.0%) at the time of initial diagnosis. The median time from diagnosis of metastatic disease to the first dose of study treatment was 20.2 months (range, 0.7270.80 months), and the median number of lines of previous therapy was 1 (range, 0-7). The most common sites of metastases were lymph nodes (65.0%) and bone (40.0%).

The 20 participants treated with ACP combination therapy received a median of 10 treatment cycles, with 4 participants (20.0%) receiving 30 or more treatment cycles, and 1 participant receiving a maximum of 39 cycles. A total of 7 participants (35.0%) received amivantamab and carboplatin/pemetrexed combination therapy for at least 12 months.

Supportive Efficacy Results

As of the CCO (15 November 2022), confirmed PRs per RECIST v.1.1 were observed for 7 out of 19 participants, giving an ORR of 36.8% (95% CI: 16.3%, 61.6%).

After a median follow-up of 22.0 months (range, 1.4-28.1 months), 4 participants remained on active treatment, of which 2 continued without progression and 2 continued therapy beyond progression with clinical benefit.

A spider plot of the best investigator-assessed percentage change in target lesion SoD as a function of time showed 10 participants achieving a reduction in target lesion diameter of at least 30%.

Among the 7 responders, the median DOR was 6.67 months (95% CI: 3.71, 21.75). Of the 7 responding participants, 5 (71.43%) had a DOR ≥6 months (3 with ongoing response at clinical cutoff, of which 2 responders were treated beyond RECIST-defined PD).

Median PFS was 7.85 months (95% CI: 5.49, 9.69 months); the 6-month and 12-month PFS rates for this population were 69% (95% CI: 44%, 88%) and 27% (95% CI: 10%, 47%), respectively.

The median TTF was 8.21 months (95% CI: 4.14, 15.28). The 9-month and 12-month event-free rates for TTF in this population were 40% (95% CI: 19%, 60%) and 35% (95% CI: 16%, 55%), respectively.

As of the CCO, 11 participants (55.0%) died. The median OS was 22.77 months (95% CI: 8.08, NE), with 45.0% of participants censored. The estimated 12-month survival rate was 65% (95% CI: 40%, 82%), while the estimated 18-month survival rate was 60% (95% CI: 36%, 78%).

Supportive Phase 3 Study 61186372NSC3001 (hereafter PAPILLON)

PAPILLON study has been assessed in the procedure Rybrevant II-10.

Biomarker Analyses

Across arm B and C at baseline 100% of NSCLC patients had tumours positively tested for EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (66.6% of participants had the EGFR exon 19del mutation and 33.4% had the EGFR exon 21 L858R mutation).

The Applicant clarified that the participants were not required to undergo local or central testing to confirm EGFR Exon 19del or Exon 21 L858R mutation status at the time of enrolment. Instead, a confirmation of EGFR Exon 19del or Exon 21 L858R mutation status based on local testing performed prior to osimertinib therapy administered prior to enrolment on MARIPOSA-2. Per protocol, all participants received prior osimertinib, which was given as first-line systemic therapy for 70.5% of participants and second-line therapy for 29.4% of participants.

The current information in the SmPC section 5.1 on testing EGFR Exon 19del or Exon 21 L858R mutation status in MARIPOSA-2 has been amended to clearly state that the testing has not been repeated once the EGFR mutation status has been previously established at the time of initial diagnosis or prior 3rd generation TKI therapy. The following amendment is proposed to align the current information on testing in the SmPC sections 4.2 and 5.1 with the newly received information on testing in MARIPOSA-2:

for EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (testing could have been performed at or after the time of locally advanced or metastatic disease diagnosis. Testing did not need to be repeated once EGFR mutation status has been previously established).

2.4.3. Discussion on clinical efficacy

MARIPOSA-2 pivotal study

Design and conduct of clinical study

MARIPOSA-2 is an ongoing, randomized, open-label, multicentre Phase 3 study planned as three arm study to compare the combination of lazertinib, amivantamab, carboplatin and pemetrexed (LACP/ACPL in arm A) versus CP (arm B) and ACP (arm C) versus CP (arm B). The patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations progressing on or after prior Osimertinib were randomized 2:2:1 to receive LACP/ACPL:CP:ACP.

Selection of patients with NSCLC expressing EGFR Exon 19del or Exon 21 L858R mutations to be randomized in the study and the overall inclusion/exclusion criteria are adequate to identify a population with advanced EGFRm NSCLC progressing on/after osimertinib that would benefit from the targeted therapy.

To support the sought indication, two of the three arms, namely arm B and C comparing the efficacy and safety of ACP (Arm C) versus CP (Arm B) are taken into consideration and constitute the pivotal data of MARIPOSA-2 study.

The study includes a screening phase, a treatment phase, and a follow-up phase.

After screening and enrolment, eligible participants were randomly assigned to study treatment in a 2:2:1 ratio (LACP/ACP-L:CP:ACP). Randomization was stratified by osimertinib line of therapy (first-line versus second-line), history of brain metastases (yes versus no), and Asian race (yes versus no).

Treatments

The patients in the ACP arm received amivantamab in the RP2 ChD regimen established in the Phase 1 CHRYSALIS study for amivantamab in combination with carboplatin and pemetrexed. The treatment continued until disease progression, death, or unacceptable toxicity. Continuation of study treatment after confirmed disease progression was allowed after approval from the medical monitor, if the investigator believed the participant was deriving clinical benefit. The regimen, as well as the sequence of components administration is adequately reflected in the SmPC 4.2 and 5.1.

Patients in the CP arm received carboplatin for up to 4 cycles and pemetrexed in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression.

Objectives/endpoints

The choice of PFS as primary endpoint is acceptable, in line with the relevant CHMP guideline. A blinded, independent central review (BICR) assessment of the primary endpoint PFS was planned which is adequate, taking in account the open-label design.

OS is assessed as a key secondary endpoint which is in line with the anticancer guideline when PFS is chosen as primary endpoint.

The other secondary endpoint tested sequentially is ORR. Test for ORR was to be conducted before the test for OS.

The other secondary efficacy endpoints (DoR, Intracranial response- related endpoints, TSST, PFS2, TTSP and PROs) were not tested for type-1 error, are acceptable

Statistical analysis plan

The changes made (SAP amendment 1, 23 June 2022, CSP amendment 3, 27 June 2022) stated that a biomarker-driven subgroup analysis was removed. Moreover, a second (dual) primary hypothesis was defined to independently evaluate the efficacy of both the ACP versus CP arms and lazertinib plus ACP versus CP arms. The alpha spend intended for the biomarker analysis was repurposed to support the testing of what became two primary hypotheses.

Paramount for the assessment of the potential impact of the changes made on study conclusions is the time-point for the amendment(s) implementation with which follows that only a limited amount of primary efficacy endpoint data will have been available. In this respect, worth considering is also that given the unbalanced allocation (2:2:1), the number of randomised subjects will have been approximately half that many in the ACP arm as compared with the LACP and CP arm.

The SAP amendment 1/CSP amendment 3 was formally implemented until the end of June 2022, approximately only 7 months after the screening of the first subject (17 November 2021). The number of subjects randomised has not been clarified but according to the Applicant approximately 59 patients across the study had then completed a disease evaluation, and the Sponsor had only received blinded data from the BICR vendor on 12 of these patients.

Further, in considering the study outcomes it was found unlikely that any potential impact on the type I error could have impacted the statistical evidence to an extent that will have altered study conclusions (PFS, ACP vs CP: HR: 0.48, 95% CI: 0.36, 0.64, p <0.0001).

Hence, the changes made were accepted.

Statistical analysis planned and performed

The original SAP was approved 16 February 2022. The submitted SAP version is amendment 3, dated 19 May 2023. Besides the changes as discussed above (SAP amendment 1), neither amendment 2 nor 3 raised any concern.

The subject for the current application was ACP. The pre-defined hypothesis testing of the primary efficacy endpoints and key secondary efficacy endpoints were nonetheless performed as planned for LACP/ACP-L (Arm A) versus CP (Arm B) and ACP (Arm C) versus CP (Arm B), respectively according to the multiple testing procedure. This is endorsed.

The main features of the statistical analysis plan (that still applied) were presented already in the original version of the study protocol (9 July 2021). Overall, tests and analysis models were according to convention and were accepted.

No interim analysis was planned for the primary endpoint. The primary efficacy analysis was performed based on all randomised subjects. This was endorsed.

In the primary analysis of PFS by BICR, the censoring of subjects did not completely follow the rules as preferred by EMA. However, a predefined analysis showed that not censoring for missing more than 1 disease assessments provided an almost identical outcome to the one observed in the primary analysis.

To address the censoring of subjects who were randomised and not treated in the CP arm, a sensitivity analysis for the PFS by BICR was performed in which these subjects (n=20) were assumed to have been event-free until the clinical cut-off. This analysis supported the robustness of the primary analysis of the primary endpoint.

The multiple testing procedure relied on a graphical approach applied in a group sequential design setting and was acceptable. Analyses were performed according to plan despite that the LACP/ACP-L arm (arm A) was no longer subject to the current application.

Intracranial PFS was defined as a secondary endpoint and was not included in the multiple testing procedure. The first interim analysis of OS was planned at the time of the final PFS analysis.

The final OS analysis has been planned to occur after 400 deaths.

Efficacy data and additional analyses

Patient disposition

Overall, 657 participants were randomized in study 2:1, 263 to the CP arm, 131 to the ACP arm, and 263 to the LACP/ACP-L arm.

At the cut-off date for the current primary analysis (final analysis for primary endpoint) of 10 July 2023, 33% of patients remained on the study treatment (51.5% in the ACP arm and 22.6% in the CP arm) and 67% that discontinued the treatment mostly due to progressive disease overrepresented in the CP arm in comparison with ACP arm (63% in CP arm and 31.5% in CP).

No important imbalance is seen in discontinuations due to physician decision. On the other hand, higher discontinuation due to patients refusing further study treatment is noticed again in the control CP arm than in experimental ACP arm (8.6% in CP vs 2.3% in ACP arm).

Major protocol deviations and amendments

The major protocol deviations were clearly described and balanced distributed across the three arms.

Baseline characteristics

Overall, the study population in the full analysis set (FAS) (N=657 randomized ACP:CP= 131:263) was considered comparable across the two arms. The median age was 62 (range: 31;85), and 37.8% of participants were ≥65 years of age, which is considered adequate with the intended population. A total of 60.4% of patients were female, 48.2% were Asian.

Majority of the patients had adenocarcinoma (99%), stage IV, were not former smoker (65.5%) and had baseline ECOG 1 (60.4%). Brain metastases were present at baseline in 45.2% of patients. Overall, all patients in FAS had EGFR mut positive NSCLC. Among EGFR mutations, the Exon 19del was detected in 69.2% of patients and Exon 21 L858R in 30.8% of the patients in FAS.

Among prior therapies for lung cancer, systemic therapy in locally advanced or metastatic setting was received by the overall patient population. Roughly 70% of patients received one line and 30% of patients 2 lines of prior systemic therapy. Regarding the prior osimertinib treatment, in accordance with study protocol Osimertinib was prior administered for overall study population, for 70.5% of patients as first line and for 29.4% of patients as second line.

The study population is representative of the sought indication.

Primary endpoint

PFS by BICR

At the cutoff date for final PFS analysis 10 July 2023, after a median follow-up of 8.6 months, the maturity grade was reached with totally 371 PFS events across the three arms, including 245 events in the two arm of interest, arm B and C, i.e. 171 (65%) events in CP arm and 74(56.5%) events in ACP arm, respectively.

The PFS analysis by BICR showed a statistically significant benefit with amivantamab addition to CP HR 0.48 (0.36, 0.64); p-value<0.0001 and clinically relevant PFS gain in this setting of 2 months (median PFS 6.28 (5.55;8.41) months in ACP arm vs 4.17 (4.04;4.44) months in CP arm). An imbalance in the dropouts (20 in the CP arm and 1 in the ACP arm) between randomization and treatment administration was observed. The impact on PFS was addressed by a sensitivity analysis (PFS by BICR Assuming Untreated CP Arm Participants Were Event-free at CCO) which showed that PFS remained statistically significant (HR=0.65 [95% CI: 0.49, 0.85]; nominal p=0.0017).

The primary PFS analysis was not completely in accordance with EMA's censoring rules. However, according to supplementary PFS analyses including an analysis not censoring for missing more than one disease evaluation prior PD/death: HR (95% CI) 0.48 (95% CI: 0.36, 0.63; nominal p<0.0001) confirms the robustness of PFS primary analysis by a fusion of FDA-EMA censoring rules. This addresses the ITT principle (treatment policy strategy) according to EMA's policy and is considered supportive for the robustness of PFS gain.

A statistically significant PFS benefit was observed with investigator assessment of PFS (HR=0.41 [95% CI: 0.30, 0.54], nominal p<0.0001), with a median PFS of 8.18 months (95% CI: 6.80, 10.94) in the ACP arm compared with 4.21 months (95% CI: 4.04, 4.47) in the CP arm. The agreement rate on the event status between Investigator and BICR was 89.4% in CP arm and 87% in ACP arm.

The benefit was observed across all pre-defined clinically relevant subgroups. The 95% CI of the PFS HR was crossing the unity only in the subgroup over 75 years and the subgroup with weight over 80 kg, however no conclusion can be drawn due to the small size of these subgroups.

Secondary endpoints

Objective response rate (ORR) was the first secondary endpoint sequentially tested after the primary endpoint was met. ORR was assessed in the patients with measurable disease at baseline that

represents the majority of ITT population (130 of the 131 patients in ACP arm and 260 of the 263 patients in CP arm). ORR by BICR further support the benefit with amivantamab addition to CP with ORR of 63.8% in ACP arm compared with the CP arm 36.2% ORR with statistically significant odds ratio of 3.10 ((95% CI: 2.00, 4.80; p<0.0001). Similar results were observed for best overall response.

DoR: The response (CR or PR) lasts longer in the ACP arm than in CP arm (median DoR 6.90 months in ACP compared with 5.55 months in the CP arm).

Overall survival

The results of the second interim analysis of OS become available during the procedure. The second interim analysis was event driven, preplanned when approximately 300 OS events (75% of total events) had been observed in all 3 arms (approximately 189 OS events in ACP and CP arms combined).

With a total of 208 OS events observed across ACP and CP arms (approx. 50% maturity), the second interim OS analysis performed at CCO of 26 April 2024 shows an OS difference of 2 months with ACP over CP (17.74 (15.97, 22.37) from 15.34 (13.73, 16.76), HR = 0.73; 95% CI: 0.54, 0.99; p=0.0386). This, however, is not statistically significant (the 2 sided alpha level of significance was set at 0.0142).

