Janssen Research & Development *

Clinical Protocol

Protocol Title

A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

PAPILLON

Protocol 61186372NSC3001; Phase 3
Version: Amendment 3

JNJ-61186372 (amivantamab)

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United States (US) sites will conduct this study under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number(s):

IND:	135405
EudraCT NUMBER:	2020-000633-40
EU Trial NUMBER:	2023-506033-29

Status:	Approved
Date:	07 August 2023
Prepared by:	Janssen Research & Development
EDMS number:	EDMS-ERI-205634813, 5.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	07 Aug 2023
Amendment 2	12 Aug 2022
Amendment 1	20 May 2021
Original Protocol	17 Jul 2020

Amendment 3 (07 August 2023)

Overall Rationale for the Amendment: To continue providing participants access to study treatment and collect data of clinical relevance/importance while reducing the burden on participants after the primary analysis by adding open-label extension (OLE) and long-term extension (LTE) phases to the study.

In addition, template changes related to the upcoming transition to European Union (EU)/European Economic Area (EEA) Clinical Trial Regulations (CTR), and other template-related changes have been added to the protocol.

The changes made to the clinical protocol 61186372NSC3001 as part of Protocol Amendment 3 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.16 (Appendix 16: Protocol Amendment History).

Section Number and Name	Description of Change	Brief Rationale
Changes related to adding an OLE Phase and an LTE Phase to the study.		
Synopsis (Overall Design); 4.1.4 Open-label Extension Phase and Long-term Extension Phase (new subheading)	A description of the new OLE and LTE phases was added, with cross-references to the newly added appendices.	To add the new OLE and LTE phases to the overall study design.
Synopsis (Study Treatment Groups and Duration); 4.4 End of Study Definition	Stated that a final analysis for overall survival is planned to occur approximately 48 months after the first participant is randomized. Added an end of study definition.	To keep the final analysis for overall survival and the end of study distinct.
1.2 Schema, Figure 1 (Schematic Overview of the Study Design)	The schematic was revised to add the new OLE and LTE phases.	To add the 2 new phases (OLE and LTE) to the study design.
1.3 Schedule of Activities (SoA): Table 1, Table 2; 10.11 Appendix 11: Optional Crossover After Disease Progression to Second-Line Amivantamab Monotherapy (Arm B Only): Table 20, Table 21	Added text in parenthesis after each table title to indicated that these Schedules of Activities were applicable only to the main study.	To distinguish the Schedules of Activities in the main study from those in the OLE and LTE phases.

Section Number and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Treatment (Bullet #5)	Revised text as shown below (bold font denotes added text): Documented radiographic (RECIST v1.1) disease progression by BICR **(except during the OLE and LTE phases, during which investigator assessment will be used)**, unless treatment beyond disease progression has been approved by the Medical Monitor.	To clarify that disease progression will not be determined by blinded independent central review (BICR) during the OLE and LTE phases.
8.1.1 Disease Assessments	Added text specifying that, during the OLE/LTE Phase, disease assessments, treatment decisions, and confirmation of disease progression can be made based on investigator assessment by RECIST v1.1.	To clarify that these items will not be determined by BICR during the OLE and LTE phases.
10 (Appendix 1: Abbreviations)	New abbreviations used during Amendment 3 were added.	To provide a comprehensive list of abbreviations.
10.7 Appendix 7: Clinical Laboratory Tests	Text referring to the Schedule of Activities during the OLE Phase was added.	To distinguish clinical laboratory tests performed during the OLE Phase from those performed in the main study.
10.11 Appendix 11: Optional Crossover After Disease Progression to Second-Line Amivantamab Monotherapy (Arm B Only)	Cross-references to study conduct/information and study assessments/procedures after transition to the OLE Phase were added.	To keep study conduct and assessments after transition to the OLE Phase distinct from what will be done during the optional crossover phase of the main study.
10.14 Appendix 14: Open-label Extension (new appendix)	The study design was changed to include a new study phase (an OLE Phase), whose purpose is to continue providing participants access to study treatment and collect data of clinical relevance/importance while reducing the burden on participants after the primary analysis is complete. Instructions on eligibility criteria to cross over to second-line amivantamab monotherapy (Arm B Only), study treatment administration, study procedures, and a Schedule of Activities for the OLE Phase are provided in the new appendix. During the OLE Phase, patient-reported outcomes (PROs) will be collected for 1 year after disease progression, reducing the data collection frequency from every 3 months to every 6 months.	To provide detailed information on study conduct during the OLE Phase.
10.15 Appendix 15: Long-term Extension Phase (new appendix)	The study design was changed to include a new study phase (an LTE Phase) whose purpose is to continue providing participants access to study treatment while further reducing the burden on participants after the final analysis for overall survival is complete. In this appendix, instructions on eligibility criteria to cross over to second-line	To provide detailed information on study conduct during the LTE Phase.

Section Number and Name	Description of Change	Brief Rationale
	amivantamab monotherapy (Arm B Only), study treatment administration, study procedures, and a Schedule of Activities for the LTE Phase are provided in the new appendix. During the OLE Phase, PROs will not be collected.	
Changes related to the upcoming EU CTR transition, and other template-specific changes.		
Cover page	The EU trial number was added.	To comply with the upcoming EU CTR transition.
Synopsis	The IND number, EudraCT Number, and EU trial number were added.	To comply with the upcoming EU CTR transition.
5.4 Screen Failures	Added the text shown below: "This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS."	To comply with the current protocol template.
6.1 Study Treatments Administered	Additional text related to study treatment was added.	To comply with the current protocol template.
10.2.4 Data Protection	Minor changes were made to text.	To comply with the current protocol template.
	Text related to measures by the sponsor to mitigate possible adverse effect in the event of a data security breach was added.	To comply with the upcoming EU CTR transition.
10.2.7 Publication Policy/Dissemination of Clinical Study Data	Minor changes were made to text.	To comply with the current protocol template.
Throughout the protocol	Minor editorial and formatting changes were made.	Minor errors, discrepancies, or omissions were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

IND: 135405
EudraCT NUMBER: 2020-000633-40
EU Trial NUMBER: 2023-506033-29

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) tyrosine kinase receptors that is being developed for the treatment of solid tumors, including EGFR-mutated non-small cell lung cancer (NSCLC). In approximately 10% of patients with EGFR-mutated NSCLC, EGFR is activated through one of a group of heterogenous, in-frame base pair insertions in EGFR Exon 20, collectively referred to as EGFR Exon 20 insertion (Exon 20ins) mutations. NSCLC arising from Exon 20ins mutations is distinguished by de novo resistance to currently approved EGFR tyrosine kinase inhibitors (EGFR TKIs), including third-generation EGFR TKIs such as osimertinib.

In the absence of effective targeted therapies, platinum-based doublet chemotherapy remains the standard of care for first-line therapy in patients with EGFR Exon 20ins mutated NSCLC. Platinum-based doublet chemotherapy is associated with an objective response rate (ORR) of approximately 30% and median progression-free survival (PFS) of approximately 5 months in patients with advanced NSCLC and EGFR L858R or Exon 19del mutations. Given their similar underlying biology, the activity of platinum-doublet chemotherapy is expected to be similar in patients with EGFR Exon 20ins disease.

In a Phase 1 Study (61186372EDI1001) of amivantamab for the treatment of NSCLC, antitumor activity was seen in a majority of participants with Exon 20ins mutations who received amivantamab as monotherapy. The combination of amivantamab with chemotherapy in participants with EGFR mutated NSCLC is also being evaluated in this study. As of 20 October 2020, 16 patients have been dosed with the combination amivantamab and chemotherapy (carboplatin and pemetrexed). Preliminary safety analysis of the combination is consistent with the monotherapy experience of amivantamab and chemotherapy alone. Preliminary pharmacokinetic (PK) data suggests no impact of chemotherapy on amivantamab exposure.

This randomized, multicenter, Phase 3 study seeks to demonstrate the improved efficacy of combining amivantamab with standard of care carboplatin-pemetrexed chemotherapy (Arm A) compared with carboplatin-pemetrexed chemotherapy (Arm B) in the first-line treatment of patients with EGFR Exon 20ins NSCLC.

OBJECTIVES AND ENDPOINTS

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 blinded independent central review
Key Secondary	
To further assess the clinical benefit achieved with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Objective response rate • Overall survival
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

PFS=progression free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Other secondary and exploratory objectives and endpoints are described in the protocol.

Hypothesis

The hypothesis is that amivantamab, when given in combination with standard of care carboplatin-pemetrexed chemotherapy (Arm A), will prolong PFS compared with standard of care carboplatin-pemetrexed chemotherapy (Arm B) in patients with locally advanced or metastatic NSCLC characterized by EGFR Exon 20ins activating mutations.

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 (see protocol Section 4.1.2). 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 (see protocol Section 10.11).

Following the primary analysis for efficacy, the study will transition to an open-label extension (OLE) Phase (see details provided in Section 10.14 [Appendix 14]). Participants will be provided the option to continue treatment in the OLE Phase until the final analysis for overall survival, after which the study will transition to a long-term extension (LTE) Phase.

Participants who continue to benefit from study treatment(s), as determined by their investigator, at the time of the OLE Phase may continue to receive access to study treatment(s) within the study by transferring to the LTE Phase, where only serious adverse event data and study treatment accountability will be collected.

The LTE Phase (see details provided in Section 10.15 [Appendix 15]) will begin after the final analysis for overall survival, and will continue until the discontinuation criteria described in Section 7.1 are met, or until 2 years after local marketing authorization is obtained for the studied indication, whichever occurs first.

The extension phases will begin after approval of Amendment 3 by health authorities of countries in which this study is still being conducted at the time of transition, and by study site ECs/IRBs. In addition, for transition to the LTE Phase (after final analysis for overall survival), prior notification from the sponsor will be needed.

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.

NUMBER OF PARTICIPANTS

Approximately 300 eligible participants will be stratified based on Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no), and assigned randomly in a 1:1 ratio into 1 of 2 treatment arms.

STUDY TREATMENT GROUPS AND DURATION

Study treatment will be administered open-label, without blinding, in 21-day cycles, until disease progression or until the participant meets another criterion for discontinuation of study treatment.

Arm A (amivantamab plus chemotherapy):

- 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
- 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

Arm B (chemotherapy):

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

A final analysis for overall survival is planned to occur approximately 48 months after the first participant is randomized.

End of Study Definition:

The end of study/study completion is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study.

EFFICACY EVALUATIONS

Tumor response will be assessed by BICR according to RECIST v1.1. Baseline disease assessments should be performed no more than 28 days prior to randomization. On-study imaging will occur at regular intervals, as defined in the Schedule of Activities, until radiographic disease progression is documented.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected from participants receiving amivantamab for the measurement of serum amivantamab.

IMMUNOGENICITY EVALUATIONS

Blood samples will be collected and analyzed for antibodies to amivantamab using a validated immunoassay. Other immunogenicity analyses may be performed to further characterize any immune responses generated.

