25 April 2024
EMA/CHMP/111303/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rybrevant

International non-proprietary name: Amivantamab

Procedure No. EMEA/H/C/005454/II/0010

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Background information on the procedure 6
1.1. Type II variation 6
1.2. Steps taken for the assessment of the product 7

2. Scientific discussion 7
2.1. Introduction 7
2.1.1. Problem statement 7
2.1.2. About the product 8
2.1.3. The development programme/compliance with CHMP guidance/scientific advice 9
2.1.4. General comments on compliance with GCP 11
2.2. Non-clinical aspects 11
2.2.1. Ecotoxicity/environmental risk assessment 11
2.2.2. Non-clinical aspects conclusion 11
2.3. Clinical aspects 11
2.3.1. Introduction 11
2.3.2. Pharmacokinetics 13
2.3.3. Pharmacodynamics 25
2.3.4. Discussion on clinical pharmacology 26
2.3.5. Conclusions on clinical pharmacology 28
2.4. Clinical efficacy 28
2.4.1. Dose response study(ies) 28
2.4.2. Main study(ies) 29
2.4.3. Discussion on clinical efficacy 62
2.4.4. Conclusions on the clinical efficacy 68
2.5. Clinical safety 68
2.5.2. Discussion on clinical safety 91
2.5.3. Conclusions on clinical safety 94
2.5.4. PSUR cycle 95
2.6. Risk management plan 95
2.7. Update of the Product information 97
2.7.1. User consultation 97

3. Benefit-Risk Balance 97
3.1. Therapeutic Context 97
3.1.1. Disease or condition 97
3.1.2. Available therapies and unmet medical need 98
3.1.3. Main clinical studies 98
3.2. Favourable effects 98
3.3. Uncertainties and limitations about favourable effects 99
3.4. Unfavourable effects 99
3.5. Uncertainties and limitations about unfavourable effects 100
3.6. Effects Table 101
3.7. Benefit-risk assessment and discussion 102
3.7.1. Importance of favourable and unfavourable effects 102
3.7.2. Balance of benefits and risks 103

3.7.3. Additional considerations on the benefit-risk balance 103
3.8. Conclusions 103

4. Recommendations 103

List of abbreviations

ACP	Amivantamab + carboplatin - pemetrexed
AEs	adverse events
AUC	area under the curve
BICR	blinded independent central review
CBR	clinical benefit rate
CCO	clinical cutoff
CI	confidence interval
COVID	coronavirus disease
CP	carboplatin-pemetrexed
CR	complete response
CRF	case report form
CSR	clinical study report
ctDNA	circulating tumor deoxyribonucleic acid
C_{trough}	serum concentration immediately prior the next study treatment administration
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EoT	End of Treatment
EQ-5D-5L	EuroQol five-dimensional descriptive system (5-level version)
EU	European Union
FDA	Food and Drug Administration
FIH	first-in human
FOIA	Freedom of Information Act
HR	hazard ratio
HRQoL	health-related quality of life
IV	Intravenous
MET	mesenchymal-epithelial transition
MMRM	mixed-effects model for repeated measures
NE	not evaluable
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival after first subsequent therapy
PK	pharmacokinetic(s)

PR	partial response
PRO	patient-reported outcomes
PROMIS-PF	Patient-Reported Outcomes Measurement Information System – Physical Function
QW	Once weekly
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2CD	recommend Phase 2 combination dose
RP2ChD	recommended Phase 2 chemotherapy combination dose
RP2D	recommended Phase 2 dose
RWE	real-world evidence
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation *(Note: in the context of the response analysis, SD has been used in few instances as the abbreviation of "stable disease")*
SDV	source data verification
SOC	standard of care
TKIs	tyrosine kinase inhibitor
TMF	trial master file
tSDV	targeted source data verification
TTST	time to subsequent therapy
TTD	time from randomization to discontinuation of all study treatments for any reason
TTSP	time to symptomatic progression

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 5 October 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 first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations for RYBREVANT, based on the final results from study 61186372NSC3001 listed as a Specific Obligation in the Annex II of the Product Information; this is a global, open-label, randomized Phase 3 study of ACP compared to CP alone in participants with newly diagnosed, locally advanced or metastatic NSCLC characterized by EGFR exon 20ins. The primary objective of the PAPILLON 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, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II and Annex IV of the PI. Consequently, the MAH proposes a switch from conditional marketing authorisation to full marketing authorisation given the fulfilment of the SOB. As part of the application, the MAH also requests an extension of the market protection by one additional year.

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.

Scientific advice

The MAH received Scientific Advice from the CHMP on 25 June 2020 (EMEA/H/SA/4472/1/2020/II). 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

Timetable	Actual dates
Submission date	5 October 2023
Start of procedure:	28 October 2023
CHMP Rapporteur Assessment Report	21 December 2023
PRAC Rapporteur Assessment Report	3 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Request for supplementary information (RSI)	25 January 2024
CHMP Rapporteur Assessment Report	25 March 2024
PRAC Rapporteur Assessment Report	27 March 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	18 April 2024
Opinion	25 April 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

State the claimed the therapeutic indication

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

RYBREVANT in combination with carboplatin and pemetrexed is indicated for the first-line treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations.

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 L858R, are found in 80% to 85% of patients with EGFR mutations, while tumors characterized by one of a group of heterogenous, in-frame base pair insertions in EGFR exon 20 (exon 20ins) are identified in up to 10% of patients with EGFR mutations (Vyse 2019).

Management

Several EGFR TKIs have been approved for use as the first-line treatment of NSCLC patients with tumours characterized by EGFR exon 19del and L858R and mutations, which has resulted in significantly improved patient outcomes, with improved response rates, prolonged disease control, and an improved overall survival of 32 to 39 months (Ramalingam 2020). However, these TKIs, approved for the treatment of common EGFR mutations (exon 19del and L858R), are largely ineffective against exon 20ins mutations (Yang 2023). As a result, there are no approved targeted therapies available for the first-line treatment of EGFR exon 20ins mutated NSCLC, and platinum-based doublet chemotherapy remains the standard of care for first-line treatment of newly diagnosed patients with advanced or metastatic EGFR exon 20ins NSCLC, although with poor health outcomes as evidenced by RWE (ie, median real world PFS of 6.6 months and median real world OS of 17.4 months; Information Summary 2021).

In summary, EGFR exon 20ins NSCLC is a serious and life-threatening disease with overall survival among the worst for NSCLC patients. Although driven by EGFR driver mutations, patients with EGFR exon 20ins NSCLC have not benefitted from SOC EGFR TKIs or other therapeutic approaches at the time of initial diagnosis and, therefore, remain a population with significant unmet medical need

2.1.2. About the product

Amivantamab, a bispecific antibody targeting EGFR and MET, 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. Through its ability to bind to the wild-type, external domains of EGFR, amivantamab can bypass the steric hindrance resulting from EGFR exon 20ins mutations and downregulate activity

of the activated pathway. Based on data from the FIH Study 61186372EDI1001 (hereafter referred to as CHRYSALIS), amivantamab was granted conditional approval as a monotherapy by EMA on 9 December 2021 for patients with EGFR exon 20ins mutations whose disease has progressed on or after platinum-based chemotherapy.

The indication as adopted by the CHMP is:

Rybrevant in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating EGFR Exon 20 insertion mutations.

Table 1: Recommended dosage of Rybrevant every 3 weeks, when used in combination with carboplatin and pemetrexed

Body weight at baselinea	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.

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 or in combination therapy (see Figure 1).

Key efficacy and safety data to support the current proposed product information update for ACP in exon 20ins NSCLC are derived from the pivotal Phase 3 PAPILLON study and the supportive Phase 1 CHRYSALIS study (ACP cohort [n=20 for safety and n=5 for efficacy]).

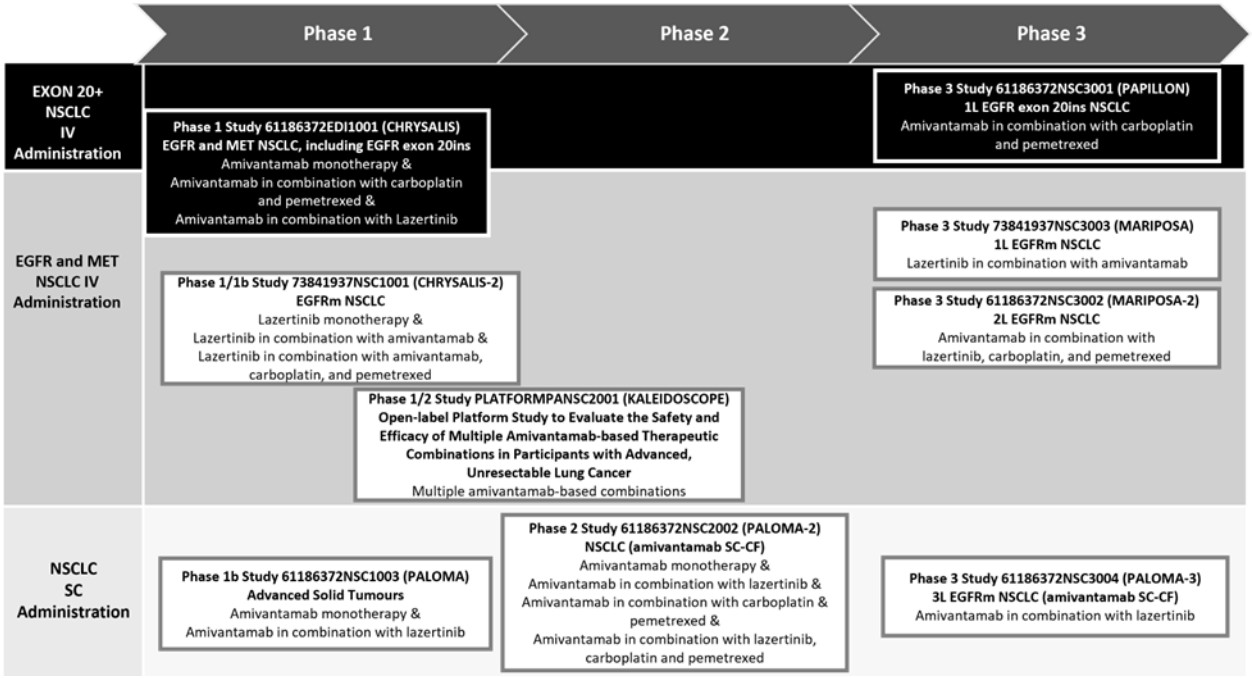


Figure 1: Clinical Development Program for Amivantamab in Patients with Locally Advanced or Metastatic NSCLC

The Applicant's clinical development program was designed in consultation with Health Authorities globally.

Phase 3 Scientific Advice

The Applicant sought Scientific Advice from the CHMP on the Phase 3 PAPILLON study in June 2020, more specifically (1) on the major design aspects and (2) whether the outcome could support a potential registration of ACP for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations.

The CHMP generally agreed with the major design aspects (target population, SOC CP, primary endpoint, secondary endpoints, and statistical assumptions), the PK plan, and the approach to confirm exon20ins mutations in participants before enrollment.

(Co-) Rapporteur Pre-submission Meetings

A Pre-submission Meeting was held with the Rapporteur and Co-rapporteur Agencies (Dr Filip Josephson, Sweden) and (Dr Johanna Lähteenvuo, Finland) on 16 August 2023 and 05 September 2023, respectively. The main objectives of these meetings were to present the topline results of the final analysis of the PAPILLON study to seek input from the Rapporteur and Co-Rapporteur on the overall regulatory strategy supporting the planned extension of indication submission for amivantamab and to fulfill the specific obligation needed to convert the existing conditional marketing authorization for amivantamab into a standard marketing authorization in the EU.

Overall, the meetings with the (Co-) Rapporteurs identified no barriers to proceed with the Type II Variation. The Co-Rapporteur confirmed that the study was conducted as requested, and the data presented was clear and consistent, and therefore should be a good basis for the Benefit-Risk Assessment. The Rapporteur indicated that there were no concerns with the top line results provided, and the data would be suitable for assessment.

2.1.4. General comments on compliance with 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

2.2.1. Ecotoxicity/environmental risk assessment

With regards to the Environmental Risk Assessment ((ERA), 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. As amivantamab is a monoclonal antibody and is consequently classified as a protein, no ERA for amivantamab is required.

2.2.2. Non-clinical aspects conclusion

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

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 2: Overview of the Clinical Studies

Study number/name[a] Cohort (if applicable) Status SCE data cutoff	Study Design	Treatment regimen	Study Population/Sample Size (Actual)
61186372NSC3001 PAPILLON ongoing CCO 03 May 2023	A Phase 3, randomized, open-label study. The study consists of two arms: Arm A: treatment with ACP. Arm B: treatment with CP. Participants from Arm B with disease progression confirmed by BICR are given the option to enter the Crossover phase, where they receive amivantamab monotherapy.	**Main Study:** Arm A (ACP): Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) by IV infusion once weekly up to 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 until disease progression. Pemetrexed 500 mg/m2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression. Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles. Arm B (CP): Pemetrexed 500 mg/m2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression. Carboplatin AUC 5 on Day 1 of each 21-day cycle, for up to 4 cycles. **Crossover Phase:** 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.	At least ≥18 years of age with treatment-naïve, locally advanced or metastatic NSCLC characterized by EGFR exon 20ins activating mutations (main study: N=308, crossover phase: N=65).
61186372EDI1001[b] CHRYSALIS Ongoing **Chemotherapy Combination Cohort** CCO 15 November 2022	A Phase 1, first-in-human, open-label, dose escalation study in subjects with advanced NSCLC. After confirmation of the safety of the regimen, a total of 20 participants with advanced NSCLC who were eligible to receive SOC carboplatin- pemetrexed (no specific driver mutation required) were enrolled in this cohort and treated with ACP in a 21-day cycle.	Carboplatin and pemetrexed were administered in accordance with local guidelines and labeling. Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) by IV infusion once weekly up to 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 until disease progression.	**Study Population:** At least ≥18 years of age. Histologically or cytologically confirmed NSCLC that was metastatic or unresectable. Participants could be diagnosed with EGFR mutated or EGFR wild-type NSCLC. **Sample Size** Of the 20 participants enrolled in the chemotherapy combination cohort, 5 had treatment-naïve EGFR exon 20ins NSCLC, consistent with the PAPILLON study population. This SCE includes supportive efficacy results from the 5 participants with treatment-naïve EGFR exon 20ins NSCLC.

AUC=area under the curve; AUC5= 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 20ins= exon 20 insertion; EoT=end of trial; NSCLC= non-small cell lung cancer; IV=intravenous.
[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.

Study number/name[a] Cohort (if applicable) Status SCE data cutoff	Study Design	Treatment regimen	Study Population/Sample Size (Actual)

[b] This study consists of different cohorts in which participants either receive amivantamab and lazertinib combination therapy or amivantamab and carboplatin/pemetrexed combination therapy (chemotherapy combination cohort). Only information regarding the chemotherapy combination cohort is included in this table and SCE

2.3.2. Pharmacokinetics

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

The clinical pharmacology data, relevant for this application, originates from 2 ongoing studies evaluating amivantamab as monotherapy and in combination with standard of care carboplatin and pemetrexed (CP) in participants with exon 20ins NSCLC (Table 3). The PK data cut-off date for the pivotal PAPILLON study was 09 February 2023. The PK data cut-off date for participants with NSCLC enrolled in the chemotherapy combination Part 1 cohort (hereafter referred to as "ACP cohort") of the CHRYSALIS study was 15 November 2021. ACP treatment was compared to amivantamab monotherapy using PK data from the amivantamab monotherapy cohorts of the CHRYSALIS study, with a PK cut-off of 26 February 2021, and from the PAPILLON study, with a PK cut-off of 09 February 2023.

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

Study Number	Phase	Population	Amivantamab Dose	Number of Participants Dosed
61186372NSC3001 (PAPILLON)	3	Participants with advanced or metastatic NSCLC with EGFR exon 20 insertions	Amivantamab in combination with carboplatin and pemetrexed (ACP, RP2ChD Q3W): Baseline body weight <80 kg 1400 mg IV Cycle 1 Day1/2 (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 Day1/2 (Day 1=350 mg, Day 2=1400 mg), Day 8, Day 15, and Cycle 2 Day 1 (QW) 2100 mg IV Cycle3+ Day 1 (Q3W)	ACP arm: 151
			Not applicable while receiving CP. After crossover from CP to amivantamab monotherapy: Amivantamab in 21-day cycles as follows: 1400 mg (1750 mg if body weight is ≥80 kg) by IV infusion QW up to Cycle 2 Day 1, then 1750 mg (2100 mg if body weight is ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3	Total CP arm: 155 Crossover: n=56[a]
61186372EDI1001 (CHRYSALIS)	1	Participants with advanced NSCLC	Amivantamab monotherapy: Part 1 (dose escalation): 140, 350, 700, 1050, 1400, and 1750 mg Part 2 (dose expansion, RP2D Q2W): 1050 mg (body weight <80 kg) or 1400 mg (body weight ≥80 kg)	413
61186372EDI1001 (CHRYSALIS)	1	Participants with advanced NSCLC	Amivantamab in combination with carboplatin and pemetrexed (ACP, RP2ChD Q3W): Baseline body weight <80 kg 1400 mg IV Cycle 1 Day1/2 (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 Day1/2 (Day 1=350 mg, Day 2=1400 mg), Day 8, Day15, and Cycle 2 Day 1 (QW) 2100 mg IV Cycle 3+ Day 1 (Q3W)	20

[a] After BICR-confirmed disease progression, eligible participants from CP arm were given the option to enter the Crossover phase, where they received amivantamab monotherapy in a 21-day cycle.

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 the ACP cohort of the CHRYSALIS study and in the ACP arm of the

PAPILLON study. Further, serum amivantamab concentrations of samples obtained from participants treated with amivantamab monotherapy in the CP arm after crossover to amivantamab monotherapy of the PAPILLON study were included.

In the PAPILLON study, for the ACP arm, serum samples were collected on Day 1 of Cycle 1 and on Day 2 of Cycle 1, at predose and EOI and at Day 1 of Cycles 2, 3, 5, 7, 9, 11 and 13, at predose and EOI. The same sampling schedule applies to participants in the CP arm after crossover to amivantamab monotherapy.

In the CHRYSALIS study ACP cohort, serum samples were collected on Day 1 of Cycle 1 at predose and EOI, Day 2 of Cycle 1 at predose, EOI, and 2, 24, 72 hours after EOI and on Day 1 of Cycle 2 at predose, EOI, and 2, 24, 72, 168, and 336 hours after EOI. Additionally, predose and EOI samples were collected for each dose.

All PK parameters were calculated using conventional non-compartmental methods using actual times of blood sampling, unless otherwise stated in the CSR.

The population PK analysis was performed using nonlinear mixed effects modelling, using standard methodology and adherence to regulatory guidelines for population PK analyses.

Phase 3 PAPILLON study

Blood samples were collected at the designated timepoints for the evaluation of amivantamab PK from participants in the ACP arm and participants in the CP arm after crossover to amivantamab monotherapy. In total, 207 participants (151 participants from the ACP arm and 56 participants from the CP arm who crossed over to amivantamab monotherapy) were included in the study and had received at least 1 dose of amivantamab and had at least 1 evaluable post-baseline amivantamab concentration measurement.

Mean serum concentrations of amivantamab appeared to be comparable at all timepoints when given in combination with CP in the ACP arm and when given as monotherapy following crossover from the CP arm, after IV infusion of 1400/1750 mg amivantamab QW up to Cycle 2 Day 1, then 1750/2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3 (Figure 2).

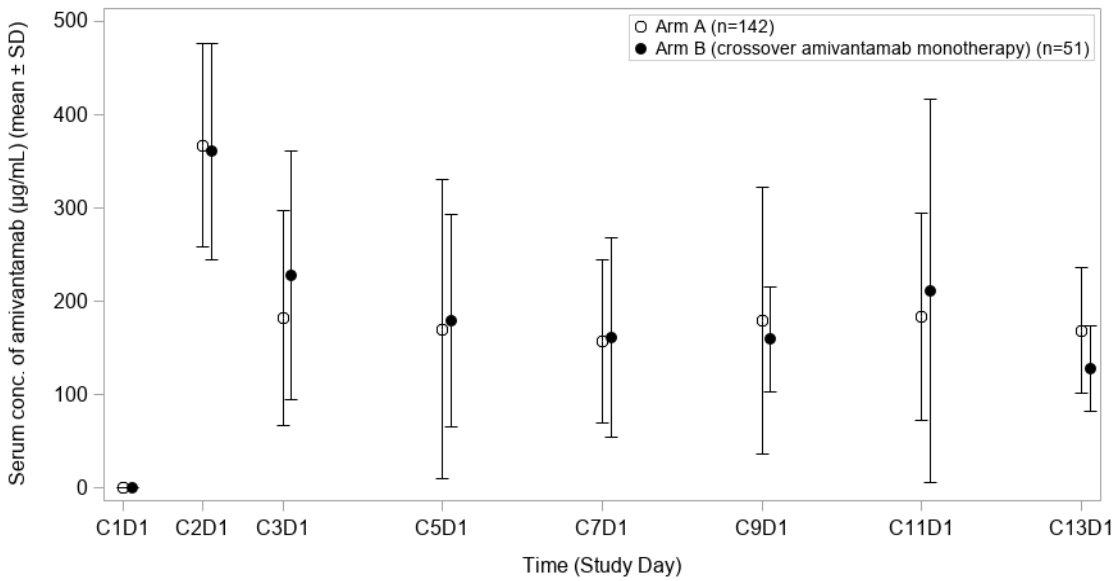


Figure 2: Mean (SD) Serum Predose Concentration-time Profiles of Amivantamab After IV Infusion of Amivantamab Administered Q3W in Combination With or Without CP (PAPILLON Study: Pharmacokinetics Data Analysis Set)

Population pharmacokinetic analysis

A population PK analysis was performed using the nonlinear mixed effect modelling software NONMEM (version 7.5.0). The FOCE method with the INTERACTION option was used.

A previous model, developed on data collected after monotherapy treatment in CHRYSALIS (13440 rich and sparse serum concentration samples from 413 subjects; see procedure number EMEA/H/C/005454/0000), was used as a starting point for the model describing pooled PK data from the CHRYSALIS and PAPILLON studies.

Data

The pooled PK dataset included 16321 amivantamab PK concentrations from 639 participants with EGFR mutated NSCLC, where 433 participants were from CHRYSALIS (413 treated with amivantamab monotherapy [these data were included in the previous model analysis] and 20 treated with ACP) and 206 participants were from PAPILLON (151 treated with ACP and 55 treated with amivantamab monotherapy after crossover from CP). Individual amivantamab serum concentrations versus time after the previous dose, stratified by study, are shown in Figure 3. Because the percentage of posttreatment samples below the limit of quantification (BLQ) was low (0.8%), the BLQ samples were omitted from the analysis.

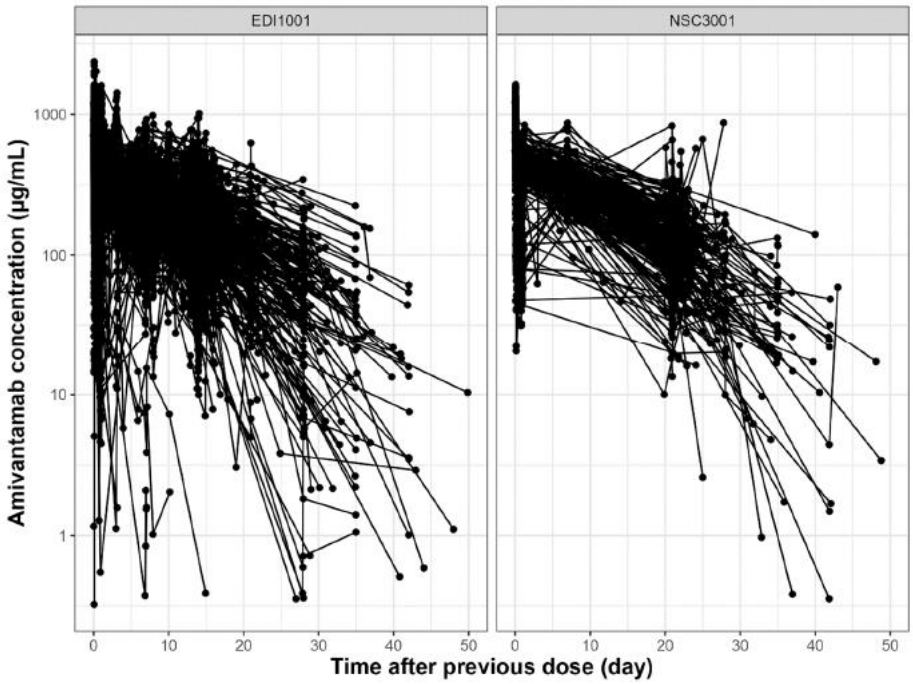


Figure 3: Scatter plot of amivantamab serum concentration versus time after previous dose stratified by study (EDI1001 = CHRYSALIS; NSC3001 = PAPILLON).

Model

The PK of amivantamab was described using a 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination. The model was parameterized in terms of linear CL, V_1, Q, V_2, V_{max}, and K_m. Inter-individual variability (IIV) was estimated for CL, V_1, and V_2; IIV for V_{max} was removed from the starting model as it was not normally distributed around zero. The residual variability was proportional (additive on logarithmic scale). Covariate relationships were reassessed: baseline

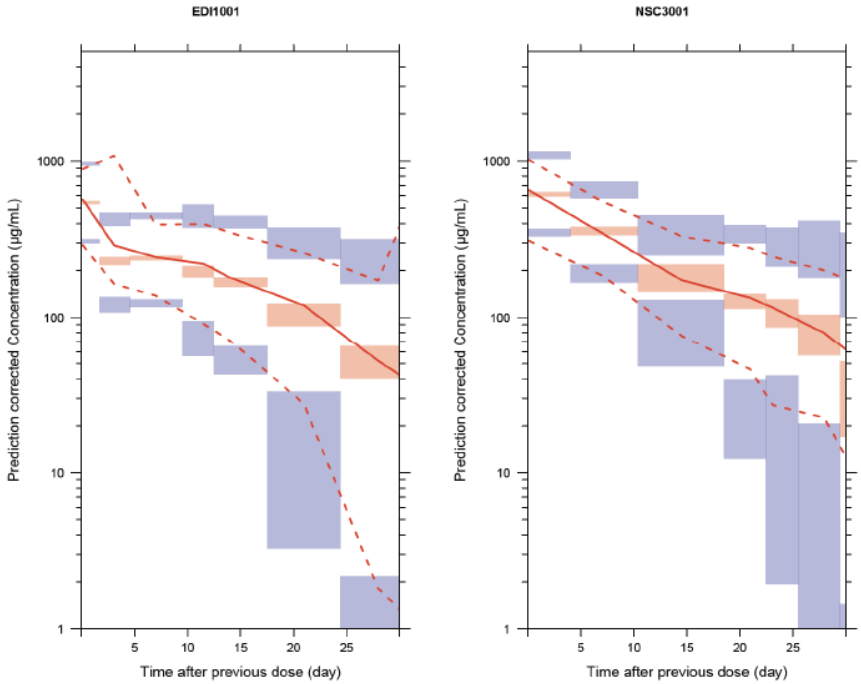
demographics (age, weight, sex, race), baseline serum albumin, and combination with chemotherapy (yes or no) were explored as potential covariates in a full covariate model, and a backward elimination step was used to remove nonsignificant relationships. The final model included body weight, sex, age, 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). The parameter estimates of the final model are presented in Table 4, prediction corrected VPCs, stratified by study, are presented in Figure 4, and summary statistics of individual (secondary) PK parameters, derived based on post hoc parameter estimates of participants in PAPILLON, are presented in Table 5.

Table 4: Parameter estimates in the final population PK model on pooled PK data from the CHRYSALIS and PAPILLON studies.

Parameters	Estimate	Standard Error	RSE%	IIV/Residual (CV%)	Shrinkage (%)
CL (L/h)	0.00956	0.000246	2.58		
V_1 (L)	2.51	0.0361	1.44		
V_2 (L)	2.25	0.0752	3.34		
Q (L/h)	0.125	0.0147	11.7		
V_{max} (mg/h)	0.596	0.0635	10.7		
K_m (µg/mL)	3.71	1.61	43.3		
WT on CL (unitless)	0.531	0.0577	10.9		
WT on V_1 and V_2 (unitless)	0.468	0.0467	9.98		
Sex Male on CL (unitless)	0.236	0.0328	13.9		
Sex Male on V_1 (unitless)	0.150	0.0261	17.4		
Age on CL (unitless)	-0.241	0.0555	23.0		
Albumin on CL (unitless)	-0.489	0.115	23.5		
IIV CL	0.0718	0.0073	10.2	27.3	7.4
IIV V_1	0.0463	0.00772	16.7	21.8	11.4
IIV V_2	0.258	0.0477	18.5	54.3	20.8
Residual Variance	0.0542	0.00235	4.33	23.6	4.5

Estimates in relative percentage scale for IIV and residual error. CV% calculated as 100×sqrt(exp(var)-1), where var represents the variance estimate for log-normally distributed random effects and residual. Shrinkage is based on the SD and is calculated as 100×(1-SD(ETA)/ω).

CL (L/h)=0.00956×(WT in kg/60)$^{0.531}$×(1+0.236 if male) × (Age in years/63)$^{-0.241}$×(Albumin in g/L/40)$^{-0.489}$; V_1 (L)=2.51×(WT in kg/60)$^{0.468}$ ×(1+0.150 if male); V_2 (L)=2.25×(WT in kg/60)$^{0.468}$.



Solid red lines represent the median, and dashed lines represent 5% and 95% percentiles of the prediction-corrected observed values. Orange and blue shaded areas represent the 95% CI of the median, 5% and 95% percentiles of the prediction-corrected simulated concentrations based on 1,000 PPK simulations.

Figure 4: Prediction corrected visual predictive check for the final population PK model stratified by study (EDI1001 = CHRYSALIS; NSC3001 = PAPILLON).

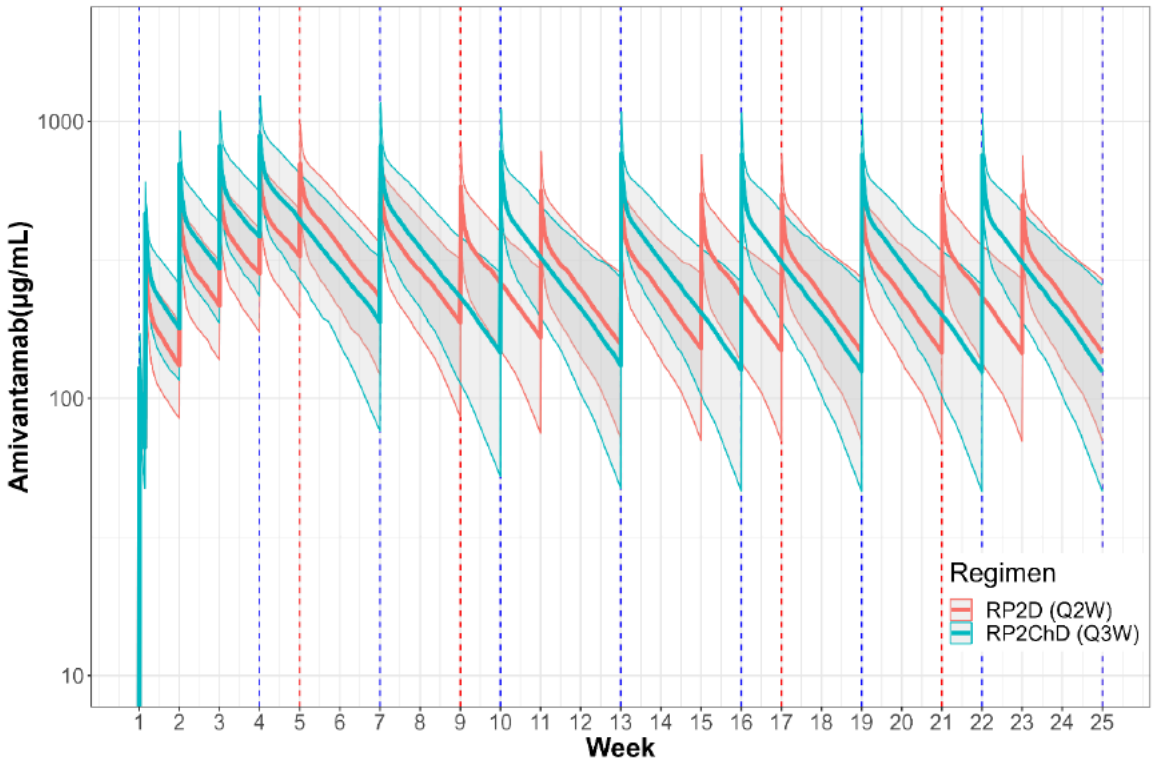
Table 5: Summary of (secondary) PK parameters derived based on post hoc parameter estimates of participants in PAPILLON.