Given the alpha allocated to this interim analysis, the study will continue to the final analysis for OS, which is planned to be conducted when approximately 400 OS events have been observed in all 3 arms (approximately 250 OS events in ACP vs. CP arms combined). Results are anticipated by mid-year 2025. The MAH will submit the results of the final OS analysis as recommended by the CHMP (REC).

Intracranial PFS and ORR by BICR

According to baseline disease characteristics 120 patients (45.6%) in the CP arm and 58 (44.3%) in the ACP arm, had a history of brain metastasis.

The intracranial response endpoints were not multiplicity corrected.

Intracranial PFS as assessed by BICR was presented for ITT population suggesting benefit with addition of amivantamab to CP with HR of 0.55 (95%CI 0.38, 0.79) and nominal p 0.0011. The observed intracranial PFS difference was maintained with extended median follow up, at IA2 (CCO of 26 April 2024):ACP vs CP (12.45 vs 8.90 months) and HR=0.65 (0.49, 0.84);p= 0.0012. Of note, the IA2 analysis was neither multiplicity controlled, nor prespecified.

A 12% difference of intracranial ORR in favour of ACP regimen in patients with measurable disease at baseline is also observed: Objective response rate 7 (23.3%) in ACP and 10 (16.7%) in the CP arm, respectively. The median duration of intracranial response among responders was also longer with ACP vs CP: 13.27 (1.41, NE) vs 2.23 (1.38, NE).

Subsequent systemic therapies -time related endpoints: PFS2 and TTST

A longer median time to initiation of subsequent anti-cancer therapy was observed in the ACP arm of 12.16 (10.71, 14.29) months compared with the CP arm 6.60 (6.11, 7.39) with a HR of 0.51 (0.39, 0.65); P<0.0001. The median PFS2 was also longer for the patients receiving subsequent anticancer treatment in ACP arm in comparison with those in CP arm with HR PFS2 0.64 (0.48, 0.85); P=0.0020.

Overall, the results of the secondary endpoints that, per protocol, were not type 1 error tested are however supporting the benefit with a first line regimen with amivantamab add-on to CP.

Patient-reported Outcomes

Overall, the PRO outcomes indicated that HRQoL were unchanged from baseline in both treatment arms. However, the open-label design of the study, absence of type 1 error control precludes solid inferences. Moreover, equivalence claim without known assay sensitivity are not supported.

Biomarker Analyses

The current information in the SmPC section 4.2 and 5.1 on testing EGFR Exon 19del or Exon 21 L858R mutation status in MARIPOSA-2 has been amended to clearly state that the testing has not been repeated once the EGFR mutation status has been previously established at the time of initial diagnosis or prior 3rd generation TKI therapy.

The proposed indication sought is covering use after any 3rd generation EGFR TKI, whereas the study was performed in patients exclusively pretreated with osimertinib. Amivantamab does not bind to the kinase domain, but rather to the extracellular domain of EGFR. TKI's bind to the kinase domain which is entirely different and localised intracellularly. Therefore, resistance mutations selected by EGFR TKIs are not anticipated to impact amivantamab binding. Consequently, the efficacy seen post osimertinib may be extrapolated to use after any EGFR targeting TKI. As a result, the indication was revised to remove "3rd generation" from the wording in 4.1 of the SmPC.

2.4.4. Conclusions on the clinical efficacy

A clinically relevant PFS gain, along with a trend towards improved OS, is shown when amivantamab is added to chemotherapy, compared to chemotherapy alone, in patients that have progressed on osimertinib. Efficacy in patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI has been established. The final OS results will be submitted as a Recommendation by Q3 2025.

2.5. Clinical safety

Introduction

The key safety data are derived from the safety population in pivotal study 61186372NSC3002 (hereafter referred to as MARIPOSA-2). The safety analysis set (SAS) consisted of the patients in the pivotal study who received any study treatment. Of the patients in the SAS, 130 patients received amivantamab + carboplatin and pemetrexed (ACP) treatment and 243 patients received carboplatin and pemetrexed (CP) treatment. Data are presented as off data cut-off (DCO) 10 July 2023.

Supportive safety data are derived from ACP treated patients in study 61186372NSC3001 (hereafter referred to as PAPILLON, DCO 03 May 2023) and study 61186372EDI1001 (hereafter referred to as CHRYSALIS, DCO 15 Nov 2022) and presented together. Safety data derived from ACP treated patients in the MARIPOSA-2, PAPILLON, and CHRYSALIS studies are also presented as a combined safety cohort (n=301).

Comparisons with amivantamab monotherapy are made when considered relevant.

Table 26: Overview of clinical study data

Study	Study Design	Study Population	Role in SCS CCO	Treatment	Number of Participants	Median Total Duration of Treatment (months)[7]
MARIPOSA-2[1] 61186372NSC3002	Ongoing, randomized, open-label, multicenter Phase 3	Patients with EGFRm NSCLC, whose disease has progressed on or after treatment with the third-generation TKI osimertinib	**Pivotal** (ACP: integrated) 10 Jul 2023	**ACP**[4]	**n=130**	**6.31**
				CP[4]	**n=243**	**3.68**
PAPILLON[2] 61186372NSC3001	Ongoing, randomized, open-label, multicenter Phase 3	Patients with treatment-naïve, locally advanced or metastatic NSCLC with EGFR exon 20ins	**Supportive** (integrated) 03 May 2023	**ACP**[4]	**n=151**	**9.72**
CHRYSALIS[3] 61186372EDI1001	Ongoing, FIH, open-label, multicenter, multicohort Phase 1	**Chemotherapy Combination Cohort (ACP)** Patients with advanced NSCLC (no specific driver mutation was required)	**Supportive** (integrated) 15 Nov 2022	**ACP**[4]	**n=20**	**7.49**
		Amivantamab Monotherapy Patients with locally advanced or metastatic NSCLC, after disease progression on or after platinum-based chemotherapy	**Pooled ADR analyses only** (not integrated) 30 Mar 2021	**A**[5]	**n=380**[6]	**4.14**

[1]In addition to comparing ACP (Arm C) and CP treatment (Arm B), MARIPOSA-2 also compares efficacy and safety of a combination of the novel third-generation EGFR TKI, lazertinib, with amivantamab, carboplatin, and pemetrexed (Arm A) versus CP (Arm B) in the same patient population. There was a dosing schedule change to Arm A driven by a USM during the execution of the study, and participants receiving the updated dosing schedule have had limited follow-up. As a result, this comparison, and the results of Arm A, are not in scope of this SCS. The study also contains an extension cohort, which compares the efficacy and safety of combining lazertinib with ACP (ACP-L regimen) versus the ACP regimen in approximately 90 additional participants. Follow-up for the extension cohort is ongoing and the primary analysis has not been conducted. As a result, data from the extension cohort is also not in scope of this SCS.

[2]In addition to the ACP treatment (Arm A), PAPILLON also has a CP treatment (Arm B). The results of Arm B are not in scope of this SCS, as the AE profile for CP is well established.

[3]CHRYSALIS evaluated amivantamab monotherapy and 2 different combination regimens (amivantamab with CP and amivantamab with lazertinib), and included n=380 participants who received the RP2D of amivantamab monotherapy and n=20 participants who received the RP2CD of amivantamab in combination with CP (ie, CC Cohort). Data from amivantamab in combination with lazertinib are not included in the SCS.

[4]A 21-day treatment cycle was used with ACP and CP combination therapy:
A: amivantamab 1,400 mg (1,750 mg if body weight ≥80 kg) by IV infusion once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.
C: carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles.
P: pemetrexed 500 mg/m^2 (with vitamin supplementation) on Day 1 of each 21-day cycle, until disease progression.

[5]A 28-day treatment cycle was used with amivantamab monotherapy: amivantamab weekly for the first 4 doses (at 1,050 mg for <80 kg, 1,400 mg for ≥80 kg), followed by Q2W dosing for subsequent cycles.

[6]The 2 different pooled ADR populations are:
- n=510, including 130 participants treated with ACP from MARIPOSA-2 + 380 participants treated with amivantamab monotherapy from CHRYSALIS.
- n=661, including 130 participants treated with ACP from MARIPOSA-2 + 380 participants treated with amivantamab monotherapy from CHRYSALIS + 151 participants treated with ACP from PAPILLON.

All safety analyses are based on the safety analysis set (SAS), which includes all participants who received at least one dose of the investigational product or its comparator.

Patient exposure

Overall extent of exposure

Table 27: Treatment disposition (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Subjects ongoing any study agent	55 (22.6%)	67 (51.5%)	74 (43.3%)	141 (46.8%)
Discontinued all study agents[a]	188 (77.4%)	63 (48.5%)	97 (56.7%)	160 (53.2%)
Reason for discontinuation[b]				
Progressive disease	152 (62.6%)	41 (31.5%)	62 (36.3%)	103 (34.2%)
Adverse event	10 (4.1%)	14 (10.8%)	17 (9.9%)	31 (10.3%)
Adverse event - COVID-19 related	0	1 (0.8%)	2 (1.2%)	3 (1.0%)
Subject refused further study treatment	21 (8.6%)	3 (2.3%)	12 (7.0%)	15 (5.0%)
Physician decision*	5 (2.1%)	5 (3.8%)	2 (1.2%)	7 (2.3%)
Death	0	0	1 (0.6%)	1 (0.3%)
Non-compliance with study drug	0	0	1 (0.6%)	1 (0.3%)
Other	0	0	2 (1.2%)	2 (0.7%)

[a] Subjects are included in the Amivantamab + Chemotherapy (ACP) group if they discontinued amivantamab, carboplatin, and pemetrexed. Subjects are included in the Chemotherapy group if they discontinued carboplatin and pemetrexed.
[b] The reason for discontinuation for all study agents is the reason of discontinuation for the last study agent received.
Note: Adverse events that are considered COVID-19 related (associated) are based on events that code to a COVID-19 MedDRA term and events that are identified via the COVID-19 Case of AEs form
*In MARIPOSA-2 the category of physician decision included participants who discontinued treatment due to clinical progressive disease in the absence of radiographic progressive disease. This was not the case in PAPILLON or CHRYSALIS.

Duration of exposure

Table 28: Summary of duration and treatment cycles (safety analysis set)

	CP			ACP							
	MARIPOSA-2			MARIPOSA-2				CHRYSALIS + PAPILLON			
	Total	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed
Analysis set: Safety	243	243	243	130	130	130	130	171	171	171	171
Duration of treatment (months)											
N	243	243	243	130	130	130	130	171	171	171	171
Mean (SD)	4.20 (3.148)	1.90 (0.747)	4.20 (3.149)	6.49 (3.862)	6.29 (4.029)	2.02 (0.617)	6.40 (3.825)	10.43 (6.412)	10.20 (6.454)	2.06 (0.632)	9.50 (6.322)
Median	3.68	2.10	3.68	6.31	6.19	2.10	6.21	9.26	9.17	2.14	8.31
Range	(0.0; 15.9)	(0.0; 5.0)	(0.0; 15.9)	(0.0; 14.7)	(0.0; 14.7)	(0.0; 3.1)	(0.0; 14.7)	(0.1; 28.1)	(0.0; 28.1)	(0.0; 3.8)	(0.0; 28.1)
Total number of treatment cycles received											
N	243	243	243	130	130	130	130	171	171	171	171
Mean (SD)	6.63 (4.336)	3.49 (0.929)	6.63 (4.337)	9.72 (5.367)	9.37 (5.562)	3.65 (0.776)	9.55 (5.292)	14.66 (8.512)	14.07 (8.422)	3.71 (0.739)	13.43 (8.322)
Median	6.00	4.00	6.00	9.00	9.00	4.00	9.00	14.00	13.00	4.00	12.00
Range	(1.0; 23.0)	(1.0; 5.0)	(1.0; 23.0)	(1.0; 22.0)	(1.0; 22.0)	(1.0; 4.0)	(1.0; 22.0)	(1.0; 39.0)	(1.0; 39.0)	(1.0; 4.0)	(1.0; 39.0)

Note: Percentages are calculated with the number of subjects in each treatment group as denominator.

	ACP			
	COMBINED			
	Total	Amivantamab	Carboplatin	Pemetrexed
Analysis set: Safety	301	301	301	301
Duration of treatment (months)				
N	301	301	301	301
Mean (SD)	8.73 (5.791)	8.51 (5.862)	2.05 (0.625)	8.16 (5.595)
Median	7.69	7.66	2.10	7.39
Range	(0.0; 28.1)	(0.0; 28.1)	(0.0; 3.8)	(0.0; 28.1)
Total number of treatment cycles received				
N	301	301	301	301
Mean (SD)	12.52 (7.711)	12.04 (7.677)	3.68 (0.755)	11.75 (7.416)
Median	12.00	11.00	4.00	11.00
Range	(1.0; 39.0)	(1.0; 39.0)	(1.0; 4.0)	(1.0; 39.0)

Note: Percentages are calculated with the number of subjects in each treatment group as denominator.

The mean dose intensity for amivantamab was 91.49% (range 2.7-107-0). For carboplatin, the mean dose intensity was 100.04% (range 100.0-105.1) in the ACP arm compared to 100.36% (range 100.0-

112.6) in the CP arm, and for pemetrexed the mean dose intensity was 100.11% (range 100.0-113.2) in the APC arm compared to 100.01% (range 100.0-101.8) in the CP arm.

Adverse events

Adverse events overview

TEAEs are defined as AEs that occurred or worsened in severity from the initial administration of study treatment until 30 days after the last dose of study treatment or start of subsequent anticancer therapy (whichever was earlier). The severity of TEAEs was graded according to the NCI-CTCAE toxicity grade Version 5.0, and AEs were coded using MedDRA Version 25.0. Analyses of TEAEs were performed by subgroups of participants defined by age, sex, race, baseline hepatic and renal function, ECOG PS, weight, brain metastasis, and smoking history.