BIOMARKER EVALUATIONS

Blood samples and tumor tissue collected at Screening and during the study may be evaluated for biomarkers relevant to cancer to understand the molecular biology of the tumor, efficacy observed with amivantamab, and mechanisms of acquired resistance to amivantamab.

SAFETY EVALUATIONS

Safety will be assessed by physical examinations, laboratory tests, vital signs, electrocardiograms, left ventricular ejection fraction, monitoring of adverse events, and concomitant medication usage.

STATISTICAL METHODS

The statistical hypothesis is that amivantamab and carboplatin-pemetrexed chemotherapy (Arm A) will reduce the risk of either progression or death compared with standard of care carboplatin-pemetrexed chemotherapy (Arm B). A total of 200 PFS events will provide approximately 90% power to detect a hazard

ratio (HR) of 0.625 that corresponds to at least 3-month improvement in the median PFS (5 months for chemotherapy and 8 months for the combination of amivantamab with chemotherapy) with a stratified log-rank test (2-sided alpha = 0.05). The total sample size needed for the study is approximately 300 participants (150 per group). The sample size calculation takes into consideration an annual dropout rate of 5%.

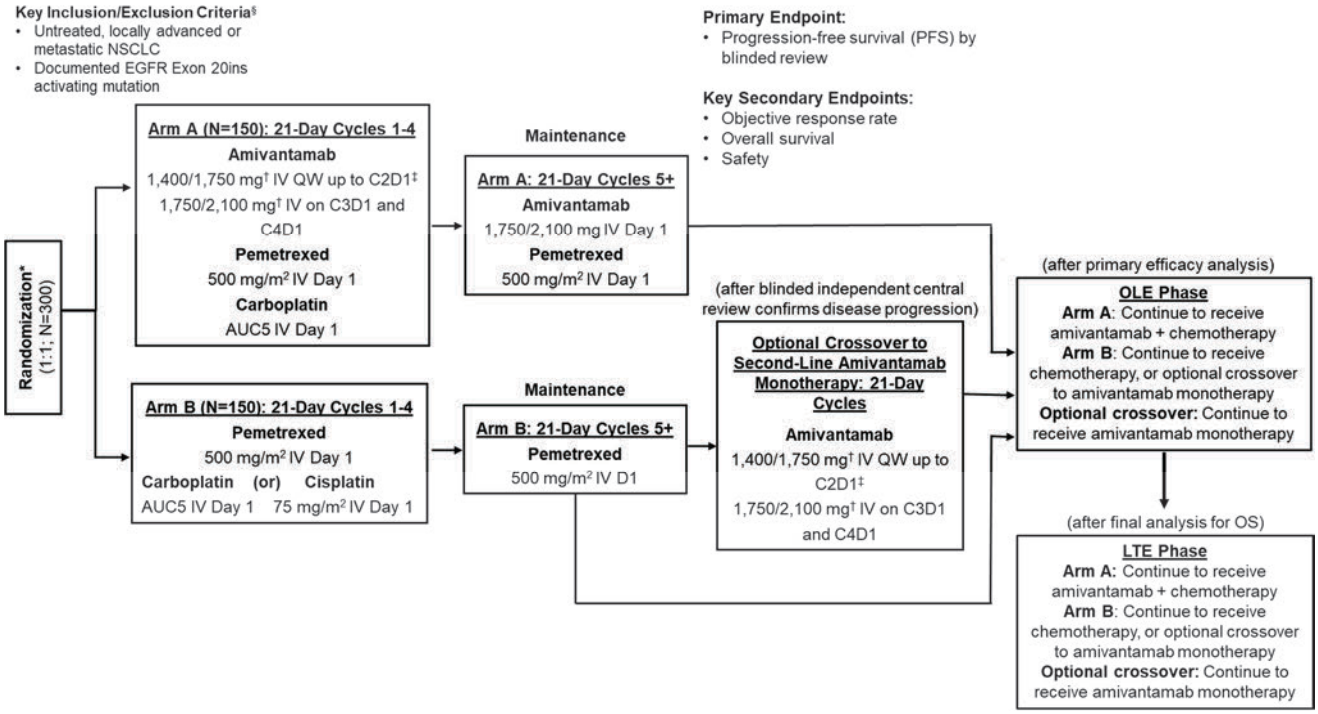
The primary efficacy endpoint of PFS by BICR will be analyzed by stratified log-rank test using the Breslow approach for handling ties. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

To control the overall type I error rate for the hypotheses testing of primary and secondary endpoints at 5%, a sequential testing strategy will be used. If the testing for the primary endpoint of PFS is statistically significant, key secondary endpoints including ORR and overall survival will be sequentially tested, with an overall 2-sided alpha of 0.05.

Safety data will be summarized for all participants who receive at least 1 dose of study treatment. Data for PK, immunogenicity, patient-reported outcomes, and biomarkers will be summarized for participants who receive at least 1 dose of study treatment and provide an evaluable measurement for that endpoint at least once post baseline. Details of the hierarchical testing procedure, analyses of other secondary or exploratory endpoints and analyses of data after crossover to amivantamab monotherapy will be specified in the Statistical Analysis Plan.

1.2. Schema

Figure 1: Schematic Overview of the Study Design



AUC=area under the concentration-time curve; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; IV=intravenously; LTE=long-term extension; OLE=open-label extension; 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

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities for Study Assessments/Procedures (Main Study Only)

Study Phase		Treatment (21 Days/Cycle)								End of Treatment	Follow-up (Visit/Call)	
Cycle		Cycle 1				Cycle 2	Cycle 3	Cycle 4	Cycle 5+	30 Days After		
Cycle Day	Screening	1	2	8	15	1	1	1	1	Last Dose*	Q12W	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	Notes
STUDY PROCEDURES Treatment cycles are 21 days in duration. In Arm A, amivantamab is administered in Cycle 1 on Days 1, 2, 8 and 15, then once every 3 weeks on Day 1 of each 21-day cycle. Assessments during in-clinic dosing days should be performed prior to administration of study treatment unless otherwise stated. Starting with Cycle 2 Day 1: if a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule (except disease assessments) should be delayed accordingly to ensure sampling relative to amivantamab dose administration. Investigator must confirm that the participant meets treatment criteria before administration of study treatment/s. *End of Treatment visit should occur 30 days after the last dose or before starting the next anti-cancer treatment, whichever occurs first. In Follow-up phase, collect data until the end of study unless the participant has died, is lost to follow-up, or has withdrawn consent.												
Screening Assessments												
Informed consent	X											Must be signed before any study-related procedures.
Inclusion/exclusion criteria	X											Confirm all criteria are met before randomization.
Demography	X											
Disease characteristics	X											
Medical history	X											
ECOG performance status	X	X				X	X	X	X	X		
Serology	X											HIV antibody, HBsAg, HBsAb, HBcAb, anti-HCV antibody, HBV viral load (if needed) and HCV viral load (if needed). Please refer to exclusion criterion 10.
Coagulation	X											
Urinalysis	X											
Pregnancy test (serum or urine)	X	X	As clinically indicated, according to local regulation requirements, or following the local practice of the center									Women of child-bearing potential only. Required at Screening and within 72 hours before the first dose of study treatment. If local regulations mandate pregnancy testing before administration of study treatment, the test should be completed within 72 hours before Day 1 of each cycle or monthly, whichever is more frequent.
Hematology/chemistry (up to 72h predose)	X	X		X	X	X	X	X	X	X		Laboratory assessments are listed in Appendix 7. Results of the screening assessments must be reviewed by the Investigator prior to enrollment; laboratory assessments must be reviewed by the Investigator prior to infusion of chemotherapy and/or amivantamab. Additional testing as needed, per local guidelines and practice for the purposes of chemotherapy dosing, with clinically significant abnormalities reported as adverse events. If chemotherapy and amivantamab are administered on different days, obtain hematology/chemistry before each study treatment. Hematology/chemistry schedule on C1D8 and C1D15 applies to both Arm A and Arm B.

Study Phase		Treatment (21 Days/Cycle)								End of Treatment	Follow-up (Visit/Call)	
Cycle		Cycle 1				Cycle 2	Cycle 3	Cycle 4	Cycle 5+	30 Days After Last Dose*		
Cycle Day	Screening	1	2	8	15	1	1	1	1		Q12W	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	Notes
Efficacy Assessments												
CT/MRI tumor imaging	X	6 weeks (+1 week) from randomization, every 6 weeks (±1 week) for the first 18 months, then every 12 weeks (±1 week) afterward										Use same method throughout study (Section 8.1). Continue until disease progression by BICR. If a participant receives study treatment beyond documented disease progression, continue disease assessments as scheduled and review clinical benefit with the Medical Monitor after each disease assessment. Imaging obtained as standard of care before signing the ICF, but within 28 days of randomization, may be used for the Screening assessment.
Brain MRI	X	As clinically indicated										
Symptomatic progression events		X										Collect continuously from randomization (including during the Follow-up Phase)
Survival/disease status											X	
Subsequent anticancer therapy											X	Collect information on type of therapy, treatment start date, treatment stop date, objective disease response and progression
Safety Assessments (predose, except as noted)												
12-lead ECG	X	X					X					Single ECG at Screening. Triplicate ECG at C1D1 (preinfusion of study treatment) and C3D1 (≤30 min post-infusion [of amivantamab in Arm A; of carboplatin in Arm B]). If performed within 72 h before the first dose of study treatment, the assessment does not need to be repeated at C1D1.
ECHO or MUGA	X											At Screening and then as clinically indicated
Vital signs	X	X	X	X	X	X	X	X	X	X		Heart rate, BP, respiratory rate, temperature, and O_2 saturation before administration of chemotherapy on Day 1 of each cycle. Also ≤30 min before amivantamab infusion, 30 min intervals (±5 minutes) during each amivantamab infusion, and at end of infusion (+5 minutes). If chemotherapy and amivantamab are administered on different days, obtain vital signs before each study treatment. If C1D1 dosing of amivantamab is delayed, vital signs scheduled for C1D1 should be collected on C1D2 and vital signs scheduled for C1D2 should be collected on C1D3. Vital signs on C1D2 are not required for Arm B as no C1D2 visit is required.