	PAPILLON (N=206)
CL (L/day)	
Mean (SD)	0.277 (0.0838)
Median [Min, Max]	0.263 [0.132, 0.590]
Gmean (GCV)	0.266 (30.4)
Total volume of distribution (L)	
Mean (SD)	5.34 (1.81)
Median [Min, Max]	4.95 [2.75, 16.8]
Gmean (GCV)	5.12 (27.8)
Terminal $t_{1/2}$ associated with linear clearance (day)	
Mean (SD)	14.4 (6.40)
Median [Min, Max]	13.3 [5.84, 79.7]
Gmean (GCV)	13.7 (31.9)

Terminal $t_{1/2}$ is the beta half-life of a 2-compartment model calculated using the linear clearance (CL), Q, V1 and V2 estimated.

Simulations

The comparability of the approved RP2D (Q2W) regimen and the proposed RP2ChD (Q3W) regimen was evaluated through simulated amivantamab PK profiles for the two regimens, respectively, using post hoc parameter estimates of participants in PAPILLON. For both regimens, steady state was reached by Week 13, and the mean serum $AUC_{1\text{-week,ss}}$ was approximately 1.9-fold higher at steady state compared to the first dose (Table 6).



Vertical dashed lines indicate Q2W (red) or Q3W (blue) treatment cycle. Shaded areas indicate 5th to 95th percentile of the prediction intervals.

Figure 5: Simulated amivantamab serum concentration versus time profiles by regimen, using post hoc parameter estimates of participants in PAPILLON.

Table 6: Summary of simulated amivantamab exposure by regimen.

	RP2D (Q2W) regimen: 1050/1400 mg QW in Cycle 1, 1050/1400 mg Q2W from Cycle 2; 28-days per cycle (N=206)	RP2ChD (Q3W) regimen: 1400/1750 mg QW through Cycle 2 Day 1, 1750/2100 mg Q3W from Cycle 3; 21-days per cycle (N=206)
$C_{trough,C2D1}$ (µg/mL)		
Median [min, max]	325 [144, 610]	383 [165, 717]
G_{mean} (GCV)	315 (27.4 %)	373 (26.4 %)
$C_{trough,ss}$ (µg/mL)		
Median [min, max]	145 [28.1, 349]	124 [10.4, 378]
G_{mean} (GCV)	140 (43.3 %)	116 (56.3 %)
$AUC_{1\text{-}week,1st\ full\ dose}$ (µg/mL*h)		
Median [min, max]	27200 [12200, 45400]	35900 [16400, 60800]
G_{mean} (GCV)	26700 (22.1 %)	35500 (21.9 %)
$AUC_{1\text{-}week,C2D1}$ (µg/mL*h)		
Median [min, max]	76100 [37500, 138000]	92800 [44100, 171000]
G_{mean} (GCV)	73700 (24.8 %)	91800 (24.1 %)
$AUC_{1\text{-}week,ss}$ (µg/mL*h)		
Median [min, max]	51000 [27400, 93300]	68400 [38800, 124000]
G_{mean} (GCV)	50100 (25.6 %)	67200 (23.4 %)

Compared with the approved RP2D (Q2W) regimen, the RP2ChD (Q3W) regimen had higher trough concentrations after QW (ie, predose of Cycle 2 Day 1 dose [$C_{trough,C2D1}$]) and comparable trough concentrations at steady state ($C_{trough,ss}$), supporting the selected recommended doses for the RP2ChD regimen. Simulation results stratified by body weight (<80 kg versus ≥80 kg) are provided in Figure 6. In both body weight subgroups, the PK exposures were comparable between the RP2D (Q2W) regimen and the RP2ChD (Q3W) regimen.

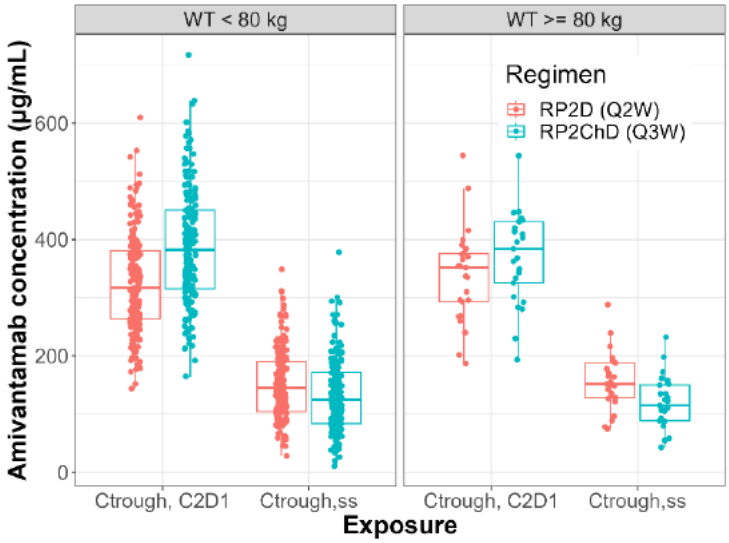
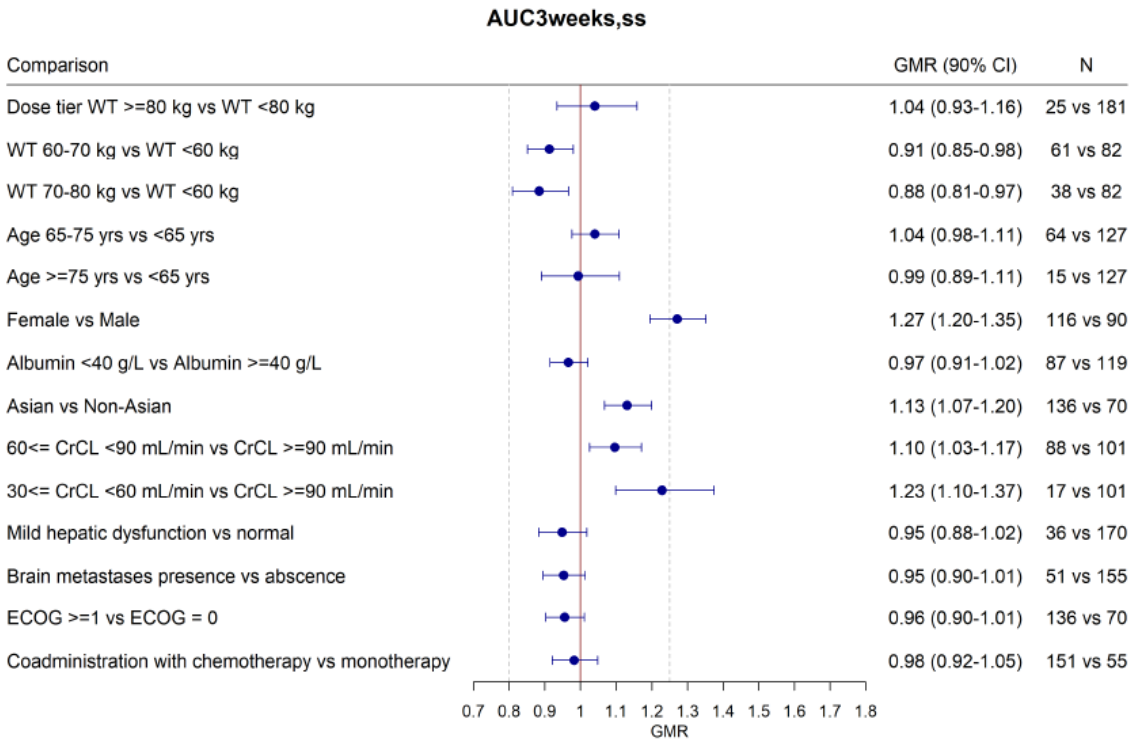


Figure 6: Simulated amivantamab exposure by dosing regimen stratified by body weight using post hoc parameter estimates of participants in PAPILLON.

A comparison of amivantamab steady-state exposure parameters ($C_{eoi,ss}$ and $AUC_{3weeks,ss}$) 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 PAPILLON study, assuming all participants received the scheduled doses of the RP2ChD regimen. Subgroups were considered to have comparable exposure if the estimated GMR and 90% CI limits were not entirely outside the 80% to 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, with one dependent variable (exposure in logarithmic scale) and multiple independent variables (the various patient factors). The reported adjusted GMR is the coefficient associated with each patient factor from the multivariate regression model. The forest plot of $AUC_{3weeks,ss}$ with adjusted GMR is presented in Figure 7. The trend for $C_{eoi,ss}$ (not shown) was similar to that of $AUC_{3weeks,ss}$. The forest plot shows that coadministration of amivantamab with CP did not affect amivantamab PK, consistent with the results of PK covariate model.



Filled circle + line represent GMR (+90% CI) with vertical dashed lines represent 80% (left) and 125% (right). Post hoc PK parameters of PAPILLON PK population were used in the simulations (N=206). In each subgroup comparison, only participants with nonmissing covariate values were included. GMR was adjusted with other covariates listed in the forest plot, where the effect of each covariate was estimated simultaneously using a multivariate regression model.

Figure 7: Forest plot of simulated $AUC_{3weeks,ss}$ using post hoc parameter estimates of participants in PAPILLON.

Special populations

Renal impairment

Based on the updated population PK model, the mild renal impairment subgroup (creatinine clearance 60 to 90 mL/min) had comparable exposure to the normal renal function group (creatinine clearance ≥90 mL/min). Based on the estimated GMR (adjusted for correlated covariates), the subgroup of moderate renal impairment (creatinine clearance 30 to 60 mL/min) had 23% higher $AUC_{3weeks,ss}$ than the subgroup of subjects with normal renal function. This difference is not considered clinically relevant.

Hepatic impairment

Based on the updated population PK model, the mild hepatic impairment subgroup (based on National Cancer Institute Organ Dysfunction Working Group criteria) had comparable exposure to the normal hepatic function group.

Sex

Based on the updated population PK model, males had higher CL and central volume of distribution than females. Based on the estimated GMR (adjusted for correlated covariates), females had 27% higher $AUC_{3weeks,ss}$ than males (ie, males had 21% lower amivantamab $AUC_{3weeks,ss}$ than females). This difference is not considered clinically relevant.

Race

Based on the updated population PK model, subgroups of race (Asian versus non-Asian, Japanese versus non-Japanese, Chinese versus non-Chinese, African American versus non-African American) tended to have comparable exposure.

Body weight

Participants with higher body weight tended to have lower exposure at the same dose. Subgroups of weight (<80 kg, ≥80 kg) had comparable exposure when participants in the ≥80 kg group received a higher dose, supporting the weight-tiered flat dosing.

Based on the estimated GMR (adjusted for correlated covariates), body weight subgroups of 60 to 70 kg and 70 to 80 kg had 9% and 12% lower $AUC_{3weeks,ss}$ in comparison to the weight subgroup of <60 kg, respectively.

Age

Based on the updated population PK model, age is a significant covariate on CL; however, subgroups of age (<65, ≥65 to <75, ≥75 years) had comparable exposure.

Immunogenicity data analysis

Method

The possible generation of anti-amivantamab antibodies was assessed in participants, from the CHRYSALIS and PAPILLON studies, treated with ACP or amivantamab monotherapy. 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 PAPILLON study, serum samples were collected prior to the administration of amivantamab on Day 1 of Cycles 1, 2, 3, 5, 7, 9, 11, and 13, and at the end of treatment visit.

In the CHRYSALIS study, serum samples were collected prior to the first administration of amivantamab on Day 1 of Cycles 1, 2, 4, 6, 9, 11, 13, 15, and 17, and every 26 cycles thereafter until the end of treatment and at the follow up 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 PAPILLON study consisted of 198 participants (143 participants from the ACP arm and 55 participants from the CP arm who crossed over to amivantamab monotherapy) who had appropriate samples, whereas the immunogenicity analysis population in the CHRYSALIS study consisted of 365 participants (18 participants who received ACP and 347 participants who received amivantamab as monotherapy) who had appropriate samples (Table 7).

Table 7: Summary of the incidence of immunogenicity to amivantamab in participants in the PAPILLON and CHRYSALIS studies.

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[b]
61186372NSC3001 (PAPILLON)	Amivantamab in combination with carboplatin and pemetrexed (ACP, RP2ChD Q3W): 1400 mg (<80 kg) or 1750 mg (≥80 kg) IV infusion QW up to C2D1; 1750 mg (<80 kg) or 2100 mg (≥80 kg) on C3D1 and C4D1	143[c]	0 (0.0%)	143 (100.0%)
	After crossover from CP to amivantamab monotherapy: 1400 mg (<80 kg) or 1750 mg (≥80 kg) IV infusion QW up to C2D1; 1750 mg (<80 kg) or 2100 mg (≥80 kg) on C3D1 and onwards	55	0 (0.0%)	55 (100.0%)
61186372EDI1001 (CHRYSALIS)	Amivantamab monotherapy: 140 mg, 350 mg, 700 mg, 1050 mg, 1400 mg, 1750 mg IV infusion	347[d]	3 (0.9%)	344 (99.1%)
61186372EDI1001 (CHRYSALIS)	Amivantamab in combination with carboplatin and pemetrexed (ACP, RP2ChD Q3W): 1400 mg (<80 kg) or 1750 mg (≥80 kg) C1 to C2 IV infusion Q3W; 1750 mg (<80 kg) 2100 mg (≥80 kg) C3 onwards IV Q3W	18	0 (0.0%)	18 (100.0%)

[a] Participants who had 1 or more evaluable samples obtained after their first amivantamab administration.
[b] Denominator is number of participants with appropriate samples for antibodies to amivantamab.
[c] In 1 participant, all post-baseline ADA samples contained drug concentrations greater than the assay drug tolerance limit (>400 µg/mL). This participant was excluded from the ADA descriptive statistics.
[d] In 25 participant, all post-baseline ADA samples contained drug concentrations greater than the assay drug tolerance limit (>400 µg/mL) and were excluded from the ADA descriptive statistics.

In the CHRYSALIS study, 3 participants were positive for antibodies to amivantamab. The shape of the serum concentration-time profiles of the participants who tested positive for antibodies to amivantamab did not deviate from the serum concentration-time profiles of the participants who tested negative for antibodies to amivantamab (see procedure number EMEA/H/C/005454/0000). None of the participants in the PAPILLON study were positive for antibodies to amivantamab. The overall incidence of antibodies to amivantamab in all treated participants was low, with all ADA positive participants having low titers.

Pharmacokinetic interaction studies

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

Coadministration with CP had no impact on amivantamab exposure, neither based on review of observed data nor based on the population PK analysis.

2.3.3. Pharmacodynamics

Please refer to procedure number EMEA/H/C/005454/0000 for details on the pharmacodynamics (PD) of amivantamab monotherapy. No new PD data are available.

Exposure-response modelling

Exposure-response (E-R) analyses were conducted for the efficacy and safety results from PAPILLON. The E-R population included 151 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. The E-R analysis for safety included selected common TEAEs related to amivantamab administration. Analyses were performed with R (version 4.2.2 or greater).

Efficacy

The E-R relationships for PFS by BICR (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.

A weak, but not statistically significant, trend of positive E-R for PFS by BICR was observed across exposure tertiles, using the log-rank test. After accounting for brain metastases and sex, E-R for PFS by BICR was insignificant (flat) in multivariate Cox-PH modelling. The flat E-R for PFS by BICR suggests that the RP2ChD Q3W dose regimen provided adequate exposure for efficacy.

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 any grade rash, paronychia, constipation, and hypoalbuminemia increased slightly with the increase of amivantamab exposure. These adverse events are consistent with the known safety profile of amivantamab monotherapy.

No apparent relationship between amivantamab exposure and nausea was identified.

2.3.4. Discussion on clinical pharmacology

In the current application, the PK is mainly descriptive and population PK modelling has been applied to characterise the PK of amivantamab when administered as monotherapy and in combination with carboplatin and pemetrexed (CP) in subjects with exon 20ins NSCLC.

The clinical pharmacology data originates from 2 ongoing studies – CHRYSALIS and PAPILLON – evaluating amivantamab as monotherapy and in combination with standard of care CP in participants with exon 20ins NSCLC. The general distribution, metabolism, and excretion characteristics, dose proportionality and time dependency of amivantamab administered as monotherapy are described in procedure number EMEA/H/C/005454/0000 and are based on data on 413 participants treated with amivantamab monotherapy in the CHRYSALIS study (mainly sparse PK sampling and population PK modelling).

For the current application, additional data have been collected on 20 participants treated with amivantamab in combination with CP in the CHRYSALIS study, 151 participants treated with amivantamab in combination with CP in the PAPILLON study, and 55 participants treated with amivantamab monotherapy (after crossover from CP) in the PAPILLON study.

The bioanalytical methods were assessed during procedure number EMEA/H/C/005454/0000 and were found acceptable. Both the bioanalytical and immunogenicity methods have for the studies in this application been transferred to another site where the methods were acceptably re-validated and the bioanalytical method also cross-validated to the previous site.

The recommended phase 2 in combination with chemotherapy dose (RP2ChD) Q3W regimen evaluated in PAPILLON was selected to accommodate the chemotherapy Q3W dose schedule and to achieve trough concentrations at the end of the QW dosing period and at steady state that are comparable to the approved recommended phase 2 dose (RP2D) Q2W regimen. The comparability of the dosing regimens was further evaluated in the population PK analysis.

The PK of amivantamab was evaluated in a population PK analysis on pooled data on amivantamab administered as monotherapy and amivantamab administered in combination with CP, from the CHRYSALIS and PAPILLON studies. The starting model was the model developed on monotherapy data from the CHRYSALIS study (procedure number EMEA/H/C/005454/0000). The structural model was a 2-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination. Covariate relationships were reassessed on the pooled data, and new statistically significant relationships were identified. The starting model contained body weight as covariate on CL and V_1, and sex as covariate on CL. These relationships were retained in the final model, and in addition, age and albumin were identified as covariates on CL, sex was identified as a covariate on V_1, and body weight was identified as a covariate on V_2 (same exponent as for V_1). Body weight and sex are correlated and included as covariates on the same two parameters, which may affect the magnitude of the estimated effect sizes and hamper the interpretability.

The η-shrinkage is relatively low for all parameters in the final model (7.4 – 21%), which implies that post hoc estimates are likely to be representative of the variability in the population. It should be noted though, that the number of samples per subject varies a lot and there were fewer samples per subject in PAPILLON than in CHRYSALIS, which means that the shrinkage is likely higher in the subpopulation that received amivantamab in combination with CP than in the subpopulation that received monotherapy treatment. Nevertheless, since the first line treatment (in combination with CP) is the most relevant indication to reflect in the SmPC, and since most subjects receiving amivantamab as first line treatment were in the PAPILLON study, it is considered acceptable to present total volume of distribution and terminal elimination half-life, derived based on post hoc estimates of participants in PAPILLON, in Section 5.2 of the SmPC. The Applicant has provided arguments for why they consider it

more appropriate to also base the reported clearance on summary statistics of individual post hoc parameter estimates of participants in the PAPILLON study, instead of using the population parameter estimate (it reflects the clearance in the target patient population, considering both covariate distributions and correlation between covariates, and it uses the same method as the reported terminal half-life). The arguments are accepted, and it is also clearly stated in the SmPC that the total volume of distribution, the terminal half-life, and the clearance are based on individual parameter estimates.

The pcVPC indicates an underprediction of data at early time points after dose in the CHRYSALIS study; however, overall, the model describes the observed data well, especially data from the PAPILLON study. The model is therefore considered adequate for the current descriptive purpose.

The RP2ChD (Q3W) regimen was selected to achieve trough concentrations at the end of QW dosing period and at steady state that are comparable to the approved RP2D (Q2W) regimen. The simulations show that the RP2ChD regimen had higher trough concentrations after QW (ie, predose of Cycle 2 Day 1 dose [$C_{trough,C2D1}$]) than the RP2D regimen, which is expected since the weekly dose is higher with the RP2ChD regimen. At steady state, the trough concentrations ($C_{trough,ss}$) are slightly lower following the RP2ChD regimen compared to the RP2D regimen. For the RP2ChD regimen, the achieved trough concentrations (both $C_{trough,C2D1}$ and $C_{trough,ss}$) are comparable between subjects weighing <80 kg and subjects weighing ≥80 kg, supporting the weight cut-off and the proposed doses for subjects weighing <80 kg and subjects weighing ≥80 kg, respectively.

In the SmPC, the current statement regarding accumulation is based on NCA results, comparing $AUC_{1\text{-}week}$ after the 1st dose in Cycle 2 (maximum exposure) to the $AUC_{1\text{-}week}$ after the 1st full dose, of the RP2D regimen. The Applicant has proposed to base the updated statement on simulations from the population PK model. It is considered acceptable to base the statement on the presented simulations, and the SmPC is now providing information on the accumulation to the maximum exposure (after the first dose in Cycle 2; 2.6- to 2.8-fold, depending on dosing regimen) as well as the accumulation to steady state (1.9-fold for both the RP2D and the RP2ChD regimens).

A direct comparison between the exposure following the RP2ChD regimen and the exposure following the RP2D regimen is not included in the SmPC. This is considered acceptable since the currently approved monotherapy treatment in second line, with the RP2D (Q2W) regimen, will likely be of little relevance once the indication for first line treatment in combination with CP is accepted.

For evaluation of covariate effects, the Applicant has compared steady-state exposure parameters in specific subgroups by presenting the estimated GMR and its 90% CI for the exposure metrics for a given covariate stratum relative to the reference stratum. To account for the correlation between covariates, the GMR was adjusted with other covariates, which is considered good practice, since the correlation between covariates otherwise may hamper the comparison of exposure metrics derived using post hoc parameter estimates. Subgroups were considered to have comparable exposure if the estimated GMR and 90% CI limits were not entirely outside the 80% to 125% range.

It is agreed with the Applicant that although the covariate effects of sex, age, and albumin were statistically significant, none of these covariates are considered clinically relevant. The only covariate considered clinically relevant is body weight, and the effect of body weight is accounted for in the proposed dosing, which recommends a higher dose for subjects weighing ⩾80 kg, compared to subjects weighing <80 kg.

Coadministration with CP was not identified as a covariate in the population PK analysis, and the observed pre-dose concentrations of amivantamab, in the PAPILON study, appear comparable for participants who received amivantamab as monotherapy and participants who received amivantamab in combination with CP. This was expected since there is no overlapping pathway of elimination between amivantamab (mAb) and CP (small molecule drugs).

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

The exposure-response (E-R) analysis for efficacy (PFS by BICR) revealed a flat E-R relationship, which was expected given the narrow exposure range in PAPILLON (body weight-tiered flat dosing). The E-R analysis for safety revealed a minor increase in toxicity with increasing exposure, which is in agreement with the known safety profile of amivantamab.

2.3.5. Conclusions on clinical pharmacology

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

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

Amivantamab in combination with carboplatin and pemetrexed was first evaluated in the Part 1 chemotherapy combination cohort in the Phase 1 CHRYSALIS study where the RP2ChD was established based on pharmacokinetic, pharmacodynamic, safety, and efficacy data. Favorable therapeutic efficacy was demonstrated when participants with advanced NSCLC were treated with amivantamab at a dose of 1,400 mg (1,750 mg if body weight is ≥80 kg) once weekly up to 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 in combination with carboplatin and pemetrexed, administered in accordance with local guidelines and labeling.

Pharmacokinetic evaluation confirmed that similar amivantamab exposures were obtained with the Q3W RP2ChD in the chemotherapy combination cohort and the Q2W RP2D used with the monotherapy cohorts in the CHRYSALIS study. Furthermore, amivantamab exposure was not impacted by the co-administration of carboplatin and pemetrexed.

Subsequently, the RP2ChD Q3W dosing regimen, as confirmed in the CHRYSALIS chemotherapy combination cohort, was used in the Phase 3 pivotal PAPILLON study. The pharmacokinetic simulation results demonstrated that the key amivantamab exposure metrics (eg, AUC, $C_{trough,C2D1}$, and $C_{trough,ss}$) were comparable between the RP2D Q2W dosing regimen and the RP2ChD Q3W dosing regimen, supporting Q3W as an alternative regimen (PopPK-ER).

Overall, favorable therapeutic efficacy at the RP2ChD was demonstrated in the PAPILLON study and an exposure-response analysis (PopPK-ER) supports the adequacy of the proposed dosing regimen, as outlined below:

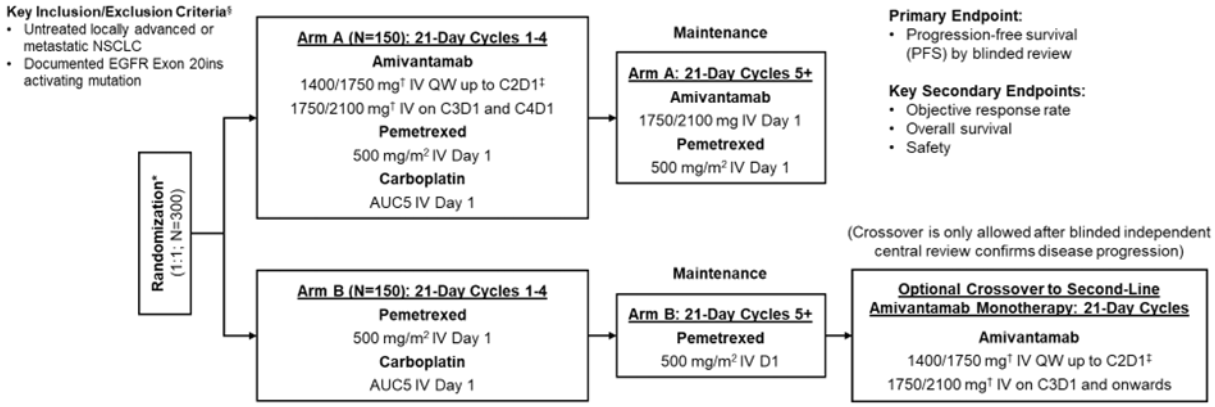
- Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) once weekly up to Cycle 2 Day 1, then 1,750 mg (2,100 mg if body weight is ≥80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.
- Pemetrexed 500 mg/m^2 (with vitamin supplementation) on Day 1 of each 21-day cycle, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression.

- Carboplatin area under the concentration-time curve 5 mg/mL per minute (AUC 5) on Day 1 of each 21-day cycle, for up to 4 cycles.

2.4.2. Main study(ies)

PAPILLON Study (Pivotal)

PAPILLON is a global, open-label, randomized Phase 3 study, designed to demonstrate improved efficacy of amivantamab in combination with CP versus CP alone for the first-line treatment of patients with EGFR exon 20ins NSCLC. The study design is shown in Figure 8.



AUC=area under the concentration-time curve; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; IV=intravenously; QW=once weekly; TKI=tyrosine kinase inhibitor.

* Stratification factors: Brain metastases (yes vs no); ECOG performance status (0 vs 1); prior EGFR TKI use (yes or no)

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

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

Figure 8: Study Design PAPILLON (61186372NSC3001)

This efficacy section presents the results of the primary analysis from the PAPILLON study based on a cut-off date of 03 May 2023.

2.4.2.1. OVERALL DESIGN

The study will include a Screening phase, a Treatment phase, and a Follow-up phase. Participants must complete screening procedures within 28 days before randomization. Imaging of disease sites will occur at regular intervals, as defined in the Schedule of Activities, until objective radiographic disease progression.

The Treatment phase for each participant will begin on Cycle 1 Day 1 and continue until the End of Treatment Visit, approximately 30 days after discontinuation of study treatment.

Participants who discontinue assigned study treatment for any reason will be followed for subsequent therapy, disease status, and survival in the Follow-up phase. This phase starts after the End of Treatment visit and continues until the end of study, death, loss to follow-up, or withdrawal of consent, whichever comes first.

Continuation of study treatment after disease progression may be allowed. A participant in Arm B with disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as confirmed by blinded independent central review (BICR), may be allowed to cross-over to amivantamab monotherapy.

An Independent Data Monitoring Committee will be commissioned for this study for the periodic review of safety and tolerability data, as well as planned efficacy analyses.

End of Study Definition

The end of study is planned to occur approximately 48 months after the first participant is randomized. Subjects who continue to receive study drug or who are in Follow-up after the data cutoff will continue to be monitored.

Methods

Study participants

The target population consisted of approximately 300 adult participants with treatment naïve, EGFR exon 20ins mutated locally advanced or metastatic NSCLC.

Screening for eligible participants was performed within 28 days before randomization, including submission of local test results for EGFR exon 20ins mutation status, submission of a tumor biopsy sample for central confirmation of EGFR exon 20ins, submission of peripheral blood samples for ctDNA analysis, baseline radiographic assessment of disease sites, and baseline brain magnetic resonance imaging.

Participants crossing over to second-line amivantamab monotherapy were rescreened to ensure eligibility was met to receive amivantamab.

Inclusion/Exclusion Criteria

The key eligibility criteria for inclusion in the study were as follows:

• Participants had to be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study took place).

• Participants had to have:

– histologically or cytologically confirmed, locally advanced or metastatic, nonsquamous NSCLC with documented primary EGFR exon 20ins mutations

– measurable disease according to RECIST v1.1

– ECOG performance status 0 or 1.

– adequate organ and bone marrow function.

The key exclusion criteria from the study were as follows:

Participants having received any prior systemic treatment for locally advanced or metastatic disease including prior therapy with investigational EGFR TKI agents targeting Exon20ins mutations, including TAK788 or poziotinib, with evidence of synchronous NSCLC disease, or with untreated brain metastases were excluded from participation in the study.

Crossover Phase

The key eligibility criteria for inclusion in the Crossover phase were as follows

• Participants could not have received any intervening systemic anti-cancer therapy or investigational therapy following discontinuation of assigned Arm B (CP arm) study treatment.

• Any unresolved toxicities from prior therapy should have resolved to NCI-CTCAE ≤Grade 1 severity (except for alopecia, which may be Grade 2) at the time of starting amivantamab monotherapy.

• Participants had to have:

– ECOG performance status 0 or 1.

– adequate organ and bone marrow function.

Treatments

Participants received the following study treatments during the Treatment phase:

Arm A (ACP arm):

· Amivantamab 1,400 mg (1,750 mg if body weight is ≥80 kg) by intravenous (IV) infusion once weekly up to 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 until disease progression.

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

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

Arm B (CP arm):

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

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

Participants were to discontinue study treatment for documented radiographic (RECIST v1.1) disease progression (confirmed by BICR) or if they met another criterion for discontinuation of study treatment. 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.

Participants who discontinued assigned study treatment for any reason were followed for subsequent therapy, disease status, survival, and symptomatic progression in the Follow-up phase. This phase started after the EoT Visit and continued until the end of study, death, loss to follow-up, or withdrawal of consent from participation in the study, whichever came first.

Crossover Phase

Eligible participants from Arm B (CP arm), after disease progression confirmed by BICR, were given the option to enter the Crossover phase where they received amivantamab monotherapy Q3W according to the amivantamab dose described above for Arm A (ACP arm).

After screening (which had to be performed within 28 days of the first dose of amivantamab monotherapy), all participants in the Crossover phase received amivantamab monotherapy as follows:

· 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.

Crossover participants could not initiate treatment with amivantamab earlier than 21 days or later than 90 days after their last dose of chemotherapy, regardless of the time of progression.

Pre- and Post-infusion Medications for Chemotherapy
Pre-and post-infusion medications for chemotherapy are summarized below.

• Corticosteroids, folic acid, and vitamin B12 were administered concomitantly with pemetrexed according to local prescribing information or per standard local practice.

• Participants were permitted to receive other pre-treatment or concomitant treatment for pemetrexed or carboplatin as recommended by local prescribing information, local practice guidelines, or as clinically indicated.

• Concomitant medications for the symptomatic treatment of related toxicities, supportive care and other medications considered necessary for the participant's well-being, and localized, limited radiotherapy of short duration for palliative purposes was permitted under certain conditions.

Pre- and Post-infusion Medications for Amivantamab

Required prophylactic or predose medications were to be administered to all participants per the protocol to prevent or lessen the severity of IRRs, rash, and nausea.

Prophylactic treatment for IRRs included:

• Required:

– IV administration of a glucocorticoid (ie, dexamethasone 20 mg [Cycle 1 Day 1]; dexamethasone 10 mg or methylprednisolone 40 mg [Cycle 1 Day 2]) 45 to 60 minutes prior to study treatment infusion.