Table 29: Overall summary of treatment-emergent adverse events (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Subjects with 1 or more:				
AEs	227 (93.4%)	130 (100.0%)	171 (100.0%)	301 (100.0%)
Grade 3 or greater AEs	117 (48.1%)	94 (72.3%)	129 (75.4%)	223 (74.1%)
Maximum toxicity grade				
Grade 1	30 (12.3%)	2 (1.5%)	3 (1.8%)	5 (1.7%)
Grade 2	80 (32.9%)	34 (26.2%)	39 (22.8%)	73 (24.3%)
Grade 3	94 (38.7%)	62 (47.7%)	97 (56.7%)	159 (52.8%)
Grade 4	20 (8.2%)	29 (22.3%)	24 (14.0%)	53 (17.6%)
Grade 5	3 (1.2%)	3 (2.3%)	8 (4.7%)	11 (3.7%)
Serious AEs	49 (20.2%)	42 (32.3%)	66 (38.6%)	108 (35.9%)
AEs leading to discontinuation of any study agent	9 (3.7%)	24 (18.5%)	45 (26.3%)	69 (22.9%)
AEs leading to discontinuation of Amivantamab	-	20 (15.4%)	22 (12.9%)	42 (14.0%)
AEs leading to discontinuation of Carboplatin	4 (1.6%)	9 (6.9%)	17 (9.9%)	26 (8.6%)
AEs leading to discontinuation of Pemetrexed	8 (3.3%)	14 (10.8%)	36 (21.1%)	50 (16.6%)
AEs leading to drug interruption of any study agent[c]	81 (33.3%)	84 (64.6%)	123 (71.9%)	207 (68.8%)
AEs leading to interruption of Amivantamab[c]	-	78 (60.0%)	116 (67.8%)	194 (64.5%)
AEs leading to interruption of Carboplatin[c]	57 (23.5%)	40 (30.8%)	42 (24.6%)	82 (27.2%)
AEs leading to interruption of Pemetrexed[c]	81 (33.3%)	64 (49.2%)	97 (56.7%)	161 (53.5%)
AEs leading to dose reduction of any study agent	37 (15.2%)	53 (40.8%)	79 (46.2%)	132 (43.9%)
AEs leading to reduction of Amivantamab	-	22 (16.9%)	59 (34.5%)	81 (26.9%)
AEs leading to reduction of Carboplatin	31 (12.8%)	36 (27.7%)	30 (17.5%)	66 (21.9%)
AEs leading to reduction of Pemetrexed	31 (12.8%)	36 (27.7%)	43 (25.1%)	79 (26.2%)
AEs leading to death[b]	3 (1.2%)	3 (2.3%)	8 (4.7%)	11 (3.7%)
Related AEs leading to death[a,b]	1 (0.4%)	2 (1.5%)	3 (1.8%)	5 (1.7%)
COVID-19 associated AEs[d]	26 (10.7%)	29 (22.3%)	46 (26.9%)	75 (24.9%)
COVID-19 associated serious AEs[d]	0	2 (1.5%)	5 (2.9%)	7 (2.3%)
COVID-19 associated non-serious AEs[d]	26 (10.7%)	27 (20.8%)	42 (24.6%)	69 (22.9%)
COVID-19 associated grade 3 or greater AEs[d]	0	2 (1.5%)	5 (2.9%)	7 (2.3%)
COVID-19 associated AEs[d] leading to death	0	0	2 (1.2%)	2 (0.7%)

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.
[c] Excludes infusion related reactions.
[d] COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term and events that are identified via the COVID-19 Case of AEs form.
[adapted from tsfae01.rtf] [xcp_oncology/z61186372_73841937/dbr_dwh_mariposa2/re_scs_mariposa2/tsfae01.sas] 07SEP2023, 16:33

Adverse events by system organ class and preferred term

Table 30: Number of subjects with treatment-emergent adverse events with frequency of at least 10% in combined ACP group by system organ class and preferred term (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Subjects with 1 or more AEs	227 (93.4%)	130 (100.0%)	171 (100.0%)	301 (100.0%)
System organ class Preferred term				
Gastrointestinal disorders	147 (60.5%)	112 (86.2%)	148 (86.5%)	260 (86.4%)
Nausea	90 (37.0%)	58 (44.6%)	71 (41.5%)	129 (42.9%)
Constipation	72 (29.6%)	50 (38.5%)	70 (40.9%)	120 (39.9%)
Stomatitis	21 (8.6%)	41 (31.5%)	44 (25.7%)	85 (28.2%)
Vomiting	42 (17.3%)	32 (24.6%)	35 (20.5%)	67 (22.3%)
Diarrhoea	16 (6.6%)	18 (13.8%)	38 (22.2%)	56 (18.6%)
Skin and subcutaneous tissue disorders	62 (25.5%)	102 (78.5%)	157 (91.8%)	259 (86.0%)
Rash	12 (4.9%)	56 (43.1%)	87 (50.9%)	143 (47.5%)
Dermatitis acneiform	7 (2.9%)	26 (20.0%)	59 (34.5%)	85 (28.2%)
Dry skin	4 (1.6%)	15 (11.5%)	20 (11.7%)	35 (11.6%)
Pruritus	17 (7.0%)	20 (15.4%)	12 (7.0%)	32 (10.6%)
Infections and infestations	81 (33.3%)	92 (70.8%)	135 (78.9%)	227 (75.4%)
Paronychia	1 (0.4%)	48 (36.9%)	92 (53.8%)	140 (46.5%)
COVID-19	25 (10.3%)	27 (20.8%)	38 (22.2%)	65 (21.6%)
Blood and lymphatic system disorders	154 (63.4%)	95 (73.1%)	126 (73.7%)	221 (73.4%)
Neutropenia	101 (41.6%)	74 (56.9%)	98 (57.3%)	172 (57.1%)
Anaemia	97 (39.9%)	51 (39.2%)	81 (47.4%)	132 (43.9%)
Thrombocytopenia	72 (29.6%)	57 (43.8%)	64 (37.4%)	121 (40.2%)
Leukopenia	68 (28.0%)	37 (28.5%)	60 (35.1%)	97 (32.2%)
General disorders and administration site conditions	122 (50.2%)	95 (73.1%)	126 (73.7%)	221 (73.4%)
Oedema peripheral	15 (6.2%)	42 (32.3%)	55 (32.2%)	97 (32.2%)
Fatigue	47 (19.3%)	36 (27.7%)	34 (19.9%)	70 (23.3%)
Asthenia	40 (16.5%)	34 (26.2%)	30 (17.5%)	64 (21.3%)
Pyrexia	25 (10.3%)	15 (11.5%)	27 (15.8%)	42 (14.0%)
Metabolism and nutrition disorders	98 (40.3%)	74 (56.9%)	127 (74.3%)	201 (66.8%)
Decreased appetite	51 (21.0%)	40 (30.8%)	60 (35.1%)	100 (33.2%)
Hypoalbuminaemia	21 (8.6%)	29 (22.3%)	67 (39.2%)	96 (31.9%)
Hypokalaemia	15 (6.2%)	24 (18.5%)	37 (21.6%)	61 (20.3%)
Hypomagnesaemia	9 (3.7%)	13 (10.0%)	25 (14.6%)	38 (12.6%)
Hypocalcaemia	9 (3.7%)	16 (12.3%)	20 (11.7%)	36 (12.0%)
Hyponatraemia	16 (6.6%)	13 (10.0%)	21 (12.3%)	34 (11.3%)
Injury, poisoning and procedural complications	6 (2.5%)	82 (63.1%)	85 (49.7%)	167 (55.5%)
Infusion related reaction	1 (0.4%)	76 (58.5%)	76 (44.4%)	152 (50.5%)
Investigations	99 (40.7%)	53 (40.8%)	103 (60.2%)	156 (51.8%)
Alanine aminotransferase increased	67 (27.6%)	26 (20.0%)	52 (30.4%)	78 (25.9%)
Aspartate aminotransferase increased	57 (23.5%)	19 (14.6%)	49 (28.7%)	68 (22.6%)
Weight decreased	17 (7.0%)	14 (10.8%)	24 (14.0%)	38 (12.6%)
Gamma-glutamyltransferase increased	25 (10.3%)	7 (5.4%)	24 (14.0%)	31 (10.3%)
Respiratory, thoracic and mediastinal disorders	73 (30.0%)	51 (39.2%)	80 (46.8%)	131 (43.5%)
Dyspnoea	18 (7.4%)	14 (10.8%)	25 (14.6%)	39 (13.0%)
Cough	29 (11.9%)	14 (10.8%)	23 (13.5%)	37 (12.3%)
Musculoskeletal and connective tissue disorders	58 (23.9%)	47 (36.2%)	56 (32.7%)	103 (34.2%)
Back pain	18 (7.4%)	13 (10.0%)	18 (10.5%)	31 (10.3%)

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

2.5.1.1. Adverse drug reactions

All terms previously identified as amivantamab-related ADRs and ADRs identified in the PAPIILLON study were included in the current report.

ADR methodology

The primary data source used for determination of new ADR terms for amivantamab was the MARIPOSA-2 study. Any TEAEs with an absolute incidence of 1) 10% or higher in the ACP arm and 2) a difference of 5% or higher in ACP arm as compared to the CP arm were selected for further analysis to determine if they should be classified as ADRs. This analysis included assessment of the difference between the exposure-adjusted rates in the ACP and CP arms. Additionally, all TEAEs (regardless of frequency) were reviewed for potential plausible biological or pharmacological association with amivantamab. Where possible, similar PTs were grouped together to assess specific medical concepts.

All SAEs and TEAEs that were grade ≥3 were thoroughly reviewed for potential plausible biological or pharmacological association with amivantamab. In addition, a comprehensive review of laboratory abnormalities with incidence of ≥20% in the ACP arm that also worsened from baseline and demonstrated a consistent up or down trend of mean values over time was conducted.

ADRs

Two existing ADRs that are grouped terms had new PTs added to their grouping:

- Nail toxicity (grouped term) had 1 new PT added (nail bed disorder)
- Rash (grouped term) had 1 new PT added (rash follicular)

In the PAPILLON study, pyrexia and haemorrhoids were identified as new ADRs. Additionally, three existing ADRs that are grouped terms had new PTs added to their grouping based on data from the PAPILLON study:

- Nail toxicity (grouped term) had 3 new PTs added (nail bed inflammation, nail dystrophy, nail infection)
- Stomatitis (grouped term) had 1 new PT added (angular cheilitis)
- Dry skin (grouped term) had 1 new PT added (xerosis)

ADRs pertaining to ACP treatment

VTE was identified as a new ADR pertaining to ACP combination treatment in the PAPILLON study.

In the MARIPOSA-2 study, neutropenia and thrombocytopenia were identified as new ACP ADRs and included in the SmPC 4.8.

2.5.1.1.1. ADR presentation in the SmPC

The ADR presentation in the SmPC 4.8 is based on pooled safety data from 301 ACP treated patients in the MARIPOSA-2, PAPILLON, and CHRYSALIS studies, i.e., the combined safety data set presented throughout this report.

Table 31: Adverse reactions in patients receiving amivantamab in combination with carboplatin and pemetrexed

System organ class Adverse reaction	Frequency category	Any Grade (%)	Grade 3-4 (%)
Blood and lymphatic system disorders			
Neutropenia	Very common	57	39
Thrombocytopenia		40	12
Metabolism and nutrition disorders			
Decreased appetite	Very common	33	1.3
Hypoalbuminaemia*		32	3.7
Hypokalaemia		20	6.6
Hypomagnesaemia		13	1.3
Hypocalcaemia		12	1.0
Nervous system disorders			
Dizziness*	Common	10	0.3
Vascular disorders			
Venous thromboembolism*	Very common	14	3.0
Eye disorders			
Other eye disorders*	Common	7.3	0
Visual impairment*		3.0	0
Growth of eyelashes	Uncommon	0.3	0
Keratitis		0.3	0
Uveitis		0.3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease*	Common	2.3	1.7
Gastrointestinal disorders			
Nausea	Very common	43	1.0
Constipation		40	0.3
Stomatitis*		39	3.0
Vomiting		22	2.0
Diarrhoea		19	2.3
Abdominal pain*	Common	11	0.3
Haemorrhoids		9.3	0.7
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	26	4.3
Aspartate aminotransferase increased		23	0.7
Blood alkaline phosphatase increased	Common	10	0.3
Skin and subcutaneous tissue disorders			
Rash*	Very common	83	14
Nail toxicity*		53	4.3
Dry skin*		16	0
Pruritus		10	0
Musculoskeletal and connective tissue disorders			
Myalgia	Common	5.0	0.7
General disorders and administration site conditions			
Fatigue*	Very common	43	4.7
Oedema*		40	1.3
Pyrexia		14	0
Injury, poisoning and procedural complications			
Infusion related reaction	Very common	50	3.0

* Grouped terms

2.5.1.2. Treatment related adverse events

Overall, 99.2% (129/130) of the patients in the ACP arm and 86.4% (210/243) in the CP arm had TEAEs considered related to any of the study agents by the investigator. Of the patients who received amivantamab, 98.5% (128/130) experienced TEAEs considered related to amivantamab treatment.

The most frequently reported related TEAEs were consistent with the known safety profiles of the individual components. TEAEs considered related to amivantamab were rash, dermatitis acneiform, paronychia, and stomatitis, predominantly associated with the on-target activity against the EGFR pathway, and hypoalbuminemia and peripheral oedema, associated with on-target activity against the MET pathway. Furthermore, IRRs, also known to be associated with amivantamab treatment, were among the related TEAEs.

Treatment related TEAEs grade >3 were reported for 66.9% of the patients in the ACP arm vs. 35.4% in the CP arm. Of the patients who received amivantamab, 41.5% (54/130) experienced grade >3 TEAEs related to amivantamab treatment.

2.5.1.3. Adverse events by severity

Grade 3 or higher TEAEs were reported for 72.3% of the patients in the ACP arm compared to 48.1% in the CP arm.

There were nine commonly reported grade ≥3 TEAEs (defined as occurring in ≥5% of participants in the ACP or CP arm of MARIPOSA-2, supportive ACP, or combined ACP): neutropenia, leukopenia, anaemia, thrombocytopenia, ALT increased, hypokalaemia, rash, IRR, and paronychia.