Study Phase		Treatment (21 Days/Cycle)								End of Treatment	Follow-up (Visit/Call)	
Cycle		Cycle 1				Cycle 2	Cycle 3	Cycle 4	Cycle 5+	30 Days After Last Dose*		
Cycle Day	Screening	1	2	8	15	1	1	1	1		Q12W	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	Notes
Physical examination	X	X				X	X	X	X	X		Screening will include, at a minimum, height, weight, general appearance, and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. On Day 1 of each cycle, directed physical examination of involved organs and other body systems will be performed as indicated, with clinically significant abnormalities reported as adverse events. If chemotherapy and amivantamab are administered on different days, obtain symptom-directed physical examination before each study treatment.
Adverse events	X											Continuous from the time ICF is signed through 30 days after the last dose of study treatment (or >30 days, if considered related to study treatment)
Prior and concomitant medications	X											Record all prescription and over-the-counter treatments administered up to 28 days before randomization through 30 days after the last dose of study treatment (or the start of a subsequent systemic anti-cancer therapy, if earlier). For participants with Grade 3 or 4 adverse events considered related to study drug, record concomitant medications through the end of follow-up of that adverse event.
Preinfusion Medications												
Folic acid **(Arm A/B)**	Daily from 7d before first dose of pemetrexed to 21d after last dose of pemetrexed											
Vitamin B12 **(Arm A/B)**	One dose within 7 days of Cycle 1 Day 1, then every 3 cycles afterward. May be administered on the same day as pemetrexed.											
Corticosteroid **(Arm A/B)**	Day -1	X	X			X	X	X	X			Day before, day of, and day after each pemetrexed dose, or per local regulations and practice
Preinfusion medications for amivantamab **(Arm A only)**		X	X	X	X	X	X	X	X			See Section 6.6.2. Record all preinfusion medications.
Randomization & Study Treatment												
Randomization		X										Start study treatment within 3 days of randomization
Pemetrexed administration **(Arm A/B)**		X				X	X	X	X			On Day 1 of each cycle, pemetrexed should be the first administered study treatment. Creatinine clearance must be determined prior to administration of pemetrexed.
Carboplatin administration **(Arm A/B)**		X				X	X	X				On Day 1 of Cycles 1-4, carboplatin should be administered after pemetrexed (and before amivantamab [Arm A]).
Amivantamab administration **(Arm A only)**		X	X	X	X	X	X	X	X			See Section 6.2.1 for guidance if changes are required to scheduled doses of amivantamab.
Patient-Reported Outcomes (predose on dosing days)												
EQ-5D-5L, EORTC-QLQ-C30, PROMIS-PF		X					X		C5, 7, 9, etc.	X	Every 12 weeks	On C1D1, the Patient-Reported Outcomes data can be collected 24 hours before the first dose. Continue in Follow-up phase for 1 year, regardless of whether subsequent therapy has been started
Pharmacokinetics and Immunogenicity (See Table 2)												

Study Phase		Treatment (21 Days/Cycle)								End of Treatment	Follow-up (Visit/Call)	
Cycle		Cycle 1				Cycle 2	Cycle 3	Cycle 4	Cycle 5+	30 Days After		
Cycle Day	Screening	1	2	8	15	1	1	1	1	Last Dose*	Q12W	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±3	±3	±3	+7	±14	Notes
Biomarkers (predose on dosing days)												
Tumor biopsy	X									X		Provide at least 10 slides (up to 15 when available) or equivalent material. At Screening, submission of archival or fresh tumor biopsy sample for central mutation analysis is mandatory. The screening sample must be obtained at or after the time of diagnosis of locally advanced or metastatic disease. Post-progression, obtain biopsy within 30 days of disease progression, if clinically feasible, before the next anticancer therapy.
ctDNA blood sample	X						X			X		If participant receives study treatment/s beyond disease progression, collect additional samples at each post-progression disease assessment.
Exploratory biomarkers serum sample	X									X		

BICR=blinded independent central review; BP=blood pressure; C#D#=Cycle # Day #; CT=computerized tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; d=day; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol 5-dimensional descriptive system (5-level version); h=hour; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; min=minutes; MUGA=multigated acquisition; MRI=magnetic resonance imaging; O2=oxygen; PROMIS-PF=Patient-Reported Outcomes Measurement Information System – Physical Function; Q3W=every 3 weeks; Q12W=every 12 weeks.

Table 2: Collection Times for Pharmacokinetics and Immunogenicity Samples Among Participants Receiving Amivantamab (Arm A in Main Study Only)

Study Phase	Treatment				End of Treatment
Cycle	Cycle 1[a]		Cycle 2	Cycles 3, 5, 7, 9, 11, and 13	30 Days After Last Dose
Cycle Day	1	2	1[b]	1[b]	-
Dosing Visit Window (days)	-	-	±1	±3	+7
Pharmacokinetic Samples[c]					
Preinfusion (0-2 hr before planned amivantamab)	X	X	X	X	
End of infusion (0-15 min after amivantamab)	X	X	X	X	
At End of Treatment Visit					X
Immunogenicity Samples[c]					
Preinfusion (0-2 hr before planned amivantamab)	X		X	X	
At End of Treatment Visit					X

a. If Cycle 1 Day 1 dosing of amivantamab is delayed, samples scheduled for Cycle 1 Day 1 should be collected on Cycle 1 Day 2, and samples scheduled for Cycle 1 Day 2 should be collected on Cycle 1 Day 3.
b. If a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule should be delayed accordingly to ensure sampling relative to amivantamab dose administration.
c. Separate blood draws are not required for amivantamab PK and immunogenicity when collected at the same time point.

2. INTRODUCTION

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) tyrosine kinase receptors that is being developed for the treatment of solid tumors. Amivantamab has demonstrated anti-tumor activity in preclinical models of EGFR and MET-driven non-small cell lung cancer (NSCLC), through 3 distinct mechanisms of action: 1) inhibition of ligand binding, 2) receptor degradation, and 3) antibody-dependent cellular cytotoxicity (ADCC). Early clinical experience with amivantamab has demonstrated durable responses in subjects with various types of EGFR-driven or MET-driven NSCLC that are resistant to currently available EGFR-targeted or MET-targeted therapies, including subjects with EGFR mutations characterized by one of a group of heterogenous, in-frame base pair insertions in EGFR Exon 20 (Exon 20ins). Based on its observed activity in the latter population, amivantamab achieved Breakthrough Therapy Designation status by the United States (US) Food and Drug Administration (FDA) in March 2020 for the monotherapy treatment of patients with NSCLC characterized by EGFR Exon 20ins mutations, after prior treatment with platinum-based doublet chemotherapy. This study will explore whether the addition of amivantamab to first-line standard of care doublet chemotherapy will further improve disease control and clinical benefit as compared to chemotherapy alone.

The term "study treatment" throughout the protocol refers to study drug (amivantamab) or to carboplatin or pemetrexed. For the most comprehensive nonclinical and clinical information regarding amivantamab, refer to the latest version of the Investigator's Brochure (IB) and Addenda.[12] For further information regarding carboplatin and pemetrexed, refer to the local prescribing information for each product.[2,5]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Background

Cancer is a leading cause of death worldwide. Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer (almost 20% of cancer deaths); NSCLC accounts for 80% to 85% of lung cancers.[3] Adenocarcinoma is a subset of NSCLC and the most common type of lung cancer, comprising 40% of lung cancers.[31] Five-year survival rates for NSCLC depend on the stage at diagnosis, ranging from 57% for localized cancer to 5% for cancer that has spread to distant locations.[28] In patients with metastatic NSCLC, clinical guidelines recommend testing for activating mutations, which are observed in approximately 50% of adenocarcinomas.[17,24]

The identification of these "driver" activating mutations has provided an opportunity to specifically inhibit the constitutively activated pathway using targeted tyrosine kinase inhibitors (TKIs). Among patients with NSCLC adenocarcinoma, the most prevalent of these driver mutations are those that result in the activation of EGFR, which are identified in more than 15% of patients with

adenocarcinoma[20] and up to 50% of the corresponding Asian population.[13] The most commonly occurring EGFR mutations, L858R and Exon 19del, are sensitive to approved EGFR TKIs, which are associated with high response rates (approximately 60% to 80%), prolonged duration of response, and median progression free survival (PFS) of approximately 10-19 months.[26] As a result, these EGFR TKIs are considered first-line therapy for patients with NSCLC and EGFR L858R or Exon 19del mutations.

In approximately 10% of EGFR-mutated NSCLC, EGFR is activated through one of a group of heterogenous, in-frame base pair insertions in EGFR Exon 20, collectively referred to as EGFR Exon 20ins mutations. Although EGFR Exon 20ins-mutated NSCLC is believed to share a similar biology with other EGFR-mutated NSCLC, the unique protein structure associated with this group of EGFR mutations prevents effective binding by approved EGFR TKIs, by sterically hindering access to the receptor active site. Thus, NSCLC arising from Exon 20ins mutations is distinguished by de novo resistance to currently approved EGFR TKIs, including third-generation TKIs such as osimertinib.[29] Correspondingly, recently presented real-world evidence suggests inferior therapeutic outcomes with the non-standard use of EGFR TKI in the first-line setting, as compared to chemotherapy. [6] As a result, no EGFR TKI or other targeted therapy is approved for the treatment of patients with EGFR Exon 20ins NSCLC.

In the absence of effective targeted therapies, platinum-based doublet chemotherapy remains the standard of care for first-line therapy in patients with EGFR Exon 20ins-mutated NSCLC. The efficacy of combination chemotherapy in patients with advanced NSCLC and EGFR L858R or Exon 19del mutations includes an objective response rate (ORR) of approximately 30% and median PFS of approximately 5 months.[14,16,25] The efficacy of combination chemotherapy, which is not dependent on EGFR, is expected to be similar in patients with Exon 20ins mutations.

2.2. Rationale for Amivantamab Therapy for EGFR EXON 20ins Disease

2.2.1. Clinical Studies of Amivantamab

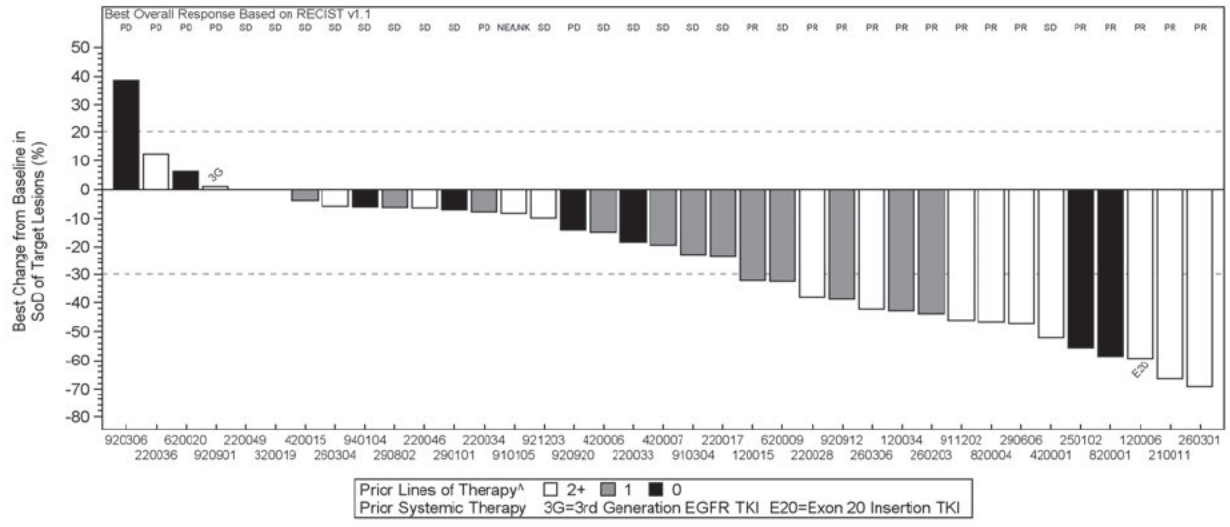
Amivantamab is being developed based on the hypothesis that a bispecific antibody, by targeting the extracellular domain of each receptor (EGFR and MET), will demonstrate activity against tumors resistant to EGFR TKIs, either through primary resistance (EGFR Exon 20ins) or through the two most frequent mechanisms of resistance to current EGFR therapies: 1) secondary/tertiary mutations in EGFR, and 2) MET amplification or mutation. In the first-in-human Study 61186372EDI1001, amivantamab has shown clinical proof-of-concept for this approach by demonstrating activity in patients with NSCLC disease characterized by activating mutations of EGFR and/or MET, including EGFR Exon 20ins mutations. Early clinical experience with amivantamab in this patient population suggests that it has activity as a monotherapy that is at least equivalent to current standard of care platinum-based doublet chemotherapy, validating the approach of targeting these mutations via their extracellular domain, rather than the TKI-resistant active site.