– Administration of antihistamine (diphenhydramine 25 to 50 mg or equivalent), given either IV 15 to 30 minutes or orally 30 to 60 minutes prior to each amivantamab infusion.

– Administration of antipyretic (paracetamol 650 to 1,000 mg or equivalent), given either IV 15 to 30 minutes or orally 30 to 60 minutes prior to each amivantamab infusion.

• Optional:

– Glucocorticoid (IV or oral) given from Cycle 1, Day 8 and onwards

– Histamine H2 antagonist (ranitidine 50 mg or equivalent) given IV at any cycle

– Antiemetic (ondansetron 16 mg IV or 8 mg oral or equivalent) given at any cycle.

Post-infusion medications could be prescribed and continued for up to 48 hours after infusion of study treatment if clinically indicated for the management of IRRs or other infusion-related symptoms. These included IV or oral glucocorticoids, antihistamines, antipyretics (paracetamol), opiates (meperidine), and antiemetics administered as specified in the protocol. The administration of post-infusion medications and use of supportive-care measures was at the discretion of the investigator.

Objectives

The primary objective of the PAPILLON study is to compare efficacy, as demonstrated by PFS, in participants treated with ACP versus CP alone.

Table 8: Objectives and Endpoints for the PAPILLON Study

Objectives	Endpoints
Primary	
To compare the efficacy, as demonstrated by PFS, in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone	• PFS (using RECIST v1.1 guidelines), as assessed by BICR
Secondary	
To further assess the clinical benefit achieved with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Objective response • Duration of response • Overall survival • Time to subsequent therapy • PFS after first subsequent therapy • Time to symptomatic progression
To assess the safety in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone*	• Incidence and severity of adverse events and laboratory abnormalities, assessment of vital signs, and physical examination abnormalities
To assess the relationship between pharmacokinetics or immunogenicity and selected endpoints (including but not limited to efficacy, safety and/or PRO)*	• Serum amivantamab concentrations and anti-amivantamab antibodies
To assess health-related quality of life and disease-related symptoms in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone*	• EORTC-QLQ-C30 • PROMIS-PF
Exploratory	**Endpoints**
To further assess the clinical benefit achieved with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Time to treatment discontinuation
To explore genetic biomarkers predictive of improved outcome in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone*	• Tumor genetics by NGS of ctDNA and genetic analysis of tumor biopsy material at baseline, on therapy, and at progression • Circulating mutant allele frequencies by NGS of ctDNA at baseline, on therapy, and at progression
To explore mechanisms of resistance to amivantamab in combination with chemotherapy*	• Tumor protein markers by immunohistochemistry (eg, EGFR, MET) at baseline and at progression • Changes in tumor genetics, relative to baseline, by NGS of ctDNA and genetic analysis of tumor biopsy material at progression
To assess health-related quality of life in participants treated with amivantamab in combination with chemotherapy, versus chemotherapy alone*	• EQ-5D-5L

BICR=blinded independent central review; ctDNA=circulating tumor deoxyribonucleic acid; EGFR=epidermal growth factor receptor; EORTC-QLQ-C30= European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L= EuroQol five-dimensional descriptive system (5-level version); MET=mesenchymal-epithelial transition; NGS=next-generation sequencing; PFS=progression-free survival; PROMIS-PF= Patient-Reported Outcomes Measurement Information System – Physical Function; RECIST=Response Evaluation Criteria in Solid Tumors
*results not included in this SCE.

Outcomes/endpoints

2.4.2.1.1. Efficacy Endpoint Definitions

- PFS was defined as the time from randomization until the date of objective disease progression based on BICR using RECIST v1.1 or death (by any cause), whichever comes first.
- ORR was defined as the percentage of participants with best response of complete response or partial response, as defined by RECIST v1.1.
- DOR was defined as the time from the date of first document response (complete response or partial response) until the date of documented progression or death, whichever comes first.
- OS was defined as the time from the date of randomization until the date of death due to any cause.
- TTST was defined as 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.
- PFS2, defined as 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.
- TTSP was defined as 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 required either a change in anticancer treatment and/or clinical intervention to manage symptoms, or death, whichever comes first.

- Patient reported outcomes:

☐ EORTC-QLQ-C30, measures cancer patients' symptoms and functioning for all cancer types.

☐ PROMIS-PF, assesses physical function, including upper, central, and lower extremity functions and instrumental activities of daily living.

Crossover Phase

The efficacy analyses for the Crossover phase were exploratory and aimed to further characterize the efficacy of amivantamab, when administered as a monotherapy in a 21 day cycle, following disease progression with standard of care CP. Data were summarized descriptively, and endpoints analyzed included ORR, DOR, PFS, OS, TTST, and safety.

2.4.2.1.2. ctDNA and Biomarker Collection

To be eligible for the study, each participant must have a documented EGFR Exon 20ins activating mutation, as assessed before screening by local testing of tissue or ctDNA, as per standard of care. Provision of an unstained, tumor tissue sample (archival or recently collected) is required for each participant before randomization. If possible, the tissue provided for central analysis should be from the same biopsy utilized for local testing and identification of Exon 20ins.

Additional blood samples will be collected during the study and may be evaluated for ctDNA to assess changes in the levels or types of genetic alterations observed over time, and to monitor for the emergence of potential markers of resistance to the study therapy.
Blood samples will also be collected at time points for potential analysis of circulating biomarkers (eg, cytokines, growth factors) in samples taken prior to and after exposure to study treatment(s). Changes in circulating markers may be assessed in pre- and post-treatment samples and levels correlated with response to study treatments.
Additional biomarkers (eg, DNA, RNA, and protein) relevant to cancer and/or metabolism of study treatments may also be assessed in blood and tissue samples collected during the study to better understand the disease and mechanisms of response or resistance to study therapy.

The local testing of plasma or tissue specimens for the detection of EGFR Exon 20ins mutations was performed in accordance with the study eligibility criteria using the validated and/or CE-marked IVD assays listed in Table 9. The central testing using validated CE-marked assays was also performed with the objective of confirming the local testing results using both tissue and plasma specimens retrospectively. For tissue, confirmatory testing was conducted with the Thermo Fisher Oncomine Dx Target Test (ODxTT) and the AmoyDx® LC10 test. AmoyDx was used exclusively to support central testing in China, given the local requirement. Plasma confirmatory testing was conducted with the Guardant Health Guardant360 test. According to external data for test methods for other EGFR activating mutations (Ex19del, or exon 21 L858R substitution mutations or T790M mutations), if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

Table 9: Local Tests Used to Determine Exon 20ins Mutation Status (Study 61186372NSC3001)

Local Test	Number of Participants Enrolled
ROCHE COBAS ASSAY	39
LIFE TECH/THERMO FISHER ONCOMINE DX	28
SITE SPECIFIC LOCAL ASSAY	26
AMOYDX	16
PCR CLAMP	12
ILLUMINA TRUSIGHT	11
GUARDANT 360	8
PANAMUTYPER	8
QIAGEN ASSAY	8
FOUNDATIONONE	7
ENTROGEN	6
ONCOMINE FOCUS ASSAY	6
IDYLLA	5
ONCOMINE COMPREHENSIVE	5
TEMPUS	5
EASYPGX	3
GENESWELL DROPLET DIGITAL	3
DIATECH	2
ONCOMINE PRECISION	2
PIERIANDX	2
QIASEQ	2
AMPLISEQ FOR ILLUMINA FOCUS PANEL	1
AVENIO TUMOR TISSUE EXPANDED KIT	1
CARIS	1
GENEREADER	1
ILLUMINA FLOWCELL	1
ILLUMINA MISEQ	1
ION S5 SYSTEM (THERMO FISHER)	1
IVD, MARKED COMMERCIAL KIT	1
LABORATORY DEVELOPED TEST ON ION PROTON/ S5 PRIME	1
NEO GENOMICS	1
NEOTYPE	1
ONCOMINE THERMOFISHER	1
ONCOPRO NCCN LUNG PANEL	1
RMH200SOLID PANEL	1
SEMA4	1

Sample size

A total of 200 PFS events was to provide approximately 90% power to detect a hazard ratio (HR) of 0.625 corresponding to at least a 3-month improvement in the median PFS based on the assumptions of 5 months for chemotherapy and 8 months for the combination of amivantamab with chemotherapy with a log-rank test and based on a two-sided alpha=0.05.

Taking into consideration an annual dropout rate of 5%, the total sample size needed for the study was then approximately 300 subjects (150 per group).

Assuming a 15-month recruitment period, 200 PFS events were expected to occur approximately 18 months after the first subject had been randomised.

Randomisation

Participants were randomly assigned to Arm A (ACP arm) or Arm B (CP arm) using an IWRS. The randomisation was balanced by using randomly permuted blocks and was stratified by ECOG

performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no).

Blinding (masking)

This is an open-label study.

Statistical methods

The study was initiated on 02 December 2020 with the screening of the first participant and is ongoing. The current analysis is based on data through a clinical cut-off date of 03 May 2023, that is, the date of the last observation recorded as part of the database for the final analysis of the primary endpoint.

Statistical analysis plan

The submitted Statistical Analysis Plan was approved and is dated 04 March 2021. There was no amendment to the SAP.

As was predefined, all tests have been conducted at a 2-sided alpha level of 0.05, and 95% CI have been provided, unless stated otherwise. All efficacy endpoints have been analysed using the Full Analysis Set (definition below).

In addition, there exists a Statistical Analysis Plan Addendum. The addendum was approved on 20 April 2023, and, hence, before the data cut-off date. This document provides additional clarification and changes regarding some of the pre-planned analyses including time to symptomatic progression, PFS2, the analysis of PROMIS-PF and ECG reporting.

With this document it was clarified that TKI use was to be dropped as a stratification factor from all analyses. The levels of prior TKI use (yes/no) are heavily skewed and one of the levels is extremely under-represented, with 4 participants in the full analysis set (n=308) enrolled with prior TKI use. Furthermore, subgroup analyses using prior TKI use were omitted.

Analysis sets

The Full Analysis set was to include all randomised subjects to be analysed according to assigned treatment.

The safety population was to include all randomised subjects who had received at least one dose of study treatment.

Primary endpoint

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 blinded independent central review (BICR) using RECIST v1.1. Participants who had not progressed or had not died at the time of analysis was to be censored at their last evaluable RECIST v1.1 assessment date.

Key censoring rules for PFS were as follows:

Situation	***Date of censoring***
No evaluable baseline or postbaseline disease assessment	Censored at the date of randomisation

Lost to follow-up or withdraw from the 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 assessment*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visists

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

Estimand(s)

Estimands for both the primary and the key secondary endpoints, ORR and OS, were defined in the SAP.

For PFS the scientific question of interest was described as "What is the relative effect of amivantamab in combination with chemotherapy, versus chemotherapy alone in prolonging PFS in patients with EGFR mutation Exon 20ins positive, locally advanced or metastatic NSCLC?"

The population-level summary was defined as the hazard ratio (HR) and 95% CI of Arm A (amivantamab plus chemotherapy) vs Arm B (chemotherapy alone).

The intercurrent events and their corresponding strategies were as follows:

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

Primary endpoint analysis

The treatment effect of Arm A was to be compared to Arm B based on a log rank test initially to be stratified by ECOG performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no) using the Breslow approach for handling ties. As described (above), the stratification factor prior EGFR TKI use was dropped (from all analyses) since only 4 participants enrolled with prior TKI use.

The p-value generated from the stratified log-rank test was used for the primary hypothesis testing. The hazard ratio and corresponding 95% confidence interval was estimated based on a stratified Cox's regression 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 (K-M) method. The Kaplan-Meier PFS curve was to be plotted by treatment group. In addition, PFS rates with 95% CI was to be estimated by the K-M method at landmarks (e.g. at 6-month, 12-month, and 18-month, etc.) and reported for each treatment group. The number and percentage of participants who had a PFS event or

were censored were to be reported and reasons for PFS event and censoring were to be be summarized.

A similar analysis was to be carried out for the optional crossover arm that was to consist of BICR confirmed progressed subjects from Arm B but be limited to descriptive summaries only (median PFS with 95% CI and PFS rates with 95% CI to be estimated by the Kaplan-Meier method at landmarks).

For the assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis on pre-specified subgroups was to be conducted and be graphically displayed using Forest plots.

Sensitivity analyses (PFS)

For the assessment of PFS primary analysis robustness, the following sensitivity analyses/assessments were planned:

A sensitivity analysis using an unstratified log-rank test.

The proportional hazards assumption was to be examined by plotting log(-log[estimated survival distribution function]) against log(survival time). In addition, a treatment by logarithm-transformed time interaction term was to be added into the primary Cox model and tested. A p-value greater than 0.05 for the interaction term where then to be interpreted as no statistical evidence against the proportional hazard assumption.

Supplementary analyses (PFS)

Censored for Death/PD after Start of Subsequent Anticancer Therapy

A supplementary analysis was planned to be performed using progression or death prior to the start of the subsequent anticancer therapy as events. Participants 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. A similar analysis was to be carried out for the crossover arm as well.

Not Censored for Missing More Than One Disease Evaluation

An additional supplementary analysis was to be performed using all progression or death, whichever occurred first, as event regardless of missed/unevaluable disease assessment for 2 or more consecutive visits. A similar analysis was to be carried out for crossover arm as well.

Analysis of key secondary endpoints

OS

OS is defined as the time from the date of randomisation 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.

OS was to be analysed using the similar methodology and model as for the primary analysis of PFS provided there were sufficient events available for a meaningful analysis.

A sensitivity analysis using a non-stratified log-rank test could be performed as supportive analysis.

A similar analysis was to be carried out for crossover arm but be limited to descriptive summaries only (median OS with 95% CI and OS rates with 95% CI will be estimated by Kaplan-Meier method at landmarks).

In addition, a supplementary analysis was planned to be carried out using Inverse Probability of Censoring Weighting (IPCW) (Cole and Hernán, 2004) to adjust for confounding from treatment crossover. The weights to reduce the bias was to be estimated from baseline covariates and time-dependent covariates predictive of treatment crossover such as baseline disease burden, occurrence of serious adverse event before crossover, based on a logistic regression model. Analysis using rank preserving failure time model (Robins and Tsiatis, 1991)1 was also to be conducted to estimate true treatment effect on OS in crossover arm. The hazard ratio and the corresponding 95% CI was to be estimated based on a Cox regression analysis using both the methods.

ORR

ORR 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 further anticancer therapy was received, were not to be included in the numerator for the ORR calculation. Participants who did not have a tumour response assessment for any reason was 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 ECOG performance status (0 or 1) and history of brain metastases (yes or no), and prior EGFR TKI use (yes or no; this stratification factor was later dropped).

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.

The same analysis will be carried out for ORR based on confirmed PR or CR from subsequent assessments. The confirmation by subsequent assessments should be performed not less than 4 weeks after the criteria for PR or CR are first met.

Multiplicity

To control the overall type I error rate for the hypotheses testing of primary and secondary endpoints at 5%, a hierarchical fixed sequence testing strategy was predefined.

If the testing for the primary endpoint of PFS was statistically significant, the key secondary endpoints, i.e., ORR and OS, were to be sequentially tested, each with an overall 2-sided alpha of 0.05. The test for ORR was to be conducted before the test for OS.

The analysis of OS will be conducted at two time points:

• An interim analysis of OS was planned at the time of the final PFS analysis when approximately 85 deaths overall were anticipated. Based on the O'Brien Fleming alpha spending approach, a 2-sided alpha of 0.0008 was planned to be allocated to the interim analysis.

• The final planned OS analysis will be conducted approximately 48 months after the first participant was randomised, when approximately 210 deaths overall have been anticipated. The final OS analysis will be conducted at a 2-sided alpha of 0.0498.

Interim Analyses

Not applicable insofar that there was no interim analysis of the primary endpoint planned nor performed.

Independent Data Monitoring Committee

An IDMC was be commissioned for periodic review of safety and tolerability data, as well as planned efficacy analyses, if needed.

According to the study CSR the IDMC consisted of two medical experts and one statistician. The IDMC periodically reviewed safety and tolerability data. Per protocol, the first IDMC meeting was held on 02 August 2021 (CCO: 02 June 2021), when a total of 39 participants had been randomised and at least 20 participants had been treated with 2 cycles of protocol-based treatment. In total, 4 IDMC meetings were held through the CCO for this current CSR (03 May 2023).

Crossover Phase

Data from the Crossover phase have been summarized descriptively. Endpoints analysed include ORR, DOR, PFS, OS, TTST, and safety.

Results

All efficacy analyses for the PAPILLON study were performed using the FAS, which included all randomized participants, classified according to their assigned treatment arm regardless of the actual treatment received.

Participant flow

In total 542 participants were screened and of these 234 were not randomized due to screen failure. In half of the cases of screening failure (130 patients), the patients met the exclusion criteria. Of the exclusion criteria, the most common reason for screen failure was untreated brain metastases, which occurred in 10.3% of all screened participants (56/542). The next largest group of screening failures comprises the patients not meeting the inclusion criteria (104 patients). Of these, the most common reason was not adequate organ and bone marrow function to allow the study treatment.

Recruitment

Study period: The study was initiated on 02 December 2020 (ie, the date that the first participant was screened) and is currently ongoing. This clinical study report describes data through a clinical cut-off 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).

Study initiation date: 02 December 2020

Data cut-off date, primary analysis, final for PFS: 03 May 2023

Study PAPILLON is still ongoing.

Study centres: This study enrolled participants from 131 centres across 25 countries/territories.

The population for PAPILLON comprised participants with treatment naïve, EFGR exon 20ins mutated locally advanced or metastatic NSCLC. One hundred fifty-three (153) participants were randomized into the ACP arm and 155 participants were randomized into the CP arm. Two participants who were randomised to the ACP arm did not receive any dose of study treatment due to withdrawal of consent prior to first dosing.

- All participants randomised in the study (n=308) were included in the Full Analysis Set which was used for the efficacy analyses.

- Participants who received at least 1 dose of study treatment (n=306) were included in the Safety Analysis Set.

Table 10: Treatment Disposition; Safety Analysis Set (Study 61186372NSC3001)

	CP	ACP	Total
Analysis set: Safety	155	151	306
Subjects ongoing	24 (15.5%)	70 (46.4%)	94 (30.7%)
Discontinued all study treatment	131 (84.5%)	81 (53.6%)	212 (69.3%)
Reason for discontinuation[a]			
Progressive disease	107 (69.0%)	50 (33.1%)	157 (51.3%)
Adverse event	14 (9.0%)	14 (9.3%)	28 (9.2%)
Adverse event - COVID-19 related	0	2 (1.3%)	2 (0.7%)
Subject refused further study treatment	5 (3.2%)	12 (7.9%)	17 (5.6%)
Non-compliance with study drug	2 (1.3%)	1 (0.7%)	3 (1.0%)
Death	1 (0.6%)	1 (0.7%)	2 (0.7%)
Physician decision	0	1 (0.7%)	1 (0.3%)
Other	2 (1.3%)	2 (1.3%)	4 (1.3%)

[a] The reason for discontinuation for all study treatment is the reason of discontinuation for the last study treatment 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

Conduct of the study

Protocol amendments

Table 11: Summary of protocol amendments

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	12 August 2022
Amendment 1	20 May 2021
Original Protocol	17 Jul 2020

Amendment 1 (20 May 2021)

To provide clarifications to the current protocol and to provide the latest combination therapy data from the Phase 1 Study 61186372EDI1001.

Amendment 2 (12 August 2022)

To clarify that tumour imaging assessments should continue until objective disease progression by blinded central independent review (BICR) has been documented, to clarify steps beyond disease progression and symptomatic progression, and to add appropriate action in the event of toxic epidermal necrolysis (TEN) occurrence, as requested by Health Authority.

Protocol Deviations

An overview of the major protocol deviations is provided in Table 12. These major protocol deviations were considered unlikely to influence the interpretation of study results or pose a safety risk to the participants.

Table 12: Summary of Subjects with Major Protocol Deviations; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP	Total
Analysis set: Full	155	153	308
Subjects with major protocol deviations	4 (2.6%)	5 (3.3%)	9 (2.9%)
Entered but did not satisfy criteria	1 (0.6%)	1 (0.7%)	2 (0.6%)
Received wrong treatment or incorrect dose	2 (1.3%)	0	2 (0.6%)
Received a disallowed concomitant treatment	0	1 (0.7%)	1 (0.3%)
Other	2 (1.3%)	3 (2.0%)	5 (1.6%)

Note: Subjects may appear in more than one category.

At the time of the CCO, 10 major protocol deviations were identified in 9 participants (2.9%) (5 participants [3.3%]) in the ACP arm and 4 participants [2.6%] in the CP arm). Of note, 1 participant in the CP arm had 2 major protocol deviations.

Baseline data

Demographic and Other Baseline Characteristics

Table 13: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP	Total
Analysis set: Full	155	153	308
Age, years			
N	155	153	308
Mean (SD)	60.0 (12.01)	59.3 (11.92)	59.6 (11.95)
Median	62.0	61.0	62.0
Range	(30; 92)	(27; 86)	(27; 92)
18-25	0	0	0
26-50	32 (20.6%)	34 (22.2%)	66 (21.4%)
51-64	60 (38.7%)	63 (41.2%)	123 (39.9%)
65-74	48 (31.0%)	44 (28.8%)	92 (29.9%)
>=75	15 (9.7%)	12 (7.8%)	27 (8.8%)
Sex			
N	155	153	308
Female	93 (60.0%)	85 (55.6%)	178 (57.8%)
Male	62 (40.0%)	68 (44.4%)	130 (42.2%)
Race[a]			
N	152	151	303
American Indian or Alaska Native	2 (1.3%)	1 (0.7%)	3 (1.0%)
Asian	89 (58.6%)	97 (64.2%)	186 (61.4%)
Black or African American	0	2 (1.3%)	2 (0.7%)
White	60 (39.5%)	49 (32.5%)	109 (36.0%)
Multiple[b]	0	1 (0.7%)	1 (0.3%)
Unknown	1 (0.7%)	1 (0.7%)	2 (0.7%)
Ethnicity			
N	155	153	308
Hispanic or Latino	9 (5.8%)	13 (8.5%)	22 (7.1%)
Not Hispanic or Latino	145 (93.5%)	137 (89.5%)	282 (91.6%)
Not Reported	0	2 (1.3%)	2 (0.6%)
Unknown	1 (0.6%)	1 (0.7%)	2 (0.6%)
Weight, kg			
N	155	153	308
Mean (SD)	67.7 (14.02)	63.8 (14.64)	65.8 (14.44)
Median	66.5	61.8	65.0

	CP	ACP	Total
Range	(37; 112)	(39; 127)	(37; 127)
<80 kg	128 (82.6%)	132 (86.3%)	260 (84.4%)
>=80 kg	27 (17.4%)	21 (13.7%)	48 (15.6%)
Height, cm			
N	155	153	308
Mean (SD)	164.4 (8.76)	163.7 (9.44)	164.1 (9.09)
Median	164.0	163.0	163.8
Range	(145; 185)	(146; 191)	(145; 191)
Body mass index, kg/m^2			
N	155	153	308
Mean (SD)	25.0 (4.61)	23.6 (4.14)	24.3 (4.43)
Median	24.2	23.4	23.8
Range	(16; 43)	(16; 39)	(16; 43)
Baseline ECOG score			
N	155	153	308
0	55 (35.5%)	54 (35.3%)	109 (35.4%)
1	100 (64.5%)	99 (64.7%)	199 (64.6%)
History of smoking			
N	155	153	308
Yes	64 (41.3%)	65 (42.5%)	129 (41.9%)
No	91 (58.7%)	88 (57.5%)	179 (58.1%)

Key: ECOG = Eastern Cooperative Oncology Group
[a] In some regions reporting of Race is not required.
[b] Multiple includes one subject who selected Black or African American and White.
Note: N's for each parameter reflect non-missing values.

EGFR exon 20ins mutation status was determined by local testing using tissue (92.2%) and/or plasma (7.8%) samples. Central testing was concordant with local testing in 97.2% of the samples with a valid AmoyDx® LC10 tissue test result. Central testing was concordant with local testing in 74.2% of the samples with a valid central Guardant 360® CDx plasma test result.

Table 14: Summary of Baseline Disease Characteristics; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP	Total
Analysis set: Full	155	153	308
History of brain metastasis			
N	155	153	308
No	119 (76.8%)	118 (77.1%)	237 (76.9%)
Yes	36 (23.2%)	35 (22.9%)	71 (23.1%)
Prior EGFR TKI use[a]			
N	155	153	308
No	152 (98.1%)	152 (99.3%)	304 (98.7%)
Yes	3 (1.9%)	1 (0.7%)	4 (1.3%)
Initial diagnosis NSCLC subtype			
N	155	153	308
Adenocarcinoma	153 (98.7%)	151 (98.7%)	304 (98.7%)
Large cell carcinoma	1 (0.6%)	0	1 (0.3%)
Squamous cell carcinoma	0	0	0
Other	1 (0.6%)	2 (1.3%)	3 (1.0%)
Histology grade at initial diagnosis[b]			
N	142	146	288
Poorly differentiated	17 (12.0%)	24 (16.4%)	41 (14.2%)
Moderately differentiated	27 (19.0%)	27 (18.5%)	54 (18.8%)
Well differentiated	8 (5.6%)	11 (7.5%)	19 (6.6%)
Other	90 (63.4%)	84 (57.5%)	174 (60.4%)
Cancer stage at initial diagnosis			
N	149	153	302
IA	4 (2.7%)	2 (1.3%)	6 (2.0%)
IB	6 (4.0%)	4 (2.6%)	10 (3.3%)

	CP	ACP	Total
IIA	1 (0.7%)	0	1 (0.3%)
IIB	5 (3.4%)	1 (0.7%)	6 (2.0%)
IIIA	5 (3.4%)	5 (3.3%)	10 (3.3%)
IIIB	5 (3.4%)	7 (4.6%)	12 (4.0%)
IIIC	2 (1.3%)	1 (0.7%)	3 (1.0%)
IVA	54 (36.2%)	62 (40.5%)	116 (38.4%)
IVB	67 (45.0%)	71 (46.4%)	138 (45.7%)
Location of metastasis at screening[c]			
N	153	151	304
Bone	80 (52.3%)	71 (47.0%)	151 (49.7%)
Liver	31 (20.3%)	18 (11.9%)	49 (16.1%)
Brain	36 (23.5%)	35 (23.2%)	71 (23.4%)
Lymph node	114 (74.5%)	102 (67.5%)	216 (71.1%)
Adrenal gland	19 (12.4%)	10 (6.6%)	29 (9.5%)
Lung	120 (78.4%)	113 (74.8%)	233 (76.6%)
Other	64 (41.8%)	71 (47.0%)	135 (44.4%)
Histology grade at screening[b]			
N	143	145	288
Poorly differentiated	16 (11.2%)	27 (18.6%)	43 (14.9%)
Moderately differentiated	28 (19.6%)	26 (17.9%)	54 (18.8%)
Well differentiated	11 (7.7%)	11 (7.6%)	22 (7.6%)
Other	88 (61.5%)	81 (55.9%)	169 (58.7%)
Cancer stage at screening			
N	155	153	308
IIIB	0	3 (2.0%)	3 (1.0%)
IIIC	0	1 (0.7%)	1 (0.3%)
IVA	70 (45.2%)	67 (43.8%)	137 (44.5%)
IVB	85 (54.8%)	82 (53.6%)	167 (54.2%)
Time since initial lung cancer diagnosis (months)			
N	155	153	308
Mean (SD)	8.49 (18.092)	5.89 (14.525)	7.20 (16.442)
Median	1.84	1.77	1.84
Range	(0.6; 95.9)	(0.5; 80.8)	(0.5; 95.9)
Time since metastatic disease diagnosis (months)			
N	154	151	305
Mean (SD)	2.29 (3.088)	2.23 (3.799)	2.26 (3.452)
Median	1.61	1.51	1.54
Range	(0.3; 30.7)	(0.2; 40.0)	(0.2; 40.0)

Key: EGFR = epidermal growth factor receptor, NSCLC = non-small cell lung cancer, TKI = tyrosine kinase inhibitor
[a] Protocol allowed for prior TKI therapy if certain criteria were met per exclusion criterion 1.
[b] Other includes unknown histology grade.
[c] Subjects can be counted in more than one category.

Prior Therapies

A total of 22 participants (7.2%) received prior systemic therapy, 106 participants (34.6%) received prior radiotherapy, and all participants (100%) received prior cancer-related surgery (including tumor biopsies performed for diagnosis). Most of the prior systemic therapy was in an adjuvant/neoadjuvant setting. Four participants (1.3%) received TKI therapy in a palliative setting. The most common systemic therapies received were platinum compounds (7 participants [4.6%] in the ACP arm and 12 participants [7.7%] in the CP arm), and vinca alkaloids and analogues (5 participants [3.3%] in the ACP arm and 4 participants [2.6%] in the CP).

Table 15: Prior Therapies for Lung Cancer; Safety Analysis Set (Study 61186372NSC3001)

	CP	ACP	Total
Analysis set: Safety	155	151	306
Total number of subjects with any prior therapies for lung cancer	155 (100.0%)	151 (100.0%)	306 (100.0%)
Prior systemic therapy	14 (9.0%)	8 (5.3%)	22 (7.2%)
Prior radiotherapy	59 (38.1%)	47 (31.1%)	106 (34.6%)
Prior cancer-related surgery[a]	155 (100.0%)	151 (100.0%)	306 (100.0%)
Prior systemic therapy			
Adjuvant/Neo-adjuvant			
Adjuvant	12 (7.9%)	7 (4.5%)	19 (6.2%)
Neo-Adjuvant	0	1 (0.6%)	1 (0.3%)
Palliative			
Palliative[b,c]	3 (2.0%)	1 (0.6%)	4 (1.3%)

a Prior cancer-related surgery includes tumor biopsies performed for diagnosis.

b Palliative was captured on the eCRF as Curative/Palliative/Any other intent.

c One subject received both adjuvant and palliative therapy.

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

Exposure

The median follow-up in the study was 14.9 months. The median duration of treatment in the ACP arm was 9.72 months (9.26 months [range: 0.0; 26.9] for amivantamab, 2.14 months [range: 0.0; 3.8] for carboplatin, and 8.34 months [range: 0.0; 24.9] for pemetrexed). The median duration of treatment in the CP arm was 6.74 months (2.14 months [range: 0.0; 3.9] for carboplatin and 6.74 months [range: 0.0; 25.3] for pemetrexed).

Numbers analysed

Table 16: Number of Subjects in Each Analysis Set; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP	Total
Full analysis set	155	153	308
Safety analysis set	155 (100.0%)	151 (98.7%)	306 (99.4%)
Pharmacokinetics analysis set	NA	151 (98.7%)	NA
Immunogenicity analysis set	NA	144 (94.1%)	NA

Outcomes and estimation

Primary endpoint PFS by BICR

As of the CCO of 03 May 2023, after a median follow-up of 14.92 months, there were 216 BICR-assessed PFS events in total meeting the targeted number of events required for PFS analysis per the SAP.

Table 17: Summary of Progression-free Survival by BICR - Stratified Analysis; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP
Analysis set: FAS	155	153
Event	132 (85.2%)	84 (54.9%)
Censored	23 (14.8%)	69 (45.1%)
Time to event (months)		
25th percentile (95% CI)	4.21 (3.48, 4.40)	6.70 (5.39, 7.72)
Median (95% CI)	6.70 (5.59, 7.33)	11.37 (9.79, 13.70)
75th percentile (95% CI)	9.95 (8.87, 11.01)	NE (16.62, NE)
Range	(0.0+, 23.6+)	(0.0+, 23.6+)
6-month event-free rate (95% CI)	0.51 (0.43, 0.59)	0.77 (0.69, 0.83)
12-month event-free rate (95% CI)	0.13 (0.08, 0.19)	0.48 (0.39, 0.56)
18-month event-free rate (95% CI)	0.03 (0.01, 0.09)	0.31 (0.22, 0.40)
p-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.395 (0.296, 0.528)

Key: BICR = blinded independent central review, ECOG = Eastern Cooperative Oncology Group, PS = performance status
[a] p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors ACP.
Note: + = censored observation, NE = not estimable

Table 18: Summary of Progression-free Survival Events and Reasons for Censoring by BICR; Full Analysis Set (Study JNJ61186372NSC3001)

	CP	ACP
Analysis set: Full	155	153
Subjects with event	132 (85.2%)	84 (54.9%)
Progressive disease	126 (81.3%)	75 (49.0%)
Death without progressive disease	6 (3.9%)	9 (5.9%)
Subjects censored	23 (14.8%)	69 (45.1%)
Reason for censoring		
Study cut-off	20 (12.9%)	60 (39.2%)
No PD or death prior to >= 2 consecutively missing or unevaluable assessments	2 (1.3%)	4 (2.6%)
Lost to follow-up	1 (0.6%)	1 (0.7%)
Withdrawal of consent to study participation	0	4 (2.6%)

Key: BICR = blinded independent central review
[a] Includes subjects who were randomized but never treated.