Table 32: Most commonly reported grade 3 or higher TEAEs

Adverse Event	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	CHRYSALIS+PAPILLON (n=171)	COMBINED (n=301)
At Least 1 TEAE				
Grade 3+ Incidence	117 (48.1%)	94 (72.3%)	129 (75.4%)	223 (74.1%)
Grade 3	94 (38.7%)	62 (47.7%)	97 (56.7%)	159 (52.8%)
Grade 4	20 (8.2%)	29 (22.3%)	24 (14.0%)	53 (17.6%)
Grade 5	3 (1.2%)	3 (2.3%)	8 (4.7%)	11 (3.7%)
Neutropenia				
Grade 3+ Incidence	52 (21.4%)	59 (45.4%)	57 (33.3%)	116 (38.5%)
Grade 3	39 (16.0%)	40 (30.8%)	40 (23.4%)	80 (26.6%)
Grade 4	13 (5.3%)	19 (14.6%)	17 (9.9%)	36 (12.0%)
Grade 5	0	0	0	0
Leukopenia				
Grade 3+ Incidence	23 (9.5%)	26 (20.0%)	18 (10.5%)	44 (14.6%)
Grade 3	21 (8.6%)	24 (18.5%)	16 (9.4%)	40 (13.3%)
Grade 4	2 (0.8%)	2 (1.5%)	2 (1.2%)	4 (1.3%)
Grade 5	0	0	0	0
Anemia				
Grade 3+ Incidence	23 (9.5%)	15 (11.5%)	19 (11.1%)	34 (11.3%)
Grade 3	23 (9.5%)	15 (11.5%)	19 (11.1%)	34 (11.3%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Thrombocytopenia				
Grade 3+ Incidence	22 (9.1%)	19 (14.6%)	18 (10.5%)	37 (12.3%)
Grade 3	15 (6.2%)	9 (6.9%)	10 (5.8%)	19 (6.3%)
Grade 4	7 (2.9%)	10 (7.7%)	8 (4.7%)	18 (6.0%)
Grade 5	0	0	0	0
Alanine aminotransferase increased				
Grade 3+ Incidence	10 (4.1%)	7 (5.4%)	6 (3.5%)	13 (4.3%)
Grade 3	10 (4.1%)	7 (5.4%)	6 (3.5%)	13 (4.3%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Hypokalemia				
Grade 3+ Incidence	6 (2.5%)	6 (4.6%)	14 (8.2%)	20 (6.6%)
Grade 3	5 (2.1%)	4 (3.1%)	11 (6.4%)	15 (5.0%)
Grade 4	1 (0.4%)	2 (1.5%)	3 (1.8%)	5 (1.6%)
Grade 5	0	0	0	0
Rash				
Grade 3+ Incidence	0	8 (6.2%)	17 (9.9%)	25 (8.3%)
Grade 3	0	8 (6.2%)	17 (9.9%)	25 (8.3%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Infusion Related Reaction				
Grade 3+ Incidence	0	7 (5.4%)	2 (1.2%)	9 (3.0%)
Grade 3	0	7 (5.4%)	2 (1.2%)	9 (3.0%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Paronychia				
Grade 3+ Incidence	0	3 (2.3%)	10 (5.8%)	13 (4.3%)
Grade 3	0	3 (2.3%)	10 (5.8%)	13 (4.3%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0

Note: Commonly reported is defined as occurring ≥5% of participants in the ACP or CP arm.

2.5.1.4. Adverse events leading to dose adjustments

2.5.1.4.1. Dose reduction due to adverse events

Table 33: Number of subjects with TEAEs leading to any study treatment dose reduction with frequency of at least 7% in any treatment group by system organ class and preferred term (safety analysis set)

	CP			ACP			
	Total	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed
Analysis set: Safety	243	243	243	130	130	130	130
Subjects with 1 or more AEs leading to any study treatment dose reduction	37 (15.2%)	31 (12.8%)	31 (12.8%)	53 (40.8%)	22 (16.9%)	36 (27.7%)	36 (27.7%)
System organ class Preferred term							
Blood and lymphatic system disorders	29 (11.9%)	25 (10.3%)	22 (9.1%)	22 (16.9%)	4 (3.1%)	21 (16.2%)	18 (13.8%)
Neutropenia	16 (6.6%)	15 (6.2%)	13 (5.3%)	14 (10.8%)	3 (2.3%)	14 (10.8%)	11 (8.5%)
Thrombocytopenia	14 (5.8%)	12 (4.9%)	13 (5.3%)	9 (6.9%)	1 (0.8%)	9 (6.9%)	9 (6.9%)
Gastrointestinal disorders	3 (1.2%)	3 (1.2%)	3 (1.2%)	7 (5.4%)	2 (1.5%)	5 (3.8%)	4 (3.1%)
Stomatitis	0	0	0	4 (3.1%)	1 (0.8%)	3 (2.3%)	3 (2.3%)
Infections and infestations	0	0	0	8 (6.2%)	5 (3.8%)	3 (2.3%)	3 (2.3%)
Paronychia	0	0	0	2 (1.5%)	2 (1.5%)	0	0
Skin and subcutaneous tissue disorders	0	0	0	11 (8.5%)	10 (7.7%)	1 (0.8%)	1 (0.8%)
Rash	0	0	0	8 (6.2%)	7 (5.4%)	1 (0.8%)	1 (0.8%)

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

2.5.1.4.2. Dose interruption due to adverse events

Table 34: Number of subjects with TEAEs leading to any study treatment interruption with frequency of at least 7% in any treatment group by system organ class and preferred term (safety analysis set)

	CP			ACP			
	Total	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed
Analysis set: Safety	243	243	243	130	130	130	130
Subjects with 1 or more AEs leading to any study treatment Interruption[a]	81 (33.3%)	57 (23.5%)	81 (33.3%)	84 (64.6%)	78 (60.0%)	40 (30.8%)	64 (49.2%)
System organ class Preferred term							
Blood and lymphatic system disorders	46 (18.9%)	32 (13.2%)	46 (18.9%)	40 (30.8%)	35 (26.9%)	22 (16.9%)	30 (23.1%)
Neutropenia	32 (13.2%)	25 (10.3%)	32 (13.2%)	30 (23.1%)	26 (20.0%)	19 (14.6%)	23 (17.7%)
Anaemia	13 (5.3%)	7 (2.9%)	13 (5.3%)	7 (5.4%)	5 (3.8%)	3 (2.3%)	5 (3.8%)
Thrombocytopenia	12 (4.9%)	8 (3.3%)	12 (4.9%)	13 (10.0%)	11 (8.5%)	5 (3.8%)	7 (5.4%)
Leukopenia	7 (2.9%)	4 (1.6%)	7 (2.9%)	12 (9.2%)	10 (7.7%)	5 (3.8%)	8 (6.2%)
Infections and infestations	20 (8.2%)	12 (4.9%)	20 (8.2%)	33 (25.4%)	30 (23.1%)	14 (10.8%)	28 (21.5%)
COVID-19	7 (2.9%)	6 (2.5%)	7 (2.9%)	12 (9.2%)	12 (9.2%)	7 (5.4%)	10 (7.7%)
Paronychia	0	0	0	8 (6.2%)	6 (4.6%)	2 (1.5%)	6 (4.6%)
Gastrointestinal disorders	1 (0.4%)	1 (0.4%)	1 (0.4%)	9 (6.9%)	8 (6.2%)	3 (2.3%)	4 (3.1%)
Stomatitis	0	0	0	3 (2.3%)	2 (1.5%)	1 (0.8%)	1 (0.8%)
Skin and subcutaneous tissue disorders	0	0	0	20 (15.4%)	19 (14.6%)	3 (2.3%)	9 (6.9%)
Dermatitis acneiform	0	0	0	7 (5.4%)	7 (5.4%)	0	2 (1.5%)
Rash	0	0	0	11 (8.5%)	10 (7.7%)	2 (1.5%)	6 (4.6%)

Key: AE = adverse event
[a] Excludes infusion related reactions.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

2.5.1.5. Adverse events of special interest

Adverse events of special interest (AESIs) of pneumonitis/ILD, IRR, and rash were prospectively identified based upon the identified safety profile of amivantamab. VTE was identified as a risk for the combination of amivantamab and lazertinib as a result of a signal detected in the MARIPOSA study and was added as an AESI for the MARIPOSA-2 study. VTE was also identified as an ADR for the ACP combination in the PAPILLON study.

Table 35: Number of subjects with treatment-emergent AESIs by category and preferred term (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Subjects with 1 or more AEs	38 (15.6%)	115 (88.5%)	162 (94.7%)	277 (92.0%)
Special interest category Preferred term				
Rash	30 (12.3%)	92 (70.8%)	155 (90.6%)	247 (82.1%)
Rash	12 (4.9%)	56 (43.1%)	87 (50.9%)	143 (47.5%)
Dermatitis acneiform	7 (2.9%)	26 (20.0%)	59 (34.5%)	85 (28.2%)
Folliculitis	0	8 (6.2%)	6 (3.5%)	14 (4.7%)
Dermatitis	0	4 (3.1%)	7 (4.1%)	11 (3.7%)
Rash pustular	0	4 (3.1%)	6 (3.5%)	10 (3.3%)
Acne	1 (0.4%)	3 (2.3%)	5 (2.9%)	8 (2.7%)
Rash maculo-papular	4 (1.6%)	3 (2.3%)	4 (2.3%)	7 (2.3%)
Erythema	4 (1.6%)	2 (1.5%)	3 (1.8%)	5 (1.7%)
Rash erythematous	1 (0.4%)	3 (2.3%)	0	3 (1.0%)
Rash macular	1 (0.4%)	2 (1.5%)	1 (0.6%)	3 (1.0%)
Rash pruritic	1 (0.4%)	1 (0.8%)	2 (1.2%)	3 (1.0%)
Skin lesion	0	1 (0.8%)	2 (1.2%)	3 (1.0%)
Pustule	0	0	2 (1.2%)	2 (0.7%)
Rash papular	0	0	2 (1.2%)	2 (0.7%)
Rash follicular	0	1 (0.8%)	0	1 (0.3%)
Drug eruption	1 (0.4%)	0	0	0
Infusion Related Reaction	1 (0.4%)	76 (58.5%)	76 (44.4%)	152 (50.5%)
Infusion related reaction	1 (0.4%)	76 (58.5%)	76 (44.4%)	152 (50.5%)
VTE	11 (4.5%)	13 (10.0%)	29 (17.0%)	42 (14.0%)
Deep vein thrombosis	3 (1.2%)	9 (6.9%)	12 (7.0%)	21 (7.0%)
Pulmonary embolism	7 (2.9%)	4 (3.1%)	12 (7.0%)	16 (5.3%)
Embolism	2 (0.8%)	2 (1.5%)	3 (1.8%)	5 (1.7%)
Venous thrombosis	0	2 (1.5%)	1 (0.6%)	3 (1.0%)
Thrombosis	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Venous thrombosis limb	0	0	2 (1.2%)	2 (0.7%)
Renal vein thrombosis	1 (0.4%)	0	0	0
Pneumonitis/Interstitial Lung Disease	0	2 (1.5%)	5 (2.9%)	7 (2.3%)
Pneumonitis	0	1 (0.8%)	5 (2.9%)	6 (2.0%)
Interstitial lung disease	0	1 (0.8%)	0	1 (0.3%)

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

The median time to first onset of rash after first administration of study treatment in the ACP arm was 16.0 days (range 1-282) vs. 9.0 days (range 2-169) for the CP arm.

The median time to onset of an IRR in the ACP arm was 60.0 minutes (range 1-809), and most IRRs occurred during the first infusion.

The median time to first onset of a VTE event after the first administration of study treatment in the ACP arm was 71.0 days (range 15-233) vs. 43.0 days (range 9-92) in the CP arm) For a majority of participants in both the ACP and CP arms, the first VTE event occurred in the absence of concomitant

anticoagulant use at the time of the event (13/13 participants in the ACP arm, 8/11 participants in the CP arm).

The median time to first onset of events of pneumonitis/ILD after first administration of study treatment in the ACP arm was 127.0 days (range 39-215).

Table 36: Characteristics of the AESI of rash (grouped term)

Adverse Event Characteristic	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	CHRYSALIS+PAPILLON (n=171)	COMBINED (n=301)
Incidence (all grades)	30 (12.3%)	92 (70.8%)	155 (90.6%)	247 (82.1%)
Grade 3+	0	13 (10.0%)	29 (17.0%)	42 (14.0%)
Serious	0	1 (0.8%)	7 (4.1%)	8 (2.7%)
Treatment Discontinuation	0	3 (2.3%)	4 (2.3%)	7 (2.3%)
amivantamab	NA	3 (2.3%)	3 (1.8%)	6 (2.0%)
carboplatin	0	0	0	0
pemetrexed	0	1 (0.8%)	2 (1.2%)	3 (1.0%)
Drug Interruption	0	19 (14.6%)	33 (19.3%)	52 (17.3%)
amivantamab	NA	18 (13.8%)	31 (18.1%)	49 (16.3%)
carboplatin	0	2 (1.5%)	7 (4.1%)	9 (3.0%)
pemetrexed	0	9 (6.9%)	20 (11.7%)	29 (9.6%)
Dose Reduction	0	11 (8.5%)	31 (18.1%)	42 (14.0%)
amivantamab	NA	10 (7.7%)	31 (18.1%)	41 (13.6%)
carboplatin	0	1 (0.8%)	0	1 (0.3%)
pemetrexed	0	1 (0.8%)	2 (1.2%)	3 (1.0%)

Table 37*:* Characteristics of the AESI of IRR (grouped term)

Adverse Event Characteristic	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	CHRYSALIS+PAPILLON (n=171)	COMBINED (n=301)
Incidence (all grades)	1 (0.4%)	76 (58.5%)	76 (44.4%)	152 (50.5%)
Grade 3+	0	7 (5.4%)	2 (1.2%)	9 (3.0%)
Serious	0	2 (1.5%)	1 (0.6%)	3 (1.0%)
Treatment Discontinuation	0	7 (5.4%)	3 (1.8%)	10 (3.3%)
amivantamab	NA	7 (5.4%)	1 (0.6%)	8 (2.7%)
carboplatin	0	2 (1.5%)	1 (0.6%)	3 (1.0%)
pemetrexed	0	2 (1.5%)	1 (0.6%)	3 (1.0%)
Drug Interruption	1 (0.4%)	68 (52.3%)	68 (39.8%)	136 (45.2%)
amivantamab*	NA	68 (52.3%)	68 (39.8%)	136 (45.2%)
carboplatin	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
pemetrexed	1 (0.4%)	0	1 (0.6%)	1 (0.3%)
Dose Reduction	0	0	1 (0.6%)	1 (0.3%)
amivantamab	NA	0	1 (0.6%)	1 (0.3%)
carboplatin	0	0	0	0
pemetrexed	0	0	0	0

Source: Mod5.3.5.3/ISS/TSFAE23b

*Per protocol, amivantamab infusion was to be interrupted for any IRR of ≥Grade 2.