Study 61186372EDI1001 includes both a dose-escalation phase (Part 1: subjects with advanced NSCLC) and a dose-expansion phase (Part 2: subjects with advanced EGFR-mutated or MET-mutated NSCLC, after standard of care therapy). Part 1 of the study includes a chemotherapy

combination arm for participants with advanced NSCLC who are eligible for treatment with standard of care carboplatin and pemetrexed. Part 2 of the study includes expansion cohorts for amivantamab monotherapy in populations with unmet clinical need, including NSCLC characterized by the following: 1) Cohort C: EGFR resistance mutations (eg, C797S and others) and previous treatment with a third-generation EGFR TKI; 2) Cohort D: EGFR Exon 20ins disease and no previous treatment with an EGFR TKI with known activity in Exon 20ins disease; 3) Cohort MET-1: EGFR mutation with MET mutation or amplification of ≥3 copy number and previous treatment with any EGFR TKI; and 4) Cohort MET-2: Primary MET Exon 14 skipping mutation. Part 2 of the study also includes Cohort E, an expansion cohort for amivantamab in combination with lazertinib in participants with advanced EGFR-mutated NSCLC characterized by Exon19del or L858R sensitive activating mutations who have progressed after first or second-line treatment with a third-generation TKI (eg, osimertinib).

As of 30 October 2019, 252 subjects had received amivantamab in Study 61186372EDI1001, including 153 subjects treated at the recommended Phase 2 dose (RP2D) of 1,050 mg for subjects with body weight <80 kg (1,400 mg for subjects with body weight ≥80 kg). Ninety-two subjects with EGFR Exon 20ins disease had been enrolled into either Part 1 or Part 2 of the study, of which 50 subjects were treated at the amivantamab RP2D. Of these, 39 subjects had undergone at least 2 scheduled post-baseline disease assessments, or discontinued therapy. A majority of subjects with Exon 20ins NSCLC demonstrated some level of tumor response to amivantamab (Figure 2).[21]

Figure 2: Waterfall Plot of Best Percentage Change from Baseline in Sum of Diameters (SoD) of Target Lesions; Response Evaluable with ≥2 Disease Assessments and Measurable Disease at Baseline and Exon 20 Insertion at RP2D Analysis Set in Monotherapy (Amivantamab) (Study 61186372EDI1001)



RP2D: 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight >= 80 kg.
Key: SoD = Sum of Diameters, CN = copy number, RP2D = recommended phase 2 dose
^ Includes platinum doublet chemotherapy in metastatic setting.
Note: The response evaluable with >= 2 disease assessments analysis set consists of all subjects who received at least one dose of study drug and either have at least two post-baseline disease assessment or discontinued treatment for any reason prior to the second post-baseline disease assessment.
[GEFRSWF01-E20-BW.RTF] [JNJ-61186372\EDI1001\DBR BTD IND BB PED 2019 10\RE BTD BB 2019 12\PROD\GEFRSWF01-E20-BW.SAS] 20MAY2020, 07:59

The emerging safety profile of amivantamab as a monotherapy suggests it is well tolerated and is consistent with that observed with other EGFR and MET-directed therapies. Among the 252 subjects who received amivantamab, the most commonly reported treatment-emergent adverse events (TEAEs) at the data cutoff date were infusion-related reaction (62.7%), rash (31.7%) or dermatitis acneiform (28.6%), paronychia (27.8%), and hypoalbuminemia (22.2%), the majority of which were Grade 1 or 2. Grade 3 rash was reported for 2.2% of subjects. TEAEs of liver enzyme elevations in >10% of subjects included increased alanine aminotransferase (ALT) in 10.3% of subjects. Treatment-related serious adverse events were reported for 11 subjects (4.4%), with infusion-related reaction being the most frequently reported (2 subjects, 0.8%); a treatment-related serious adverse event of interstitial lung disease (ILD) was reported for 2 subjects (0.8%). TEAEs led to dose reduction for 6.7% of subjects and discontinuation of amivantamab for 3.9% of subjects. Updated efficacy and safety data of amivantamab monotherapy in patients with EGFR Exon 20ins NSCLC were recently presented at the International Association for the Study of Lung Cancer (IASLC) 2021 World Conference.[26] Results remain consistent with the previous experience with amivantamab. Updated information is also available in the latest version of the IB.[12]

2.2.2. Rationale for Chemotherapy Comparator

National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) treatment guidelines for advanced or metastatic NSCLC recommend platinum-based combination chemotherapy regimens, including carboplatin-pemetrexed or cisplatin-pemetrexed, in the first-line setting treatment of non-squamous NSCLC.[17,24] While the activity of cisplatin and carboplatin is largely considered to be similar, with no associated difference in overall survival (OS),[9] the use of cisplatin is typically reserved for therapies with curative intent, such as neoadjuvant, adjuvant, or combined chemotherapy-radiation regimens, where a potential slight benefit in ORR may outweigh greater toxicity and patient burden in patients who can tolerate it.

Carboplatin-based regimens, with their improved safety profile, are more often used in the metastatic NSCLC setting, within clinical regimens with palliative intent. The importance of improved toxicity profile and reduced infusion times associated with carboplatin administration, and the decreased need for pre-infusion and post-infusion hydration for these patients are reflected in recent reviews of real world usage patterns, which demonstrate that carboplatin-pemetrexed is the most frequently used platinum-based doublet regimen in the US for the first-line treatment of metastatic, nonsquamous NSCLC, and cisplatin-based regimens are used infrequently in this setting (<5%).[1] In addition, carboplatin and pemetrexed have been combined with the first-generation EGFR TKI gefitinib, a regimen that is recognized in the ESMO guidelines as a first-line treatment option for TKI-sensitive EGFR-mutated NSCLC.[7]

Given the above, the use of carboplatin-pemetrexed combination chemotherapy in this study ensures every enrolled subject will receive treatment with the preferred first-line regimen for EGFR Exon 20ins NSCLC, and will enable the most robust assessment of amivantamab efficacy and safety when administered in combination with carboplatin and pemetrexed in the first-line setting.

2.2.3. Rationale for Amivantamab Chemotherapy Combination

As a bispecific antibody capable of engaging the extracellular domains of both EGFR and MET receptors, amivantamab has the potential to control EGFR-mutated NSCLC independent of activating and resistance mutations within the intracellular domains of the protein, which can determine sensitivity or resistance to approved EGFR TKIs. Like the EGFR TKIs already approved for the treatment of EGFR-mutated NSCLC, a large contributor of amivantamab activity lies in its ability to target the biological driver of tumor growth, halting tumor cell division, and ultimately resulting in cell death and tumor response.

With the approval of EGFR TKIs for the treatment of NSCLC, several studies have investigated the optimal application of these agents, including potential combination with chemotherapy. While early studies evaluating the potential of EGFR TKI/chemotherapy failed to demonstrate clinical benefit, the failure to use molecular markers to select for populations with EGFR-driven disease may have confounded the interpretation of these results. With the significant improvement in efficacy observed with second-generation and third-generation EGFR TKIs relative to chemotherapy, platinum-based chemotherapies were reserved for salvage therapy after TKI failure, after tumors had developed mutations that made them resistant to targeted approaches.

More recent studies have suggested a possible benefit with EGFR TKI/chemotherapy combination treatment, and that this potential approach deserves re-evaluation. Two studies that combined gefitinib (a first-generation EGFR TKI) with carboplatin and pemetrexed demonstrated improved outcomes, as compared to gefitinib alone, in terms of ORR, PFS, and OS.[11,18] These recent results suggest potential benefit of this combined approach when appropriately applied to selected populations with EGFR-mutated NSCLC, as the use of concomitant chemotherapy may eliminate potential tumor cell populations with inherent TKI resistance, thereby delaying disease recurrence.

In addition to the suggested benefit of combining chemotherapy with targeted inhibition of the EGFR pathway, amivantamab anti-tumor activity is hypothesized to include ADCC-dependent mechanisms that are not associated with EGFR TKIs. Thus, there may be additional benefit with amivantamab/chemotherapy combinations arising from disruption of an inhibitory tumor microenvironment[8] and targeting of Fc receptor-bearing immune cells to tumor cells. Given the demonstrated activity of platinum-based doublet chemotherapy and amivantamab monotherapy in patients with EGFR Exon 20ins-mutated NSCLC, it is hypothesized that the combination of these 2 active regimens will improve patient outcomes over what has been observed with either agent alone.

The safety profile for amivantamab, which resembles that of EGFR TKIs or other monoclonal antibodies (mAb), is largely distinct from those associated with chemotherapeutic agents. Moreover, amivantamab is not a modulator of cytokines that have known effects on metabolizing enzymes and transporters, and due to the lack of common elimination pathways for amivantamab and carboplatin or pemetrexed, no relevant pharmacokinetic (PK) interactions are expected.[30]

As of 20 October 2020, 16 patients have been dosed with the combination amivantamab and chemotherapy (carboplatin and pemetrexed) in the ongoing Phase 1 study CHRYSALIS (61186372EDI1001). Preliminary safety analysis of the combination is consistent with the

monotherapy experience of amivantamab and chemotherapy alone. Preliminary PK data suggests no impact of chemotherapy on amivantamab exposure. Please refer to the latest version of the IB for additional information.[12]

This Phase 3 study seeks to demonstrate the tolerability and improved efficacy of combining amivantamab with standard of care carboplatin-pemetrexed chemotherapy as first-line treatment of patients with EGFR Exon 20ins NSCLC, compared with carboplatin-pemetrexed chemotherapy in this setting.