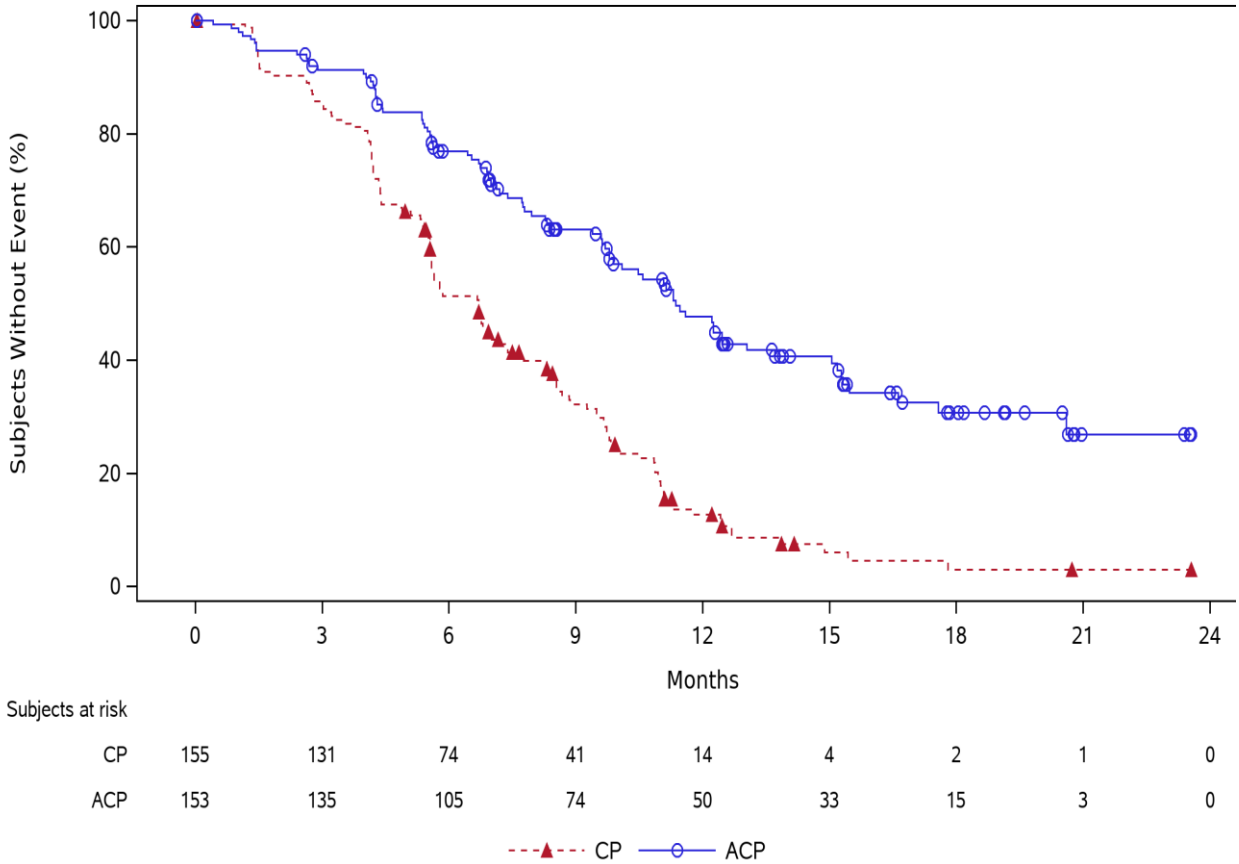


Figure 9: Kaplan-Meier Plot of Progression-free Survival by BICR; Full Analysis Set (Study 61186372NSC3001)

Of note, 65 participants of the CP arm received subsequent amivantamab monotherapy in an optional Crossover phase of the study.

Secondary Endpoint Analyses

Objective Response Rate

The ORR was assessed in participants with measurable disease at baseline and responders were defined as participants achieving either CR or PR, per RECIST v1.1 criteria. Based on the BICR assessment, 152 of the 153 participants enrolled in the ACP arm and 152 of the 155 participants enrolled in the CP arm had measurable disease at baseline and were included in the analysis of ORR.

Table 19: Summary of Objective Response Rate Based on RECIST v1.1 Criteria in Subjects With Measurable Disease at Baseline by BICR – Stratified Analysis; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP
Analysis set: FAS	155	153
Number of subjects with measurable disease at baseline	152	152
Responders (CR + PR)	72	111
Objective response rate	47.4%	73.0%
95% CI	(39.2%, 55.6%)	(65.2%, 79.9%)
p-value[a]		<0.0001
Odds ratio (95% CI)[b]		2.971 (1.844, 4.787)
Best Overall Response		
Complete Response (CR)	1 (0.7%)	6 (3.9%)
Partial Response (PR)	71 (46.7%)	105 (69.1%)
Stable Disease (SD)	62 (40.8%)	29 (19.1%)
Progressive Disease (PD)	16 (10.5%)	4 (2.6%)
Not Evaluable (NE)	2 (1.3%)	8 (5.3%)

Key: BICR = blinded independent central review, CR = complete response, ECOG = Eastern Cooperative Oncology Group, PR = partial response, PS = performance status
[a] p-value is from a logistic regression model stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).
[b] Odds ratio >1 favors ACP.
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.

An analysis of ORR based on confirmed PR or CR from subsequent assessments indicated that the anti-tumor effect was more durable with ACP, with an ORR of 67.1% (95% CI: 59.0%, 74.5%) in the ACP arm compared with 36.2% (95% CI: 28.6%, 44.4%) in the CP arm.

Duration of Response

Among the confirmed responders at the CCO of 03 May 2023, approximately 3 times as many participants maintained a response in the ACP arm compared with the CP arm (49.0% versus 18.2%. Correspondingly, the median DOR was doubled in the ACP arm (10.09 months; 95% CI: 8.48, 13.90) compared with the CP arm (5.55 months; 95% CI: 4.44, 6.93). At the time of the CCO (03 May 2023), 70 participants (46.4%) in the ACP arm and 24 participants (15.5%) in the CP arm remained on treatment.

Table 20: Summary of Duration of Response in Confirmed Responders Based on Subjects With Measurable Disease at Baseline by BICR; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP
Analysis set: Full	155	153
Number of subjects with measurable disease at baseline	152	152
Confirmed Responders (Confirmed CR + Confirmed PR)	55	102
Event	45 (81.8%)	52 (51.0%)
Censored	10 (18.2%)	50 (49.0%)
Time to event (months)		
25th percentile (95% CI)	4.17 (2.86, 4.44)	6.54 (5.39, 8.21)
Median (95% CI)	5.55 (4.44, 6.93)	10.09 (8.48, 13.90)
75th percentile (95% CI)	8.94 (6.93, 11.47)	NE (15.21, NE)
Range	(1.3+, 22.4+)	(1.4+, 22.3+)
6-month event-free rate (95% CI)	0.44 (0.30, 0.56)	0.77 (0.67, 0.85)
12-month event-free rate (95% CI)	0.11 (0.03, 0.23)	0.45 (0.34, 0.55)
18-month event-free rate (95% CI)	0.05 (0.01, 0.19)	0.35 (0.24, 0.47)

Key: BICR = blinded independent central review, CR = complete response, PR = partial response
Note: + = censored observation, NE = not estimable

Overall Survival

An interim analysis of OS was planned at the time of the final PFS analysis, when an estimated 85 deaths events were to have occurred. However, at the time of the CCO date for the final PFS analysis, after a median follow-up of 14.92 months, there were a total of 70 death events reported across both arms combined: 28 in the ACP arm and 42 in the CP arm.

Table 21: Summary of Overall Survival - Unstratified Analysis; Full Analysis Set (Study 61186372NSC3001), CCO 3 May 2023

	CP	ACP
Analysis set: FAS	155	153
Event	42 (27.1%)	28 (18.3%)
Censored	113 (72.9%)	125 (81.7%)
Time to event (months)		
25th percentile (95% CI)	13.67 (11.10, 18.37)	16.85 (13.96, NE)
Median (95% CI)	24.38 (22.08, NE)	NE (NE, NE)
75th percentile (95% CI)	25.49 (24.38, NE)	NE (NE, NE)
Range	(0.4, 26.9+)	(0.3+, 27.0+)
6-month event-free rate (95% CI)	0.97 (0.92, 0.99)	0.94 (0.89, 0.97)
12-month event-free rate (95% CI)	0.82 (0.74, 0.87)	0.86 (0.79, 0.91)
18-month event-free rate (95% CI)	0.68 (0.58, 0.76)	0.74 (0.64, 0.82)
24-month event-free rate (95% CI)	0.54 (0.37, 0.68)	0.72 (0.61, 0.81)
p-value[a]		0.1056
Hazard ratio (95% CI)[b]		0.675 (0.418, 1.090)

[a] p-value is from a log-rank test.
[b] Hazard ratio is from proportional hazards model. Hazard ratio <1 favors ACP.
Note: + = censored observation, NE = not estimable

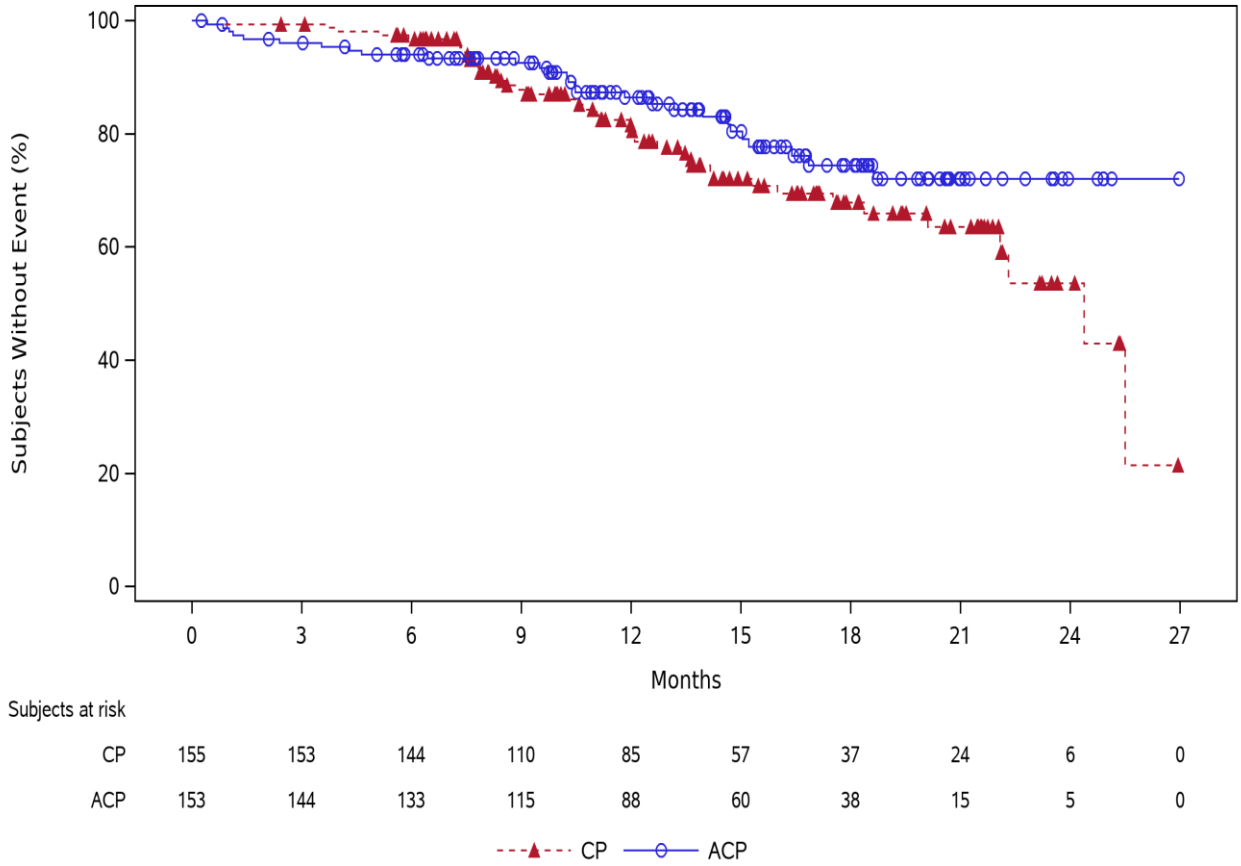


Figure 10: Kaplan-Meier Plot of Overall Survival; Full Analysis Set (Study 61186372NSC3001), CCO 3 May 2023

Table 22: Summary of Overall Survival Events and Reasons for Censoring in First 6 Months; Full Analysis Set; Study 61186372NSC3001

	CP	ACP
Analysis set: Full	155	153
Subjects with event in first 6 months	5 (3.2%)	9 (5.9%)
Death	5 (3.2%)	9 (5.9%)
Subjects censored	150 (96.8%)	144 (94.1%)
Reason for censoring		
Study cut-off	148 (95.5%)	139 (90.8%)
Withdrawal of consent to study participation	1 (0.6%)	4 (2.6%)
Lost to follow-up	1 (0.6%)	1 (0.7%)

Note: Subjects who died, were lost to follow-up, or withdrew consent from study participation after the first 6 months were censored as study cut-off.

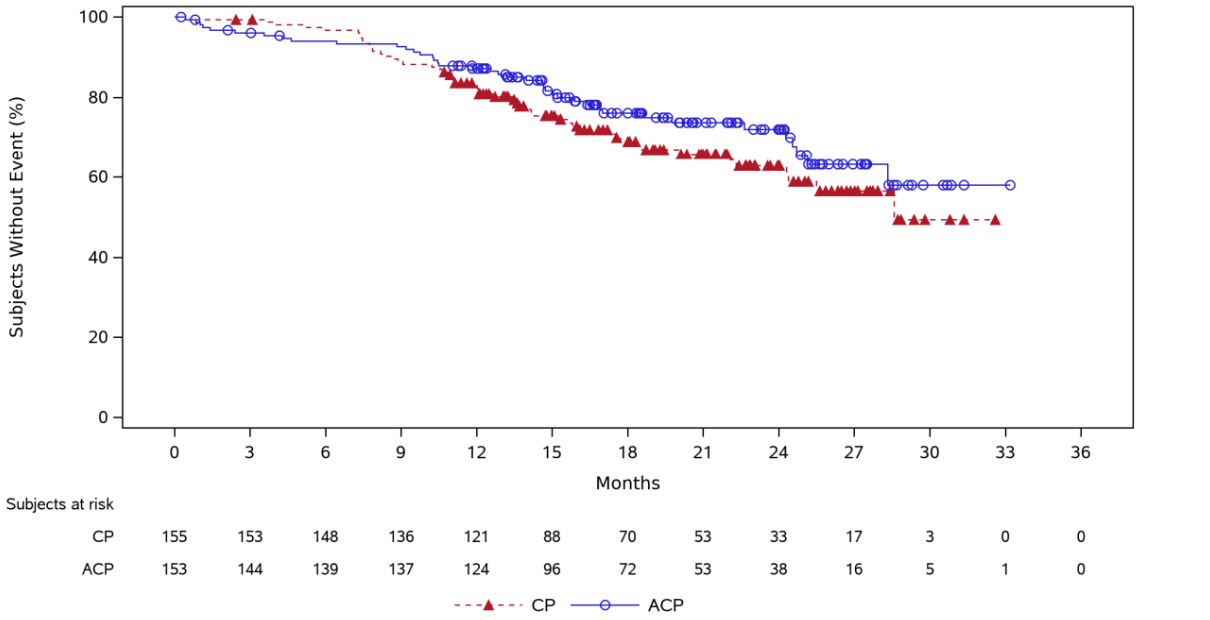
Table 23: Summary of Overall Survival Events and Reasons for Censoring; Full Analysis Set; Study 61186372NSC3001 (PAPILLON)

	CP	ACP
Analysis set: Full	155	153
Subjects with event	42 (27.1%)	28 (18.3%)
Death	42 (27.1%)	28 (18.3%)
Subjects censored	113 (72.9%)	125 (81.7%)
Reason for censoring		
Study cut-off	106 (68.4%)	115 (75.2%)
Withdrawal of consent to study participation	5 (3.2%)	9 (5.9%)
Lost to follow-up	2 (1.3%)	1 (0.7%)

Table 24: Summary of updated Overall Survival - Unstratified Analysis; Full Analysis Set; Study 61186372NSC3001 (PAPILLON), CCO 31 Oct 2023

	CP	ACP
Analysis set: Full	155	153
Event	52 (33.5%)	40 (26.1%)
Censored	103 (66.5%)	113 (73.9%)
Time to event (months)		
25th percentile (95% CI)	15.31 (12.06, 18.56)	19.75 (14.72, 24.71)
Median (95% CI)	28.58 (24.38, NE)	NE (28.32, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.4, 32.6+)	(0.3+, 33.2+)
6-month event-free rate (95% CI)	0.97 (0.92, 0.99)	0.94 (0.89, 0.97)
12-month event-free rate (95% CI)	0.83 (0.76, 0.88)	0.87 (0.81, 0.92)
18-month event-free rate (95% CI)	0.69 (0.60, 0.76)	0.76 (0.68, 0.83)
24-month event-free rate (95% CI)	0.63 (0.53, 0.71)	0.72 (0.63, 0.79)
30-month event-free rate (95% CI)	0.49 (0.33, 0.64)	0.58 (0.43, 0.71)
p-value[b]		0.1825
Hazard ratio (95% CI)[c]		0.756 (0.501, 1.142)

[a] Ad hoc OS analysis based on data available as of **31 October 2023**
[b] p-value is from a log-rank test.
[c] Hazard ratio is from proportional hazards model. Hazard ratio <1 favors ACP.
Note: + = censored observation, NE = not estimable



[gefos01.rtf] [jnj-61186372/nsc3001/dbr_120d_os/re_120d_os/gefos01.sas] 01NOV2023, 11:00

[1] Ad hoc OS analysis based on data available as of **31 October 2023**

Figure 11: Kaplan-Meier Plot of updated Overall Survival ; Full Analysis Set; Study 61186372NSC3001 (PAPILLON), CCO 31 Oct 2023

Time to Subsequent Anticancer Therapy

A significantly higher percentage of participants in the ACP arm had not initiated subsequent systemic therapy compared with the CP arm (62.1% versus 29.7%).

Table 25: Summary of Time to Subsequent Systemic Anti-cancer Therapy – Stratified Analysis; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP
Analysis set: FAS	155	153
Event	109 (70.3%)	58 (37.9%)
Censored	46 (29.7%)	95 (62.1%)
Time to event (months)		
25th percentile (95% CI)	6.34 (5.36, 7.39)	10.18 (8.18, 12.65)
Median (95% CI)	9.89 (8.57, 11.07)	17.71 (13.67, NE)
75th percentile (95% CI)	13.47 (12.02, 15.44)	NE (23.26, NE)
Range	(0.4, 25.4+)	(0.3+, 27.0+)
6-month event-free rate (95% CI)	0.79 (0.72, 0.85)	0.90 (0.84, 0.94)
12-month event-free rate (95% CI)	0.36 (0.27, 0.44)	0.68 (0.59, 0.76)
18-month event-free rate (95% CI)	0.14 (0.07, 0.23)	0.49 (0.39, 0.59)
24-month event-free rate (95% CI)	0.05 (0.01, 0.13)	0.37 (0.21, 0.53)
p-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.348 (0.250, 0.486)

Key: ECOG = Eastern Cooperative Oncology Group, PS = performance status

[a] p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours ACP.

Note: + = censored observation, NE = not estimable

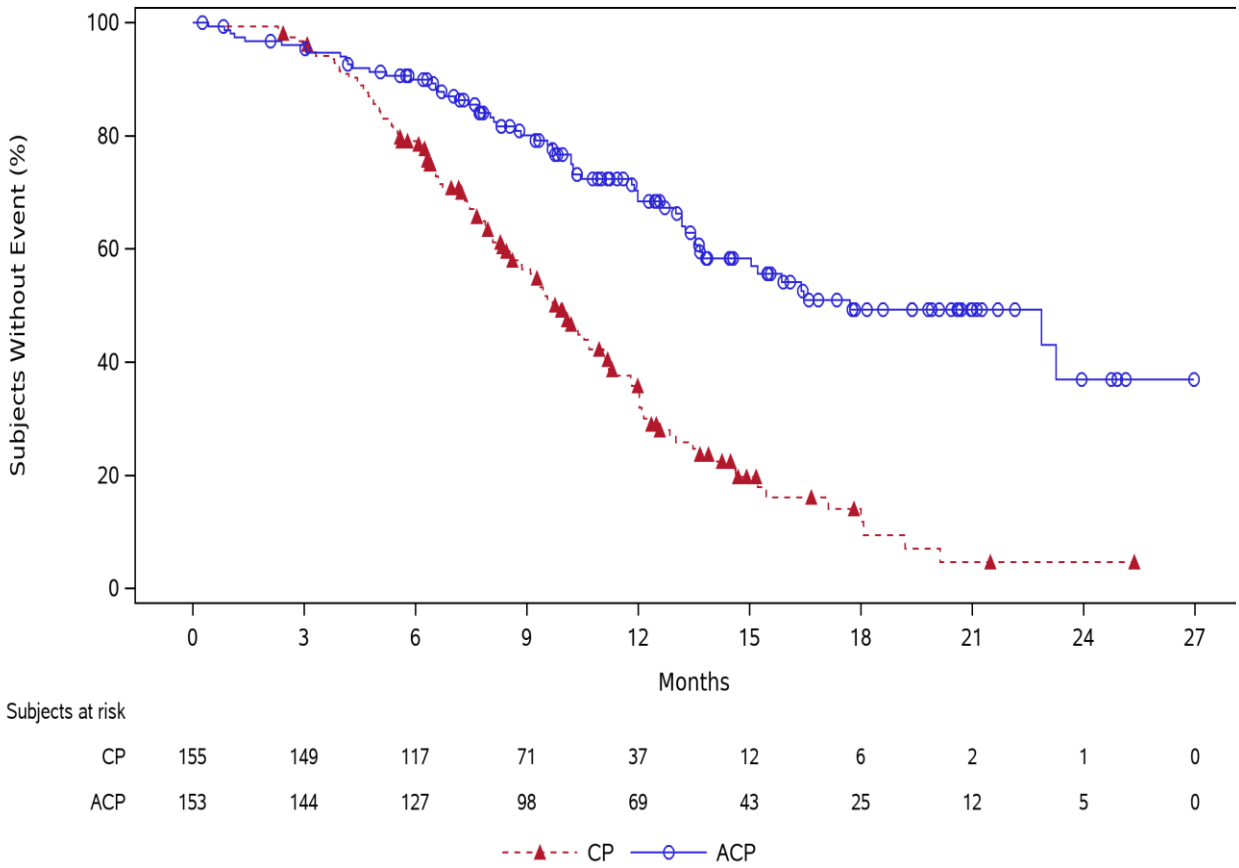


Figure 12: Kaplan-Meier Plot of Time to Subsequent Systemic Anti-cancer Therapy; Full Analysis Set (Study 61186372NSC3001)

Of the 43 participants in the ACP arm (28.1%) who received subsequent systemic therapy, just over half (23/43 participants) were prescribed chemotherapy/immunotherapy-based regimens. The remaining participants in the ACP arm received TKIs or TKI-based regimens (12/43 participants [27.9%]) and other regimens including investigational antineoplastic agents (8/43 [18.6%]). In contrast, in the 94 participants in the CP arm who received subsequent systemic therapy, 65 of whom crossed over to amivantamab monotherapy, the most frequently prescribed first subsequent systemic therapies were amivantamab or TKIs/TKI-based regimens (82/94 participants [87.2%]).

PFS After First Subsequent Therapy

Table 26: Summary of Progression-free Survival After the First Subsequent Therapy (PFS2) – Stratified Analysis; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP
Analysis set: FAS	155	153
Event	61 (39.4%)	33 (21.6%)
Censored	94 (60.6%)	120 (78.4%)
Time to event (months)		
25th percentile (95% CI)	10.68 (8.87, 12.06)	14.98 (13.67, 18.63)
Median (95% CI)	17.25 (13.96, 21.52)	NE (22.77, NE)
75th percentile (95% CI)	24.38 (21.52, NE)	NE (NE, NE)
Range	(0.0+, 26.9+)	(0.0+, 24.9+)
6-month event-free rate (95% CI)	0.95 (0.91, 0.98)	0.94 (0.89, 0.97)
12-month event-free rate (95% CI)	0.69 (0.60, 0.77)	0.86 (0.79, 0.91)
18-month event-free rate (95% CI)	0.46 (0.35, 0.57)	0.67 (0.55, 0.76)
24-month event-free rate (95% CI)	0.35 (0.23, 0.48)	0.57 (0.39, 0.72)
p-value[a]		0.0010
Hazard ratio (95% CI)[b]		0.493 (0.320, 0.759)

Key: ECOG = Eastern Cooperative Oncology Group, PS = performance status
[a] p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors ACP.
Note: + = censored observation, NE = not estimable

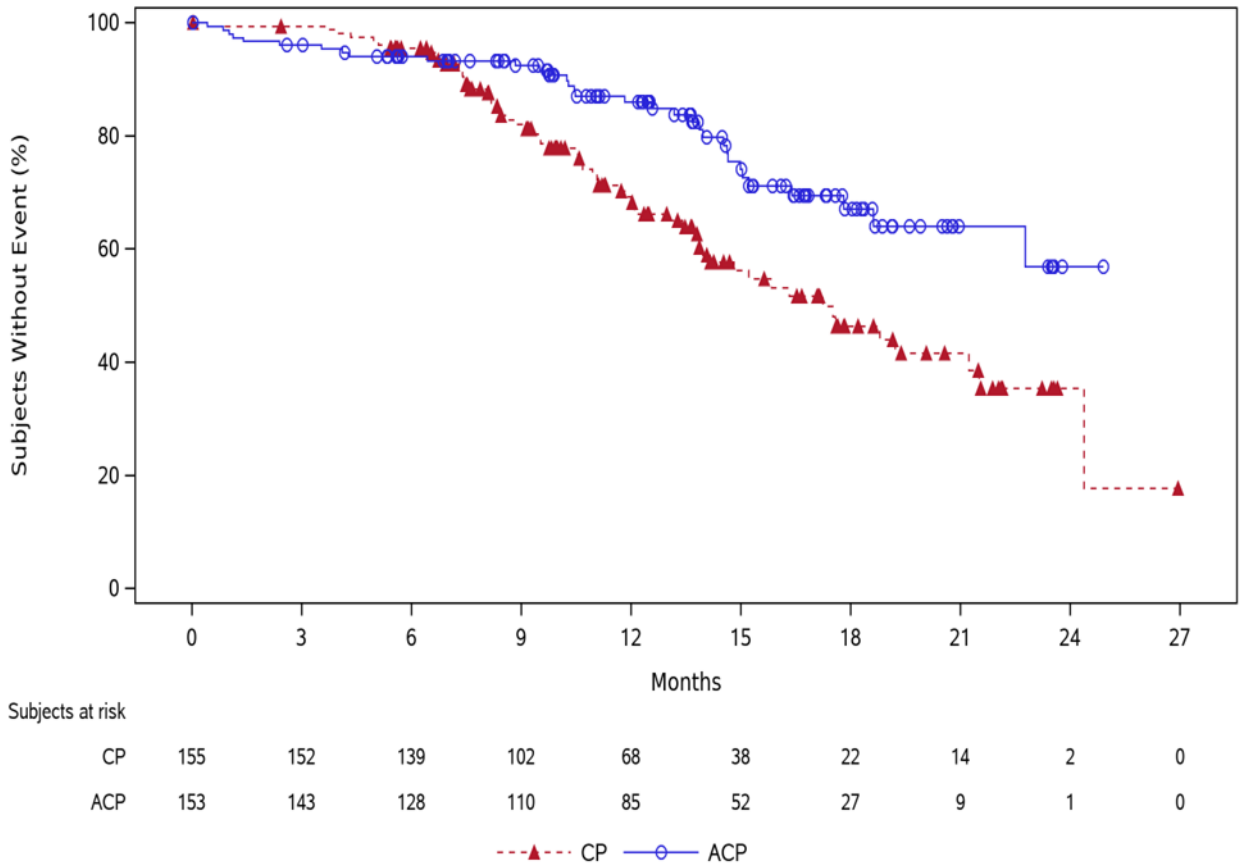


Figure 13: Kaplan-Meier Plot of Progression-free Survival After the First Subsequent Therapy (PFS2); Full Analysis Set (Study 61186372NSC3001)Time to Symptomatic Progression

Table 27: Summary of Time to Symptomatic Progression - Stratified Analysis; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP
Analysis set: FAS	155	153
Event	64 (41.3%)	45 (29.4%)
Censored	91 (58.7%)	108 (70.6%)
Time to event (months)		
25th percentile (95% CI)	7.82 (6.51, 9.40)	13.60 (9.49, 15.18)
Median (95% CI)	20.07 (13.11, NE)	NE (18.63, NE)
75th percentile (95% CI)	NE (24.38, NE)	NE (NE, NE)
Range	(0.0, 25.4+)	(0.0, 27.0+)
6-month event-free rate (95% CI)	0.82 (0.75, 0.88)	0.89 (0.83, 0.93)
12-month event-free rate (95% CI)	0.60 (0.51, 0.68)	0.77 (0.69, 0.83)
18-month event-free rate (95% CI)	0.55 (0.45, 0.63)	0.62 (0.52, 0.71)
24-month event-free rate (95% CI)	0.44 (0.30, 0.57)	0.53 (0.37, 0.67)
p-value[a]		0.0387
Hazard ratio (95% CI)[b]		0.669 (0.456, 0.982)

Key: ECOG = Eastern Cooperative Oncology Group, PS = performance status
[a] p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors ACP.
Note: + = censored observation, NE = not estimable

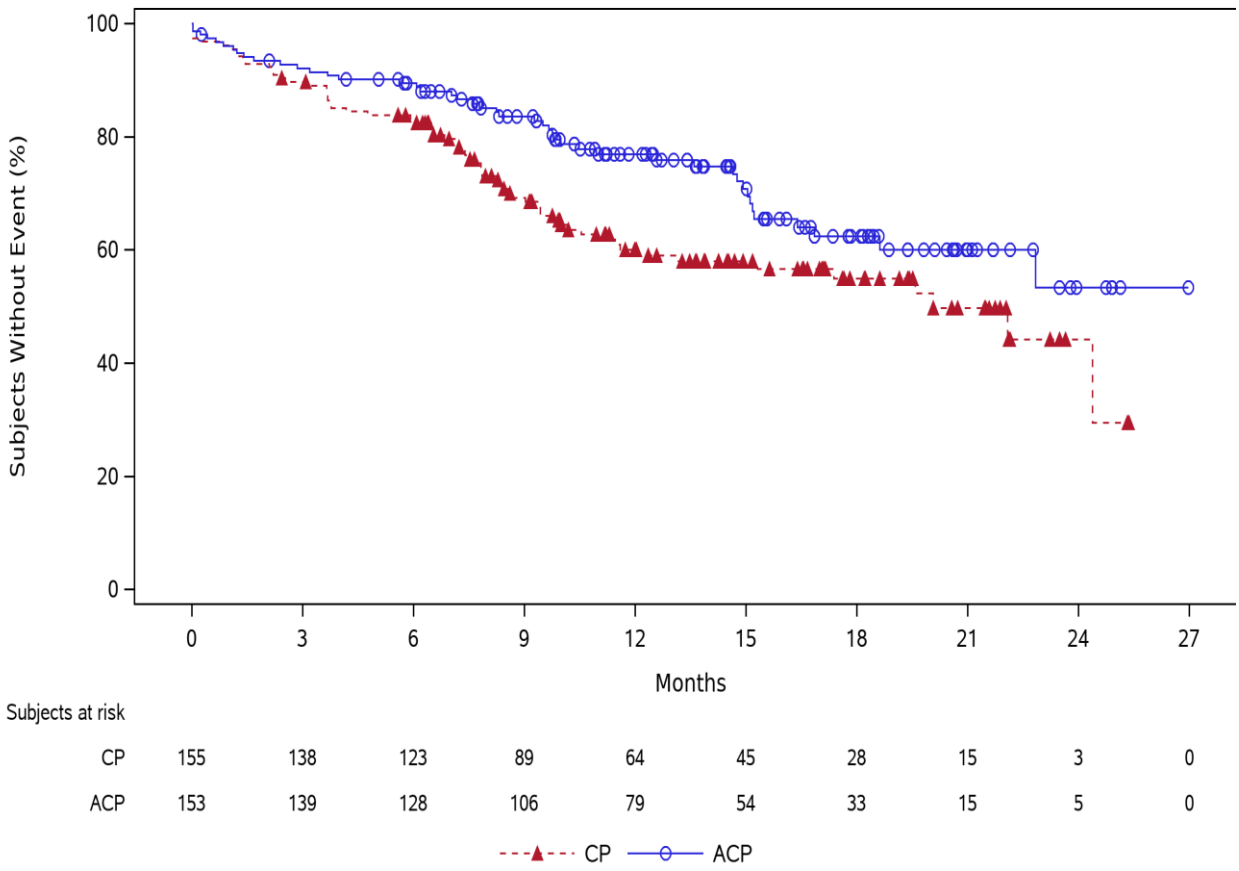


Figure 14: Kaplan-Meier Plot of Time to Symptomatic Progression; Full Analysis Set (Study 61186372NSC3001) Exploratory Efficacy Analyses

Time to Treatment Discontinuation

Table 28: Summary of Time to Treatment Discontinuation – Stratified Analysis; Full Analysis Set (Study 61186372NSC3001)

	CP	ACP
Analysis set: FAS	155	153
Event	131 (84.5%)	83 (54.2%)
Censored	24 (15.5%)	70 (45.8%)
Time to event (months)		
25th percentile (95% CI)	5.13 (4.27, 5.85)	8.02 (6.28, 9.56)
Median (95% CI)	7.46 (6.97, 8.38)	13.17 (11.76, 15.24)
75th percentile (95% CI)	11.14 (9.99, 12.29)	22.34 (18.40, NE)
Range	(0.4, 25.4+)	(0.3, 27.0+)
6-month event-free rate (95% CI)	0.66 (0.58, 0.73)	0.84 (0.77, 0.89)
12-month event-free rate (95% CI)	0.21 (0.15, 0.29)	0.58 (0.49, 0.66)
18-month event-free rate (95% CI)	0.05 (0.02, 0.11)	0.35 (0.26, 0.45)
24-month event-free rate (95% CI)	0.03 (0.01, 0.08)	0.23 (0.13, 0.35)
p-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.378 (0.283, 0.505)

Key: ECOG = Eastern Cooperative Oncology Group, PS = performance status
[a] p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors ACP.
Note: + = censored observation, NE = not estimable

Other Exploratory Efficacy Analyses

Patient-Reported Outcomes

PRO measures in this study comprised the PROMIS Physical Function 8c, EQ-5D-5L, and EORTC-QLQ-C30. The PRO analysis demonstrated that participants in the ACP arm achieved improved clinical benefits across primary and secondary endpoints compared with participants in the CP arm without compromising HRQoL. Participants in both treatment arms maintained low symptom burden and high levels of functioning while on treatment.