Table 38: Overall summary of treatment-emergent adverse events of venous thromboembolism (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Subjects with 1 or more:				
AEs	11 (4.5%)	13 (10.0%)	29 (17.0%)	42 (14.0%)
Related AEs[a]	3 (1.2%)	6 (4.6%)	14 (8.2%)	20 (6.6%)
Related to Amivantamab[a]	-	5 (3.8%)	12 (7.0%)	17 (5.6%)
Related to Carboplatin[a]	3 (1.2%)	2 (1.5%)	6 (3.5%)	8 (2.7%)
Related to Pemetrexed[a]	3 (1.2%)	3 (2.3%)	9 (5.3%)	12 (4.0%)
Grade 3 or greater AEs	7 (2.9%)	3 (2.3%)	6 (3.5%)	9 (3.0%)
Related Grade 3 or greater AEs[a]	2 (0.8%)	3 (2.3%)	4 (2.3%)	7 (2.3%)
Related to Amivantamab[a]	-	3 (2.3%)	3 (1.8%)	6 (2.0%)
Related to Carboplatin[a]	2 (0.8%)	1 (0.8%)	2 (1.2%)	3 (1.0%)
Related to Pemetrexed[a]	2 (0.8%)	2 (1.5%)	4 (2.3%)	6 (2.0%)
Maximum toxicity grade				
Grade 1	0	0	2 (1.2%)	2 (0.7%)
Grade 2	4 (1.6%)	10 (7.7%)	21 (12.3%)	31 (10.3%)
Grade 3	6 (2.5%)	3 (2.3%)	6 (3.5%)	9 (3.0%)
Grade 4	1 (0.4%)	0	0	0
Grade 5	0	0	0	0
Serious AEs	5 (2.1%)	3 (2.3%)	4 (2.3%)	7 (2.3%)
Related serious AEs[a]	2 (0.8%)	3 (2.3%)	2 (1.2%)	5 (1.7%)
Related to Amivantamab[a]	-	3 (2.3%)	2 (1.2%)	5 (1.7%)
Related to Carboplatin[a]	2 (0.8%)	1 (0.8%)	1 (0.6%)	2 (0.7%)
Related to Pemetrexed[a]	2 (0.8%)	2 (1.5%)	2 (1.2%)	4 (1.3%)
AEs leading to discontinuation of any study agent	0	1 (0.8%)	0	1 (0.3%)
AEs leading to discontinuation of Amivantamab	-	0	0	0
Related to Amivantamab[a]	-	0	0	0
AEs leading to discontinuation of Carboplatin	0	1 (0.8%)	0	1 (0.3%)
Related to Carboplatin[a]	0	1 (0.8%)	0	1 (0.3%)
AEs leading to discontinuation of Pemetrexed	0	0	0	0
Related to Pemetrexed[a]	0	0	0	0
AEs leading to drug interruption of any study agent	5 (2.1%)	2 (1.5%)	5 (2.9%)	7 (2.3%)
AEs leading to interruption of Amivantamab	-	2 (1.5%)	5 (2.9%)	7 (2.3%)
Related to Amivantamab[a]	-	2 (1.5%)	2 (1.2%)	4 (1.3%)
AEs leading to interruption of Carboplatin	3 (1.2%)	0	1 (0.6%)	1 (0.3%)
Related to Carboplatin[a]	1 (0.4%)	0	0	0
AEs leading to interruption of Pemetrexed	5 (2.1%)	2 (1.5%)	3 (1.8%)	5 (1.7%)
Related to Pemetrexed[a]	2 (0.8%)	2 (1.5%)	1 (0.6%)	3 (1.0%)
AEs leading to dose reduction of any study agent	0	0	1 (0.6%)	1 (0.3%)
AEs leading to reduction of Amivantamab	-	0	1 (0.6%)	1 (0.3%)
Related to Amivantamab[a]	-	0	1 (0.6%)	1 (0.3%)
AEs leading to reduction of Carboplatin	0	0	0	0
Related to Carboplatin[a]	0	0	0	0
AEs leading to reduction of Pemetrexed	0	0	1 (0.6%)	1 (0.3%)
Related to Pemetrexed[a]	0	0	1 (0.6%)	1 (0.3%)
AEs leading to death[b]	0	0	0	0
Related AEs leading to death[a,b]	0	0	0	0
Related to Amivantamab[a,b]	-	0	0	0
Related to Carboplatin[a,b]	0	0	0	0
Related to Pemetrexed[a,b]	0	0	0	0
COVID-19 associated AEs[c]	0	0	0	0
COVID-19 associated serious AEs[c]	0	0	0	0
COVID-19 associated non-serious AEs[c]	0	0	0	0
COVID-19 associated grade 3 or greater AEs[c]	0	0	0	0
COVID-19 associated AEs[c] leading to death	0	0	0	0

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.
[c] COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term and events that are identified via the COVID-19 Case of AEs form.

Table 39: Characteristics of the AESI of VTE

Adverse Event Characteristic	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	CHRYSALIS+PAPILLON (n=171)	COMBINED (n=301)
Incidence (all grades)	11 (4.5%)	13 (10.0%)	29 (17.0%)	42 (14.0%)
Exposure-Adjusted (all grades)	11 (11.0)	13 (18.1)	29 (19.9)	42 (19.3)
Incidence (Grade 3 +)	7 (2.9%)	3 (2.3%)	6 (3.5%)	9 (3.0%)
Exposure-Adjusted (Grade 3+)	7 (6.9)	3 (3.9)	6 (3.9)	9 (3.9)
Serious	5 (2.1%)	3 (2.3%)	4 (2.3%)	7 (2.3%)
Treatment Discontinuation	0	1 (0.8%)	0	1 (0.3%)
amivantamab	NA	0	0	0
carboplatin	0	1 (0.8%)	0	1 (0.3%)
pemetrexed	0	0	0	0
Drug Interruption	5 (2.1%)	2 (1.5%)	5 (2.9%)	7 (2.3%)
amivantamab	NA	2 (1.5%)	5 (2.9%)	7 (2.3%)
carboplatin	3 (1.2%)	0	1 (0.6%)	1 (0.3%)
pemetrexed	5 (2.1%)	2 (1.5%)	3 (1.8%)	5 (1.7%)
Dose Reduction	0	0	1 (0.6%)	1 (0.3%)
amivantamab	NA	0	1 (0.6%)	1 (0.3%)
carboplatin	0	0	0	0
pemetrexed	0	0	1 (0.6%)	1 (0.3%)

Table 40: Characteristics of the AESI of pneumonitis/ILD

Adverse Event Characteristic	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	CHRYSALIS+PAPILLON (n=171)	COMBINED (n=301)
Incidence (all grades)	0	2 (1.5%)	5 (2.9%)	7 (2.3%)
Grade 3+	0	1 (0.8%)	4 (2.3%)	5 (1.7%)
Serious	0	2 (1.5%)	4 (2.3%)	6 (2.0%)
Treatment Discontinuation	0	2 (1.5%)	5 (2.9%)	7 (2.3%)
amivantamab	NA	2 (1.5%)	5 (2.9%)	7 (2.3%)
carboplatin	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
pemetrexed	0	2 (1.5%)	5 (2.9%)	7 (2.3%)
Drug Interruption	0	0	0	0
amivantamab	NA	0	0	0
carboplatin	0	0	0	0
pemetrexed	0	0	0	0
Dose Reduction	0	0	0	0
amivantamab	NA	0	0	0
carboplatin	0	0	0	0
pemetrexed	0	0	0	0

Serious adverse event/deaths/other significant events

Serious adverse events

Table 41: Number of subjects with treatment-emergent SAEs by system organ class and preferred term (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Subjects with 1 or more SAEs	49 (20.2%)	42 (32.3%)	66 (38.6%)	108 (35.9%)
System organ class Preferred term				
Infections and infestations	13 (5.3%)	12 (9.2%)	21 (12.3%)	33 (11.0%)
Pneumonia	5 (2.1%)	0	8 (4.7%)	8 (2.7%)
COVID-19	0	2 (1.5%)	3 (1.8%)	5 (1.7%)
Sepsis	1 (0.4%)	3 (2.3%)	1 (0.6%)	4 (1.3%)
Skin infection	0	2 (1.5%)	2 (1.2%)	4 (1.3%)
Cellulitis	1 (0.4%)	0	3 (1.8%)	3 (1.0%)
Pneumonia viral	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Rash pustular	0	0	2 (1.2%)	2 (0.7%)
COVID-19 pneumonia	0	0	1 (0.6%)	1 (0.3%)
Gastroenteritis	0	1 (0.8%)	0	1 (0.3%)
Gastrointestinal infection	0	1 (0.8%)	0	1 (0.3%)
Herpes virus infection	0	1 (0.8%)	0	1 (0.3%)
Infection	0	0	1 (0.6%)	1 (0.3%)
Infectious pleural effusion	0	1 (0.8%)	0	1 (0.3%)
Neutropenic sepsis	0	1 (0.8%)	0	1 (0.3%)
Postoperative wound infection	0	0	1 (0.6%)	1 (0.3%)
Soft tissue infection	0	1 (0.8%)	0	1 (0.3%)
Bacteraemia	1 (0.4%)	0	0	0
Meningitis	1 (0.4%)	0	0	0
Pneumonia pneumococcal	1 (0.4%)	0	0	0
Respiratory tract infection	2 (0.8%)	0	0	0
Upper respiratory tract infection	1 (0.4%)	0	0	0
Gastrointestinal disorders	2 (0.8%)	5 (3.8%)	16 (9.4%)	21 (7.0%)
Diarrhoea	0	1 (0.8%)	3 (1.8%)	4 (1.3%)
Vomiting	0	1 (0.8%)	3 (1.8%)	4 (1.3%)
Nausea	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Abdominal pain	0	0	1 (0.6%)	1 (0.3%)
Cheilitis	0	0	1 (0.6%)	1 (0.3%)
Colitis	0	1 (0.8%)	0	1 (0.3%)
Duodenitis	0	0	1 (0.6%)	1 (0.3%)
Dysphagia	0	0	1 (0.6%)	1 (0.3%)
Enterocolitis	0	0	1 (0.6%)	1 (0.3%)
Gastrointestinal disorder	0	0	1 (0.6%)	1 (0.3%)
Haematemesis	0	0	1 (0.6%)	1 (0.3%)
Lower gastrointestinal haemorrhage	0	0	1 (0.6%)	1 (0.3%)
Stomatitis	0	1 (0.8%)	0	1 (0.3%)
Upper gastrointestinal haemorrhage	0	0	1 (0.6%)	1 (0.3%)
Ascites	1 (0.4%)	0	0	0
Enteritis	1 (0.4%)	0	0	0
Respiratory, thoracic and mediastinal disorders	7 (2.9%)	11 (8.5%)	9 (5.3%)	20 (6.6%)
Pulmonary embolism	3 (1.2%)	3 (2.3%)	4 (2.3%)	7 (2.3%)
Dyspnoea	2 (0.8%)	4 (3.1%)	1 (0.6%)	5 (1.7%)
Pneumonitis	0	1 (0.8%)	4 (2.3%)	5 (1.7%)
Pleural effusion	3 (1.2%)	1 (0.8%)	1 (0.6%)	2 (0.7%)
Cough	0	0	1 (0.6%)	1 (0.3%)
Dyspnoea exertional	0	1 (0.8%)	0	1 (0.3%)
Haemoptysis	0	0	1 (0.6%)	1 (0.3%)
Hydrothorax	0	1 (0.8%)	0	1 (0.3%)
Interstitial lung disease	0	1 (0.8%)	0	1 (0.3%)
Pneumothorax	0	1 (0.8%)	0	1 (0.3%)
Respiratory failure	1 (0.4%)	1 (0.8%)	0	1 (0.3%)
Blood and lymphatic system disorders	14 (5.8%)	10 (7.7%)	5 (2.9%)	15 (5.0%)
Thrombocytopenia	5 (2.1%)	4 (3.1%)	3 (1.8%)	7 (2.3%)
Neutropenia	6 (2.5%)	2 (1.5%)	2 (1.2%)	4 (1.3%)
Anaemia	2 (0.8%)	2 (1.5%)	1 (0.6%)	3 (1.0%)
Febrile neutropenia	5 (2.1%)	2 (1.5%)	1 (0.6%)	3 (1.0%)
Myelosuppression	0	2 (1.5%)	0	2 (0.7%)
Leukopenia	1 (0.4%)	0	1 (0.6%)	1 (0.3%)
Pancytopenia	1 (0.4%)	0	0	0
Metabolism and nutrition disorders	3 (1.2%)	1 (0.8%)	7 (4.1%)	8 (2.7%)
Hypokalaemia	0	1 (0.8%)	3 (1.8%)	4 (1.3%)
Hyponatraemia	0	0	2 (1.2%)	2 (0.7%)
Decreased appetite	1 (0.4%)	0	1 (0.6%)	1 (0.3%)
Dehydration	0	0	1 (0.6%)	1 (0.3%)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Hypomagnesaemia	0	0	1 (0.6%)	1 (0.3%)
Hypophagia	0	0	1 (0.6%)	1 (0.3%)
Diabetes mellitus	1 (0.4%)	0	0	0
Hypercalcaemia	1 (0.4%)	0	0	0
General disorders and administration site conditions	8 (3.3%)	4 (3.1%)	3 (1.8%)	7 (2.3%)
Asthenia	2 (0.8%)	0	2 (1.2%)	2 (0.7%)
Pyrexia	3 (1.2%)	2 (1.5%)	0	2 (0.7%)
Death	0	0	1 (0.6%)	1 (0.3%)
Fatigue	1 (0.4%)	1 (0.8%)	0	1 (0.3%)
Oedema peripheral	0	1 (0.8%)	0	1 (0.3%)
Non-cardiac chest pain	1 (0.4%)	0	0	0
Pain	1 (0.4%)	0	0	0
Nervous system disorders	4 (1.6%)	1 (0.8%)	6 (3.5%)	7 (2.3%)
Aphasia	0	0	1 (0.6%)	1 (0.3%)
Cerebral infarction	1 (0.4%)	1 (0.8%)	0	1 (0.3%)
Cerebrovascular accident	1 (0.4%)	0	1 (0.6%)	1 (0.3%)
Dizziness	0	0	1 (0.6%)	1 (0.3%)
Encephalopathy	0	0	1 (0.6%)	1 (0.3%)
Myoclonic epilepsy	0	0	1 (0.6%)	1 (0.3%)
Optic neuritis	0	1 (0.8%)	0	1 (0.3%)
Transient ischaemic attack	0	0	1 (0.6%)	1 (0.3%)
Headache	1 (0.4%)	0	0	0
Seizure	1 (0.4%)	0	0	0
Syncope	1 (0.4%)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (0.8%)	5 (2.9%)	6 (2.0%)
Rash	0	1 (0.8%)	2 (1.2%)	3 (1.0%)
Dermatitis acneiform	0	0	2 (1.2%)	2 (0.7%)
Rash maculo-papular	0	0	1 (0.6%)	1 (0.3%)
Injury, poisoning and procedural complications	2 (0.8%)	2 (1.5%)	3 (1.8%)	5 (1.7%)
Infusion related reaction	0	2 (1.5%)	1 (0.6%)	3 (1.0%)
Lumbar vertebral fracture	0	0	1 (0.6%)	1 (0.3%)
Vascular access site thrombosis	0	0	1 (0.6%)	1 (0.3%)
Procedural pain	1 (0.4%)	0	0	0
Spinal compression fracture	1 (0.4%)	0	0	0
Cardiac disorders	2 (0.8%)	3 (2.3%)	1 (0.6%)	4 (1.3%)
Supraventricular tachycardia	0	2 (1.5%)	0	2 (0.7%)
Cardio-respiratory arrest	0	0	1 (0.6%)	1 (0.3%)
Ventricular fibrillation	0	1 (0.8%)	0	1 (0.3%)
Cardiac failure	1 (0.4%)	0	0	0
Myocardial infarction	1 (0.4%)	0	0	0
Investigations	2 (0.8%)	1 (0.8%)	3 (1.8%)	4 (1.3%)
Blood creatinine increased	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Alanine aminotransferase increased	1 (0.4%)	0	1 (0.6%)	1 (0.3%)
C-reactive protein increased	1 (0.4%)	0	1 (0.6%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	1 (0.4%)	1 (0.8%)	2 (1.2%)	3 (1.0%)
Back pain	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Myalgia	0	0	1 (0.6%)	1 (0.3%)
Pain in extremity	1 (0.4%)	0	0	0
Hepatobiliary disorders	3 (1.2%)	1 (0.8%)	1 (0.6%)	2 (0.7%)
Cholecystitis acute	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Biliary obstruction	0	0	1 (0.6%)	1 (0.3%)
Hepatic cytolysis	1 (0.4%)	0	0	0
Hepatic function abnormal	2 (0.8%)	0	0	0
Renal and urinary disorders	1 (0.4%)	1 (0.8%)	1 (0.6%)	2 (0.7%)
Acute kidney injury	0	0	1 (0.6%)	1 (0.3%)
Renal impairment	1 (0.4%)	1 (0.8%)	0	1 (0.3%)
Reproductive system and breast disorders	0	0	2 (1.2%)	2 (0.7%)
Endometrial thickening	0	0	1 (0.6%)	1 (0.3%)
Ovarian mass	0	0	1 (0.6%)	1 (0.3%)
Vascular disorders	2 (0.8%)	2 (1.5%)	0	2 (0.7%)
Deep vein thrombosis	1 (0.4%)	2 (1.5%)	0	2 (0.7%)
Embolism	1 (0.4%)	0	0	0
Immune system disorders	0	0	1 (0.6%)	1 (0.3%)
Contrast media reaction	0	0	1 (0.6%)	1 (0.3%)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.6%)	1 (0.3%)
Prostate cancer	0	0	1 (0.6%)	1 (0.3%)
Psychiatric disorders	1 (0.4%)	0	1 (0.6%)	1 (0.3%)
Mental status changes	0	0	1 (0.6%)	1 (0.3%)
Confusional state	1 (0.4%)	0	0	0