2.3. Benefit-Risk Assessment

2.3.1. Risks for Study Participation

As clinical data for the combination of amivantamab plus chemotherapy are limited, unforeseen safety risks associated with the study treatments are possible. Previous studies combining EGFR TKIs or anti-EGFR mAbs with chemotherapy have shown the combinations were generally well tolerated.[11,18,21,23] Combining amivantamab with chemotherapy is expected to have a similar safety profile to combining an EGFR TKI or mAb with chemotherapy.

The safety profile for amivantamab is largely distinct from those associated with chemotherapeutic agents. However, pemetrexed has been reported to be associated with bullous and exfoliative skin toxicity as well as interstitial pneumonitis, which should be considered when evaluating and managing potential skin and pulmonary toxicities.

This study protocol includes the following elements to mitigate risks for study participants:

- Participants will be monitored closely for safety throughout the study (refer to Section 8.2), per the scheduled assessments outlined in the Schedule of Activities (Table 1).
- Dose delay and dose modification guidance is provided to manage toxicities that occur during the study (refer to Section 6.7 and Section 6.8), including specific guidance for infusion-related reactions, ILD/pneumonitis, rash, or liver test abnormalities.
- The safety of amivantamab in combination with carboplatin and pemetrexed is being investigated in a Phase 1 study (61186372EDI1001) and results from this cohort have been updated in the IB.[12]
- An Independent Data Monitoring Committee (IDMC) will review safety and tolerability data periodically (refer to Appendix 2: Regulatory, Ethical, and Study Oversight Considerations). The IDMC has reviewed safety results for amivantamab in combination with carboplatin and pemetrexed in the ongoing Phase 1 study prior to enrollment of participants in this Phase 3 study. In addition, an early IDMC meeting is planned after approximately 20 participants have been randomized and treated for 2 cycles with the protocol treatment for additional review of the safety with this combination.
- If regulatory or health authorities request region specific safety experience for amivantamab in combination with carboplatin-pemetrexed, an optional Safety Run-in may be performed to collect region/country-specific safety data (refer to Appendix 10: Safety Run-in).

2.3.2. Benefits for Study Participation

As described in the previous sections, there are no approved targeted therapies for the treatment of NSCLC with EGFR Exon 20ins mutations. Amivantamab has demonstrated significant activity as monotherapy in this disease population, and platinum-based combination chemotherapy is the accepted standard of care in the first-line setting. It is anticipated that combining these therapeutic approaches with non-overlapping mechanisms of action—targeted therapy with amivantamab and combination chemotherapy—will be more effective than either approach alone for the treatment of NSCLC with EGFR Exon 20ins mutations.

2.3.3. Benefit-Risk Assessment for Study Participation

Considering the measures taken to minimize risk to participants of this study (refer to Section 2.3.1), the potential risks of combining amivantamab and platinum-based doublet chemotherapy are justified by the anticipated benefits that may be afforded to participants with EGFR Exon 20ins-mutated metastatic NSCLC (refer to Section 2.3.2). More detailed information about known and expected benefits and risks of amivantamab can be found in the latest version of the IB for amivantamab.[12]

3. OBJECTIVES AND ENDPOINTS

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 blinded independent central review (BICR)
Secondary	
To further assess the clinical benefit achieved with amivantamab in combination with chemotherapy, versus chemotherapy alone	• Objective response rate • 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	
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; EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol five-dimensional descriptive system (5-level version); NGS = next-generation sequencing; PFS = progression free survival; PK = pharmacokinetics; PRO=patient-reported outcomes; PROMIS-PF = Patient-Reported Outcomes Measurement Information System – Physical Function; RECIST = Response Evaluation Criteria in Solid Tumors.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The hypothesis is that amivantamab, when given in combination with standard of care carboplatin-pemetrexed chemotherapy, will prolong PFS compared with carboplatin-pemetrexed in patients with locally advanced or metastatic NSCLC characterized by EGFR Exon 20ins activating mutations.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, open-label, multicenter, Phase 3 study of combination amivantamab and carboplatin-pemetrexed therapy, compared with carboplatin-pemetrexed, in patients with treatment-naïve, locally advanced or metastatic NSCLC characterized by EGFR Exon 20ins activating mutations. A target of 300 participants will be randomly assigned in this study.

The study will include a Screening phase (Section 4.1.1), a Treatment phase (Section 4.1.2), and a Follow-up phase (Section 4.1.3). An IDMC will be commissioned for this study for the periodic review of safety and tolerability data, as well as planned efficacy analyses (refer to Appendix 2: Regulatory, Ethical, and Study Oversight Considerations). Additional ad-hoc meetings may occur as needed.

A diagram of the study design is provided in Section 1.2, Schema.

4.1.1. Screening Phase

The participant must sign an informed consent form (ICF) at the beginning of the Screening phase, before the first study-related activity is conducted. Participants will be evaluated for eligibility during Screening. Participants must complete all Screening procedures within 28 days of randomization, including submission of test results for Exon 20ins mutation, submission of a tumor biopsy sample, submission of peripheral blood samples for circulating tumor deoxyribonucleic acid (ctDNA), baseline imaging of disease sites, and baseline Brain MRI.

4.1.2. Treatment Phase

The Treatment phase for each participant will begin at Cycle 1 Day 1 and continue in 21-day cycles until the End of Treatment visit, approximately 30 days after discontinuation of study treatment. Study treatment will continue until documented clinical or radiographic (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) disease progression or until the participant meets another criterion for discontinuation of study treatment (Section 7.1). Approximately 300 eligible participants will be stratified based on Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no), and assigned randomly in a 1:1 ratio into 1 of 2 treatment arms as follows:

Arm A (amivantamab plus chemotherapy):

- 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
- 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

Arm B (chemotherapy alone):

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

Disease assessments will occur as close as possible to the start of treatment (baseline screening scans), 6 weeks (+1 week) after randomization, then every 6 weeks (±1 week) for the first 18 months and then every 12 weeks (±1 week), until objective radiographic disease progression.

At each study visit during the Treatment phase, participants will undergo safety evaluations, including physical examinations and assessment of TEAEs, vital signs, concomitant medication usage, and clinical laboratory parameters. Participants will complete questionnaires for patient-reported outcomes (PROs) at selected visits. Participants will also have blood samples drawn for assessment of PK and immunogenicity parameters, and for biomarker evaluations, at selected visits. Post-progression biopsy will be obtained, if clinically feasible, within 30 days of disease progression and before the next anti-cancer therapy.

Continuation of study treatment after disease progression by RECIST v1.1, as confirmed by blinded independent central review (BICR) may be allowed after approval from the Medical Monitor, if the investigator believes the participant is deriving clinical benefit. Participants continuing treatment after documented progression will continue within the Treatment phase of the study and comply with all associated visits and procedures, including scheduled disease assessments, until the termination of study treatment.

A participant in Arm B with disease progression by RECIST v1.1, as confirmed by BICR, may cross over to amivantamab monotherapy (refer to Appendix 11: Optional Crossover After Disease Progression to Second-Line Amivantamab Monotherapy (Arm B Only)).

4.1.3. Follow-up Phase

Participants who discontinue assigned study treatment for any reason will be followed for subsequent therapy, disease status, survival, and symptomatic progression in the Follow-up phase. This phase starts from the End of Treatment Visit and continues until the end of study, death, loss to follow-up, or withdrawal of consent from participation in the study, whichever comes first. Visits (or telephone contact) will occur approximately every 12 weeks during the Follow-up phase. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the case report form (CRF) when available. Where allowed by local law, public records may be used to document death for obtaining survival status.

Note: For participants who discontinue prior to disease progression by BICR, tumor imaging should continue per schedule of activities.

4.1.4. Open-label Extension Phase and Long-term Extension Phase

Following the primary analysis for efficacy, the study will transition to an open-label extension (OLE) Phase (see details provided in Section 10.14 [Appendix 14]). Participants will be provided the option to continue treatment in the OLE Phase until the final analysis for overall survival, after which the study will transition to a long-term extension (LTE) Phase.

Participants who continue to benefit from study treatment(s), as determined by their investigator, at the time of the OLE Phase may continue to receive access to study treatment(s) within the study by transferring to the LTE Phase, where only serious adverse event data and study treatment accountability will be collected.

The LTE Phase (see details provided in Section 10.15 [Appendix 15]) will begin after the final analysis for overall survival, and will continue until the discontinuation criteria described in Section 7.1 are met, or until 2 years after local marketing authorization is obtained for the studied indication, whichever occurs first.

The extension phases will begin after approval of Amendment 3 by health authorities of countries in which this study is still being conducted at the time of transition, and by study site ECs/IRBs. In addition, for transition to the LTE Phase (after final analysis for overall survival), prior notification from the sponsor will be needed.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Study Treatment Groups

Randomization will be used to minimize bias in the assignment of participants to study treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across study treatment groups, and to enhance the validity of statistical comparisons across study treatment groups. Due to differences in safety profile, safety monitoring, premedication requirements, and administration, blinded study treatment and a placebo control will not be used.

Clinical Pharmacology Assessments

Blood samples will be analyzed for amivantamab serum concentrations and estimation of PK parameters. Immunogenicity (antibodies to amivantamab) will be evaluated for impact on PK, safety and efficacy. A population PK model will be developed as a means to derive the individual participant's exposure, for determination of participant covariates that influence the PK of amivantamab, and for exposure-response analysis to support regulatory submission.

ctDNA and Biomarker Collection

Tumor biopsy samples will be collected to evaluate pretreatment mutational status of EGFR (Exon 20ins and co-occurring EGFR mutations), MET, and other key oncogenes to characterize the tumor or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to a study treatment.

The ctDNA and serum biomarker samples may be used to better understand dynamics of tumor response and/or resistance to therapy and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Thorough scientific evaluation of any treatment before market authorization is an ethical requirement. As the benefits and risks of the combination of amivantamab and chemotherapy in this study population are not fully known, this study will evaluate the safety and clinical activity of this combination. Participants will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit. The IDMC will review evolving safety data from this study, as well as efficacy data as appropriate. Based on the mechanism of action of both study treatments, there is adequate justification, including significant unmet clinical need, for evaluating these drugs in combination for the treatment of NSCLC in participants who are eligible for this study.

All participants will undergo regular disease assessments to monitor the underlying disease. In general, these procedures are routinely performed during a participant's diagnostic workup and follow-up care; therefore, archival tumor material collected at the time of locally advanced or metastatic diagnosis may be submitted in lieu of pre-treatment biopsies. A post-progression biopsy should be performed within 30 days of the last dose of study treatment and before the start of next anticancer treatment, if clinically feasible. Although biopsy collection is associated with risk, the complication rate for these procedures is low. The data obtained from this procedure will generate valuable scientific data on the pharmacodynamic effect of the combination of these study treatments in this study population.