Time to deterioration analyses showed that median time to symptom worsening was delayed by 2 to 5 months for ACP compared to CP alone for dyspnea (HR=0.75, 95% CI: 0.55, 1.01), pain (HR=0.74, 95% CI: 0.55, 1.00), insomnia (HR=0.75, 95% CI: 0.54, 1.04), diarrhea (HR=0.67, 95% CI: 0.47, 0.95), and nausea/vomiting (HR=0.74, 95% CI: 0.55, 0.98). Time to worsening was similar between treatment arms for fatigue (HR=0.88, 95% CI: 0.68, 1.14) and appetite loss (HR=0.92, 95% CI: 0.68, 1.23)

Crossover Phase: Summary of Efficacy Data

The efficacy analyses for the Crossover phase were exploratory and aimed to further characterize the efficacy of amivantamab when administered as a monotherapy in a 21-day cycle, following disease progression with standard of care CP. Data were summarized descriptively, and endpoints analyzed included ORR, DOR, PFS, and safety.

At the time of the CCO (03 May 2023), a total of 65 participants had entered the Crossover phase and had received at least 1 dose of study treatment. A total of 35 participants (53.8%) remained on treatment with the most common reason for discontinuation being progressive disease (22/30 participants).

Overall, the efficacy data from the Crossover phase were consistent with data from the FIH study (61186372EDI1001), which led to the approval of amivantamab as monotherapy in this same patient population, with an ORR of 39.3% (95% CI: 26.5%, 53.2%) and median DOR of 11.07 months (95% CI: 5.19, not estimable). After a median follow up of 9.7 months the median PFS was 6.77 months (95% CI: 4.40, 9.59) and median OS was 17.68 months (95% CI: 12.09, not estimable).

Ancillary analyses

Sensitivity Analysis

Unstratified Analysis of PFS

The results from the unstratified analysis of PFS by BICR showed a treatment benefit with ACP (HR: 0.389 [95% CI: 0.293, 0.516]), similar to that observed in the stratified analysis

Investigator Assessment

The results of the sensitivity analysis evaluating PFS, as assessed by the treating investigator, were similarly robust (HR=0.383 [95% CI: 0.285, 0.515], p<0.0001) with a median PFS of 12.91 months (95% CI: 11.37, 16.66) in the ACP arm compared with 6.90 months (95% CI: 6.24, 8.31) in the CP arm.

Supplementary Analysis

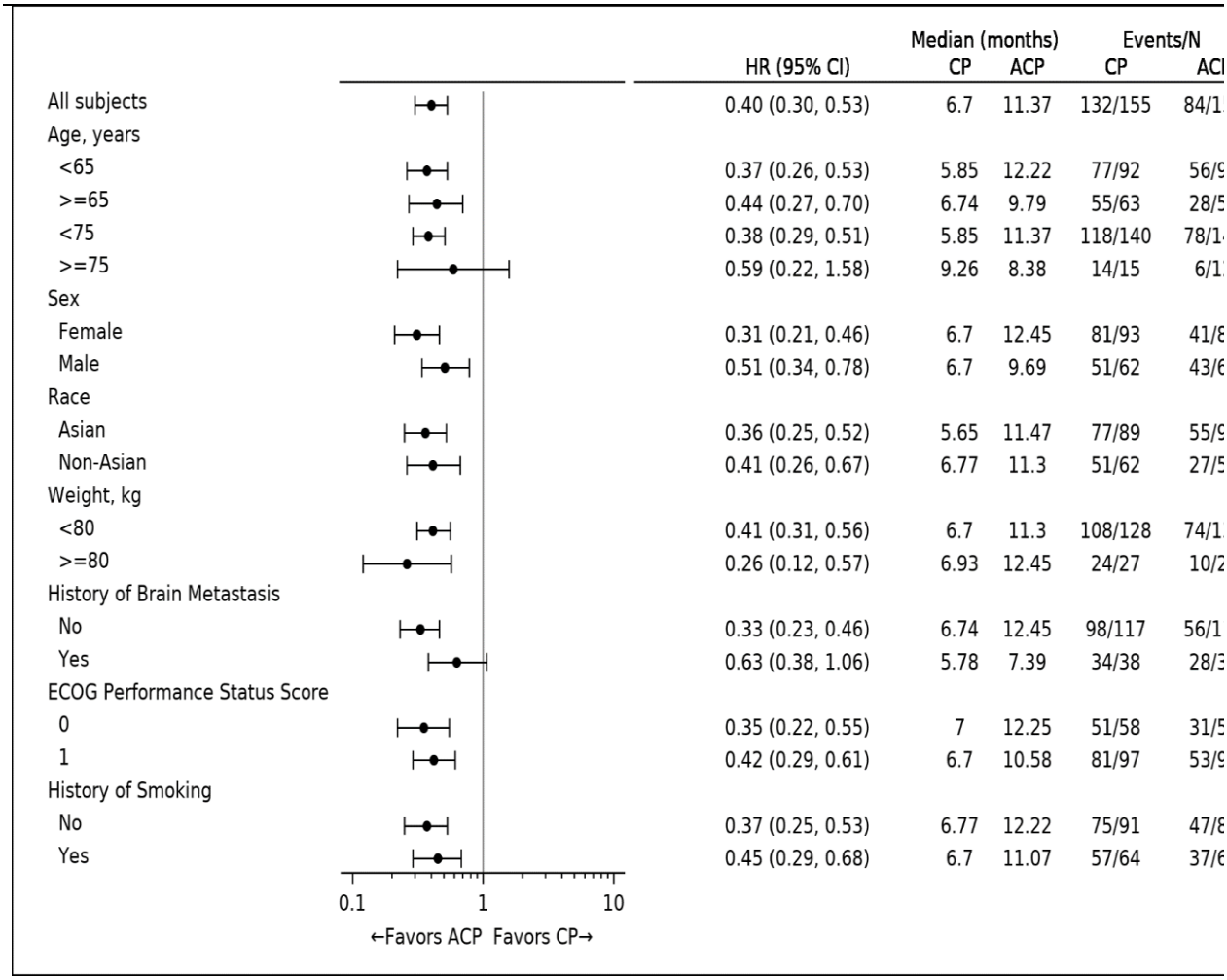
Subsequent Systemic Anti-cancer Therapy

The results from the analysis of PFS by BICR censored for subsequent anti-cancer therapy showed a treatment benefit with ACP (HR: 0.398 [95% CI: 0.298, 0.533]), similar to that observed in the primary analysis (Attachment TEFPFS01rb). When based upon investigator assessment, results from this supplementary analysis were also similar to that observed in the primary analysis.

Missing Disease Evaluations

The results from the analysis of PFS by BICR not censored for missing 2 or more consecutive visits showed a treatment benefit with ACP (HR: 0.395 [95% CI: 0.297, 0.526]), similar to that observed in the primary analysis. When based upon investigator assessment, results from this supplementary analysis were also similar to that observed in the primary analysis.

Analysis by Baseline Clinical Disease Characteristics



Key: ACP = Amivantamab + Carboplatin + Pemetrexed; CP = Carboplatin + Pemetrexed; ECOG = Eastern Cooperative Oncology Group; NE = not estimable

Figure 15: Forest Plot of Progression-free Survival by BICR for Subgroups Defined by Baseline Clinical Disease Characteristics; Full Analysis Set (Study 61186372NSC3001)

Summary of main study(ies)

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

Table 29: Summary of Efficacy for PAPILLON study

Study identifier	61186372NSC3001 EudraCT NUMBER: 2020-000633-40	
Design	Randomized, Open-label Phase 3 Study, Multicenter	
	Screening phase Treatment phase Maintenance phase Follow-up phase	28 days 21-Day Cycles 1-4 21-Days Cycles 5+

Hypothesis	Superiority		
Treatments groups	ACP		N=153 Amivantamab+ carboplatin-pemterexed
	CP		N=155 Carboplatin-pemterexed
Endpoints and definitions	Primary endpoint	PFS by BICR	PFS (using RECIST v1.1 guidelines), as assessed by blinded independent central review
	Secondary endpoint	ORR DoR OS	Objective response Duration of response Overall surviva
	Other Secondary endpoint	Time to subsequent therapy PFS after first subsequent therapy Time to symptomatic progression	
Database lock	03 May 2023		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat Final analysis of the primary endpoint			
Descriptive statistics and estimate variability	Treatment group	ACP	CP	Cross over
	Number of subject	n=153	N=155	N=65
	Primary endpoint Median PFS (months)	11.37 (9.79, 13.70)	6.70 (5.59, 7.33)	
	HR PFS (95% CI); p-value	0.395 (0.296, 0.528); p-value<0.0001	0.395 (0.296, 0.528); p-value<0.0001	

Effect estimate per comparison	Secondary endpoint ORR Odds ratio	ACP	CP
		73.0% (65.2%, 79.9%	47.4% (39.2, 55.6)
		2.971 (1.844, 4.787); p-value<0.0001	2.971 (1.844, 4.787); p-value<0.0001
	Secondary endpoint OS Median OS HR OS	Events. 42 (27.1%)	Events: 28 (18.3%)
		NE (NE, NE)	24.38 (22.08, NE)
		0.675 (0.418, 1.090); p-value=0.106	0.675 (0.418, 1.090); p-value=0.106

Clinical studies in special populations

Table 30: Number of Subjects in Each Population of the ACP Arm by Age Group; Full Analysis Set

TSIDEM03age: (Study JNJ61186372NSC3001)

	ACP				
	Age <65 yrs	Age 65-74 yrs	Age 75-84 yrs	Age 85+ yrs	Total
Efficacy population	97	44	11	1	153
Safety population	96	43	11	1	151

Supportive study(ies)

CHRYSALIS Chemotherapy Cohort: Supportive Efficacy

Study Design

CHRYSALIS is an ongoing, first-in-human, open-label, multicenter Phase 1 study to evaluate the safety, PK, and preliminary efficacy of amivantamab as monotherapy and in combination with other agents, and to determine the RP2D (amivantamab monotherapy), RP2CD (amivantamab in combination with lazertinib), and RP2ChD (amivantamab in combination with carboplatin-pemetrexed chemotherapy [ACP]) in subjects with advanced NSCLC who are 18 years of age.

The CHRYSALIS study consists of 2 parts (**Error! Reference source not found.**):

Part 1: Dose escalation and dose determination for amivantamab monotherapy and amivantamab in combination with other agents.

Part 2: Dose expansion phase. Part 2 of the study aims to evaluate clinical activity in participants with NSCLC of unmet medical need, who have a documented EGFR or MET mutation and who have progressed on SOC for metastatic disease.

Chemotherapy Combination Cohort

A chemotherapy combination cohort was added to Part 1 of the CHRYSALIS study to demonstrate the initial safety of ACP (refer to the grey shaded box in 10). In this cohort, a total of 20 participants with advanced NSCLC who were eligible to receive CP as SOC (no specific driver mutation was required) were enrolled to confirm the dosing, safety, and tolerability of the ACP regimen in a Q3W (ie, 21-day cycle) schedule.[1] In this heterogenous cohort of 20 participants, 7 had EGFR exon 20ins mutations (5 were treatment-naïve and 2 were previously-treated). There was no ACP Part 2 Expansion Cohort.

This SCE includes supportive efficacy results from the 5 participants with treatment-naïve EGFR exon 20ins NSCLC treated with ACP in the chemotherapy combination cohort, consistent with the PAPILLON population.

[1] Participants with body weight <80 kg initially received amivantamab 1400 mg by IV infusion once weekly up through Cycle 2 Day 1, then 1750 mg on Day 1 of each 21-day cycle, starting with Cycle 3. Participants with body weight ≥80 kg initially received amivantamab 1750 mg by IV infusion once weekly up through Cycle 2 Day 1, then 2100 mg on Day 1 of each 21-day cycle, starting with Cycle 3. In this cohort, participants received amivantamab in combination with carboplatin and pemetrexed, administered in accordance with local guidelines and labeling. Amivantamab and/or pemetrexed could be continued as maintenance therapy after Cycle 4.

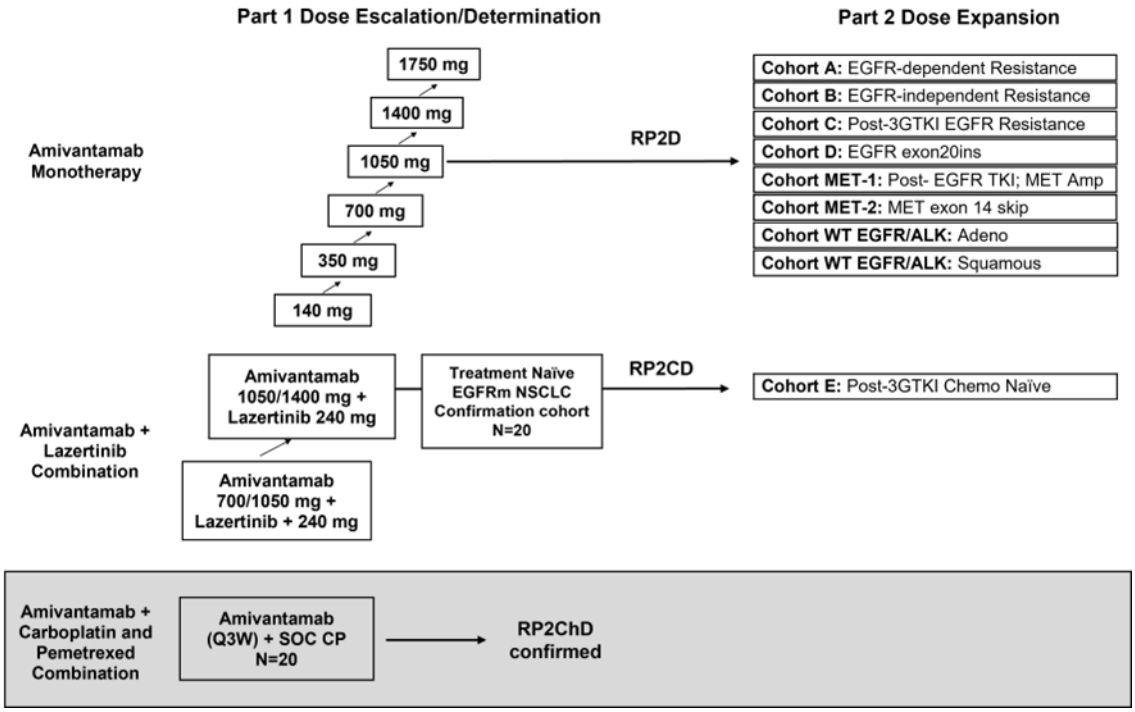


Figure 16: Study Design: CHRYSALIS

Study Population

A total of 5 participants were enrolled with treatment-naïve EGFR exon 20ins NSCLC. Overall, participants had a median age of 63 years, with 60.0% being younger than 65 years of age. There were 2 (40.0%) female participants and 3 (60.0%) male participants. Participants were white (60.0%) or Asian (40.0%).

All participants (100.0%) were diagnosed with adenocarcinoma and most participants had a cancer stage IV disease (80.0%) at the time of initial diagnosis. The median time from diagnosis of metastatic disease to the first dose of study intervention was 2.2 months (range, 0.72-3.94 months).

Supportive Efficacy Results

As of the CCO (15 November 2022), among the 5 treatment-naïve participants with EGFR exon 20ins NSCLC, 4 achieved a best response of PR, with 3 confirming, for an ORR of 60.0% (95% CI: 14.7%, 94.7%). In addition, 2 participants achieved a best response of durable SD (ie, SD for at least 11 weeks), contributing to an overall CBR of 100.0% (95% CI: 47.8%, 100.0%).

All 3 responders (100.0%) had a DOR for ≥6 months (2 with ongoing responses at clinical cutoff). The median DOR in these 3 responders was 18.14 months (95% CI: 6.64, NE), with the longest response being 21.9 months. The median duration of treatment among these responders was 25.53 months. One responder was treated beyond RECIST-defined PD.

2.4.3. Discussion on clinical efficacy

Phase 3 PAPILLON confirmatory study (SOB)

Design and conduct of clinical studies

Papillon study is an ongoing randomized, open-label, Phase 3 study comparing amivantamab add-on to

carboplatin-pemetrexed with carboplatin-pemetrexed, in advanced or metastatic NSCLC patients with activating EGFR exon 20ins mutations in the first-line setting. The study has an appropriate design to isolate amivantamab add-on effect and safety. The "open -label strategy" and the "allowed cross-over to ACP" in this population selected for EGFR exon 20ins mutated NSCLC are acceptable for ethical considerations.

The choice of carboplatin-pemetrexed followed by pemetrexed-maintenance as comparator and backbone therapy is considered acceptable as there are no approved targeted therapies available for the first-line treatment of EGFR exon 20ins mutated NSCLC, and platinum-based doublet chemotherapy remains the standard of care for first line treatment. The mandatory choice of carboplatin is disputable regarding the likely lower efficacy compared to cisplatin. However, carboplatin-pemetrexed is used in this context as backbone and the choice of a more tolerable platinum with the prospect to reduce toxicity with amivantamab add-on is considered relevant. The role of ICIs in the management of advanced EGFR-mutated NSCLC in first line remains controversial, rather more adequate after exhaustion of TKI treatment (ESMO Guidelines for Oncogene-addicted metastatic non-small-cell lung cancer, 2023).

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

After screening, eligible participants were stratified based on ECOG performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no), and randomly assigned 1:1 to treatment with either ACP (ACP arm) or CP (CP arm). In the end it was shown that only a small number of participants had been randomised with prior EGFR TKI use (4 participants). The statistical impact of this stratification factor was assessed to be negligible and prior EGFR TKI use was omitted from analysis models/tests (SAP Addendum approved on 20 April 2023, before data cut-off date). Furthermore, subgroup analyses using prior TKI use were omitted. This is acceptable.

The planned total sample size was 300. There have been no changes to the assumptions made at the planning stage or the (planned) sample size. In estimating the number of subjects needed, a HR of 0.625 had been assumed, resulting in that 200 PFS events were required for a power of approximately 90% based on a two-sided significance level of 0.05.

Selection of patients with NSCLC EGFR Exon 20ins mutation to be randomised in the study and the overall inclusion/exclusion criteria are adequate to identify a population with advanced NSCLC that would benefit from the targeted therapy. The patients crossing over to experiment arm (amivantamab monotherapy) were rescreened to ensure eligibility was met to receive amivantamab.

For eligibility evaluation, EGFR Exon 20ins mutation was detected by local testing of tumour tissue (92.2%) and/or or plasma samples (7.8%) for all 308 patients using next generation sequencing (NGS) in 55.5% of patients and/or polymerase chain reaction (PCR) in 44.5% of patients. The central testing using validated CE-marked assays was also performed with the objective of confirming the local testing results using both tissue and plasma specimens retrospectively. For tissue, confirmatory testing was conducted with the Thermo Fisher Oncomine Dx Target Test (ODxTT) and the AmoyDx® LC10 test. AmoyDx was used exclusively to support central testing in China, given the local requirement. Plasma confirmatory testing was conducted with the Guardant Health Guardant360 test. Central testing was concordant with local testing in 97.2% of the samples with a valid AmoyDx® LC10 tissue test result. Central testing was concordant with local testing in 74.2% of the samples with a valid central Guardant 360® CDx plasma test result. Section 4.2 of the SmPC is updated with information that if a plasma-based ctDNA test is negative, a tissue test should be performed whenever possible due to the risk of false negative results using plasma tests.The treatment with amivantamab and pemetrexed maintenance in ACP arm and maintenance with pemetrexed in CP arm continued until disease progression, death, or unacceptable toxicity. The regimen, as well as the sequence of

components administration is adequately reflected in the SmPC 4.2 and 5.1. 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.

Overall the study objectives reflect a study designed to evaluate efficacy of amivantamab in combination with chemotherapy, versus chemotherapy alone in mNSCLC patient with EGFR Exon 20ins mutations in first line.

The choice of PFS as primary endpoint instead of OS is acceptable despite the poor prognosis of metastatic NSCLC with EGFR Exon 20ins activating mutations. 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 key secondary endpoint which is in line with the anticancer guideline when PFS is chosen as primary endpoint. The cross-over to amivantamab monotherapy allowed for the patients with BICR confirmed progress on CP will be considered in the evaluation of the relative OS benefit in the ITT population.

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, TSST, PFS2, TTSP and PRO) are acceptable.

Conventional analysis methods have been used for the testing and estimation of amivantamab add-on treatment efficacy in comparison with chemotherapy alone. It is endorsed that the primary efficacy analysis set comprised all randomised subjects (FAS) and further, that multiplicity had been considered (in order of appearance, for PFS, ORR and OS).

No PFS interim analysis had been planned and none was performed.

The SAP (dated 04 March 2021) was finalised approximately 3 months after the study had started. There were no SAP amendments. There exists an SAP addendum (approved on 20 April 2023, before the data cut-off date). It contains a few changes and clarifications, however, nothing that raise any concern.

Where applicable, the PFS censoring rules were in alignment with the identified intercurrent events and the strategy for how to address them, which overall are endorsed. However, the censoring of subjects with missed/unevaluable disease assessment for 2 or more consecutive visits at the date of last evaluable disease assessment before the missed/unevaluable visits is not according to CHMP preferred censoring rules. Hence, the predefined supplemental analysis ignoring missed assessments is supported.

An interim analysis of OS was planned at the time of the final PFS analysis when approximately 85 deaths overall were anticipated. Based on the O'Brien Fleming alpha spending approach, a 2-sided alpha of 0.0008 was planned to be allocated to the interim analysis. The final OS analysis will be conducted at a 2-sided alpha of 0.0498.

The currently presented OS outcome is from this interim analysis. At the time of the final analysis of PFS, 70 deaths had occurred. The final OS analysis has been planned to be conducted when approximately 210 deaths overall have been observed. Initially it was expected that this was to occur approximately 48 months after the randomisation of the first subject.

Efficacy data and additional analyses

A total of 308 were randomized in study including 153 in the ACP arm and 155 in the CP arm and

constitute FAS, of which 306 patients received at least one dose of study treatment (SAF) with 2 patients randomized to the ACP arm that withdraw consent prior to first dosing.

At the cut-off date 03 May 2023, 31% of patients remained on the study treatment (46.4% in the ACP arm and 15.5% in the CP arm) and 69% that discontinued the treatment mainly due to progressive disease reported at higher rate in CP arm than in ACP arm (33% in ACP arm and 69% in CP).

No important numerical imbalance between arms is seen in the rates of AEs, death, non-compliance, physician decision or other as reason for treatment discontinuation. Higher discontinuation due to patients refusing further study treatment is noticed in the experimental ACP arm than in control CP arm (7.9% in ACP vs 3.2% in CP arm). Although imbalance favouring experimental arms might be expected in an open-label controlled study, the overall dropout rate is minor and is reasonably balanced between the arms. Across the discontinuations due to the patient refusing further study treatment (12 patients in ACP vs 5 in CP) and due to physician decision (1 in ACP vs 0 in CP), when grouping them per reason, one can observe that a balanced number of patients between arms discontinued the treatment due to AEs, specifically 4 patients in ACP vs 3 patients in CP arms. The data are not considered to bias inferences.

Two global protocol amendments were implemented, however none with a timing or dignity to raise any concerns.

The major protocol deviation overall rate is 2.9% (n=9 patients) with well-balanced rates/reasons between arms, hence there is no concerns that this could have a potential impact on the evaluation of efficacy or safety.

Baseline characteristics

Overall, the study population was considered comparable across the two arms. Asian subjects were 64% in ACP arm and 58% in CP arm (17.1%) and 18 (17.3%) in the 240 mg group and 960 mg group, respectively. The median age was 62 (range: 27 to 92), and the age group and 38.7% of participants were ≥65 years of age, which is considered adequate with the intended population. Most of the patients had an adenocarcinoma (98.7%), stage IV, were not former smoker (58%) and had baseline ECOG 1 (64.6%). Brain metastases were present at baseline in 23.1% of patients.

Among prior therapies for lung cancer a small numerical imbalance is observed in terms of prior radiotherapy (38% in CP vs 31% in ACP arm) and prior adjuvant and palliative treatment (7.9% in CP vs 4.55 in ACP arm and 2% in CP vs 0.6% in ACP arm respectively), which were more frequently reported for patients in CP arm. The difference is not considered to have impact on the efficacy result.

Exposure and follow-up

The median follow-up in the study was 14.9 months. The median duration of treatment in the ACP arm was 9.72 months (9.26 months [range: 0.0; 26.9] for amivantamab, 2.14 months [range: 0.0; 3.8] for carboplatin, and 8.34 months [range: 0.0; 24.9] for pemetrexed). The median duration of treatment in the CP arm was 6.74 months (2.14 months [range: 0.0; 3.9] for carboplatin and 6.74 months [range: 0.0; 25.3] for pemetrexed).

Primary endpoint

At the cut-off date for final PFS analysis 03 May 2023, after a median follow-up of 14.92 months, the pre-planned maturity grade was exceeded with 16 events, i.e., 132 (85.2%) events were reported in CP arm and 84 (54.9%) events in ACP arm, respectively. The PFS analysis by BICR showed statistically significant benefit with amivantamab addition to CP HR 0.395 (0.296, 0.528); p-value<0.0001 (median PFS 11.37 months in ACP arm vs 6.70 months in CP arm).

Across the reasons for PFS censoring a small imbalance in the rate for the death without progressive disease and withdrawal of consent is observed with higher rate in ACP arm. There is no indication of informative censoring disparity that could have been generated due to the open-label settings.

A clear separation of treatment arms favouring treatment with ACP is observed before 3 months on treatment, (corresponding to the completion of 4 cycles of carboplatin, pemetrexed, and amivantamab). The curves continue to separate with longer follow-up, suggesting amivantamab maintained additional effect.

Overall, the censoring rules of the primary PFS analysis, or sensitivity analyses are not in line with the general recommendations in Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (CHMP/27994/2008 Rev. 1). However, the pre-planned supplementary PFS analyses according to EMAs censoring rules (Event for PD/death after missing more than one disease evaluation and Event for PD/death after start of Subsequent Anticancer therapy) are addressing these aspects and support the results of primary PFS analysis.

A similar magnitude of benefit was observed with investigator assessment of PFS (HR=0.383; 95%CI 0.277, 0.497, p<0.0001). The agreement rate on the event status between Investigator and BICR was 99.2% in CP arm and 88.2% in ACP arm.

The PFS benefit was observed across all predefined 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 history of brain metastases, however no conclusion can be drawn due to the small size of these subgroups and exploratory character of analyses.

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, however those represents the majority of ITT population (152 of the 153 patients in ACP arm and 152 of the 155 patients in CP arm). ORR by BICR further support the benefit with amivantamab addition to CP with ORR of 73.0%in ACP arm compared with the CP arm 47.4% with statistically significant odds ratio of 2.971 (95% CI: 1.844, 4.787; p<0.0001). Similar results were observed for ORR based on confirmed PR or CR (67.1% in the ACP arm compared with 36.2% in the CP arm).

DoR: The response (CR or PR) was longer maintained in the ACP arm than in CP arm (median DoR 10.09 months in ACP compared with 5.55 months in the CP arm).

OS: At the interim analysis of OS after a median follow up of 14.92 months, the event rate was overall lower than expected, i.e. 42 (27.1%) events in CP arm and 28 (18.3%) events in ACP arm. The type I error allocated to this analysis was p 0.0008.

A numerical trend towards improved survival in ACP arm was observed with HR (95% CI) 0.675 (0.418, 1.090) p-value 0.1056.

Notably, 65 (42%) patients from CP arm crossed over to ACP arm, which should be considered for the OS gain understanding. Among the 65 patients that crossed over to ACP arm, at the time of the CCO date of 03 May 2023, after a median follow-up of 9.76 months, there were a total of 17 deaths reported. Supplementary analyses to adjust for confounding from treatment crossover were pre-planned.

At the inspection of KM curves, a detriment in OS is observed in the first 6 months and a clear separation occurs after 10 months. The review of the OS event/censoring for the first 6 months of treatment and until the cut-off of IA1 shows a trend of increased risk of death in the first months on study treatment with amivantamab addition to chemotherapy that changes towards the advantage

with ACP against CP until the cut-off for OS interim analysis. Sensitivity/supplementary OS analyses to address the cross-over will be provided with the final OS analysis expected to be provided by the MAH by Q4 2025. The narrative provided for the patients experiencing early deaths do not suggest an increased short-term toxicity in the experimental arm (for details, see section 2.5). Moreover, the difference in number of deaths between arms (9 in ACP vs 5 in CP) is not major**.**

Contrary to the planned stratified analysis, the OS interim analysis was performed using an unstratified log rank test with estimations based on what is interpreted as a non-adjusted Cox proportional hazard regression. However, a stratified OS analysis was also provided: HR: 0.717 [95% CI: 0.441, 1.165], p=0.177).

At the cut-off 31 October 2023 for the requested updated OS analysis the median follow-up for survival was approximately 20 months. The updated OS analysis with 6 additional months of follow-up supports the trend towards OS benefit with ACP observed at the primary analysis. The hazard ratio was 0.756 (95% CI: 0.501, 1.142) with a roughly 30% events (26.7% in ACP vs 33% in CP arm). The updated OS data have been reflected in section 5.1 of the SmPC.

The final OS analysis from the pivotal Phase 3 study PAPILLON was planned to occur approximately 48 months after the first participant was randomized, when approximately 210 deaths overall are anticipated and will be submitted as a Recommendation (REC) by Q4 2025.