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 25.0.
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Deaths

Per protocol, any participant death in the MARIPOSA-2 study that was attributed by the investigator explicitly to progression of disease was not to be reported as an AE (or SAE). Death due to disease progression was to be documented on the death forms. In PAPILLON and CHRYSALIS, for all deaths that
occurred <30 days after last dose of study treatment, specific information regarding the cause of death was to be reported as a grade 5 TEAE.

Table 42: Summary of deaths and cause of death (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Deaths during study	65 (26.7%)	27 (20.8%)	39 (22.8%)	66 (21.9%)
Progressive disease	56 (23.0%)	17 (13.1%)	29 (17.0%)	46 (15.3%)
Adverse event	3 (1.2%)	4 (3.1%)	6 (3.5%)	10 (3.3%)
COVID-19	0	1 (0.8%)	2 (1.2%)	3 (1.0%)
Other	6 (2.5%)	5 (3.8%)	2 (1.2%)	7 (2.3%)
Deaths within 30 days of first dose[a]	2 (0.8%)	1 (0.8%)	3 (1.8%)	4 (1.3%)
Progressive disease	2 (0.8%)	0	1 (0.6%)	1 (0.3%)
Adverse event	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Other	0	0	1 (0.6%)	1 (0.3%)
Deaths within 30 days of last dose[a]	7 (2.9%)	7 (5.4%)	8 (4.7%)	15 (5.0%)
Progressive disease	4 (1.6%)	4 (3.1%)	1 (0.6%)	5 (1.7%)
Adverse event	3 (1.2%)	3 (2.3%)	4 (2.3%)	7 (2.3%)
COVID-19	0	0	2 (1.2%)	2 (0.7%)
Other	0	0	1 (0.6%)	1 (0.3%)

Deaths due to COVID-19 are not included in the other causes of death (ie, subjects are only counted in one row).
[a] Subjects in this category will also be counted in the Deaths during study category.
[tsfdth01.rtf] [xcp_oncology/z61186372_73841937/dbr_dwh_mariposa2/re_scs_mariposa2/tsfdth01.sas] 14SEP2023, 17:25

Events of death occurring within 30 days of first study dose were defined as early deaths. In the MARIPOSA-2 study there were in total three reports of early deaths; one in the ACP arm (sepsis deemed related to study treatment) and two in the CP arm (both due to progressive disease).

Table 43: Number of subjects with TEAEs leading to death by system organ class and preferred term (safety analysis set)

	CP	ACP		
	MARIPOSA-2	MARIPOSA-2	CHRYSALIS + PAPILLON	COMBINED
Analysis set: Safety	243	130	171	301
Subjects with 1 or more AEs leading to death	3 (1.2%)	3 (2.3%)	8 (4.7%)	11 (3.7%)
System organ class Preferred term				
Respiratory, thoracic and mediastinal disorders	2 (0.8%)	1 (0.8%)	0	1 (0.3%)
Dyspnoea	1 (0.4%)	1 (0.8%)	0	1 (0.3%)
Respiratory failure	1 (0.4%)	0	0	0
Infections and infestations	1 (0.4%)	1 (0.8%)	5 (2.9%)	6 (2.0%)
Pneumonia	1 (0.4%)	0	2 (1.2%)	2 (0.7%)
COVID-19	0	0	1 (0.6%)	1 (0.3%)
COVID-19 pneumonia	0	0	1 (0.6%)	1 (0.3%)
Sepsis	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Cardiac disorders	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Cardio-respiratory arrest	0	0	1 (0.6%)	1 (0.3%)
Ventricular fibrillation	0	1 (0.8%)	0	1 (0.3%)
General disorders and administration site conditions	0	0	1 (0.6%)	1 (0.3%)
Death	0	0	1 (0.6%)	1 (0.3%)
Nervous system disorders	0	0	1 (0.6%)	1 (0.3%)
Cerebrovascular accident	0	0	1 (0.6%)	1 (0.3%)

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

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TEAEs leading to death were assessed as related to any study treatment for two participants (1.5%) in the MARIPOSA-2 ACP arm and one participant (0.4%) in the CP arm.

In the ACP arm, the two fatal TEAEs considered related to study treatment were 1) sepsis (assessed as related to carboplatin and pemetrexed), which occurred on day 15 in the setting of grade 4 leukopenia and grade 3 infectious pleural effusion and 2) ventricular fibrillation (assessed as related to amivantamab and pemetrexed). The participant with ventricular fibrillation had an unscheduled visit on day 351 without any abnormal physical findings and per the family on day 357 was in good health but suddenly became unwell. Cardiopulmonary arrest occurred during transportation to the hospital. Despite cardiopulmonary resuscitation efforts the participant died. Of note, it is unknown whether the ventricular fibrillation occurred before or after cardiopulmonary resuscitation.

In the CP arm, the one fatal TEAE considered related to study treatment was respiratory failure (assessed as related to both carboplatin and pemetrexed) that occurred on day 95 and was likely multifactorial in the setting of grade 4 pneumonia, thrombocytopenia, and neutropenia. The participant also had an ongoing grade 2 pulmonary embolism at the time of the event.

Laboratory findings

Clinical laboratory tests

Laboratory results were classified according to the NCI-CTCAE Version 5.0 and included the haematology and chemistry assessments from the protocol-specified scheduled timepoints.

Table 44: Most common haematologic laboratory test abnormalities (grade 3 or 4) during treatment

Laboratory Test	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	CHRYSALIS+PAPILLON (n=171)	COMBINED (n=301)
Anemia				
Grade 3	21 (9.0%)	16 (12.3%)	20 (11.8%)	36 (12.0%)
Grade 4	0	0	0	0
Lymphocyte Count Decreased				
Grade 3	46 (20.2%)	34 (26.6%)	19 (13.6%)	53 (19.8%)
Grade 4	4 (1.8%)	7 (5.5%)	3 (2.1%)	10 (3.7%)
Lymphocyte Count Increased				
Grade 3	2 (0.9%)	7 (5.5%)	0	7 (2.6%)
Grade 4	0	0	0	0
Absolute Neutrophil Count Decreased				
Grade 3	42 (18.0%)	42 (32.3%)	47 (27.6%)	89 (29.7%)
Grade 4	17 (7.3%)	21 (16.2%)	17 (10.0%)	38 (12.7%)
Platelet Count Decreased				
Grade 3	11 (4.7%)	11 (8.5%)	9 (5.3%)	20 (6.7%)
Grade 4	10 (4.3%)	11 (8.5%)	9 (5.3%)	20 (6.7%)
White Blood Cell Decreased				
Grade 3	40 (17.2%)	44 (33.8%)	27 (15.9%)	71 (23.7%)
Grade 4	4 (1.7%)	9 (6.9%)	6 (3.5%)	15 (5.0%)

Source: Mod5.3.5.3/ISS/TSFLAB02part1of2 and /TSFLAB02part2of2
Hematologic Laboratory Test Parameters with a Grade 3 occurrence >5% or Grade 4 occurrence >1% in the ACP or CP arm.

[a] These TEAEs are selected because their incidence is above the cut-off in at least one of the groupings, but this does not by default mean that their incidence is above the cut-off in all of the groupings.

The majority of hematologic abnormalities were grade 1 or 2. Grade 3 and 4 neutrophil and platelet count decreases were observed with a higher incidence in the ACP than in the CP arm, and this was reflected in a higher incidence of TEAEs of neutropenia and thrombocytopenia (including grade ≥3 TEAEs) in the ACP arm.

Analysis of the mean neutrophil and platelet counts over time showed a transient decrease at cycle 1 day 8 and cycle 1 day 15 in both treatment arms in MARIPOSA-2. The neutrophil and platelet counts increased through cycle 2 day 1 and stabilised thereafter. There was no consistent worsening of decreased neutrophil counts in the ACP arm compared to the CP arm. A greater proportion of participants in the ACP arm (36.2%) received a colony stimulating factor (e.g., filgastim, pegfilgastim) during the study than participants in the CP arm (22.2%). Platelet stimulating agents were utilized infrequently, e.g., thrombopoietin (2.3% ACP and 1.6% CP) and hetrombopag (2.3% ACP and 0.8% CP). The majority of reported neutropenia and thrombocytopenia events were non-serious and rarely led to treatment discontinuation. The incidence of febrile neutropenia (1.5% ACP vs 2.5% CP) and grade ≥3 bleeding events (1 participant with upper gastrointestinal haemorrhage in ACP, none in CP) was low and comparable between the treatment arms.

Table 45: Most common chemistry laboratory test abnormalities (grade 3 or 4) during treatment

Laboratory Test	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	CHRYSALIS+PAPILLON (n=171)	COMBINED (n=301)
Alanine Aminotransferase Increased				
Grade 3	13 (5.6%)	5 (3.8%)	6 (3.5%)	11 (3.7%)
Grade 4	0	0	0	0
Hypercalcemia				
Grade 3	0	0	0	0
Grade 4	3 (1.3%)	0	0	0
Hypokalemia				
Grade 3	6 (2.6%)	11 (8.5%)	15 (9.0%)	26 (8.8%)
Grade 4	2 (0.9%)	3 (2.3%)	4 (2.4%)	7 (2.4%)
Hyponatremia				
Grade 3	15 (6.4%)	14 (10.8%)	12 (7.1%)	26 (8.7%)
Grade 4	2 (0.9%)	3 (2.3%)	1 (0.6%)	4 (1.3%)

Source: Mod5.3.5.3/ISS/TSFLAB02part1of2 and /TSFLAB02part2of2
Chemistry Laboratory Test Parameters with a Grade 3 occurrence >5% or Grade 4 occurrence >1% in the ACP or CP arm.

[a] These TEAEs are selected because their incidence is above the cut-off in at least one of the groupings, but this does not by default mean that their incidence is above the cut-off in all of the groupings.

Hypokalaemia, hyponatremia, and increase in ALT are known to occur with both amivantamab monotherapy and chemotherapy. Hypokalaemia and increased AST and ALT are established amivantamab ADRs.

The majority of chemistry abnormalities were grade 1 or 2.

Table 46: Liver function test elevations (any grade) during treatment

Laboratory Test	CP	ACP		
	MARIPOSA-2 (n=243)	MARIPOSA-2 (n=130)	PAPILLON+CHRYSALIS (n=171)	COMBINED (n=301)
Increased ALT (Alanine Aminotransferase Increased)				
Grade 1	110 (47.0%)	44 (33.8%)	80 (47.1%)	124 (41.3%)
Grade 2	16 (6.8%)	5 (3.8%)	14 (8.2%)	19 (6.3%)
Grade 3	13 (5.6%)	5 (3.8%)	6 (3.5%)	11 (3.7%)
Grade 4	0	0	0	0
Increased AST (Aspartate Aminotransferase Increased)				
Grade 1	118 (50.4%)	60 (46.2%)	92 (54.1%)	152 (50.7%)
Grade 2	9 (3.8%)	5 (3.8%)	8 (4.7%)	13 (4.3%)
Grade 3	2 (0.9%)	0	1 (0.6%)	1 (0.3%)
Grade 4	0	1 (0.8%)	0	1 (0.3%)
Increased Bilirubin (Blood Bilirubin Increased)				
Grade 1	7 (3.0%)	7 (5.4%)	24 (14.1%)	31 (10.3%)
Grade 2	5 (2.1%)	2 (1.5%)	5 (2.9%)	7 (2.3%)
Grade 3	0	1 (0.8%)	1 (0.6%)	2 (0.7%)
Grade 4	0	0	0	0

Source: Mod5.3.5.3/ISS/TSFLAB02part1of2 and /TSFLAB02part2of2

Study participants were evaluated for components of the criteria for potential drug-induced hepatotoxicity (i.e., ALT or AST ≥3 times ULN and total bilirubin ≥2 times ULN). None fulfilled the criteria for Hy's Law.