As with all clinical and pharmacology studies, there are risks associated with venipuncture and multiple blood sample collection. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacology of the study treatment. This minimizes the number of venipunctures and the total volume of blood collected from each participant during the study. The total blood volume to be collected (see Section 8) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.[4]

4.3. Justification for Dose

4.3.1. Chemotherapy Dose Rationale

Participants in this study will receive chemotherapy with clinically approved doses of pemetrexed 500 mg/m^2 and carboplatin AUC 5 on the first day of every 21-day cycle. Platinum-based combination chemotherapy is a commonly used regimen for all patients with NSCLC, either alone or in approved combinations with anti-PD-1 agents, anti-PD-L1 agents, or bevacizumab, as well as investigational approaches such as in combination with an EGFR TKI. Although targeted EGFR TKIs are now standard of care for the first-line treatment of the majority of EGFR-mutated NSCLC (eg L858R, Exon19del), no targeted therapies are approved for the treatment of EGFR Exon 20ins NSCLC. Platinum-based doublet chemotherapy is therefore considered the standard of care for first-line treatment of newly diagnosed patients with advanced or metastatic EGFR Exon 20ins NSCLC and will be used as the control arm in this study. Among patients with metastatic adenocarcinoma, the combination of carboplatin and pemetrexed has become a preferred regimen based upon the superior tolerability and the ability to continue pemetrexed as a maintenance therapy in patients continuing to derive benefit after completion of combination therapy.

4.3.2. Amivantamab and Chemotherapy Combination Dose Rationale

Combination of amivantamab with standard of care carboplatin and pemetrexed chemotherapy may provide improved treatment outcomes than either regimen alone. The safety of chemotherapy combinations with EGFR-targeted monoclonal antibody therapy has been previously demonstrated in randomized, Phase 3 studies.[21,23] To optimize treatment with this potential combination, the amivantamab dosing schedule in this study allows dosing on the same 21-day chemotherapy regimen schedule.

In the ongoing Phase 1 Study 61186372EDI1001, amivantamab has been generally well tolerated up to the dose of 1,750 mg administered weekly for the first cycle, and every 2 weeks thereafter, on a 28-day cycle. No dose-limiting toxicity (DLTs) were reported during dose escalation and no maximum tolerated dose identified. Moreover, amivantamab had no apparent dose dependent TEAEs in the dose range of 350 to 1,400 mg. While the RP2D of amivantamab has been established as 1,050 mg for body weight <80 kg or 1,400 mg for body weight ≥80 kg when administered weekly for the first cycle and every 2 weeks thereafter, tolerability has been demonstrated up to a dose of 1,750 mg: of the first 5 subjects enrolled in the Phase 1 study at 1,750 mg, 3 subjects achieved treatment durations of at least 9 cycles. Of the 5 subjects enrolled at 1,750 mg, all had baseline body weight <80 kg (mean [range] body weight of 66 kg [58.0-79.4]), and 3 of these subjects were treated with 1,750 mg biweekly dosing beyond the anticipated 4 cycles planned to be administered in combination with chemotherapy (6, 8, and 9 cycles, respectively). The mean (%CV) maximum concentration and maximum exposure (AUC_{2week}) achieved after the weekly induction dosing of 1,750 mg on the 28-day cycle were 1,355 (21%) µg/mL and 10,932 (25%) µg×day/mL respectively.

Amivantamab has therefore been demonstrated to have an adequate therapeutic window using the 28-day cycle (every 2 weeks) dosing regimen. The planned amivantamab dosing according to the

21-day cycle is 1,400 mg for body weight <80 kg and 1,750 mg for body weight ≥80 kg once weekly up to Cycle 2 Day 1 (induction period), then 1,750 mg for body weight <80 kg and 2,100 mg for body weight ≥80 kg on Day 1 of each 21-day cycle, starting with Cycle 3 (maintenance period). This dosing regimen is intended to achieve equivalent exposures to every 2-week dosing regimen using the 28-day cycle.

During the induction period, the anticipated maximum serum concentration (C_{max}) achieved with 21-day cycles (4 weekly doses) will be lower than that observed for 1,750 mg with 28-day cycles (5 weekly doses) in the Phase 1 study. During the maintenance period, at the proposed dose of 2,100 mg for body weight ≥80 kg every 3 weeks, the anticipated exposures will be lower or within the already safely explored exposure range. Population PK simulation suggests that the maximum median predicted drug concentration at the proposed dose of 2,100 mg is 703 (95% confidence interval [CI]: 358, 1,372) µg/mL, which is within the observed concentration in the amivantamab monotherapy 1,750 mg cohort (Table 3). Moreover, the simulated exposure (AUC_{3weeks}) of 5,883 (95% CI: 3,004, 12,138) µg×day/mL achieved with 2,100 mg every 3 weeks is less than the observed maximum exposure after the weekly induction dosing of 1,750 mg on the 28-day cycle (Table 3). Thus, the population PK simulations demonstrate that the anticipated exposures in the 21-day cycle dosing will be within the exposures already demonstrated to be safe and tolerable in the amivantamab monotherapy cohort of the ongoing Phase 1 Study. Further, dosing of amivantamab in combination with chemotherapy is also being explored in the ongoing Phase 1 Study.

In the ongoing Phase 1 Study 61186372EDI1001, Cycle 1 PK data suggest no impact of chemotherapy on amivantamab exposure. Preliminary trough concentration comparisons suggest that higher doses of amivantamab given every 3 weeks (Q3W; 21-day cycle), are similar to the recommended dose for monotherapy given every 2 weeks (28-day cycle). Please refer to the latest version of the IB for further information.[12]

Table 3: Comparison of Observed Maximum Exposures Attained After Weekly Induction with 1,750 mg in the 28-Day Cycle and Expected Steady State Exposure Attained With 2,100 mg Every 3 Weeks in the 21-day Cycle

Dose (mg)	Regimen	Data	C_{max}, µg/mL	AUC, µg×day/mL
1,750[a]	After induction (28-day cycle)	Observed mean (CV%)	1,355 (21%)	10,932 (25%)
2,100[b]	Every 3 weeks (21-day cycle)	Simulated median (95%CI)	703 (358, 1372)	5,883 (3004, 12138)

a. Mean [range] body weight = 66 [58.0-79.4] kg.
b. Simulation for body weight ≥80 kg.

4.4. End of Study Definition

End of Study Definition

A final analysis for overall survival is planned to occur approximately 48 months after the first participant is randomized. The end of study/study completion is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement. The sponsor will establish a clinical data cutoff date for clinical study report (CSR)

analysis reporting. The data cutoff will be communicated to the sites. Subjects who continue to receive study drug or who are in Follow-up after the data cutoff will continue to be monitored. These data will be reported to the appropriate health authorities in a CSR addendum.

Study Completion Definition

A participant will be considered to have completed the study if he or she has died before the end of the study or has not prematurely discontinued the study for another reason.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days prior to randomization. Refer to Section 5.4 for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Participant must be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Participant must have histologically or cytologically confirmed, locally advanced or metastatic, nonsquamous NSCLC with documented primary EGFR Exon 20ins activating mutation (a copy of the mutation analysis must be submitted during screening) performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified (US sites) or an accredited (outside of the US) local laboratory.

3. Participant must have measurable disease according to RECIST v1.1. If only one measurable lesion exists, it may be used for the screening biopsy (if required for submission of tumor tissue) if the baseline tumor assessment scans are performed ≥14 days after the biopsy.

4. Participant must have ECOG performance status 0 or 1.

5. Participant must agree to genetic characterization of tumor status through the required pretreatment tumor biopsy (or submission of equivalent archival material), as well as baseline and periodic blood samples for analysis of tumor mutations in the bloodstream.

6. Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion or platelet transfusion within 7 days prior to the date of the laboratory test.

   - Hemoglobin ≥10 g/dL
   - Absolute neutrophil count ≥1.5×10^9/L, without use of granulocyte colony-stimulating factor (G-CSF) within 10 days prior to the date of the test
   - Platelets ≥100×10^9/L
   - ALT and aspartate aminotransferase (AST) ≤3×upper limit of normal (ULN)
   - Total bilirubin ≤1.5×ULN (participants with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits)
   - Creatinine clearance >50 mL/min as measured or calculated by Cockcroft-Gault formula

7. Participant must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

8. A female participant of childbearing potential must have a negative serum or urine test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.

9. Criterion modified per Amendment 1:

   9.1. A female participant must be (as defined in Appendix 4: Contraceptive and Barrier Guidance) either of the following:

      a. Not of childbearing potential
      b. Of childbearing potential and practicing 2 methods of contraception, including 1 highly effective, user independent method. Examples of highly effective methods of contraception are located in Appendix 4: Contraceptive and Barrier Guidance.

   Participant must agree to continue contraception throughout the study and through 6 months after the last dose of study treatment.

   Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) the woman must begin 2 methods of birth control, as described above.

10. A female participant must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study treatment.

11. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 6 months after receiving the last dose of study treatment. If the participant is vasectomized, he

must still use a condom (with or without spermicide) for prevention of passage of exposure through ejaculation, but his female partner is not required to use contraception.

A male participant who is sexually active with a woman of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository and his partner must also be practicing a highly effective method of contraception (ie, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]).

12. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study treatment.

13. Participant must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendment 1:

   1.1. Participant has received any prior systemic treatment for locally advanced or metastatic disease, with the following exceptions:

   - Prior adjuvant or neoadjuvant platinum-based doublet chemotherapy is allowed, if completed at least 12 months prior to signing the study ICF.

   - Localized radiotherapy to the lung must be completed at least 6 months prior to randomization. Palliative radiation to other sites must be completed at least 7 days prior to randomization.

   - Prior monotherapy with an approved EGFR TKI (ie, gefitinib, erlotinib, afatinib, dacomitinib, or osimertinib) as non-standard first-line therapy for the treatment of locally advanced or metastatic disease is allowed, if: 1) treatment duration did not exceed 8 weeks; 2) lack of disease response was documented (radiographically) by an increase in tumor burden (a copy of the computerized tomography [CT] report showing increase in tumor burden from baseline should be submitted); 3) associated toxicities have resolved to baseline; and 4) the EGFR TKI was discontinued at least 2 weeks or 4 half-lives prior to randomization, whichever is longer. Prior therapy with investigational EGFR TKI agents targeting Exon 20ins mutations, including TAK788 or poziotinib, is not allowed.

2. Criterion modified per Amendment 1:

   2.1. Participant has evidence of synchronous NSCLC disease (as suggested by genetic characterization or radiographic appearance).

3. Participant has untreated brain metastases (a participant with definitively, locally treated metastases who is clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization is eligible). If brain metastases are diagnosed on Screening imaging, the participant may be rescreened for eligibility after definitive treatment.