For the secondary endpoints related to subsequent therapy, a crossover from CP arm to amivantamab monotherapy was also considered as initiation of a subsequent systemic therapy.

TTST: A longer median time to initiation of subsequent anti-cancer therapy was observed in the ACP arm (17.71 months [95% CI: 13.67, NE]) compared with the CP arm (9.89 months [95% CI: 8.57,11.07]) with a HR of 0.348 (95% CI: 0.250, 0.486; nominal p<0.0001).

As subsequent therapies, the patients in the ACP arm received mostly immuno-chemotherapy followed by other TKI or other investigational agents. In the CP arm apart from the 65 patients that crossed over to ACP arm and received amivantamab, the majority (87%) received other TKI and a small proportion received chemo-immunotherapy- based therapy.

PFS2: The median PFS2 was also prolonged for the patients receiving subsequent anticancer treatment in ACP arm in comparison with those in CP arm with HR PFS2 0.493 (0.320, 0.759) p 0.0010.

Overall, the results of the secondary endpoints related to subsequent anticancer therapy are supporting the benefit with a first line regimen with amivantamab add-on to CP. The descriptive nature of these analyses must be however considered.

TTSP: Time to Symptomatic Progression is defined as the time from randomization to documentation 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, whichever comes first. TTSP, based on the investigator's assessments was longer in ACP arm compared with CP arm (HR=0.669 [95% CI: 0.456, 0.982]; nominal p=0.0387.

The exploratory endpoint time to treatment discontinuation is in line with the other secondary endpoints showing longer time to treatment discontinuation in the ACP than in CP arm.

PRO: Overall, the PRO outcomes showed that HRQoL were unchanged from baseline in both treatment arms. Time to symptoms deterioration was however longer in the ACP than in CP arm.

CHRYSALIS STUDY

Considering the very limited size of this population, additional data from 5 patients with treatment-naïve EGFR Exon 20ins mut NSCLC included in the Part 1 of Phase 1 study CHYSALIS treated with ACP are of limited relevance in the context of available statistically significant data from an RCT. In CHRYSALYS study among the 5 patients, the ORR of 60% and mDoR of 18.14 months in the 3 responders, are slightly lower than in patients from PAPILLON study ACP arm: ORR 73.0% 95%CI (65.2%, 79.9%), median DoR NE 95% CI (15.21 months; NE).

2.4.4. Conclusions on the clinical efficacy

The primary endpoint was met with a statistically significant PFS improvement with amivantamab add-on to CP compared to CP. The benefit with ACP in first line was further supported by a statistically significant improvement in ORR and longer responses with ACP as compared with CP. OS data are immature with 30% of events and no statistically significant OS benefit was shown at the interim analysis, however a trend towards OS benefit was observed. Final OS data will be submitted post-authorisation as a recommendation by Q4 2025. The study is considered positive, and the SOB fulfilled.

2.5. Clinical safety

Introduction

The most common adverse drug reaction (ADRs) previously established for amivantamab include common EGFR-associated side effects such as skin toxicity and paronychia, and MET-associated side effects such as hypalbuminaemia and oedema. Other established amivantamab ADRs are stomatitis, gastrointestinal side effects (e.g., nausea, constipation), increased aminotransferases, hypokalaemia, and infusion related reactions (IRR). The majority of these side-effects are generally low-grade. Known serious ADRs include interstitial lung disease (ILD), IRR, and rash.

The safety specification in the current RMP (version 3.0) includes IRR as an important identified risk, and hepatotoxicity as well as impaired fertility and embryofoetal toxicity as important potential risks.

The key safety data in support of the current application are derived from the PAPILLON study in patients with advanced or metastatic NSCLC with EGFR exon 20ins mutations, with data cut-off (DCO) date 03 May 2023. In total, 151 study participants were exposed to amivantamab + carboplatin and pemetrexed (ACP) treatment and 155 study participants were exposed to carboplatin and pemetrexed (CP) only in the PAPILLON study.

Supportive safety data are derived from the CHRYSALIS study in patients with advanced NSCLC (no specific driver mutation required), with DCO 15 Nov 2022. In the CHRYSALIS study, 20 participants were exposed to ACP treatment. Due to the limited number of patients, no detailed assessment of safety data pertaining to the ACP treated patients in the CHRYSALIS study has been made.

Data are also reported for an integrated data set on the in total 171 study participants exposed to ACP treatment in the PAPILLON and CHRYSALIS studies. This data set is mainly based on ACP treated participants in the PAPILLON study (151/171 [88.3%] participants). Therefore, data on the integrated safety data set are not assessed in further detail.

In the PAPILLON study, 65 patients randomised to CP only crossed over to amivantamab monotherapy after progression. Safety data of these patients are summarised separately.

Table 31: Overview of clinical studies included in the safety data evaluation

Study	Study Design	Population	Role in SCS/ CCO	Treatment	Number of Subjects	Median Total Duration of Treatment (months)[7]
PAPILLON 61186372NSC3001	Phase 3, randomized, controlled, ongoing, open-label study	Treatment-naïve, locally-advanced or metastatic NSCLC with EGFR exon 20ins mutations	**Pivotal** (integrated) 03 May 2023	**ACP**[2]	**n=151**	**9.72**
				CP[2]	**n=155**[4]	**6.74**
CHRYSALIS[1] 61186372EDI1001	Phase 1, first-in-human, dose escalation, dose expansion, multi-cohort, ongoing, open-label study	**Chemotherapy Combination Cohort (ACP)** Advanced NSCLC eligible to receive SOC carboplatin-pemetrexed (where no specific driver mutation was required)	**Supportive** (integrated) 15 Nov 2022	**ACP**[2]	**n=20**[5] 5 of 20 participants were treatment naïve with EGFR exon 20ins mutations	**7.49**
		Amivantamab Monotherapy locally advanced or metastatic NSCLC, after failure of platinum-based chemotherapy	**Pooled ADR analyses only** (not integrated) 30 Mar 2021	**A**[3]	**n=380**[6]	**4.14**

[1] 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, ACP Cohort). Data from amivantamab in combination with lazertinib are not included in the SCS.

[2] A 21-day treatment cycle was used with ACP 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, in combination with carboplatin for up to 4 cycles, and then as maintenance monotherapy until disease progression

[3] A 28-day treatment cycle was used with amivantamab monotherapy: amivantamab weekly for the first 4 doses (at 1,400 mg for <80 kg, 1,750 mg for ≥80 kg), followed by Q2W dosing for subsequent cycles.

[4] Participants from the CP arm of PAPILLON were permitted to crossover to amivantamab monotherapy (with a Q3 dosing regimen) following confirmation of disease progression by BICR.

[5] CHRYSALIS ACP population (n=20) included participants with sensitizing EGFR mutations (n=12) + KRAS (n=1) + EGFR exon 20ins mutations (n=7).

[6] Pooled ADR population (n=531) included 151 participants treated with ACP from PAPILLON + 380 participants treated with amivantamab monotherapy from CHRYSALIS.

[7] **Source:** Mod5.3.5.1/61186372NSC3001/Sec4.6.1 for PAPILLON (CCO 03May2023), Mod5.3.5.2/61186372EDI1001-IA-15Nov2022/Sec5.5 for CHRYSALIS ACP (CCO 15Nov2022), and Mod5.3.5.2/61186372EDI1001-interim/Sec3.1.6 for CHRYSALIS amivantamab monotherapy (CCO 30Mar2021)

Patient exposure

Overall extent of exposure

The ACP treatment schedule is discussed in the Clinical Efficacy section of the AR. In summary, amivantamab IV was administered once weekly for four weeks (up to cycle 2 day 1) and thereafter on day 1 of each 21-day cycle in combination with carboplatin and pemetrexed for up to four cycles. Carboplatin AUC 5 IV was administered in combination with pemetrexed 500 mg/m^2 IV on day 1 of each 21-day cycle for up to four cycles. As of cycle 5, amivantamab and pemetrexed maintenance treatment continued until disease progression or intolerable toxicity. Due to the risk of IRRs, cycle 1 amivantamab is administered as a split dose infusion over two days.

PAPILLON study

At DCO (03 May 2023), 46.4% (n=70) of the patients in the PAPILLON ACP arm compared to 15.5% (n=24) in the CP arm were still on treatment. The most common reason for treatment discontinuation in both treatment arms was progressive disease, but the proportion of discontinuations was higher in the CP arm (69.0%) compared to the ACP arm (33.1%). Discontinuations of all study treatments due to adverse events (AEs) was reported for 9.3% of the patients in the ACP arm and 9.0% of the patients in the CP arm. Discontinuations of all study treatments due to treatment emergent AEs (TEAEs) was reported for 7.9% vs. 7.7% of the patients in the ACP vs. the CP arm, respectively.

CHRYSALIS study

In CHRYSALIS ACP cohort, 20% (n=4) of the participants were still on treatment as of the DCO (15 Nov 2022). The most common reason for treatment discontinuation was progressive disease (60%). Discontinuation of all study treatments due to AEs and TEAEs was reported for 15.0% and 25.0% of the patients, respectively.

Table 32: Treatment disposition; safety analysis set

	CP	ACP		
	PAPILLON	PAPILLON	CHRYSALIS	COMBINED
Analysis set: Safety	155	151		
Subjects ongoing any study agent	24 (15.5%)	70 (46.4%)		
Discontinued all study agents[a]	131 (84.5%)	81 (53.6%)		
Reason for discontinuation[b]				
Progressive disease	107 (69.0%)	50 (33.1%)		
Adverse event	14 (9.0%)	14 (9.3%)		
Adverse event - COVID-19 related	0	2 (1.3%)		
Subject refused further study treatment	5 (3.2%)	12 (7.9%)		
Physician decision	0	1 (0.7%)		
Death	1 (0.6%)	1 (0.7%)		
Non-compliance with study drug	2 (1.3%)	1 (0.7%)		
Other	2 (1.3%)	2 (1.3%)		

Key: CP = Carboplatin + Pemetrexed; ACP = Amivantamab + Carboplatin + Pemetrexed
[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

2.5.1.1. Duration of exposure

PAPILLON study

The overall median duration of treatment in the PAPILLON ACP arm was 9.72 months compared to 6.74 months in the CP arm. The median duration of treatment with carboplatin was 2.14 months in both arms, corresponding to four treatment cycles, whereas the median duration of treatment with pemetrexed was 8.34 months (13 cycles) in the ACP arm compared to 6.74 months in the CP arm.

The participants in the ACP arm who were in the maintenance phase (amivantamab + pemetrexed) remained on amivantamab for a median duration of 9.26 months compared to 8.34 months on pemetrexed. The mean dose intensity was 99.87% for carboplatin, 99.59% for pemetrexed, and 100% for amivantamab in the ACP arm and 100% for pemetrexed and carboplatin in the CP arm.

CHRYSALIS study

In CHRYSALIS ACP cohort, the overall median duration of treatment was 7.49 months. The median duration of treatment was 2.10 months for carboplatin, 6.28 months for pemetrexed, and 7.49 months for amivantamab. The majority of the participants received the full course of carboplatin, and participants remained on amivantamab longer than pemetrexed in the maintenance phase. The mean dose intensity was 100% for carboplatin and pemetrexed and 98.34% for amivantamab.

Table 33: Summary of treatment duration and treatment cycles, safety analysis set

	CP		ACP								
	PAPILLON		PAPILLON			CHRYSALIS			COMBINED		
	Carboplatin	Pemetrexed	Amivantamab	Carboplatin	Pemetrexed	Amivantamab	Carboplatin	Pemetrexed	Amivantamab	Carboplatin	Pemetrexed
Analysis set: Safety	155	155	151	151	151						
Duration of treatment (months)											
N	155	155	151	151	151						
Mean	2.17	7.32	10.19	2.12	9.58						
(SD)	(0.463)	(4.140)	(6.085)	(0.594)	(6.009)						
Median	2.14	6.74	9.26	2.14	8.34						
Range	(0.0; 3.9)	(0.0; 25.3)	(0.0; 26.9)	(0.0; 3.8)	(0.0; 24.9)						
Total number of treatment cycles received											
N	155	155	151	151	151						
Mean	3.88	10.77	13.99	3.77	13.50						
(SD)	(0.514)	(5.768)	(7.873)	(0.668)	(7.857)						
Median	4.00	10.00	14.00	4.00	13.00						
Range	(1.0; 5.0)	(1.0; 37.0)	(1.0; 39.0)	(1.0; 4.0)	(1.0; 34.0)						
Relative dose intensity (%) [a]											
N	155	155	151	151	151						
Mean	100.00	100.00	100.00	99.87	99.59						
(SD)	(0.000)	(0.000)	(0.000)	(1.589)	(4.147)						
Median	100.00	100.00	100.00	100.00	100.00						
Range	(100.0; 100.0)	(100.0; 100.0)	(100.0; 100.0)	(80.5; 100.0)	(50.3; 100.0)						

Key: CP = Carboplatin + Pemetrexed; ACP = Amivantamab + Carboplatin + Pemetrexed
[a] Relative dose intensity (%) is calculated as the ratio of total actually received dose versus total prescribed dose.
Note: Amivantamab is administered once weekly (with the first dose split over Days 1 and 2) up to Cycle 2 Day 1 and then administered once every 3 weeks.
Source: Mod5.3.5.3/ISS/TSIEX02 (duration and intensity), Mod5.3.5.3/ISS/TSIEX01 (cycles)

Adverse events

2.5.1.2. Adverse events overview

Treatment emergent AEs (TEAEs) were defined as any AE 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).

Table 34: Overall summary of treatment-emergent adverse events, safety analysis set

	CP	ACP		
	PAPILLON	PAPILLON	CHRYSALIS	COMBINED
Analysis set: Safety	155	151		
Subjects with 1 or more:				
TEAEs	152 (98.1%)	151 (100.0%)		
Grade 3 or greater TEAEs	83 (53.5%)	114 (75.5%)		
Maximum toxicity grade				
Grade 1	13 (8.4%)	2 (1.3%)		
Grade 2	56 (36.1%)	35 (23.2%)		
Grade 3	65 (41.9%)	85 (56.3%)		
Grade 4	14 (9.0%)	22 (14.6%)		
Grade 5	4 (2.6%)	7 (4.6%)		
Serious TEAEs	48 (31.0%)	56 (37.1%)		
TEAEs leading to discontinuation of any study agent	16 (10.3%)	36 (23.8%)		
TEAEs leading to discontinuation of Amivantamab	NA	17 (11.3%)		
TEAEs leading to discontinuation of Carboplatin	3 (1.9%)	13 (8.6%)		
TEAEs leading to discontinuation of Pemetrexed	13 (8.4%)	28 (18.5%)		
TEAEs leading to drug interruption of any study agent[c]	57 (36.8%)	104 (68.9%)		
TEAEs leading to interruption of Amivantamab[c]	NA	97 (64.2%)		
TEAEs leading to interruption of Carboplatin[c]	29 (18.7%)	38 (25.2%)		
TEAEs leading to interruption of Pemetrexed[c]	56 (36.1%)	86 (57.0%)		
TEAEs leading to dose reduction of any study agent	35 (22.6%)	73 (48.3%)		
TEAEs leading to reduction of Amivantamab	NA	54 (35.8%)		
TEAEs leading to reduction of Carboplatin	18 (11.6%)	30 (19.9%)		
TEAEs leading to reduction of Pemetrexed	33 (21.3%)	41 (27.2%)		
TEAEs leading to death[b]	4 (2.6%)	7 (4.6%)		
Related TEAEs leading to death[a,b]	2 (1.3%)	3 (2.0%)		
COVID-19 associated TEAEs[d]	25 (16.1%)	44 (29.1%)		
COVID-19 associated serious TEAEs[d]	1 (0.6%)	5 (3.3%)		
COVID-19 associated non-serious TEAEs[d]	24 (15.5%)	40 (26.5%)		
COVID-19 associated grade 3 or greater TEAEs[d]	1 (0.6%)	5 (3.3%)		
COVID-19 associated TEAEs[d] leading to death	0	2 (1.3%)		

Key: CP = Carboplatin + Pemetrexed; ACP = Amivantamab + Carboplatin + Pemetrexed
TEAE = Treatment Emergent Adverse Event
[a] TEAE is assessed by the investigator as related to study agent.
[b] TEAEs 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.

2.5.1.3. Adverse events by system organ class and preferred term

The selection of commonly-reported TEAEs was based on TEAE data from the PAPILLON study and the integrated safety data set and not on the CHRYSALIS study, given the small sample size of the CHRYSALIS ACP cohort.

Table 35: Number of subjects with TEAEs with frequency of ≥5% in any treatment group by system organ class and preferred term, safety analysis set

	CP	ACP
Analysis set: Safety	155	151
Subjects with 1 or more AEs	152 (98.1%)	151 (100.0%)
System organ class Preferred term		
Skin and subcutaneous tissue disorders	53 (34.2%)	137 (90.7%)
Rash	12 (7.7%)	81 (53.6%)
Dermatitis acneiform	5 (3.2%)	47 (31.1%)
Dry skin	6 (3.9%)	16 (10.6%)
Alopecia	8 (5.2%)	13 (8.6%)
Pruritus	12 (7.7%)	10 (6.6%)
Skin ulcer	1 (0.6%)	10 (6.6%)
Erythema	8 (5.2%)	1 (0.7%)
Gastrointestinal disorders	112 (72.3%)	128 (84.8%)
Constipation	47 (30.3%)	60 (39.7%)
Nausea	65 (41.9%)	55 (36.4%)
Stomatitis	9 (5.8%)	38 (25.2%)
Vomiting	29 (18.7%)	32 (21.2%)
Diarrhoea	20 (12.9%)	31 (20.5%)
Haemorrhoids	2 (1.3%)	18 (11.9%)
Mouth ulceration	4 (2.6%)	12 (7.9%)
Abdominal pain	4 (2.6%)	11 (7.3%)
Gingival bleeding	2 (1.3%)	8 (5.3%)
Abdominal distension	10 (6.5%)	7 (4.6%)
Abdominal pain upper	8 (5.2%)	4 (2.6%)
Infections and infestations	65 (41.9%)	120 (79.5%)
Paronychia	0	85 (56.3%)
COVID-19	21 (13.5%)	36 (23.8%)
Pneumonia	10 (6.5%)	17 (11.3%)
Conjunctivitis	7 (4.5%)	9 (6.0%)
Upper respiratory tract infection	6 (3.9%)	9 (6.0%)
Urinary tract infection	8 (5.2%)	6 (4.0%)
Metabolism and nutrition disorders	81 (52.3%)	115 (76.2%)
Hypoalbuminaemia	15 (9.7%)	62 (41.1%)
Decreased appetite	43 (27.7%)	54 (35.8%)
Hypokalaemia	13 (8.4%)	32 (21.2%)
Hypomagnesaemia	15 (9.7%)	22 (14.6%)
Hypocalcaemia	3 (1.9%)	19 (12.6%)
Hyponatraemia	12 (7.7%)	19 (12.6%)
Hypophosphataemia	2 (1.3%)	10 (6.6%)
Hypoproteinaemia	3 (1.9%)	10 (6.6%)
Hyperglycaemia	11 (7.1%)	8 (5.3%)
Hyperkalaemia	0	8 (5.3%)
Blood and lymphatic system disorders	111 (71.6%)	111 (73.5%)
Neutropenia	70 (45.2%)	89 (58.9%)
Anaemia	85 (54.8%)	76 (50.3%)
Leukopenia	50 (32.3%)	57 (37.7%)
Thrombocytopenia	46 (29.7%)	55 (36.4%)
Lymphopenia	11 (7.1%)	7 (4.6%)
General disorders and administration site conditions	96 (61.9%)	107 (70.9%)
Oedema peripheral	16 (10.3%)	45 (29.8%)
Asthenia	29 (18.7%)	30 (19.9%)
Pyrexia	9 (5.8%)	24 (15.9%)
Fatigue	32 (20.6%)	23 (15.2%)
Malaise	12 (7.7%)	16 (10.6%)
Mucosal inflammation	4 (2.6%)	15 (9.9%)
Oedema	2 (1.3%)	10 (6.6%)
Investigations	93 (60.0%)	97 (64.2%)
Alanine aminotransferase increased	56 (36.1%)	50 (33.1%)
Aspartate aminotransferase increased	51 (32.9%)	47 (31.1%)
Gamma-glutamyltransferase increased	26 (16.8%)	21 (13.9%)
Weight decreased	13 (8.4%)	21 (13.9%)
Blood alkaline phosphatase increased	12 (7.7%)	19 (12.6%)
Blood lactate dehydrogenase increased	8 (5.2%)	13 (8.6%)
Blood creatinine increased	15 (9.7%)	11 (7.3%)
Injury, poisoning and procedural complications	15 (9.7%)	70 (46.4%)
Infusion related reaction	2 (1.3%)	63 (41.7%)

	CP	ACP
Respiratory, thoracic and mediastinal disorders	78 (50.3%)	63 (41.7%)
Cough	24 (15.5%)	21 (13.9%)
Dyspnoea	23 (14.8%)	16 (10.6%)
Pulmonary embolism	7 (4.5%)	12 (7.9%)
Productive cough	3 (1.9%)	9 (6.0%)
Pleural effusion	8 (5.2%)	5 (3.3%)
Nervous system disorders	48 (31.0%)	49 (32.5%)
Dizziness	15 (9.7%)	15 (9.9%)
Dysgeusia	10 (6.5%)	9 (6.0%)
Headache	14 (9.0%)	9 (6.0%)
Musculoskeletal and connective tissue disorders	50 (32.3%)	46 (30.5%)
Back pain	16 (10.3%)	17 (11.3%)
Arthralgia	14 (9.0%)	10 (6.6%)
Myalgia	5 (3.2%)	8 (5.3%)
Eye disorders	28 (18.1%)	28 (18.5%)
Lacrimation increased	8 (5.2%)	3 (2.0%)
Vascular disorders	24 (15.5%)	28 (18.5%)
Deep vein thrombosis	3 (1.9%)	10 (6.6%)
Hypertension	10 (6.5%)	1 (0.7%)
Hepatobiliary disorders	13 (8.4%)	21 (13.9%)
Hyperbilirubinaemia	6 (3.9%)	15 (9.9%)
Psychiatric disorders	26 (16.8%)	20 (13.2%)
Insomnia	20 (12.9%)	16 (10.6%)

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

[tsfae04.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae04.sas] 22JUN2023, 11:55

2.5.1.3.1. Venous thromboembolism

Table 36: Characteristics of the TEAEs VTE (grouped term)

Adverse Event Characteristic	CP	ACP		
	PAPILLON (n=155)	PAPILLON (n=151)	CHRYSALIS	COMBINED
Incidence (all grades)	14 (9.0%)	24 (15.9%)		
Exposure-Adjusted (all grades)	13.9	18.6		
Incidence (Grade 3 +)	6 (3.9%)	5 (3.3%)		
Exposure-Adjusted (Grade 3+)	5.8	3.6		
Serious	4 (2.6%)	4 (2.6%)		
Treatment Discontinuation	1 (0.6%)	0		
amivantamab	NA	0		
carboplatin	0	0		
pemetrexed	1 (0.6%)	0		
Drug Interruption	1 (0.6%)	5 (3.3%)		
amivantamab	NA	5 (3.3%)		
carboplatin	1 (0.6%)	1 (0.7%)		
pemetrexed	1 (0.6%)	3 (2.0%)		
Dose Reduction	0	1 (0.7%)		
amivantamab	NA	1 (0.7%)		
carboplatin	0	0		
pemetrexed	0	1 (0.7%)		

Source: Mod5.3.5.3/ISS/TSFAE23 (VTE all grade, Grade 3+, SAE, discontinuation, drug interruption, dose reduction), Mod5.3.5.3/ISS/TSFAE23f (VTE exposure-adjusted all grade [events per 100 P-Y]), Mod5.3.5.3/ISS/TSFAE23g (VTE exposure-adjusted Grade 3+ [events per 100 P-Y])

PAPILLON study

The VTE events were considered treatment related for 7.9% (n=12) and 0.6% (n=1) of the patients in the ACP and CP arms, respectively.

All treatment related VTEs in the ACP arm were considered by the investigator as related to amivantamab treatment and for 3.3% and 4.6% of the cases also related to carboplatin and/or pemetrexed treatment. Most VTE TEAEs were grade 1-2, and the proportion of SAEs related to VTE was equal in the two treatment arms (2.6% each).

2.5.1.4. Adverse drug reactions

All terms previously identified as ADRs with amivantamab monotherapy were retained.

The primary data source used for determination of new ADR terms for amivantamab was the PAPILLON study, which provided the only randomised and controlled data in the target population. 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 preferred terms were grouped together to assess specific medical concepts. All SAEs and TEAEs that were grade $\geq$3 were also thoroughly reviewed as well as all laboratory abnormalities. In addition, a comprehensive review of laboratory abnormalities with incidence of $\geq$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.

Pyrexia and haemorrhoids were identified as new ADRs for amivantamab. ADR pyrexia is included in the proposed SmPC section 4.8 with frequency "very common" for ACP treatment as well as amivantamab monotherapy. ADR haemorrhoids is included in 4.8 with frequency "very common" for ACP treatment and "common" for amivantamab monotherapy. Venous thromboembolism (VTE) was identified as a new ADR associated with amivantamab + chemotherapy treatment and is included in section 4.8 with frequency "very common".

Pyrexia was reported at a higher incidence in the ACP arm vs the CP arm (15.9% vs 5.8%), which also remained higher when adjusted for exposure (19.4 vs. 8.9 events per 100 P-Y). All events were grade 1 or 2 and were non-serious.

Haemorrhoids was reported at a higher incidence in the ACP arm vs the CP arm (11.9% vs 1.3%), which also remained higher when adjusted for exposure (14.4 vs 1.9 events per 100 P-Y). Most events were Grade 1 or 2 (>98%) and all events were non-serious.

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

- nail bed toxicity (grouped term) had three new PTs added (nail bed inflammation, nail dystrophy, nail infection)
- stomatitis (grouped term) had one new PT added (angular cheilitis)
- dry skin (grouped term) had one new PT added (xerosis)

The frequency of occurrence for each ADR term was calculated for the 151 patients in the PAPILLON ACP arm and a pooled data set of 531 patients consisting of the 151 patients from the PAPILLON ACP arm and 380 patients in the CHRYSALIS study who received >1 dose of amivantamab at RP2D.

Upon request from the CHMP, the Applicant presented the following ADR table to be included in section 4.8 of the SmPC displaying the ADRs for amivantamab + chemotherapy. ADRs for amivantamab monotherapy are displayed in a separate table in section 4.8 of the SmPC.

Table 37: Adverse reactions in patients receiving amivantamab in combination with carboplatin and pemetrexed

System organ class Adverse reaction	Frequency category	Any Grade (%)	Grade 3-4 (%)
Metabolism and nutrition disorders			
Hypoalbuminaemia*	Very common	41	4.0
Decreased appetite		36	2.6
Hypokalaemia		21	8.6
Hypomagnesaemia		15	2.0
Hypocalcaemia		13	1.3
Nervous system disorders			
Dizziness*	Common	9.9	0
Vascular disorders			
Venous thromboembolism*	Very common	16	3.3
Eye disorders			
Other eye disorders*	Common	7.3	0
Visual impairment*		1.3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease*	Common	2.6	2.6
Gastrointestinal disorders			
Stomatitis*	Very common	43	4.0
Constipation		40	0
Nausea		36	0.7
Vomiting		21	3.3
Diarrhoea		21	3.3
Haemorrhoids		12	1.3
Abdominal pain*		11	0.7
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	33	4.0
Aspartate aminotransferase increased		31	0.7
Blood alkaline phosphatase increased		13	0.7
Skin and subcutaneous tissue disorders			
Rash*	Very common	90	19
Nail toxicity*		62	6.6
Dry skin*		17	0
Pruritus	Common	6.6	0
Musculoskeletal and connective tissue disorders			
Myalgia	Common	5.3	1.3
General disorders and administration site conditions			
Oedema*	Very common	40	1.3
Fatigue*		34	6.0
Pyrexia		16	0
Injury, poisoning and procedural complications			
Infusion related reaction	Very common	42	1.3

2.5.1.5. Treatment related adverse events

Overall, 100% (151/151) of the patients in the ACP arm and 94.2% (146/155) of the patients in the CP arm had TEAEs considered related to at least one of the study treatments by the investigator.

The most commonly reported TEAEs considered to be related to amivantamab treatment were rash, dermatitis acneiform, and paronychia, which are associated with the on-target activity against the EGFR pathway, and hypoalbuminemia and peripheral oedema, which are associated with on-target activity against the MET pathway, as well as IRRs, which are also known to be associated with amivantamab.

Treatment related TEAEs grade ≥3 were reported for 66.2% of the patients in the ACP arm vs. 36.8% in the CP arm. These TEAEs were in line with the established ADRs of the individual treatment components.

2.5.1.6. Adverse events by severity

Table 38: Number of subjects with TEAEs toxicity grad ≥3 with frequency ≥5% in any treatment group by system organ class and preferred term, safety analysis set

	CP	ACP
Analysis set: Safety	155	151
Subjects with 1 or more AEstoxicity grade 3 or greater	83 (53.5%)	114 (75.5%)
System organ class Preferred term		
Blood and lymphatic system disorders	52 (33.5%)	58 (38.4%)
Neutropenia	35 (22.6%)	50 (33.1%)
Leukopenia	5 (3.2%)	17 (11.3%)
Anaemia	19 (12.3%)	16 (10.6%)
Thrombocytopenia	16 (10.3%)	15 (9.9%)
Infections and infestations	11 (7.1%)	31 (20.5%)
Paronychia	0	10 (6.6%)
Skin and subcutaneous tissue disorders	0	28 (18.5%)
Rash	0	17 (11.3%)
Metabolism and nutrition disorders	7 (4.5%)	23 (15.2%)
Hypokalaemia	2 (1.3%)	13 (8.6%)
General disorders and administration site conditions	9 (5.8%)	14 (9.3%)
Asthenia	4 (2.6%)	8 (5.3%)

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 Medical Dictionary for Regulatory Activities Version 25.0.
[tsfae16p5.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae16p5.sas] 22JUN2023, 11:55

Grade 3 TEAEs were reported for 85/114 (56.3%) of the patients in the ACP arm compared to 65/83 (41.9%) in the CP arm. Grade 4 TEAEs were reported for 22/114 (14.6%) of the patients in the ACP arm compared to 14/83 (9.0%) in the CP arm and grade 5 TEAEs were reported for 7/114 (4.6%) vs. 4/83 (2.6%), respectively.

Of the TEAEs grade ≥3 reported in at least 5% of the patients, the vast majority were grade 3. The TEAEs with the highest reported frequencies of grade 4 were neutropenia (9.9% in the ACP arm vs. 3.9% in the CP arm, respectively), thrombocytopenia (4.6% vs. 5.8%, respectively), and hypokalaemia (2.0% vs. 0.6%, respectively).

There were no reports of grade ≥3 treatment related TEAEs in ≥5% of the patients regarding the new amivantamab ADRs pyrexia and haemorrhoids.