Electrocardiograms

In MARIPOSA-2, ECGs were measured at screening and baseline. Further ECGs were to be performed only if clinically indicated. In PAPILLON and in the CHRYSALIS ACP, ECGs were measured at screening, at baseline, and post-infusion of amivantamab on cycle 3 day 1. The QTc intervals in all three studies were based on QTcF. Based on the maximum QTcF value for each participant on treatment, the incidence of abnormal QTcF values (≤450, >450 to 480, >480 to 500, >500 msec) and changes from baseline (≤30, >30 to 60, >60 msec) were summarized. Criteria for abnormal QTc intervals and changes from baseline were derived from the ICH E14 Guidance (ICH Harmonized Tripartite Guideline

E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs 2005).

In MARIPOSA-2, one participant in the ACP arm and one participant in the CP arm had a maximum postbaseline QTcF value >500 msec and four participants (two in each study arm) had a change from baseline in the QTcF interval >60 msec.

Safety in special populations

Age

In total, 61% (n=228) of the patients in the MARIPOSA-2 study were <65 years and 39% (n=145) were ≥65 years. Most of the patients were <75 years; 11.4% were ≥75 years. The distribution between the treatment arms was comparable (60% <65 years and 40% ≥65 years in the ACP arm vs. 62% <65 years and 38% ≥65 years in the CP arm, respectively).

The incidence of TEAEs was comparable between treatment arms and age groups.

There were no differences in grade ≥3 TEAEs or SAEs related to age in any of the treatment arms.

In the ACP arm, a higher incidence of TEAEs leading to treatment discontinuation was observed in age group ≥65 years compared to age group <65 years (36.5% in age group ≥65 years, 6.4% in age group <65 years), mainly driven by discontinuations of amivantamab (30.8% age group ≥65 years vs. 5.1% age group <65 years) and pemetrexed (23.1% age group ≥65 years vs. 2.6%% for <65 years).

Sex

In the MARIPOSA-2 study, 39.4% (n=147) of the patients were male and 60.6% (n=226) were female and the distribution was balanced between the treatment arms (37.7% male, 62.3% female in the ACP arm vs. 40.3% male and 59.7% female in the CP arm, respectively).

The incidence of TEAEs was comparable between treatment arms and subgroups based on sex.

In the ACP arm, there was a slight increase in grade ≥3 TEAEs and SAEs in male compared to female participants (77.65% grade ≥3 TEAEs in male vs. 69.1% in female participant and 36.7% SAEs in male vs. 29.6% in female participants), but the difference was <10%. In the CP arm, the difference in grade ≥3 TEAEs was somewhat greater and attributed to female sex; 52.4% in female participants vs. 41.8% in male participants.

The incidence of TEAEs leading to dose interruption was higher in male participants in the ACP arm (71.4%) compared to in female participants (60.5%), mainly attributed to differences in interruption of amivantamab. The overall incidence of treatment interruption in female patients was lower than in the supportive ACP studies (71.3%).

In both treatment arms, female participants had a slightly higher incidence of dose adjustments of carboplatin and pemetrexed than male participants.

Race

Of all participants in the MARIPOSA-2 study, 47.7% (n=178) were Asian and 49.3% (n=184) were non-Asian. Race was unknown or not reported for 11 patients. The distribution was identical between the treatment arms.

The overall incidence of TEAEs was comparable between Asian and non-Asian participants in both treatment arms.

In the ACP arm, higher incidences (≥10% difference) of grade ≥3 TEAEs, SAEs, and Covid-19 related TEAEs were observed for the Asian vs. the non-Asian population (79.0% vs. 64.1% grade ≥3 TEAEs, 40.3% vs. 23.4% SAES, and 33.9% vs. 10.9% Covid-19 TEAEs, respectively). For TEAEs grade ≥3 and SAEs the incidence in the Asian population was comparable to that in the supportive ACP studies, whereas it was lower in the non-Asian population compared to historical data.

Hepatic function at baseline

Hepatic function was defined as normal (total bilirubin ≤ ULN and AST ≤ ULN), mild (total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5 x ULN), moderate (1.5 x ULN < total bilirubin ≤ 3 x ULN), and severe (total bilirubin > 3 x ULN).

Apart from one patient with moderate hepatic impairment in the ACP arm all patients had either normal hepatic function (84.6% in the ACP arm vs. 90.5% in the CP arm) or mild hepatic impairment (14.6% in the ACP arm vs. 9.5% in the CP arm). This is in line with the distribution in supportive ACP studies. There were no participants with severe hepatic impairment in any of the treatment arms.

The subgroups were too small to allow for a meaningful comparison of TEAEs.

No formal studies of amivantamab in patients with hepatic impairment have been conducted. Based on population PK analyses no dose adjustment is recommended for patients with mild hepatic impairment, but caution is required in patients with moderate or severe hepatic impairment as amivantamab has not been studied in this patient population.

Renal function at baseline

Renal function was defined as normal (eGFR ≥90 mL/min/1.73m2), mild impairment (eGFR 60 to <90 mL/min/1.73m2), moderate impairment (eGFR 30 to <60 mL/min/1.73m2), or severe impairment (eGFR <30 mL/min/1.73m2).

In total, 46.6% (n=174) patients had normal renal function, 47.2% (n=176) had mild, and 6.2% (n=23) had moderate renal impairment at baseline. There were no participants with severe renal impairment in any of the treatment arms.

Overall, the incidence of TEAEs was comparable between subpopulations and between treatment arms.

In the ACP arm, the incidence of grade ≥3 TEAEs was higher in the subpopulation with normal renal function compared to the subpopulation with mild renal impairment (80.3% TEAEs in normal function vs. 62.7% TEAES in mild impairment, respectively). The TEAE incidence in the normal renal function subpopulation is in line with data from the supportive ACP studies whereas the incidence in the mild renal impairment subpopulation was lower compared to historical data.

Due to the limited size of the subpopulations with moderate renal impairment these are not included in the comparisons between the treatment arms.

ECOG performance score at baseline

In total, 40.2% (n=150) of the patients had ECOG performance status (ECOG PS) 0 at baseline and 59.8% (n=223) hade ECOG PS 1. The distribution was comparable between the treatment arms

(41.5% ECOG 0 and 58.5% ECOG 1 in the ACP arm vs. 39.5% ECOG 0 and 60.5% ECOG 1 in the CP arm).

The overall incidences of TEAEs, grade ≥3 TEAEs, SAEs, TEAEs leading to any dose adjustments, and Covid-19 related TEAEs were comparable between ECOG PS subgroups in both treatment arms.

Weight

In the MARIPOSA-2 study, 86.8% (n=324) of the patients were <80 kg and 13.1% (n=49) were ≥80 kg, with a comparable distribution between the treatment arms (86.9% <80 kg and 13.1% ≥80 kg in the ACP arm vs. 86.8% <80 kg and 13.2% ≥80 kg in the CP arm, respectively).

The overall incidences of TEAEs, grade >3 TEAEs, SAEs, TEAEs leading to any dose adjustments, and Covid-19 related TEAEs were comparable between weight subgroups in both treatment arms.

History of brain metastasis at baseline

In the MARIPOSA-2 study, 44.0% (n=164) of the patients had a history of brain metastasis and 56.0% (n=209) did not. The distribution between the treatment arms was comparable (43.8% with and 56.2% without history in the ACP arm vs. 44.0% with and 56.0% without in the CP arm, respectively). The distribution of history with or without brain metastasis differed from that in the supportive ACP studies (22.2% with brain metastasis vs. 77.8% without).

The overall incidence of TEAEs, grade ≥3 TEAEs, and SAEs, were comparable between the subpopulations with and without history of brain metastasis in both treatment arms.

In the ACP arm, the incidence of TEAEs leading to dose reduction was higher in the subpopulation with than the subpopulation without history of brain metastasis (50.9% vs. 32.9%, respectively). The difference was mainly related to dose reductions of carboplatin and pemetrexed. The incidence of dose reduction was also lower in the subpopulation without history of brain metastasis compared to in the supportive ACP studies.

Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interaction studies were performed for amivantamab. Since there is no overlapping pathway of elimination, no PK interactions are expected between amivantamab and CP.

Discontinuation due to adverse events

Table 47: Number of subjects with TEAEs leading to discontinuation of any study treatment with frequency of at least 2% in any treatment group by system organ class and preferred term (safety analysis set)

	CP			ACP			
	Total	Carboplatin	Pemetrexed	Total	Amivantamab	Carboplatin	Pemetrexed
Analysis set: Safety	243	243	243	130	130	130	130
Subjects with 1 or more AEs leading to discontinuation of any study treatment	9 (3.7%)	4 (1.6%)	8 (3.3%)	24 (18.5%)	20 (15.4%)	9 (6.9%)	14 (10.8%)
System organ class Preferred term							
Blood and lymphatic system disorders	4 (1.6%)	3 (1.2%)	2 (0.8%)	2 (1.5%)	0	1 (0.8%)	1 (0.8%)
Neutropenia	3 (1.2%)	2 (0.8%)	2 (0.8%)	0	0	0	0
Thrombocytopenia	2 (0.8%)	1 (0.4%)	2 (0.8%)	1 (0.8%)	0	1 (0.8%)	0
Febrile neutropenia	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.8%)	1 (0.4%)	2 (0.8%)	4 (3.1%)	3 (2.3%)	2 (1.5%)	3 (2.3%)
Pneumonitis	0	0	0	1 (0.8%)	1 (0.8%)	0	1 (0.8%)
Gastrointestinal disorders	1 (0.4%)	1 (0.4%)	0	2 (1.5%)	2 (1.5%)	2 (1.5%)	2 (1.5%)
Stomatitis	0	0	0	0	0	0	0
General disorders and administration site conditions	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (1.5%)	1 (0.8%)	0	2 (1.5%)
Fatigue	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	7 (5.4%)	7 (5.4%)	2 (1.5%)	2 (1.5%)
Infusion related reaction	0	0	0	7 (5.4%)	7 (5.4%)	2 (1.5%)	2 (1.5%)
Skin and subcutaneous tissue disorders	0	0	0	4 (3.1%)	4 (3.1%)	0	1 (0.8%)
Rash	0	0	0	2 (1.5%)	2 (1.5%)	0	1 (0.8%)

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

[tsfac06bpart1of2.rtf] [PROD/jnj-61186372/nsc3002/dbr_csr/rc_csr1/tsfac06b.sas] 08SEP2023, 08:13

Post marketing experience

There is currently no post marketing experience with amivantamab in combination with carboplatin and pemetrexed.

Post marketing information for amivantamab monotherapy has been accruing since the first marketing approval in 2021. Based on 22,364,767 milligrams distributed worldwide by the MAH from launch (21 May 2021) to 31 May 2023, the estimated exposure to amivantamab is 1,825 treatment courses. The post marketing safety profile of amivantamab monotherapy is consistent with the safety information provided in the product information. No new major safety issues have been identified.

2.5.2. Discussion on clinical safety

The safety assessment is focused on safety data from the pivotal study MARIPOSA-2 in patients with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations, whose disease has progressed on or after treatment with the third-generation EGFR TKI osimertinib, with DCO date 10 July 2023.

In the MARIPOSA-2 study, 130 participants were randomised and received amivantamab, carboplatin and pemetrexed (ACP) treatment and 243 participants were randomised and received carboplatin and pemetrexed (CP) treatment. The size of the safety database is considered acceptable. The patient exposure is acceptable and evokes no concern.

At DCO (10 July 2023), approximately twice as many patients were still on treatment in the ACP vs. the CP am (51.5% in the ACP arm vs. 22.6% in the CP arm, respectively). The lower rate of progressive disease and higher incidence of treatment discontinuations due to TEAEs in the ACP arm is acknowledged considering a higher treatment efficacy but also higher toxicity with an add-on treatment to chemotherapy in the ACP arm.

Both the median amivantamab and pemetrexed exposure was lower in the MARIPOSA-2 ACP arm compared to the ACP arms of the supportive studies. This is acknowledged considering the later treatment line in the MARIPOSA-2 study, where all patients had received ≥1 prior line of systemic therapy in the locally advanced or metastatic setting compared to 5.3% in the PAPILLON study and 75.0% in the CHRYSALIS study. Still, the addition of amivantamab to CP doublet did not result in a decrease of the cumulative administered dose of either chemotherapeutic agent in the MARIPOSA-2 study.

Almost all participants in both treatment arms in MARIPOSA-2 experienced ≥1 TEAE of any grade (100% in the ACP arm vs. 93.4% in the CP arm). As expected with an add-on therapy to standard of care, the frequency of most TEAEs was higher in the ACP arm than in the CP arm.

The most frequently occurring TEAEs in the MARIPOSA-2 ACP arm corresponded to known amivantamab ADRs pertaining to EGFR and MET inhibition. Among TEAEs with ≥10% incidence in the ACP than the CP arm were stomatitis (+22.9% in the ACP arm), rash and dermatitis acneiform (+38.2% and +17.1%, respectively), and paronychia (+36.5%), all pertaining to EGFR inhibition, and peripheral oedema (+25.9%) and hypoalbuminemia (+13.7%), pertaining to MET inhibition. The warning on rash in section 4.4 of the SmPC has been clarified for the health care professional to consider a prophylactic approach to rash prevention. This is endorsed.

The majority of all TEAEs were considered treatment related and were already adjudicated as ADRs of amivantamab and addressed in section 4.8 of the SmPC.

When it regards haematological TEAEs, normally associated with chemotherapy, neutropenia and thrombocytopenia were more commonly reported in the ACP than in the CP arm (neutropenia +15.3%, thrombocytopenia +14.2%% in the ACP arm). For amivantamab monotherapy, the incidence of neutropenia and thrombocytopenia was reported to be considerably lower (4.7% neutropenia, 3.1% thrombocytopenia in the CHRYSALIS study). Thus, neutropenia and thrombocytopenia were identified as new ADRs pertaining to ACP treatment and included in the ADR table in the SmPC 4.8. This is endorsed.