4. Participant has a history of leptomeningeal disease.

5. Participant has history of spinal cord compression that has not been treated definitively with surgery or radiation.

6. Participant has uncontrolled tumor-related pain (symptomatic lesions amenable to palliative radiotherapy [eg, bone metastases or metastases causing nerve impingement] should be treated prior to Screening).

7. Participant has a medical history of ILD, including drug-induced ILD, or radiation pneumonitis.

8. Criterion modified per Amendment 1:

   8.1. Participant has an active malignancy (ie, ongoing, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

   a. Non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.
   b. Skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
   c. Non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
   d. Localized prostate cancer (N0M0):
      - with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance,
      - with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence,
      - or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
   e. Breast cancer:

- adequately treated lobular carcinoma in situ or ductal carcinoma in situ,
- or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.

f. Malignancy that is considered cured with minimal risk of recurrence

9. Participant has a history of clinically significant cardiovascular disease including, but not limited to:

- Diagnosis of deep vein thrombosis or pulmonary embolism within 1 month prior to randomization or any of the following within 6 months prior to randomization: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated clots, are not exclusionary.
- Prolonged corrected QT interval by Fridericia's (QTcF) >480 msec, clinically significant cardiac arrhythmia, or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate)
- Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg
- Congestive heart failure defined as New York Heart Association (NYHA) Class III-IV or hospitalization for congestive heart failure (any NYHA class) within 6 months of study Day 1 (refer to Appendix 6: New York Heart Association Criteria)
- Pericarditis/clinically significant pericardial effusion
- Myocarditis
- Baseline left ventricular ejection fraction below the lower limit of normal as assessed by screening echocardiogram (ECHO) or multigated acquisition scan.

10. Participant has at Screening:

- Positive hepatitis B (hepatitis B virus [HBV]) surface antigen (HBsAg).

  Note: Participants with a prior history of HBV demonstrated by positive hepatitis B core antibody are eligible if they have at Screening 1) a negative HBsAg and 2) an HBV deoxyribonucleic acid (DNA; viral load) below the lower limit of quantification, per local testing. Participants with a positive HBsAg due to recent vaccination are eligible if HBV DNA (viral load) is below the lower limit of quantification, per local testing.
- Positive hepatitis C (hepatitis C virus [HCV]) antibody (anti-HCV)

  Note: Participants with a prior history of HCV who have completed antiviral treatment and have subsequently documented HCV ribonucleic acid (RNA) below the lower limit of quantification per local testing are eligible.
- Other clinically active infectious liver disease.

11. Criterion modified per Amendment 1:

    11.1. Participant is known to be positive for human immunodeficiency virus (HIV) and meets one of the following criteria:

    - Not receiving highly active antiretroviral therapy (ART)
    - Had a change in antiretroviral therapy within 6 months of the start of screening
    - Receiving antiretroviral therapy that may interfere with study treatment (consult Sponsor for review of medication prior to enrollment)
    - CD4 count <350 at screening
    - AIDS-defining opportunistic infection within 6 months of start of screening
    - Not agreeing to start ART and be on ART >4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled).

12. Participant has an uncontrolled illness, including but not limited to the following:

    - Diabetes
    - Ongoing or active bacterial infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week before randomization]), symptomatic viral infection, or any other clinically significant infection
    - Active bleeding diathesis
    - Impaired oxygenation requiring supplemental oxygen
    - Psychiatric illness/social situation that would limit compliance with study requirements

13. Participant had major surgery (eg, requiring general anesthesia) or significant traumatic injury within 4 weeks of randomization, will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

14. Participant has a contraindication to the use of carboplatin or pemetrexed (refer to local prescribing information for each agent[2,5]). Participant has a history of hypersensitivity to, or cannot take, vitamin B12 or folic acid.

15. Participant has a history of hypersensitivity to the excipients of amivantamab (refer to the IB[12]).

16. Participant has received a live or live attenuated vaccine within 3 months before randomization.

17. Participant has received an investigational intervention (including investigational vaccines) within 6 weeks before randomization.

18. Participant is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment.

19. Participant plans to father a child while enrolled in this study or within 6 months after the last dose of study treatment.

20. Participant has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators must ensure that all study enrollment procedures have been completed during the screening period and the subject continues to meet eligibility at the time of randomization, is clinically stable and is expected to initiate therapy within 72 hours of randomization. The required source documentation to support meeting the enrollment criteria are noted in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.6.3 for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Agree to use sun protective measures (such as a hat, sunglasses, and protective clothing), limit prolonged exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) from baseline until the last dose of study treatment. Avoid unnecessary exposure to sunlight. Use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥30 (refer to Section 6.8.2.1).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by

the sponsor study-site contact for completeness. This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Participants who are determined to be eligible for the study after their condition changes must sign a new ICF.

6. STUDY MEDICATION AND CONCOMITANT THERAPY

Refer to the Investigational Product Preparation Instructions (IPPI) or the study Site Investigational Product and Procedures Manual (SIPPM) for detailed guidance on amivantamab dosage and administration.

6.1. Study Treatments Administered

For this study, "study treatment" refers to JNJ-61186372 (amivantamab), carboplatin, and pemetrexed.

Study treatment administration must be captured in the source documents and the CRF. Study-site personnel will instruct participants on how to store and administer required premedications at home as required for this protocol.

Amivantamab will be manufactured and provided under the responsibility of the sponsor. Refer to the latest version of the IB for a list of excipients.

For information related to study treatment overdose, refer to Section 6.9, Treatment of Overdose.

6.2. Dosage and Administration of Study Treatment

6.2.1. Scheduled Dosage and Timing

Administration of study treatment should begin within 3 days of randomization. The scheduled dosage and timing of each study treatment are outlined in Table 4. On Day 1 of each cycle in which combination therapy is administered, they should occur in the following order: 1) pemetrexed, 2) carboplatin, and 3) amivantamab.

The proposed timing for carboplatin and pemetrexed should be according to the local guidelines and regulatory labeling (eg, pemetrexed can be given over approximately 10 to 15 minutes and carboplatin can be given over approximately 30 to 60 minutes). Refer to IPPI for detailed information on amivantamab administration. Due to the multiple infusions in Arm A, dosing should be scheduled to begin with sufficient time to accommodate all infusions on Cycle 1 Day 1.

If, however, delays in initiation of therapy leave insufficient time on Cycle 1 Day 1 for full amivantamab dosing, the initial split dose of amivantamab (Cycle 1 Days 1 and 2) may be delayed (until Cycle 1 Days 2 and 3), with corresponding changes to scheduled activities (PK and vital signs), and should be reported in the electronic case report form (eCRF) as a dose delay. If amivantamab treatment is delayed from Cycle 1 Day 1 to Day 2 and Cycle 1 Day 2 to Day 3, appropriate premedications should be administered before amivantamab infusion. Please refer to Table 6 for premedications required with amivantamab.

Table 4: Scheduled Dosages and Timing of Study Treatments, by Study Visit (21-Day Cycles)

Study Visit Study Treatment (Study Arm)	Study Treatment Dosage
Cycle 1 Day 1	
Pemetrexed (Arm A + Arm B)	500 mg/m^2
Carboplatin (Arm A + Arm B)	AUC 5; maximum of 750 mg
Amivantamab (Arm A only)	350 mg
Cycle 1 Day 2	
Amivantamab (Arm A only)	1,050 mg (if <80 kg) 1,400 mg (if ≥80 kg)
Cycle 1 Day 8	
Amivantamab (Arm A only)	1,400 mg (if <80 kg) 1,750 mg (if ≥80 kg)
Cycle 1 Day 15	
Amivantamab (Arm A only)	1,400 mg (if <80 kg) 1,750 mg (if ≥80 kg)
Cycle 2 Day 1	
Pemetrexed (Arm A + Arm B)	500 mg/m^2
Carboplatin (Arm A + Arm B)	AUC 5; maximum of 750 mg
Amivantamab (Arm A only)	1,400 mg (if <80 kg) 1,750 mg (if ≥80 kg)
Cycles 3-4 Day 1	
Pemetrexed (Arm A + Arm B)	500 mg/m^2
Carboplatin (Arm A + Arm B)	AUC 5; maximum of 750 mg
Amivantamab (Arm A only)	1,750 mg (if <80 kg) 2,100 mg (if ≥80 kg)
Cycles 5+ Day 1	
Pemetrexed (Arm A + Arm B)	500 mg/m^2
Amivantamab (Arm A only)	1,750 mg (if <80 kg) 2,100 mg (if ≥80 kg)

AUC=area under the concentration-time curve 5 mg/mL per minute.

Amivantamab should typically be administered Q3W but if amivantamab dosing needs to align with a delayed dose of chemotherapy then it can be administered at an interval between 2 and 4 weeks (see Appendix 9: Dosing Synchronization for Arm A). Any missed scheduled doses should be discussed with the Medical Monitor prior to redosing. If a dose is delayed on Cycle 1 Day 8 and/or Cycle 1 Day 15 it will not be made up. If a dose is delayed in Cycle 2 or beyond, then the dates of the subsequent doses will be scheduled based on the timing of the previous dose

of amivantamab. If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing.

6.2.2. Chemotherapy

Chemotherapy will be supplied as carboplatin (600 mg/vial, with concentration 10 mg/mL in a 60 mL vial) and pemetrexed (500 mg/vial powder for concentration for solution for infusion). Refer to the local prescribing information for each agent for a list of excipients.[2,5]

6.2.3. Amivantamab

Amivantamab is supplied for this study in a glass vial containing 350 mg/vial with concentration 50 mg/mL, 7 mL per vial. Amivantamab will be manufactured and provided under the responsibility of the sponsor. Refer to the latest version of the IB for a list of excipients.[12]

The dosage of amivantamab will be based on the participant's body weight at Screening. Qualified site personnel will administer amivantamab as an intravenous (IV) infusion in 21-day cycles as follows:

- Once weekly (with the first dose split over Days 1-2) up to Cycle 2 Day 1: 1,400 mg (1,750 mg if body weight is ≥80 kg)
- Cycles 3+: 1,750 mg (2,100 mg if body weight is ≥80 kg) on Day 1 of each 21-day cycle

Amivantamab will be administered by IV using the escalating infusion rate regimen as specified in the IPPI. The product must be infused via a peripheral vein for all Cycle 1 doses; infusion via central line is allowed for subsequent dosing starting with the Cycle 2 Day 1 dose. In cases where peripheral access may be limiting to treatment administration, earlier use of a central line for amivantamab infusion in Cycle 1 starting after Cycle 1 Day 8 may be considered, only after prior approval with the Medical Monitor.

Infusion durations that exceed the planned length of time due to IV bag overfill, minor equipment calibration factors, and/or participant factors not under the control of administering personnel will not be considered protocol deviations. The actual infusion time should be accurately recorded. Refer to IPPI for information describing the stability and administration of amivantamab.