2.5.1.7. Adverse events leading to dose modification and dose interruption

2.5.1.7.1. Dose reduction due to adverse events

Table 39: Number of subjects with TEAEs leading to dose reduction of any study treatment with frequency of ≥5% in any treatment group by system organ class and preferred term, safety analysis set

	CP			ACP			
	Reduction of Any	Reduction of Carboplatin	Reduction of Pemetrexed	Reduction of Any	Reduction of Amivantamab	Reduction of Carboplatin	Reduction of Pemetrexed
Analysis set: Safety	155			151			
Subjects with 1 or more AEs leading to dose reduction	35 (22.6%)	18 (11.6%)	33 (21.3%)	73 (48.3%)	54 (35.8%)	30 (19.9%)	41 (27.2%)
System organ class Preferred term							
Skin and subcutaneous tissue disorders	0	0	0	25 (16.6%)	25 (16.6%)	0	2 (1.3%)
Rash	0	0	0	14 (9.3%)	14 (9.3%)	0	1 (0.7%)
Blood and lymphatic system disorders	24 (15.5%)	13 (8.4%)	22 (14.2%)	22 (14.6%)	1 (0.7%)	19 (12.6%)	21 (13.9%)
Neutropenia	8 (5.2%)	4 (2.6%)	8 (5.2%)	14 (9.3%)	1 (0.7%)	10 (6.6%)	13 (8.6%)
Thrombocytopenia	13 (8.4%)	10 (6.5%)	12 (7.7%)	10 (6.6%)	0	10 (6.6%)	10 (6.6%)
Infections and infestations	4 (2.6%)	1 (0.6%)	4 (2.6%)	20 (13.2%)	20 (13.2%)	2 (1.3%)	2 (1.3%)
Paronychia	0	0	0	12 (7.9%)	12 (7.9%)	0	0

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

[tsfae09p5.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae09p5.sas] 13JUL2023, 22:36

2.5.1.7.2. Dose interruption due to adverse events

Table 40: Number of subjects with TEAEs leading to drug interruption of any study treatment with frequency of ≥5% in any treatment group by system organ class and preferred term, safety analysis set

	CP			ACP			
	Interruption of Any	Interruption of Carboplatin	Interruption of Pemetrexed	Interruption of Any	Interruption of Amivantamab	Interruption of Carboplatin	Interruption of Pemetrexed
Analysis set: Safety	155			151			
Subjects with 1 or more AEs leading to drug interruption	56 (36.1%)	29 (18.7%)	56 (36.1%)	104 (68.9%)	97 (64.2%)	38 (25.2%)	86 (57.0%)
System organ class Preferred term							
Infections and infestations	21 (13.5%)	5 (3.2%)	21 (13.5%)	40 (26.5%)	38 (25.2%)	7 (4.6%)	30 (19.9%)
Paronychia	0	0	0	13 (8.6%)	13 (8.6%)	1 (0.7%)	5 (3.3%)
COVID-19	12 (7.7%)	2 (1.3%)	12 (7.7%)	12 (7.9%)	12 (7.9%)	1 (0.7%)	10 (6.6%)
Skin and subcutaneous tissue disorders	1 (0.6%)	0	1 (0.6%)	36 (23.8%)	34 (22.5%)	7 (4.6%)	22 (14.6%)
Rash	0	0	0	18 (11.9%)	17 (11.3%)	5 (3.3%)	11 (7.3%)
Dermatitis acneiform	0	0	0	8 (5.3%)	7 (4.6%)	1 (0.7%)	5 (3.3%)
Blood and lymphatic system disorders	23 (14.8%)	18 (11.6%)	23 (14.8%)	35 (23.2%)	28 (18.5%)	17 (11.3%)	27 (17.9%)
Neutropenia	11 (7.1%)	8 (5.2%)	11 (7.1%)	25 (16.6%)	20 (13.2%)	16 (10.6%)	18 (11.9%)
Thrombocytopenia	8 (5.2%)	4 (2.6%)	8 (5.2%)	9 (6.0%)	8 (5.3%)	1 (0.7%)	4 (2.6%)
Anaemia	11 (7.1%)	7 (4.5%)	11 (7.1%)	8 (5.3%)	4 (2.6%)	2 (1.3%)	8 (5.3%)
Metabolism and nutrition disorders	3 (1.9%)	0	3 (1.9%)	17 (11.3%)	13 (8.6%)	4 (2.6%)	13 (8.6%)
Hypokalaemia	0	0	0	10 (6.6%)	8 (5.3%)	3 (2.0%)	6 (4.0%)

Key: AE = adverse event
Note: The table excludes infusion related reactions.
Note: Subjects are counted only once for any given event within each study treatment, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

[tsfae10p5.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae10p5.sas] 13JUL2023, 22:36

2.5.1.8. Adverse events of special interest

Adverse events of special interest (AESIs) were prospectively identified based upon the identified safety profile of amivantamab, for the purposes of additional safety data collection and/or analysis.

There were no new AESIs identified during the study, by either the study team's ongoing review of cumulative safety data, or the IDMC's periodic review of unblinded safety data. Predefined AESIs per protocol were rash (grouped term), IRR, and pneumonitis/ILD (grouped term).

Table 41: Number of subjects with TEAEs of interest by special interest category and preferred term, safety analysis set

	CP	ACP
Analysis set: Safety	155	151
Subjects with 1 or more AEs of Interest	30 (19.4%)	139 (92.1%)
Special interest category		
Preferred term		
Rash	28 (18.1%)	135 (89.4%)
Rash	12 (7.7%)	81 (53.6%)
Dermatitis acneiform	5 (3.2%)	47 (31.1%)
Dermatitis	3 (1.9%)	6 (4.0%)
Rash pustular	0	6 (4.0%)
Acne	0	5 (3.3%)
Folliculitis	1 (0.6%)	5 (3.3%)
Rash maculo-papular	2 (1.3%)	4 (2.6%)
Pustule	0	2 (1.3%)
Rash papular	1 (0.6%)	2 (1.3%)
Rash pruritic	0	2 (1.3%)
Skin lesion	1 (0.6%)	2 (1.3%)
Erythema	8 (5.2%)	1 (0.7%)
Rash macular	0	1 (0.7%)
Infusion Related Reaction	2 (1.3%)	63 (41.7%)
Infusion related reaction	2 (1.3%)	63 (41.7%)
Pneumonitis/ILD	0	4 (2.6%)
Pneumonitis	0	4 (2.6%)

Key: AE = adverse event, ILD = interstitial lung disease
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.

[tsfae03.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae03.sas] 22JUN2023, 11:55

Table 42: Time to onset of TEAEs of special interest by special interest category, safety analysis set

	CP	ACP
Analysis set: Safety	155	151
Infusion Related Reaction		
Subjects with any infusion related reactions	2 (1.3%)	63 (41.7%)
Time to first onset (hours)		
Median	5041.05	0.98
Range	(5041.1; 5041.1)	(0.1; 8066.5)
Rash		
Subjects with any rashes	28 (18.1%)	135 (89.4%)
Time to first onset (days)		
Median	37.50	10.00
Range	(1.0; 341.0)	(1.0; 310.0)
Pneumonitis/ILD		
Subjects with any pneumonitis/ILDs	0	4 (2.6%)
Time to first onset (days)		
Median	-	128.00
Range	-	(13.0; 188.0)

Key: ILD = interstitial lung disease
Note: Subjects may be counted multiple times per category. Mean, SD, median and range is calculated only for subjects with corresponding adverse events.

[tsfae03tt.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae03tt.sas] 22JUN2023, 17:04

IRRs generally occurred rapidly after the first treatment administration in the ACP arm (median 0.98 hours), but the range was wide (0.1-8066.5 hours). Only two IRRs were reported in the CP arm. Upon request from the CHMP, the Applicant has included information about the potential late time to onset of IRRs in section 4.8 of the SmPC.

All four of the pneumonitis events reported in the ACP arm were grade 3. The median time to onset was 128 days, with a very wide range (13.0-188.0 days). No pneumonitis events were reported in the CP arm.

Serious adverse event/deaths/other significant events

2.5.1.9. Serious adverse events

Table 43: Number of subjects with SAEs by system organ class and preferred term, safety analysis set

	CP	ACP
Analysis set: Safety	155	151
Subjects with 1 or more SAEs	48 (31.0%)	56 (37.1%)
System organ class Preferred term		
Infections and infestations	10 (6.5%)	18 (11.9%)
Pneumonia	4 (2.6%)	6 (4.0%)
COVID-19	1 (0.6%)	3 (2.0%)
Cellulitis	1 (0.6%)	2 (1.3%)
Rash pustular	0	2 (1.3%)
Skin infection	0	2 (1.3%)
COVID-19 pneumonia	0	1 (0.7%)
Infection	0	1 (0.7%)
Pneumonia viral	0	1 (0.7%)
Postoperative wound infection	1 (0.6%)	1 (0.7%)
Sepsis	1 (0.6%)	1 (0.7%)
Appendicitis	1 (0.6%)	0
Enterocolitis infectious	1 (0.6%)	0
Gastrointestinal disorders	4 (2.6%)	10 (6.6%)
Vomiting	1 (0.6%)	3 (2.0%)
Diarrhoea	1 (0.6%)	2 (1.3%)
Abdominal pain	0	1 (0.7%)
Cheilitis	0	1 (0.7%)
Duodenitis	0	1 (0.7%)
Enterocolitis	0	1 (0.7%)
Lower gastrointestinal haemorrhage	0	1 (0.7%)
Ascites	1 (0.6%)	0
Gastrointestinal haemorrhage	1 (0.6%)	0
Respiratory, thoracic and mediastinal disorders	14 (9.0%)	8 (5.3%)
Pneumonitis	0	4 (2.6%)
Pulmonary embolism	4 (2.6%)	4 (2.6%)
Dyspnoea	5 (3.2%)	1 (0.7%)
Haemoptysis	1 (0.6%)	1 (0.7%)
Pleural effusion	5 (3.2%)	1 (0.7%)
Hypoxia	1 (0.6%)	0
Metabolism and nutrition disorders	5 (3.2%)	6 (4.0%)
Hypokalaemia	1 (0.6%)	3 (2.0%)
Decreased appetite	0	1 (0.7%)
Dehydration	0	1 (0.7%)
Hypomagnesaemia	0	1 (0.7%)
Hyponatraemia	1 (0.6%)	1 (0.7%)
Hypophagia	1 (0.6%)	1 (0.7%)
Hyperglycaemia	1 (0.6%)	0
Malnutrition	1 (0.6%)	0
Blood and lymphatic system disorders	11 (7.1%)	5 (3.3%)
Thrombocytopenia	5 (3.2%)	3 (2.0%)
Neutropenia	0	2 (1.3%)
Anaemia	6 (3.9%)	1 (0.7%)
Febrile neutropenia	3 (1.9%)	1 (0.7%)
Leukopenia	0	1 (0.7%)
Myelosuppression	1 (0.6%)	0
Skin and subcutaneous tissue disorders	0	5 (3.3%)
Dermatitis acneiform	0	2 (1.3%)
Rash	0	2 (1.3%)
Rash maculo-papular	0	1 (0.7%)
Nervous system disorders	5 (3.2%)	4 (2.6%)
Cerebrovascular accident	0	1 (0.7%)
Encephalopathy	0	1 (0.7%)
Myoclonic epilepsy	0	1 (0.7%)
Transient ischaemic attack	0	1 (0.7%)
Depressed level of consciousness	1 (0.6%)	0
Dysarthria	1 (0.6%)	0
Headache	1 (0.6%)	0
Lacunar infarction	1 (0.6%)	0
Syncope	1 (0.6%)	0
Vertebrobasilar insufficiency	1 (0.6%)	0
General disorders and administration site conditions	6 (3.9%)	3 (2.0%)
Asthenia	1 (0.6%)	2 (1.3%)
Death	1 (0.6%)	1 (0.7%)
Fatigue	1 (0.6%)	0
General physical health deterioration	1 (0.6%)	0
Influenza like illness	1 (0.6%)	0
Pain	1 (0.6%)	0

	CP	ACP
Investigations	2 (1.3%)	3 (2.0%)
Alanine aminotransferase increased	1 (0.6%)	1 (0.7%)
Blood creatinine increased	1 (0.6%)	1 (0.7%)
C-reactive protein increased	0	1 (0.7%)
Aspartate aminotransferase increased	1 (0.6%)	0
Injury, poisoning and procedural complications	2 (1.3%)	2 (1.3%)
Infusion related reaction	0	1 (0.7%)
Lumbar vertebral fracture	0	1 (0.7%)
Femur fracture	1 (0.6%)	0
Incisional hernia	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	4 (2.6%)	2 (1.3%)
Back pain	0	1 (0.7%)
Myalgia	0	1 (0.7%)
Arthralgia	1 (0.6%)	0
Bone pain	1 (0.6%)	0
Pain in extremity	1 (0.6%)	0
Pathological fracture	1 (0.6%)	0
Reproductive system and breast disorders	0	2 (1.3%)
Endometrial thickening	0	1 (0.7%)
Ovarian mass	0	1 (0.7%)
Cardiac disorders	2 (1.3%)	1 (0.7%)
Cardio-respiratory arrest	0	1 (0.7%)
Acute myocardial infarction	1 (0.6%)	0
Pericardial effusion	1 (0.6%)	0
Hepatobiliary disorders	1 (0.6%)	1 (0.7%)
Biliary obstruction	0	1 (0.7%)
Cholecystitis acute	0	1 (0.7%)
Jaundice cholestatic	1 (0.6%)	0
Immune system disorders	0	1 (0.7%)
Contrast media reaction	0	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6%)	1 (0.7%)
Prostate cancer	0	1 (0.7%)
Cancer pain	1 (0.6%)	0
Renal and urinary disorders	0	1 (0.7%)
Acute kidney injury	0	1 (0.7%)
Ear and labyrinth disorders	1 (0.6%)	0
Hypoacusis	1 (0.6%)	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.

[tsfae05.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae05.sas] 16JUN2023, 17:55

Among the most frequently reported SAEs (reported in ≥2% of participant in any of the arms) were pneumonia and pneumonitis (4.0% and 2.6% in the ACP arm vs. 2.6% and 0% in the CP arm), COVID-19 (2.0% in the ACP arm vs. 0.6% in the CP arm), pulmonary embolism (2.6% in both treatment arms), dyspnoea and pleural effusion (0.7% for both in the ACP arm vs. 3.2% for both in the CP arm), hypokalaemia (2.0% in the ACP arm vs. 0.6% in the CP arm), thrombocytopenia and anaemia (2.0% and 0.7% in the ACP arm vs. 3.2% and 3.9% in the CP arm). No individual SAE was reported in >5% of the patients in any treatment arm.

Haematological SAEs, which correlate to the known chemotherapy safety profile, occurred at low and generally comparable frequencies in both treatment arms. Amivantamab related SAEs dermatitis acneiform, rash, and pneumonitis were only reported in the ACP arm.

2.5.1.10. Deaths

Per protocol, all deaths within 30 days of the last dose were required to have an associated AE reported, even if due to progressive disease.

The table below lists the reasons for death as recorded in the AE CRF page within 30 days of the last dose or until the start of subsequent anticancer therapy (if earlier).

Table 44: Summary of death and cause of death, full analysis set

	CP	ACP	Total
Analysis set: Full	155	153	308
Deaths during study[a]	42 (27.1%)	28 (18.3%)	70 (22.7%)
Progressive disease	30 (19.4%)	20 (13.1%)	50 (16.2%)
Adverse event	9 (5.8%)	4 (2.6%)	13 (4.2%)
Other	3 (1.9%)	2 (1.3%)	5 (1.6%)
COVID-19	0	2 (1.3%)	2 (0.6%)
Deaths within 30 days of last dose[a,b]	7 (4.5%)	7 (4.6%)	14 (4.5%)
Adverse event	4 (2.6%)	3 (2.0%)	7 (2.3%)
Progressive disease	2 (1.3%)	1 (0.7%)	3 (1.0%)
COVID-19	0	2 (1.3%)	2 (0.6%)
Other	1 (0.6%)	1 (0.7%)	2 (0.6%)
Deaths within 30 days of last dose (main study)[b,c]	4 (2.6%)	7 (4.6%)	11 (3.6%)
Adverse event	2 (1.3%)	3 (2.0%)	5 (1.6%)
COVID-19	0	2 (1.3%)	2 (0.6%)
Other	1 (0.6%)	1 (0.7%)	2 (0.6%)
Progressive disease	1 (0.6%)	1 (0.7%)	2 (0.6%)

[a] Subjects who died during the crossover phase are included.
[b] Subjects who died within 30 days will be counted in deaths during study as well.
[c] Subjects who died during the crossover phase are excluded.
NOTE: Deaths due to COVID-19 are not included in the other causes of death (ie, subjects are only counted in one row).
[tsfdth01a.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfdth01a.sas] 24JUL2023, 12:42

The TEAEs leading to death are listed in the table below.

Table 45: Number of subjects with TEAEs leading to death by system organ class and preferred term, safety analysis set

	CP	ACP
Analysis set: Safety	155	151
Subjects with 1 or more AEs leading to death	4 (2.6%)	7 (4.6%)
System organ class Preferred term		
Infections and infestations	1 (0.6%)	4 (2.6%)
COVID-19	0	1 (0.7%)
COVID-19 pneumonia	0	1 (0.7%)
Pneumonia	0	1 (0.7%)
Sepsis	1 (0.6%)	1 (0.7%)
Cardiac disorders	1 (0.6%)	1 (0.7%)
Cardio-respiratory arrest	0	1 (0.7%)
Acute myocardial infarction	1 (0.6%)	0
General disorders and administration site conditions	1 (0.6%)	1 (0.7%)
Death	1 (0.6%)	1 (0.7%)
Nervous system disorders	0	1 (0.7%)
Cerebrovascular accident	0	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	1 (0.6%)	0
Dyspnoea	1 (0.6%)	0

Key: AE = adverse event
Note: Per protocol, all deaths within 30 days of last dose were required to have an associated AE reported, even if due to progressive disease. 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.
[tsfae12.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae12.sas] 22JUN2023, 11:55

Three events of death in the ACP arm were assessed as being related to study treatment (one event [cardiorespiratory arrest] related to amivantamab and two events [COVID-19 pneumonia and sepsis] related to both carboplatin and pemetrexed). Additionally, two events in the CP arm were assessed as being related to study treatment (one event [death of unknown reason] related to carboplatin and pemetrexed and one event [sepsis] related to pemetrexed).

On a retrospective review of the baseline scan by the investigator, it was observed that the participant in the ACP arm with death deemed related to amivantamab by the investigator (cardiorespiratory arrest) had tumour infiltration of the heart when they presented with vomiting, abdominal pain, and fever on Day 24 of the study. During hospitalisation, the participant received multiple antiemetics,

including Haldol®, and had a cardiorespiratory arrest due to ventricular fibrillation on Day 25, requiring ICU admission. The participant subsequently passed away on Day 26, after the institution of comfort care measures. The investigator deemed the event related to the tumour infiltration of the heart in the setting of possible disease progression triggering the ventricular fibrillation complicated with QTcF prolongation due to antiemetics and mild hypokalaemia, and less likely due to amivantamab.

Six out of the seven TEAEs in the ACP arm leading to death occurred within the first 90 days of Cycle 1 Day 1 compared with one death in the CP arm. Within the ACP arm, these six deaths included one event each of cardiorespiratory arrest, sepsis, CVA, death, COVID-19, and COVID-19 pneumonia. Each of these deaths was a unique event in participants with comorbidities with no clear pattern of aetiology identified. As described above, the participant with cardiorespiratory arrest had tumour infiltration of the heart and received multiple antiemetics. The participant with sepsis had a 3-day history of diarrhoea, with consequent complications of severe dehydration, and passed away on Day 4 of ICU admission with septic shock. The participant with CVA had cardiovascular risk factors (smoking [66 packs/year] and substance use [heroin and cocaine]), presented with stroke, and passed away on Day 13 of hospitalisation after receiving comfort care. The event of 'Death' was reported in a participant with a medical history of atrial fibrillation and hydropneumothorax while the participant was being transported to hospital via ambulance in the setting of disease progression. There were two deaths associated with COVID-19 with one participant dying after a prolonged hospitalisation of 26 days.

There were no reports of deaths related to the established amivantamab ADR IRR.

Laboratory findings

2.5.1.11. Clinical chemistry laboratory tests

Table 46: Most common haematologic laboratory test abnormalities (grade 3 or 4) during treatment

Laboratory Test	CP	ACP		
	PAPILLON (n=155)	PAPILLON (n=151)	CHRYSALIS	COMBINED
Decreased Neutrophil Count				
Grade 3	27 (17.5%)	39 (26.0%)		
Grade 4	8 (5.2%)	15 (10.0%)		
Decreased White Blood Cell				
Grade 3	15 (9.7%)	21 (14.0%)		
Grade 4	1 (0.6%)	5 (3.3%)		
Anemia				
Grade 3	20 (13.0%)	17 (11.4%)		
Grade 4	0	0		
Decreased Platelet Count				
Grade 3	11 (7.1%)	7 (4.7%)		
Grade 4	8 (5.2%)	8 (5.3%)		

Source: Mod5.3.5.3/ISS/TSFLAB06
Hematologic Laboratory Test Parameters with a Grade 3 occurrence >5% or Grade 4 occurrence >1% in the ACP or CP arm of PAPILLON or Combined ACP in Table 23.

A somewhat higher incidence of grade 3 and 4 `white blood cell decreased´ and `neutrophil count decreased´ was observed in the ACP compared to the CP arm, which was reflected in a higher incidence of AEs of neutropenia (including grade ≥3 AEs) in the ACP arm. Analysis of the mean neutrophil count over time showed a transient decrease at Cycle 1 Day 8 in both treatment arms, which was slightly more pronounced in the ACP arm. The neutrophil counts in both arms increased through Cycle 2 Day 1, with another transient but less marked decrease for both arms at the 3

subsequent measurements. The neutrophil counts stabilised in both arms from Cycle 6 Day 1 onwards. There was no consistent worsening of neutrophil count decreased in the ACP arm compared to the CP arm. Most haematology laboratory abnormalities in both treatment arms were grade 1-2.

Table 47: Most common chemistry laboratory test abnormalities (grade 3 or 4) during treatment

Laboratory Test	CP	ACP		
	PAPILLON (n=155)	PAPILLON (n=151)	CHRYSALIS	COMBINED
Hypokalemia				
Grade 3	1 (0.7%)	12 (8.2%)		
Grade 4	1 (0.7%)	4 (2.7%)		
Hypoalbuminemia				
Grade 3	1 (0.7%)	11 (7.4%)		
Grade 4	0	0		
Hyponatremia				
Grade 3	5 (3.3%)	11 (7.4%)		
Grade 4	1 (0.7%)	0		
Hypomagnesemia				
Grade 3	1 (0.7%)	1 (0.7%)		
Grade 4	0	2 (1.4%)		

Source: Mod5.3.5.3/ISS/TSFLAB06

Hematologic Laboratory Test Parameters with a Grade 3 occurrence >5% or Grade 4 occurrence >1% in the ACP or CP arm of PAPILLON or Combined ACP in Table 24.

Increased AST and ALT have been previously identified as ADRs with amivantamab monotherapy and are also known to occur with carboplatin and pemetrexed.

Table 48: Liver function test elevations (any grade) during treatment

Laboratory Test	CP	ACP		
	PAPILLON (n=155)	PAPILLON (n=151)	CHRYSALIS	COMBINED
Increased ALT				
Grade 1	59 (38.6%)	75 (50.0%)		
Grade 2	24 (15.7%)	13 (8.7%)		
Grade 3	2 (1.3%)	6 (4.0%)		
Grade 4	0	0		
Increased AST				
Grade 1	93 (60.8%)	86 (57.3%)		
Grade 2	2 (1.3%)	7 (4.7%)		
Grade 3	2 (1.3%)	1 (0.7%)		
Grade 4	0	0		
Increased Bilirubin				
Grade 1	18 (11.8%)	22 (14.7%)		
Grade 2	5 (3.3%)	4 (2.7%)		
Grade 3	0	1 (0.7%)		
Grade 4	0	0		

Source: Mod5.3.5.3/ISS/TSFLAB06

Participants in each treatment arm 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 a potential Hy's Law.

2.5.1.12. Electrocardiograms

Single 12-lead ECGs were collected at Screening, while 12-lead ECGs were collected in triplicate with approximately two minutes apart pre dose on Cycle 1 Day 1 and post dose on Cycle 3 Day 1. Data were available for 128/151 participants (84.8%) in the ACP arm and 144/155 participants (92.8%) in the CP arm.

Mean changes from baseline in a majority of cases were small and not considered clinically meaningful by the investigator. One participant in the ACP arm had an aggregate QTcF value >500 msec, while four participants (three in the ACP arm and one in the CP arm) had a change from baseline in the QTcF interval that exceeded 60 msec. All had either multiple concomitant medications for hypertension and diabetes or had received concomitant medications known to cause QTcF prolongation. The study treatment continued uninterrupted in all cases.

Safety in special populations

The safety data in special populations summarised below are derived from the PAPILLON study. Overall, data on the subgroups in the CHRYSALIS ACP cohort were too small to allow for meaningful comparison of TEAEs and are therefore not discussed in further detail.

2.5.1.13. Age

In the PAPILLON study, 61% (n=188) of the patients were <65 years and 39% (n=118) were ≥65 years. Nine percent of the patients were ≥75 years. The distribution between the treatment arms was comparable (64% <65 years and 36% ≥65 years in the ACP arm vs. 59% <65 years and 41% ≥65 years in the CP arm, respectively).

The incidence of TEAEs was comparable between treatment arms and age groups (≥95%).

In the ACP arm, a higher incidence (≥10% difference) of TEAEs leading to treatment discontinuation was observed in age group ≥65 years compared to age group <65 years, mainly driven by discontinuations of carboplatin and pemetrexed (30.9% for ≥65 years vs. 19.8% for <65 years, respectively).

In the CP arm, a higher incidence (≥10% difference) was observed in age group ≥65 years compared to age group <65 years for grade ≥3 TEAEs (61.9% for age ≥65 years vs. 47.8% for age <65 years), SAEs (39.7% vs. 25.0%), and TEAEs leading to interruption (50.8% vs. 27.2%) or reduction (27.0% vs. 13.0%) of carboplatin or pemetrexed.

In both treatment arms, the incidence of TEAEs were generally higher in age group ≥65 years compared to <65 years. The differences in TEAE frequencies in both treatment arms were mainly related to carboplatin and pemetrexed.

Covid-19 related TEAEs were less common in the age group ≥65 years compared to age group <65 years in both treatment arms (ACP: 20.0% vs. 34.4%, CP: 14.3% vs. 17.4%).

2.5.1.14. Sex

In the PAPILLON study, 42% (n=129) of the participants were male and 58% (n=177) were female. The distribution was comparable between the treatment arms (44% male, 56% female in the ACP arm vs. 40% male and 60% female in the CP arm, respectively).

A higher incidence (≥10% difference) of grade ≥3 TEAEs was observed in the female compared to the male population in the CP arm (58.1% vs. 46.8%, respectively), whereas no such difference was noted in the ACP arm.

2.5.1.15. Race

Of all participants in the PAPILLON study, 60% (n=185) were Asian and 37% (n=114) were non-Asian. Race was unknown or not reported for seven patients. The distribution was comparable between the treatment arms (65% Asian, 35% Non-Asian in the ACP arm vs. 59% Asian and 41% non-Asian in the CP arm, respectively).

In the ACP arm, a higher incidence (≥10% difference) of Covid-19 related TEAEs was observed for the Asian vs. the non-Asian population (35.4% vs. 19.2%, respectively). Covid-19 related TEAEs were reported at similar frequencies across Asian and non-Asian patients in the CP arm (15.7% vs. 16.1%, respectively).

In both treatment arms, a higher incidence (≥10% difference) of TEAEs leading to treatment discontinuation and treatment reduction was observed for the non-Asian vs. Asian population (ACP: 30.8% vs. 19.8% discontinuation, 55.8% vs. 44.8% reduction, CP: 14.5% vs. 5.6% discontinuation, 29.0% vs. 18.0% reduction, respectively). The TEAEs were mainly related to carboplatin and pemetrexed.

2.5.1.16. Hepatic impairment

There were no participants in any of the treatment arms in the PAPILLON study with moderate (1.5 x ULN < total bilirubin ≤ 3 x ULN), or severe (total bilirubin > 3 x ULN) hepatic impairment. In the PAPILLON study, 91% (n=278) hade normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN) and 9% (n=28) mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5 x ULN), at baseline.

The subgroups were too small to allow for a meaningful comparison of TEAEs. Based on the population pharmacokinetic analyses there were no statistically significant or clinically relevant effects on the exposure of amivantamab due to mild hepatic impairment. 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.

2.5.1.17. Renal impairment

There were no participants with severe renal impairment (eGFR <30 mL/min/1.73m2) in any treatment arm in the PAPILLON study. In total, 69% (n=212) had normal renal function (eGFR ≥90 mL/min/1.73m2), 31% (n=87) had mild renal impairment (eGFR 60 to <90 mL/min/1.73m2), and 2% (n=7) hade moderate renal impairment (eGFR 30 to <60 mL/min/1.73m2) at baseline. The distribution between the ACP and CP arms was similar (76% normal, 22.5% mild impairment in the ACP arm vs. 63% normal and 34% mild impairment in the CP arm, respectively).

There was a higher incidence (>10% difference) of TEAEs leading to treatment discontinuation in the subgroup with mild renal impairment vs. normal renal function in the ACP arm (41.2% vs. 19.1%, respectively). No differences of this magnitude were noted in the CP arm.

2.5.1.18. ECOG performance status

In the PAPILLON study, 36% (n=109) patients had ECOG performance status 0 and 64% (n=197) had ECOG performance status 1 at baseline. The distribution was equal between the two treatment arms.

In the ACP arm, a higher incidence (≥10% difference) in the ECOG 1 vs. ECOG 0 subgroup was observed for TEAEs grade ≥3 (79.4% ECOG 1 vs. 68.5% ECOG 0) and SAEs (44.3% in ECOG 1 vs. 24.1% in ECOG 0).

2.5.1.19. Smoking history

In the PAPILLON study, 42% (n=127) had a history of smoking and 58% (n=179) did not. The distribution was equal between the two treatment arms. There were no consistent trends in TEAEs observed within or between the treatment arms.

2.5.1.20. Weight

In the PAPILLON study, 84% (n=258) of the patients were weighing <80 kg and 16% (n=49) ≥80 kg. The distribution was similar between the treatment arms. The subgroups were too small to allow for meaningful comparison of TEAEs.

2.5.1.21. Brain metastasis

In total 23% (n=70) of the patients in the PAPILLON study had a history of brain metastasis and 77% (n=236) did not. The distribution was equal between the treatment arms.

In the ACP arm, there were no incidence differences ≥10% for any of the reported parameters between the subgroup with a history of brain metastasis vs. without history of brain metastasis.

In the CP arm, the subgroup without a history of brain metastasis vs. with history of brain metastasis had a ≥10% higher incidence of grade ≥3 TEAEs (56.3% without vs. 44.4% with history of brain metastasis) and SAEs (34.5% vs. 19.4%).

Crossover ph ase

Participants in the CP arm of PAPILLON were permitted to crossover to amivantamab monotherapy following disease progression and confirmation by BICR. This phase of the study was not randomised or controlled. The safety analyses were exploratory and aimed to further characterise the safety of amivantamab in a Q3W dosing schedule.

At DCO, a total of 65 participants had entered the crossover phase and had received at least one dose of study treatment (amivantamab monotherapy). At the time of the DCO, 35 participants (53.8%) remained on treatment. The most common reason for discontinuation of study treatment was progressive disease (22/30 participants). The median follow-up in the crossover phase was 9.76 months and the median duration of treatment was 4.93 months (8 treatment cycles).

Table 49: Overall summary of TEAEs. PAPILLON crossover analysis set and CHRYSALIS exon 20ins + prior chemotherapy at RP2D safety population

	Amivantamab Monotherapy		
	PAPILLON (Q3W)	CHRYSALIS (Q2W)	
	Crossover Analysis Set	Exon 20ins + prior chemotherapy at RP2D Safety Population	
Median Follow-up	9.76 months CCO 03 May 2023	14.5 months CCO 30 Mar 2021	6.5 months CCO 08 Jun 2020
Analysis set	65	153	114
Subjects with 1 or more:			
AEs	64 (98.5%)	153 (100.0%)	113 (99.1%)
Related AEs[a]	64 (98.5%)	150 (98.0%)	112 (98.2%)
Grade 3 or greater AEs	24 (36.9%)	64 (41.8%)	40 (35.1%)
Related grade 3 or greater AEs[a]	16 (24.6%)	30 (19.6%)	18 (15.8%)
Maximum toxicity grade			
Grade 1	2 (3.1%)	4 (2.6%)	1 (0.9%)
Grade 2	38 (58.5%)	85 (55.6%)	72 (63.2%)
Grade 3	22 (33.8%)	49 (32.0%)	31 (27.2%)
Grade 4	0	4 (2.6%)	1 (0.9%)
Grade 5	2 (3.1%)	11 (7.2%)	8 (7.0%)
Serious AEs	17 (26.2%)	44 (28.8%)	34 (29.8%)
Related serious AEs[a]	8 (12.3%)	13 (8.5%)	10 (8.8%)
AEs leading to discontinuation of study agent	7 (10.8%)	18 (11.8%)	11 (9.6%)
Related to study agent[a]	4 (6.2%)	8 (5.2%)	5 (4.4%)
AEs leading to drug interruption of study agent[c]	22 (33.8%)	55 (35.9%)	40 (35.1%)
Related to study agent[a,c]	14 (21.5%)	32 (20.9%)	24 (21.1%)
AEs leading to dose reduction of study agent	8 (12.3%)	22 (14.4%)	15 (13.2%)
Related to study agent[a]	8 (12.3%)	22 (14.4%)	15 (13.2%)
AEs leading to death[b]	2 (3.1%)	11 (7.2%)	8 (7.0%)
Related AEs leading to death[a,b]	0	0	0
COVID-19 associated AEs[d]	15 (23.1%)	3 (2.0%)	1 (0.9%)
COVID-19 associated serious AEs[d]	0	0	0
COVID-19 associated non-serious AEs[d]	15 (23.1%)	3 (2.0%)	1 (0.9%)

[a] An AE is assessed by the investigator as related to study treatment.
[b] AEs leading to death are based on AE outcome of Fatal. Per protocol, all deaths within 30 days of last dose were required to have an associated AE reported, even if due to progressive disease.
[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 sources: Mod5.3.5.1/61186372NSC3001/Crossover Phase Results/Tab11 and Mod5.3.5.2/61186372EDI1001-interim/Tab12 and 2LE20/Mod5.3.5.2/61186372EDI1001/Tab24

Crossover participants could not initiate treatment with amivantamab earlier than 21 days, or later than 90 days after their last dose of chemotherapy in the main study, regardless of the time of progression. AEs which occurred after 30 days of last dose of chemotherapy in the main study and before the first dose of amivantamab in the crossover phase were not considered treatment emergent.