The TEAE VTE incidence was identified as a concern regarding the amivantamab + lazertinib arm of the MARIPOSA-2 study (not part of the current application). In parallel, VTE was identified as a new ADR pertaining to ACP treatment in a recently completed procedures. In line with this, the incidence of TEAE VTE was higher in the ACP than in the CP arm in the MARIPOSA-2 study (18.1% vs. 11.0% respectively, exposure adjusted).

Other established amivantamab ADRs with a higher reported incidence in the ACP arm were IRRs (+58.1% in the ACP arm) and hypokalaemia (+12.3%).

The ADR presentation in the SmPC 4.8 is based on safety data from a total of 301 ACP treated patients in the MARIPOSA-2, PAPILLON, and CHRYSALIS studies, i.e., the combined safety data set used for comparison throughout this report. This pooling of safety data, as decision basis for ADR presentation in the SmPC, is endorsed.

Grade ≥3 TEAEs were reported in 72.3% of the patients in the ACP arm and in 48.1% of the patients in the CP arm, respectively.

The total incidence of TEAEs leading to dose reduction or interruption of any study treatment was significantly higher for participants exposed to ACP (40.8% dose reduction, 64.6% dose interruption) compared to participants exposed to CP (15.2% dose reduction, 33.3% dose interruption). Dose reduction and interruption of amivantamab was reported for 16.9% and 60.0% of the patients in the ACP arm, respectively. The higher incidence of dose reduction or interruption in the ACP compared to the CP arm was mainly attributed to known amivantamab TEAEs such as stomatitis, paronychia, rash, and dermatitis acneiform.

The majority of TEAEs leading to dose reductions and interruptions in both the ACP and CP arms were haematologic and resulted in dose reductions of carboplatin and pemetrexed on relatively comparable levels. The single most common reason for dose reduction or interruption of any study treatment in both study arms was neutropenia (10.8% reduction, 23.1% interruption in the ACP arm vs. 6.6% reduction and 13.2% interruption in the CP arm, respectively).

In total, 18.5% of the patients in the ACP arm discontinued any study agent due to TEAEs compared to 3.7% in the CP arm. TEAEs leading to treatment discontinuation of amivantamab was reported for 15.4% of the patients in the ACP arm.

The difference between the study arms was attributed to known amivantamab TEAEs, particularly pneumonitis (0.8% in the ACP arm vs. 0% in the CP arm), IRR (5.4% vs. 0%), and rash (1.5% vs. 0%), which all led to discontinuation of amivantamab.

The overall incidence of SAEs was higher in the ACP than the CP arm, with SAEs reported in 42/130 participants (32.3%) in the ACP arm and 49/243 participants (20.2%) in the CP arm and comparable with the incidence in the supportive ACP studies (38.6%).

At DCO, 27 participants (20.8%) in the ACP arm and 65 participants (26.7%) in the CP arm had died during the study. The most common reason for death was progressive disease (13.1% vs. 23.0% in the ACP and CP arms, respectively). Deaths within 30 days of first study treatment dose (`early death´) was equally uncommon in both study arms (one patient in the ACP arm and two in the CP arm, respectively).

The proportion of deaths within 30 days of last study treatment dose was higher in the ACP than in the CP arm. This is endorsed considering the longer treatment exposure in the ACP arm. Of these, two in the ACP arm (sepsis and ventricular fibrillation/cardiopulmonary arrest) and one in the CP arm (respiratory failure) were considered related to study treatment.

2.5.3. Conclusions on clinical safety

Overall, the TEAEs and SAEs in the ACP arm of the MARIPOSA-2 study are in line with what has previously been reported for amivantamab treated patients in earlier as well as corresponding treatment lines. These include well-known EFGR and MET inhibitor TEAEs such as rash, dermatitis acneiform, hypoalbuminemia, hypokalaemia, and IRR.

Neutropenia and thrombocytopenia are new ADRs pertaining to ACP treatment.

Overall, the safety profile of ACP is considered manageable and acceptable in its context.

2.5.4. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content:

Safety concerns

List of Safety Concerns	
Important Identified Risks	Infusion-related reaction
Important Potential Risks	Hepatotoxicity
	Impaired fertility and embryofetal toxicity
Missing Information	None

No new safety concerns have been identified.

Pharmacovigilance plan

There are no additional pharmacovigilance activities for Rybrevant.

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Infusion-related reaction	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 • Recommendations to administer RYBREVANT in a setting with appropriate medical support, for administration of pre-infusionmedicinal products, for RYBREVANT initial infusion administration in split doses on Week 1 (Days 1 and 2), and for RYBREVANT administration via specific infusion rates are provided in SmPC Sections 4.2 and 4.4, and PL Section 3. • Recommendations regarding the management of IRRs (eg, interruption or discontinuation of infusion, administration of supportive medicinal products) are provided in SmPC Sections	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	4.2 and 4.4, and PL Section 4. • Patients with side effects during infusion of RYBREVANT should notify their doctor or nurse immediately, as described in PL Sections 2 and 4. • Legal status. **Additional risk minimization measures:** • None	
Hepatotoxicity	**Routine risk minimization measures:** • SmPC Section 4.8 (ALT, AST, and ALP increased) • PL Section 4 • Legal status. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Impaired fertility and embryofetal toxicity	**Routine risk minimization measures:** • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • The potential harmful effects of EGFR inhibition on embryofoetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of amivantamab, are provided in SmPC Section 4.6 and PL Section 2. • Patients should notify their doctor or nurse immediately about a potential or confirmed pregnancy before and during treatment with RYBREVANT, as described in PL Section 2. • Legal status. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Routine risk minimisation measures remain sufficient to mitigate the risks of Rybrevant.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Greece.

2.7.1. User consultation

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

there have not been revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The new indication for Rybrevant is in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).

3.1.2. Available therapies and unmet medical need

The current SOC for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations (EGFRm NSCLC) is a third-generation EGFR TKI, most commonly osimertinib. Despite improved initial disease control as first-line therapy, nearly all patients will develop resistance to third-generation EGFR TKIs and their disease will progress. There are currently no targeted therapies approved for patients with EGFRm NSCLC whose disease has progressed on or after a third-generation EGFR TKI, although evidence indicates that the disease continues to be heavily dependent on signaling through the EGFR pathway (Remon 2016). The NCCN and ESMO treatment guidelines for advanced or metastatic NSCLC recommend platinum-based combination chemotherapy regimens, including carboplatin/pemetrexed or cisplatin/pemetrexed for patients with EGFRm NSCLC whose disease has progressed on or after a third-generation EGFR TKI (Hendriks 2023; NCCN 2023; Planchard 2018).

3.1.3. Main clinical studies

The pivotal study for this application is MARIPOSA-2 study. MARIPOSA-2 is an ongoing, randomized, open-label, multicentre Phase 3 study planned as three arm study to compare the combination of lazertinib (L), amivantamab (A), carboplatin (C) and pemetrexed (P) (LACP/ACPL in arm A) versus CP (arm B) and ACP (arm C) versus CP (arm B).

The part of MARIPOSA-2 relevant for the sought indication consists of arm B (CP) and arm C (ACP) comparing the benefit with addition of amivantamab to platinum-based doublet in patients with NSCLC EGFR Exon 19 deletions or Exon 21 L858R substitution mutation that has progressed on or after osimertinib.

3.2. Favourable effects

At the cut-off date for primary analysis of 10 July 2023, the primary endpoint, PFS (BICR) benefit with ACP vs CP was met, showing statistically significant PFS (BICR) advantage with ACP vs CP with HR 0.48 (0.36, 0.64); p-value <0.0001 and PFS increase of 2 months (median PFS 6.28 months in ACP arm vs 4.17 months in CP arm). The robustness of PFS benefit is supported by sensitivity analyses. The PFS benefit was observed in all predefined clinically relevant subgroups.

The second interim OS analysis performed at CCO of 26 April 2024 shows an OS difference of 2 months with ACP over CP (17.74 (15.97, 22.37) from 15.34 (13.73, 16.76), HR = 0.73; 95% CI: 0.54, 0.99; p=0.0386). However, this did not reach the threshold of statistical significance (p=0.0142, 2-sided).

3.3. Uncertainties and limitations about favourable effects

At the second interim analysis, the OS difference observed was not statistically significant. Results of the final OS analysis will be submitted (Q2/Q3 2025) as a Recommendation.

3.4. Unfavourable effects

The most frequently occurring TEAEs in the ACP arm corresponded to known amivantamab ADRs pertaining to EGFR and MET inhibition. Among TEAEs by PT with ≥10% incidence in the ACP than the CP arm were stomatitis (+22.9%), rash and dermatitis acneiform (+38.2% and +17.1%, respectively), and paronychia (+36.5%), all pertaining to EGFR inhibition, and peripheral oedema (+25.9%) and hypoalbuminemia (+13.7%), pertaining to MET inhibition. IRR and hypokalaemia, established amivantamab ADRs, also occurred with higher incidences in the ACP arm (+58.1% and +12.3%, respectively).

Grade ≥3 TEAEs were reported in 72.3% of the patients in the ACP arm and in 48.1% of the patients in the CP arm, respectively (mainly haematological TEAEs in both treatment arms).

Grade 4 TEAEs were reported for 22.3% vs. 8.2% of the patients in the ACP vs. CP arms and grade 5 TEAEs in 2.3% vs. 1.2%, respectively.

The overall incidence of SAEs was higher in the ACP than the CP arm, with SAEs reported in 32.3% of the patients in the ACP arm compared to 20.2% in the CP arm. There was no treatment-specific pattern of the reported PTs of SAEs. The SAEs with the highest incidence in the ACP arm were thrombocytopenia and dyspnoea (four patients each), and sepsis and COVID-19 (three patients each).

In total, 18.5% of the patients in the ACP arm discontinued any study agent due to TEAEs compared to 3.7% in the CP arm. The difference was mainly attributed to discontinuation of amivantamab, which was reported for 15.4% of the patients in the ACP arm. The most common TEAEs leading to amivantamab discontinuation were established amivantamab ADRs such as IRR (5.4%), rash (1.5%), and pneumonitis (0.8%).

At DCO, 27 participants (20.8%) in the ACP arm and 65 participants (26.7%) in the CP arm had died during the study. The most common reason for death was progressive disease (13.1% vs. 23.0% in

the ACP and CP arms, respectively). Of these, two in the ACP arm (sepsis and ventricular fibrillation/cardiopulmonary arrest) and one in the CP arm (respiratory failure) were considered related to study treatment. None were reported to be associated with amivantamab treatment.

Neutropenia and thrombocytopenia were identified as new ADRs pertaining to ACP treatment.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 48: Effects Table for Amivantamab in Combination With Carboplatin and Pemetrexed for the Treatment of Patients With Advanced NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations After Osimertinib

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
			Amivantamab + carboplatin + pemetrexed N=131	Carboplatin + pemetrexed N=263	
Favourable Effects					
Primary endpoint	Median PFS by BICR(months) HR (95% CI); p-value		6.28 (5.55;8.41) 0.48 (0.36, 0.64) <0.0001	4.17 (4.04;4.44)	Statistically significant
Secondary endpoints	ORR (95% CI) DOR Median, months OS IA2 Number of events HR (95% CI); p-value		63.8% 6.90 49.6% 0.73 (0.54, 0.99); p=0.0386	36.2% 5.55 54.4%	Statistically significant Benefit not statistically significant at IA2
Unfavourable Effects					
			Amivantamab + carboplatin + pemetrexed N=130*	Carboplatin + pemetrexed N=243*	
TEAEs	Any Neutropenia Thrombocyto-penia	%	100% 56.9% 43.8%	93.4% 41.6% 29.6%	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
	VTE**		10.0%	4.5%	
Treatment related TEAEs	Any Grade ≥3	%	99.2% 66.9%	86.4% 35.4%	
Grade ≥3 TEAEs	Any Neutropenia Thrombocyto-penia VTE**	%	72.3% 45.4% 14.6% 2.3%	48.1% 21.4% 9.1% 2.9%	
SAEs	Any VTE**	%	32.3% 2.3%	20.2% 2.1%	
TEAEs leading to disc.	Any Grade ≥3	%	18.5% 13.1%	3.7% 2.9%	
Deaths due to TEAEs	Any	%	2.3%	1.2%	

Abbreviations: IRR = Infusion Related Reaction, VTE = venous thromboembolism

Notes:* The safety population is based on the Safety Analysis Set, consisting of the 373 participants in the MARIPOSA-2 study who received any study treatment.

**Grouped term

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the MARIPOSA-2 study have shown a statistically significant PFS gain with amivantamab. Correspondingly, ORR was increased. At the second interim analysis there is a nominal OS benefit, albeit not statistically significant. There is no concern of a detrimental effect on OS. The Applicant will submit the results of the final OS analysis once available to fulfil the CHMP Recommendation (expected mid-year 2025).

The safety dataset is sufficiently large to describe the safety profile of amivantamab in combination with carboplatin + pemetrexed. This is in line with the safety profile previously reported for amivantamab monotherapy and seems manageable with dose reductions and interruptions.

Notably, the initially applied indication was covering use after any 3rd generation TKI, whereas the study was performed in patients exclusively pretreated with osimertinib. Amivantamab does not bind to the kinase domain, but rather to the extracellular domain of EGFR. EGFR-targeting TKI bind to the kinase domain which is located intracellularly. Therefore, resistance mutations selected by EGRF targeting TKIs are not anticipated to impact amivantamab binding. The efficacy of amivantamab has been proven in patients pre-treated with osimertinib. For the reason given above, it appears reasonable to extrapolate its efficacy to patients pretreated with any EGFR-targeting TKI. As a result, the indication was revised to remove "3rd generation" from the finally agreed wording.

3.7.2. Balance of benefits and risks

The beneficial effect of amivantamab on PFS outweighs the added toxicity, which is considered manageable and in line with the known safety profile of amivantamab.

3.8. Conclusions

The overall B/R of amivantamab is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI) for RYBREVANT, based on the final results from study 61186372NSC3002 (MARIPOSA 2); this is a randomized, open label, multicenter Phase 3 study that compares efficacy and safety of amivantamab in combination with carboplatin and pemetrexed (ACP) with carboplatin and pemetrexed (CP). The primary objective of the MARIPOSA 2 study is to compare efficacy, as demonstrated by PFS, in participants treated with ACP versus CP alone. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the EU RMP has also been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Rybrevant-H-C-5454-II-11.

Attachments

1. SmPC, Annex II, Labelling and Package Leaflet (clean and changes highlighted) as adopted by the CHMP on 25 July 2024.