Most of the TEAEs were considered related to amivantamab (98.5%). Most of the TEAEs were low grade (61.6%) with grade ≥3 TEAEs reported in 24 participants (36.9%). The most frequently occurring grade ≥3 TEAEs were pneumonia (5 participants [7.7%]), hypoalbuminemia (4 participants [6.2%]), and rash and dermatitis acneiform (3 participants each [4.5%]). The most frequently reported treatment related grade ≥3 TEAEs were rash and dermatitis acneiform, and hypoalbuminemia.

TEAEs were mostly manageable with treatment interruption and dose reduction, with only four participants (6.2%) discontinuing amivantamab treatment due to TEAEs considered related to amivantamab.

Most participants (63 [96.9%]) in the crossover phase had at least one AESI (grouped term rash, IRR, and grouped term pneumonitis/ILD).

Rash was reported in 55 participants (84.6%), with most of the rash events being grade 1 or 2 (9.2% grade 3). The median time to first onset of event of rash following first administration of amivantamab in the crossover phase was 12 days. IRRs were reported in 32 participants (49.2%). All IRR events were grade 1 or 2, with the exception of one participant (1.5%) who experienced a grade 3 IRR. One

participant (1.5%) had an IRR event considered as serious. Dose interruption due to IRR occurred in 27 participants (41.5%). One participant (1.5%) discontinued amivantamab treatment due to IRR and no participant had a dose reduction due to IRR. The median time to first onset of event of IRR following first administration of amivantamab was 1.08 hours. One participant had an initial, late-appearing IRR on Day 274. Pneumonitis/ILD was reported in two participants (3.1%). The median time to first onset of event of pneumonitis/ILD was 43 days.

TEAEs leading to dose reduction of amivantamab was reported for eight participants (12.3%) in the crossover phase, with the most common TEAEs being paronychia (five participants [7.7%]) and rash and dermatitis acneiform (two participants [3.1%] each). A total of 22 participants (33.8%) had TEAEs leading to study treatment interruption, with the most frequently reported TEAEs being Covid-19 infections (six participants [9.2%]) and pneumonia (four participants [6.2%]). Amivantamab discontinuation due to TEAEs was reported for seven participants (10.8%). All TEAEs occurred in single participants and included pleural effusion, performance status decreased, grade 2 pneumonitis, grade 1 ILD, pneumonia, IRR, and dermatitis acneiform.

SAEs were reported in 17 participants (26.2%), of which eight were assessed as related to amivantamab by the treating investigator. The most frequently occurring SAE was pneumonia (four participants [6.2%]), of which only one event was considered related to amivantamab by the treating investigator. Covid-associated TEAEs occurred in 15 participants (23.1%); all events were low grade and not serious.

Fatal TEAEs were observed in two participants (3.1%); both events were assessed as unrelated to amivantamab by the treating investigator.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with amivantamab.

Discontinuation due to adverse events

Table 50: Number of subjects with TEAEs leading to discontinuation of any study treatment with frequency of ≥1% in any treatment group by system organ class and preferred term, safety analysis set

	CP			ACP			
	Discontinued Any	Discontinued Carboplatin	Discontinued Pemetrexed	Discontinued Any	Discontinued Amivantamab	Discontinued Carboplatin	Discontinued Pemetrexed
Analysis set: Safety	155			151			
Subjects with 1 or more AEs leading to discontinuation of any study treatment	16 (10.3%)	3 (1.9%)	13 (8.4%)	36 (23.8%)	17 (11.3%)	13 (8.6%)	28 (18.5%)
System organ class Preferred term							
Infections and infestations	2 (1.3%)	0	2 (1.3%)	8 (5.3%)	6 (4.0%)	5 (3.3%)	6 (4.0%)
Pneumonia	0	0	0	2 (1.3%)	1 (0.7%)	1 (0.7%)	2 (1.3%)
Skin infection	0	0	0	2 (1.3%)	1 (0.7%)	1 (0.7%)	0
Blood and lymphatic system disorders	5 (3.2%)	2 (1.3%)	3 (1.9%)	6 (4.0%)	0	3 (2.0%)	4 (2.6%)
Anaemia	1 (0.6%)	0	1 (0.6%)	3 (2.0%)	0	2 (1.3%)	1 (0.7%)
Neutropenia	2 (1.3%)	1 (0.6%)	1 (0.6%)	3 (2.0%)	0	1 (0.7%)	3 (2.0%)
Thrombocytopenia	3 (1.9%)	2 (1.3%)	1 (0.6%)	1 (0.7%)	0	1 (0.7%)	1 (0.7%)
Skin and subcutaneous tissue disorders	1 (0.6%)	0	1 (0.6%)	6 (4.0%)	4 (2.6%)	0	3 (2.0%)
Dermatitis acneiform	0	0	0	2 (1.3%)	2 (1.3%)	0	0
Rash	1 (0.6%)	0	1 (0.6%)	2 (1.3%)	1 (0.7%)	0	2 (1.3%)
Skin ulcer	0	0	0	2 (1.3%)	1 (0.7%)	0	1 (0.7%)
General disorders and administration site conditions	2 (1.3%)	0	2 (1.3%)	4 (2.6%)	0	1 (0.7%)	3 (2.0%)
Asthenia	0	0	0	2 (1.3%)	0	0	2 (1.3%)
Fatigue	0	0	0	2 (1.3%)	0	1 (0.7%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	1 (0.6%)	0	1 (0.6%)	4 (2.6%)	4 (2.6%)	1 (0.7%)	4 (2.6%)
Pneumonitis	0	0	0	4 (2.6%)	4 (2.6%)	1 (0.7%)	4 (2.6%)
Injury, poisoning and procedural complications	0	0	0	3 (2.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Infusion related reaction	0	0	0	3 (2.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)
Metabolism and nutrition disorders	1 (0.6%)	0	1 (0.6%)	3 (2.0%)	0	1 (0.7%)	2 (1.3%)
Decreased appetite	0	0	0	3 (2.0%)	0	1 (0.7%)	2 (1.3%)

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.
Note: 'Discontinued Any' in Amivantamab combination arm includes subjects with any given event that led to the discontinuation of either amivantamab, carboplatin, or pemetrexed.
'Discontinued Any' in chemotherapy combination arm includes subjects with any given event that led to the discontinuation of either carboplatin or pemetrexed.

[tsfae06p1.rtf] [jnj-61186372/nsc3001/dbr_csr1/re_csr1/tsfae06p1.sas] 18JUL2023, 17:20

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 approval in 2021. Based on 22,364,767 milligrams distributed worldwide by the Company from launch 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 major safety issues have been identified.

2.5.2. Discussion on clinical safety

The safety assessment is focused on safety data from the PAPILLON study in patients with advanced or metastatic NSCLC with EGFR exon 20ins mutations, with DCO date 03 May 2023. In the PAPILLON study, 151 study participants were exposed to amivantamab + carboplatin and pemetrexed (ACP) treatment and 155 study participants were exposed to carboplatin and pemetrexed (CP) only. Supportive data were also derived from 65 patients initially randomised to the CP arm in the PAPILLON study who crossed over to amivantamab monotherapy upon progression. The size of the dataset is considered acceptable.

Supportive safety data were derived from the CHRYSALIS study in patients with advanced NSCLC without specific driver mutation required who were exposed to ACP (DCO 15 Nov 2022). In the CHRYSALIS study, 20 patients received ACP treatment. n. Due to the limited number of patients, the safety data derived from the CHRYSALIS study generally have to be interpreted with caution and no detailed assessment of safety data pertaining to the ACP treated patients in the CHRYSALIS study has been made.

Overall, the ACP and CP arms in the PAPILLON study were well balanced regarding distribution of age, sex, race, hepatic and renal impairment, and ECOG performance status, although it is noted that the patients in the ACP arm were somewhat younger, had somewhat better renal function and were more of Asian origin compared to in the CP arm (64% <65 years in the ACP arm vs. 59% in the CP arm; 22% mild renal impairment in the ACP arm vs. 34.5% in the CP arm, 65% Asian in the ACP arm vs. 59% in the CP arm, respectively).

The majority of participants in both arms received the intended four cycles of carboplatin, and participants in the ACP arm remained on pemetrexed treatment longer than in the CP arm. The addition of amivantamab to CP doublet, thus, did not affect the cumulative administered dose of either chemotherapeutic agent. Overall, the patient exposure is acceptable and evokes no concern.

Almost all participants in both treatment arms of the PAPILLON study experienced ≥1 TEAE (100% of participants in the ACP arm and 98.1% of participants 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 ACP arm were in line with previously established TEAEs of amivantamab and pertaining to EFGR and MET inhibition. Among the EGFR-associated TEAEs were rash and dermatitis acneiform (53.6% and 31.1% in the ACP arm vs. 7.7% and 3.2% in the CP arm, respectively), stomatitis (25.2% vs. 5.8%), diarrhoea (20.5% vs. 12.9%), and paronychia (56.3% vs. 0%). Also, the MET-associated TEAEs hypoalbuminaemia (41.1% vs. 9.7%) and peripheral oedema (29.8% vs. 10.3%) were more common in the ACP arm.

Grade ≥3 TEAEs were reported in 75.5% of the patients in the ACP arm and in 53.5% of the patients in the CP arm. Apart from TEAEs rash, paronychia, and hypokalaemia, which are all associated with amivantamab treatment, the majority of the grade ≥3 TEAEs were haematological and possibly related to the CP part of the treatment rather than amivantamab. This is supported by the fact that the haematological TEAEs were better balanced between the treatment arms than the other grade ≥3 TEAEs. Febrile neutropenia occurred at low frequencies in both treatment arms (2.6% in the ACP arm vs. 1.9% in the CP arm).

Other reported amivantamab related TEAEs, with existing warnings in the SmPC, were IRRs and pneumonitis. IRR was more common in the ACP arm than the CP arm (41.7% vs. 1.3%, respectively). The vast majority of IRRs were Grade 1-2 (96.8%) and generally occurred rapidly after the first treatment administration in the ACP arm (median 0.98 hours). This information has been reflected in section 4.8 of the SmPC. Pneumonitis was rare and occurred in four (2.6%) patients in the ACP arm compared to 0% in the CP arm. Hence, there does not seem to be any synergistic toxicity when combining amivantamab and pemetrexed, for which pneumonitis is reported as an uncommon but potentially serious ADR. Information on pneumonitis is already reflected in SmPC sections 4.2, 4.4 and 4.8. All pneumonitis events (n=4) were grade 3.

Covid-19 associated infections were more frequently reported in the ACP than in the CP arm (23.8% vs. 13.5%). More than 50% of Covid-19 related AEs in both treatment arms were reported from east Asia, consistent with the spread of the pandemic. Furthermore, twice as many patients were receiving ACP treatment compared to CP treatment in China during the pandemic surge between December

2022 and January 2023. With regards to haematological TEAEs normally associated with chemotherapy, neutropenia (58.9% in the ACP arm vs. 45.2% in the CP arm) and thrombocytopenia (36.4% vs. 29.7% in the ACP and CP arms, respectively) were reported with a somewhat higher incidence in the ACP than the CP arm.

The incidence of VTE TEAEs was higher in the ACP compared to the CP arm (≥1 TEAE in 15.9% patients in the ACP arm vs. 9.0% in the CP arm), but with comparable levels of grade ≥3 VTE TEAEs (3.3% vs. 3.9%) and VTE SAEs (2.6% in both treatment arms). The VTE events were considered treatment related for 7.9% (n=12) and 0.6% (n=1) of the patients in the ACP and CP arms, respectively. When adjusted for treatment exposure (events/100 person-years), the incidence rates were still higher in the ACP arm than the CP arm (18.6 vs. 13.9).

Although there is an increased risk of VTEs in patients with advanced/metastatic cancer and in patients receiving chemotherapy, the adjusted incidence rates of VTEs indicate a higher risk of VTEs in amivantamab treated patients. Hence, VTE should be considered a new ADR for amivantamab. Upon request by the CHMP, the Applicant agreed that VTE is a new ADR associated with amivantamab + chemotherapy treatment and it is now included in section 4.8 of the SmPC.

Pyrexia and haemorrhoids were identified as new amivantamab ADRs regardless of treatment as monotherapy or in combination with chemotherapy. Pyrexia was reported for 15.9% vs. 5.8% of the patients in the ACP and CP arms, respectively. Haemorrhoids were reported for 11.9% vs. 1.3% of the patients in the ACP and CP arms, respectively. Pyrexia and haemorrhoids are included in the SmPC section 4.8 with frequencies very common for amivantamab + chemotherapy.

Overall, approximately twice as many patients in the ACP arm compared to the CP arm had any of the treatment components reduced (48.3% vs. 22.6%, respectively) or interrupted (68.9% vs. 36.1%, respectively) due to TEAEs. The differences were mainly attributed to dose reduction and interruption of amivantamab and known amivantamab TEAEs (rash, dermatitis acneiform, paronychia). Apart from neutropenia and rash, the frequency of most individual TEAEs leading to dose reduction or interruption was generally low (<10%).

Dose reductions due to haematologic TEAEs, which are known to be associated with chemotherapy, were comparable across treatment arms.

Prospectively identified AESIs, based on the established safety profile of amivantamab, included rash (grouped term), IRR, and pneumonitis/ILD (grouped term). As expected, the AESI frequency was significantly higher in the ACP arm than the CP arm, with at least one AESI reported for 92.1% of the patients in the ACP arm compared to 19.4% of the patients in the CP arm. Overall, the frequencies of the reported AESIs were in line with the previously established frequencies reported in the SmPC. Dose discontinuations due to rash, IRR, or pneumonitis were rare.

The median time to onset of rash in the ACP arm was 10 days vs. 37.5 days in the CP arm. Overall, the AESI rash was manageable with supportive care and dose adjustments. Dose discontinuations due to rash were rare (1.3% vs. 0.6% in the ACP vs. CP arm, respectively).

Overall, the AESI rash was manageable with supportive care and dose adjustments. Dose discontinuations due to rash were rare (1.3% vs. 0.6% in the ACP vs. CP arm, respectively). Overall, the AESI of IRR was manageable through protocol defined premedication and supportive care. As noted above, discontinuations due to IRRs were rare (2.0% in the ACP arm, 0% in the CP arm).

The range of time to onset was very wide for all these AESIs, not least for IRR with an upper boundary of 8066.5 hours, i.e., >330 days. It is noted that the premedication with dexamethasone prior to cycle 1 day 1 amivantamab has been increased to 20 mg but withheld at 10 mg prior to cycle 1 day 2

(compared with the current approved version of the SmPC). Given the fact that most IRRs occurred within an hour of cycle 1 day 1 this is endorsed.

The overall incidence of SAEs was somewhat higher in the ACP than the CP arm, with SAEs reported in 56/151 participants (37.1%) in the ACP arm and 48/155 participants (31.0%) in the CP arm. Overall, the frequencies of the reported AESIs are in line with the frequencies reflected in section 4.8 of the SmPC.

At DCO, in total 70 patients had died (28 [18.3%] in the ACP arm and 42 [27.1%] in the CP arm). The main reason for death was progressive disease (13.1% vs. 19.4% in the ACP and CP arms, respectively).

TEAEs leading to death were reported for seven patients (4.6%) in the ACP arm compared to four patients (2.6%) in the CP arm. Apart from the two deaths related to COVID-19, there were no obvious imbalances in TEAEs leading to death between the treatment arms. Of all deaths, 3/7 in the ACP arm and 2/4 in the CP arm were assessed as being related to any of the study drugs, but none were reported to be associated with amivantamab and there were no reports of deaths related to the established amivantamab ADR IRR.

The results of laboratory parameters were comparable between treatment arms. There were no reports of drug induced hepatoxicity fulfilling the criteria for Hy's Law.

QTcF prolongation was reported for 5/272 (1.8%) participants (four in the ACP arm, one in the CP arm). All cases were confounded by comorbidities or concomitant medications known to cause QTcF prolongation. Study treatment continued uninterrupted in all cases.

It is acknowledged that the general incidence of TEAEs was higher in patients $\geq$65 years vs. <65 years and in patients with ECOG performance status 1 vs. 0 in both treatment arms. The differences were generally greater in the ACP than the CP arm, which is expected with an add-on treatment to chemotherapy. The generally higher incidence of TEAEs in the non-Asian vs. Asian study population was mainly related to chemotherapy and not amivantamab. Thus, overall, amivantamab toxicity seems to be manageable with supportive measures and dose adjustments.

Overall, the safety data of amivantamab monotherapy administered Q3W in the PAPILLON crossover phase was consistent with the data of amivantamab monotherapy Q2W in the CHRYSALIS study and with the safety data of amivantamab combination therapy in the PAPILLON ACP arm. The TEAE PTs reported in the crossover phase were in line with established amivantamab ADRs. This also applied for grade $\geq$3 TEAEs (36.9%), SAEs (26.2%), treatment related TEAEs (98.5%), treatment related TEAEs grade $\geq$3 (24.6%), and discontinuation due to TEAEs (10.8%).

In summary, the overall safety profile of ACP treatment was in line with the established safety profile of amivantamab monotherapy and seems tolerable and manageable with dose interruption and dose reductions.

2.5.3. Conclusions on clinical safety

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

Pyrexia and haemorrhoids are considered new amivantamab related ADR. VTE was identified as a new ADR associated with amivantamab + chemotherapy treatment.

Overall, the safety profile of ACP is considered manageable.

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 3.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.3 with the following content:

Safety concerns

Table 51: List of Safety Concerns

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

No changes to the safety concerns were identified as part of this application.

Pharmacovigilance plan

Routine pharmacovigilance remains sufficient to address the safety concerns of Rybrevant.

Risk minimisation measures

Table 52: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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 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 embryofetal 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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	

No new risk minimisation measures were identified as part of this application. Existing measures remain sufficient to mitigate Rybrevant safety concerns.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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 is:

RYBREVANT in combination with carboplatin and pemetrexed is indicated for the first-line treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations.

The inclusion criteria of the pivotal study required histologically or cytologically confirmed NSCLC that was metastatic or unresectable. Thus, the term advanced is used in the meaning unresectable.

Among 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 L858R, are found in 80% to 85% of patients with activating EGFR mutations, while tumors characterized by one of a group of heterogenous, in-frame base pair insertions in EGFR exon 20 (exon 20ins) are identified in up to 10% of patients with EGFR mutations (Vyse 2019).

3.1.2. Available therapies and unmet medical need

Several EGFR TKIs have been approved for use in the front-line therapy of NSCLC patients with tumors characterized by EGFR exon 19 del and L858R and mutations, which has resulted in significantly improved patient outcomes, with improved response rates, prolonged disease control, and an improved overall survival of 32 to 39 months (Ramalingam 2020). However, these TKIs are largely ineffective against the EGFR exon 20ins mutations, as they are unable to engage and inhibit the active sites of this group of EGFR mutations. As a result, there are no approved targeted therapies available for the first-line treatment of EGFR exon 20ins mutated NSCLC, and platinum-based doublet chemotherapy remains the standard of care for first-line treatment of newly diagnosed patients with advanced or metastatic EGFR exon 20ins NSCLC, although with poor health outcomes as evidenced by RWD (ie, median real-world PFS of 5.06 months and a median real-world OS of 16.23 months).

3.1.3. Main clinical studies

The pivotal study for this application is PAPILLON study intended also to fulfil the specific obligation needed to convert the existing CMA for amivantamab into a standard marketing authorization in the EU. PAPILLON is a global, multicentre, open-label, randomized Phase 3 study, designed to support the improved efficacy of amivantamab in combination with carboplatin-pemetrexed (ACP) versus carboplatin-pemetrexed (CP) for the first-line treatment of patients with EGFR exon 20ins NSCLC.

The ITT population consists of 308 randomized 1:1 including 153 in the ACP arm and 155 in the CP arm.

The Applicant sought Scientific Advice from the CHMP on the Phase 3 PAPILLON study in June 2020 on the major design aspects and generally agreed with the major design aspects (target population, SOC CP, primary endpoint, secondary endpoints, and statistical assumptions), the PK plan, and the approach to confirm exon20ins mutations in participants before enrolment. PFS was accepted as primary endpoint instead of OS despite the poor prognosis of metastatic NSCLC with EGFR Exon 20ins activating mutations. A blinded, independent central review (BICR) assessment of the primary endpoint PFS was planned taking in account the open-label design.

The key secondary endpoints ORR and OS were to be sequentially tested, each with an overall 2-sided alpha of 0.05 if the testing for the primary endpoint of PFS was statistically significant. Test for ORR was to be conducted before the test for OS.

OS is assessed as key secondary endpoint which is in line with the anticancer guideline when PFS is chosen as primary endpoint. The cross-over to amivantamab monotherapy was allowed for the patients with BICR confirmed progress on CP and will be considered in the evaluation of the relative OS benefit as will likely impact subsequent OS comparison.

The other secondary efficacy endpoints DoR, TSST, PFS2, TTSP and PRO were not tested for type 1 error.

At the cut-off date 03 May 2023, the median follow-up in the study was 14.9 months.

3.2. Favourable effects

At the cut-off date 03 May 2023, with a median follow-up in the study of 14.9 months and maturity grade suitable for the final PFS analysis, the primary endpoint, PFS (BICR) benefit with ACP vs CP was met.

The PFS analysis by BICR showed statistically significant benefit with amivantamab addition to CP HR 0.395 (0.296, 0.528); p-value<0.0001 and PFS gain of nearly 5 months (median PFS 11.37 months in ACP arm vs 6.70 months in CP arm).

A similar magnitude of benefit was observed with investigator assessment of PFS (HR=0.383; 95%CI 0.277, 0.497, p<0.0001). The agreement rate on the event status between Investigator and BICR was 99.2% in CP arm and 88.2% in ACP arm.

The PFS benefit was observed across all predefined clinically relevant subgroups.

The first secondary endpoint sequentially tested after the primary endpoint was met, ORR by BICR further support the benefit with amivantamab addition to CP with ORR of 73.0%in ACP arm compared with the CP arm 47.4% that was statistically significant.

The interim analysis of OS at the time of CCO for final PFS analysis showed a positive trend towards improved survival in ACP arm was observed with HR (95% CI) 0.675 (0.418, 1.090) p-value 0.1056.

The pre-planned sensitivity analysis using non-stratified log-rank test shows similar results with the stratified OS analysis OS HR: 0.717 [95% CI: 0.441, 1.165], p=0.177).

The updated OS analysis with additionally 6 months and totally 20 months of follow-up (cut-off 31 October 2023) supports the trend towards OS benefit with ACP observed at the primary analysis. The hazard ratio was 0.756 (95% CI: 0.501, 1.142) with a roughly 30% event maturity (26.7% in ACP vs 33% in CP arm).

Other secondary endpoints, although not type 1 -error controlled, further support the benefit with amivantamab addition to CP in first line.

3.3. Uncertainties and limitations about favourable effects

OS data are immature, however the final OS analysis from the pivotal Phase 3 study PAPILLON will be submitted as a post-authorisation measure as a Recommendation (REC) by Q4 2025.

3.4. Unfavourable effects

The key safety data were derived from the pivotal study PAPILLON study in patients with advanced or metastatic NSCLC with EGFR exon 20ins mutations (DCO 03 May 2023). The safety evaluation is based on data from 151 patients exposed to amivantamab (A) in combination with carboplatin + pemetrexed (CP) and 155 patients exposed to CP only.

Supportive safety data were derived from 20 ACP treated patients from the CHRYSALIS study and from 65 patients initially randomised to the CP arm in the PAPILLON study who crossed over to amivantamab monotherapy upon progression.

The size of the safety data set is considered acceptable.

The overall median duration of treatment exposure in the PAPILLON ACP arm was 9.72 months compared to 6.74 months in the CP arm. The median duration of exposure to amivantamab was 9.26 months.

The most frequently occurring TEAEs in the ACP arm were in line with previously established TEAEs of amivantamab and pertaining to EFGR and MET inhibition. Among EGFR inhibitor associated TEAEs by PT where a higher incidence was reported for ACP treated patients were rash (+45.9%), dermatitis acneiform (+27.9%), stomatitis (+19.4%), and paronychia (+56.3%). Among MET inhibitor associated

TEAEs by PT with a higher incidence in the ACP arm were hypoalbuminaemia (+31.4%) and peripheral oedema (+19.5%). IRR, an established amivantamab ADR, also occurred with higher incidence in the ACP arm (+ 40.4%).

Pyrexia and haemorrhoids were identified as new ADRs for amivantamab. ADR pyrexia is included in the proposed SmPC section 4.8 with frequency "very common" for ACP treatment as well as amivantamab monotherapy. ADR haemorrhoids is included in 4.8 with frequency "very common" for ACP treatment and "common" for amivantamab monotherapy. Venous thromboembolism (VTE) was identified as a new ADR associated with amivantamab + chemotherapy treatment and is included in section 4.8 with frequency "very common".

With regards to TEAEs by severity, grade $\geq$3 TEAEs were reported in 75.5% of the patients in the ACP arm (mainly neutropenia, leukopenia, rash, and anaemia) vs. 53.5% in the CP arm (mainly neutropenia, thrombocytopenia, and anaemia). Grade 4 TEAEs were reported for 14.6% of the patients in the ACP arm compared to 9.0% in the CP arm and grade 5 TEAEs were reported for 4.6% vs. 2.6%, respectively.

SAEs were reported for 37.1% vs. 31.0% of the patients in the ACP vs. CP arms, respectively. The SAEs with the highest incidence in the ACP arm were pneumonia (six patients), pneumonitis, and pulmonary embolism (four patients each). Overall, SAEs by PT and the SAE incidence were comparable between the treatment arms.

During study treatment, 28 patients (18.3%) in the ACP arm and 42 (27.1%) in the CP arm died. The main reason for death was progressive disease (13.1% vs. 19.4% in the ACP and CP arms, respectively). Deaths related to TEAEs were reported for seven patients (4.6%) in the ACP arm vs. four patients (2.6%) in the CP arm. No deaths were considered being related to amivantamab.

TEAEs leading to discontinuation of any study treatment were more frequently reported in the ACP arm (23.8%) compared to the CP arm (10.3%). The difference was mainly attributed to discontinuation of amivantamab, which was reported for 11.3% of the patients in the ACP arm. The most common TEAEs leading to amivantamab discontinuation were neutropenia and anaemia (2.0% each) and well-known amivantamab ADRs such as dermatitis acneiform (1.3%), pneumonitis (2.6%), and IRR (0.7%).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 53: Effects Table for amivantamab (Rybrevant) in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations. (data cut-off: 03 May 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			Amivantamab + carboplatin + pemetrexed N=153	Carboplatin + pemetrexed N=155		
Favourable Effects						
Primary endpoint	Median PFS by BICR HR (95% CI); p-value	months	11.37 (9.79, 13.70) 0.395 (0.296, 0.528); p-value<0.0001	6.70 (5.59, 7.33)	Statistically significant	
Secondary endpoint	ORR (95% CI) Odds Ratio (95% CI)	%	73.0% (65.2%, 79.9%) 2.971 (1.844, 4.787); p-value<0.0001	47.4% (39.2, 55.6)	Statistically significant	
	OS Number of events Median OS (95% CI) HR (95% CI); p-value	months	28 (18.3%) NE (NE, NE) 0.675 (0.418, 1.090); p-value=0.106	42 (27.1%) 24.38 (22.08, NE)	Interim OS. Low maturuíty,Not statistically significant, positive trend	
Unfavourable Effects						
			Amivantamab + carboplatin + pemetrexed N=151	Carboplatin + pemetrexed N=155		
TEAEs of particular relevance for ACP treatment	Any Rash Dermatitis acneiform Stomatitis Paronychia Hypoalbumin-emia Hypokalaemia Neutropenia	%	100.0% 53.6% 31.1% 25.2% 56.3% 41.1% 21.2% 58.9%	98.1% 7.7% 3.2% 5.8% 0 9.7% 8.4% 45.2%		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	Leukopenia Thrombocyto-penia Oedema peripheral Pyrexia IRR		37.7% 36.4% 29.8% 15.9% 41.7%	32.3% 29.7% 10.3% 5.8% 1.3%		
Treatment related TEAEs	Any Grade ≥3	%	 66.2%	 36.8%		
Grade ≥3	Any	%	75.5%	53.5%		
SAE	Any Pulmonary embolism Febrile neutropenia	%	37.1% 2.6% 0.7%	31.0% 2.6% 1.9%		
TEAEs leading to disc.	Any Grade ≥3	%	23.8% 17.9%	10.3% 4.4%		
Deaths due to TEAEs	Any	%	4.6%	2.6%		

Abbreviations: IRR = Infusion related reaction

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the PAPILLON study have shown a statistically significant and robust advantage in terms of PFS with amivantamab in combination with carboplatin-pemetrexed versus carboplatin-pemetrexed in first line therapy of patients with EGFR Exon 20ins mutation advanced NSCLC. The benefit with ACP in first line was further supported by a statistically significant improvement in ORR. In terms of translation into OS benefit, due to immaturity of the data at the interim analysis only a non-statistically significant, trend towards OS benefit has been observed. This was corroborated at the updated OS analysis with 20 months median follow-up and approximately 30% OS events.

The Applicant is recommended to submit the results of the final OS analysis from the pivotal Phase 3 study PAPILLON by Q4 2025.. The safety database is considered of an acceptable magnitude for describing the safety profile in the sought indication.

The safety profile of amivantamab in combination with carboplatin + pemetrexed is in line with the safety profile previously reported for amivantamab monotherapy and seems manageable with dose reductions and interruptions. Two new ADRs for amivantamab were identified (pyrexia and

haemorrhoids) regardless of treatment as a monotherapy or in combination with chemotherapy. VTE was identified as a new ADR associated with amivantamab + chemotherapy treatment .

3.7.2. Balance of benefits and risks

The PAPILLON study has demonstrated improvement of efficacy of amivantamab as add-on to chemotherapy consisting of carboplatin-pemetrexed. The safety profile of the amivantamab + chemotherapy combination is in line with the safety profile previously reported for amivantamab monotherapy and seems manageable with dose reductions and interruptions. Therefore the benefits of the proposed combination outweigh its risks.

3.7.3. Additional considerations on the benefit-risk balance

The efficacy results from the confirmatory Phase 3 study PAPILLON in patients with EGFR Exon 20ins mut NSCLC treated with amivantamab in combination with carboplatin-pemetrexed in first line were intended to fulfil the specific obligation (SOB) in the context of the conditional marketing authorisation (CMA) of Rybrevant. The study is positive and the SOB is considered fulfilled. The data from the PAPILLON study confirms a positive B/R balance for amivantamab in the sought indication and constitute a comprehensive data package supporting granting of a marketing authorisation no longer subject to specific obligations.

3.8. Conclusions

The overall B/R of amivantamab is positive provided and the SOB fulfilled.

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, II and IIIB

Extension of indication to include amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations for RYBREVANT, based on the final results from study 61186372NSC3001 listed as a Specific Obligation in the Annex II of the Product Information; this is a global, open-label, randomized Phase 3 study of ACP compared to CP alone in participants with newly diagnosed, locally advanced or metastatic NSCLC characterized by EGFR exon 20ins. The primary objective of the PAPILLON 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, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in

accordance. Version 3.1 of the RMP has also been agreed. In addition, the MAH took the opportunity to update Annex II and Annex IV of the PI. Consequently, the MAH proposes a switch from conditional marketing authorisation to full marketing authorisation given the fulfilment of the SOB. As part of the application, the MAH also requested an extension of the market protection by one additional year.

Amendments to the marketing authorisation

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).