Amivantamab must be administered according to the procedures described in the IPPI and clinical protocol, under the supervision of qualified staff. Additional guidance is provided below:

- Do not mix or dilute amivantamab with other drugs.
- Amivantamab must not be administered as an IV push or bolus.
- Due to the risk of infusion-related reactions, equipment and agents for treating anaphylaxis (eg, epinephrine, corticosteroids, IV antihistamines, bronchodilators, oxygen, resuscitation equipment) must be available during amivantamab administration. Trained personnel (eg, resuscitation team) must also be available.

After 12 cycles of amivantamab (1 year), participants receiving the full dosage of amivantamab can skip up to 3 doses in a year and participants on a reduced dose of amivantamab (refer to

Section 6.8.2) can skip up to 2 doses in a year, as needed for life events. The skipped doses should be at least 3 months apart.

6.3. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

The instructions below on study treatment preparation, handling, and storage apply only to amivantamab and/or centrally sourced chemotherapy. For locally sourced chemotherapy, please follow the instructions on the local package insert.

All study treatment must be stored at controlled temperatures according to the requirements on the label and protected from light prior to use. Refer to the pharmacy manual/SIPPM for additional guidance on study treatment preparation, handling, and storage.

Accountability

The instructions below on study treatment apply only to amivantamab and/or centrally sourced chemotherapy. For locally sourced chemotherapy, please follow the instructions on the local package insert.

The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. The study treatment administered to the participant must be documented on the study treatment accountability form. All study treatment will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study treatment containers.

Study treatment must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment, and study treatment returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study treatment, or used returned study treatment for destruction, will be documented on the study treatment return form. When the study site is an authorized destruction unit and study treatment supplies are destroyed on-site, this must also be documented on the study treatment return form.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, syringes and vials, should be disposed of immediately in a safe manner and therefore will not be retained for study treatment accountability purposes.

Study treatment should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants participating in the study. Study treatment may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study treatments are provided in the Study Reference Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

Study Treatment Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 study treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by ECOG performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no). The interactive web response system (IWRS) will assign a unique study treatment code, which will dictate the study treatment assignment and matching study treatment kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

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

6.5. Study Treatment Compliance

The instructions below on study treatment compliance apply only to amivantamab and/or centrally sourced chemotherapy. For locally sourced chemotherapy, please follow the instructions on the local package insert.

The study personnel at the study site will account for all study treatments dispensed and for appropriate return. The certificates of delivery and return should be signed.

Amivantamab is to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms. The study treatment may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing. Amivantamab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the eCRF (including date, start, and stop times of the IV infusion, and volume infused). Dispensing of all study treatment must also be recorded in the participant's source documents.

Pemetrexed and carboplatin will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the eCRF (including date, start, and stop times of the IV infusion, and volume infused). Dispensing of all study treatment must also be recorded in the participant's source documents.

Administration of pre-infusion medications will be documented in the source documents and eCRF.

6.6. Concomitant Therapy

6.6.1. Recording Prestudy and Concomitant Therapies

Prestudy therapies administered up to 28 days before randomization must be recorded at Screening. Concomitant therapies must be recorded throughout the study beginning when the ICF is signed and continuing until 30 days after the last dose of study treatment or start of new anticancer therapy, whichever is first. Concomitant therapies used in conjunction with new or worsening adverse events considered related to study treatment should be recorded through the end of follow-up of that adverse event.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study treatment must be recorded in the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.6.2. Permitted Medications and Therapies

6.6.2.1. Pre- and Post-infusion Medications for Chemotherapy

Corticosteroids, folic acid, and vitamin B12 will be administered concomitantly with pemetrexed according to local prescribing information (Table 5) or per standard local practice.

Table 5: Concomitant Medications for Pemetrexed

Medication	Dose	Timing
Corticosteroid	Dexamethasone 4 mg orally twice daily or equivalent	1 day before, the day of, and 1 day after each dose of pemetrexed[a]
Folic Acid[b]	350-1,000 µg orally	Daily beginning 7 days prior to first infusion and continuing until 21 days after the last dose of pemetrexed
Vitamin B12	1,000 µg intramuscularly	1 dose within 7 days of Cycle 1 Day 1, then every 3 cycles afterwards. Vitamin B12 may be administered on the same day as pemetrexed

a. Dexamethasone 4 mg orally twice daily dose can be skipped on Cycle 1 Day 1, if patient is administered 20 mg IV dose of dexamethasone with amivantamab
b. Folic acid may be given either as a separate preparation or as a component of a multivitamin.

Participants may receive other pre-treatment or concomitant treatment for pemetrexed or carboplatin as recommended by local prescribing information,[2,5] local practice guidelines, or as clinically indicated. Permitted prophylactic medications may include the following:

- Appropriate prophylactic antiemetic regimens for high risk of emesis associated with carboplatin (eg, ondansetron, aprepitant, dexamethasone), in accordance with institutional practice or current NCCN and/or ESMO guidelines.
- Leukocyte-depleted blood transfusions are allowed at any time after randomization.

- G-CSFs should not be used prophylactically during Screening. Use of prophylactic colony stimulating factors may be considered after randomization as per local guidelines or prescribing information.[2,5]

Concomitant medications for the symptomatic treatment of related toxicities (Grade 1-4) may be administered according to the standard of care at the site and at the treating physician's discretion, as clinically indicated. Supportive care and other medications that are considered necessary for the participant's well-being may be given at the discretion of the investigator.

Localized, limited radiotherapy of short duration for palliative purposes may be permitted but only after discussion with and approval by the Medical Monitor.

6.6.2.2. Pre- and Post-Infusion Medications for Amivantamab

Pre-Infusion Medications

Required pre-infusion medications and optional pre-infusion medications for amivantamab are summarized in Table 6.

Table 6: Pre-Infusion Medications for Amivantamab

Cycle/Day	Medication	Dose	Route of Administration	Recommended Dosing Window Before Amivantamab Infusion
Required Pre-Infusion Medications[a,b]				
Cycle 1 Day 1	Glucocorticoid	Dexamethasone 20 mg	IV	45 to 60 minutes
Cycle 1 Day 2	Glucocorticoid	Dexamethasone 10 mg or Methylprednisolone 40 mg	IV	45 to 60 minutes
All	Antihistamine	Diphenhydramine 25 to 50 mg (or equivalent)	IV	15 to 30 minutes
			Oral	30 to 60 minutes
All	Antipyretic	Paracetamol (acetaminophen) 650 to 1,000 mg (or equivalent)	IV	15 to 30 minutes
			Oral	30 to 60 minutes
Optional Pre-Infusion Medications[a]				
Cycle 1 Day 8 and beyond	Glucocorticoid[c]	Dexamethasone 10 mg or methylprednisolone 40 mg	IV	45 to 60 minutes
			Oral	60 to 90 minutes
Any	Histamine H_2-antagonist	Ranitidine 50 mg (or equivalent)	IV	15 to 30 minutes
Any	Antiemetic	Ondansetron 8-16 mg (or equivalent)	Oral or IV	15 to 30 minutes

IV=intravenous.

a. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.

b. Participants for whom required medications are contraindicated should explore alternative medications with their study doctor. If alternative medications are not suitable for the intent above, participants are not required to take the corresponding medication.

c. Beginning with Cycle 1 Day 8, optional pre-dose steroids may be administered prior to amivantamab if clinically indicated for participants who experienced an infusion-related reaction on Cycle 1 Day 1 or Cycle 1 Day 2.

Examples of specific schedules for administration of study treatments and concomitant therapies in Arm A are shown in the following tables:

- Table 7: When amivantamab is given with carboplatin and pemetrexed (Day 1 of Cycles 1 to 4)
- Table 8: When amivantamab is given without chemotherapy (eg, Days 2, 8, and 15 of Cycle 1)
- Table 9: When amivantamab is given with pemetrexed (Day 1 of Cycles 5+)

Table 7: Suggested Order of Administration When Amivantamab is Given With Carboplatin and Pemetrexed on Day 1 of Cycles 1-4 in Arm A

Medication	Dose	Route of Administration	Recommended Dosing Window
Antiemetic for chemotherapy	Ondansetron 8 to 16 mg or equivalent[a]	IV	Start 60-90 minutes before amivantamab infusion; administer in the order indicated
	Fosprepitant/Aprepitant [a]	IV	
Antihistamine for chemotherapy	Diphenhydramine 25 mg or equivalent[a]	Oral	
Antipyretic for chemotherapy	Paracetamol (acetaminophen) 325 to 500 mg (or equivalent)[a]	Oral	
Glucocorticoid	Day 1 of Cycle 1: Dexamethasone 20 mg[b] Day 1 of Cycles 2, 3, 4: Dexamethasone 10 to 12 mg as per local practice and guidelines for chemotherapy[a]	IV	
Chemotherapy	Pemetrexed	IV	-
Chemotherapy	Carboplatin	IV	-
Antipyretic for amivantamab	Paracetamol (acetaminophen) 325 to 500 mg (or equivalent)[b]	IV or oral	Start 15-30 minutes before amivantamab infusion
Antihistamine for amivantamab	Diphenhydramine 25 mg or equivalent[b]	IV	
Study treatment	Amivantamab	IV	-

IV=intravenous.
a. Other agents/dosing can be considered/substituted as per local guidelines for chemotherapy prophylaxis.
b. Required premedications for amivantamab.

Table 8: Suggested Order of Administration When Amivantamab is Given Without Chemotherapy (eg, on Days 2, 8, and 15 of Cycle 1) in Arm A

Medication	Dose	Route of Administration	Recommended Dosing Window
Glucocorticoid[a]	Dexamethasone 10 mg or Methylprednisolone 40 mg	IV	Start 15-30 minutes before amivantamab infusion
Antipyretic	Paracetamol (acetaminophen) 650 to 1,000 mg (or equivalent)	IV or oral	
Antihistamine	Diphenhydramine 25 to 50 mg (or equivalent)	IV	
Study Treatment	Amivantamab	IV	-

IV=intravenous.
a. Pre-dose steroids are mandatory for Cycle 1 Day 2 and optional for Cycle 1 Day 8 and Cycle 1 Day 15. Beginning with Cycle 1 Day 8, optional pre-dose steroids may be administered prior to amivantamab if clinically indicated for participants who experienced an infusion-related reaction on Cycle 1 Day 1 or Cycle 1 Day 2.

Table 9: Suggested Order of Administration When Amivantamab is Given With Pemetrexed on Day 1 of Cycles 5+ in Arm A

Medication	Dose	Route of Administration	Recommended Dosing Window
Antiemetic for chemotherapy[a]	Ondansetron 8 to 16 mg or equivalent	IV/oral	Start 30-45 minutes before amivantamab infusion; administer in the order indicated
Glucocorticoid[b]	Dexamethasone 10 mg or methylprednisolone 40 mg (optional)	IV	
Antipyretic[c]	Paracetamol (acetaminophen) 650 to 1,000 mg (or equivalent)	IV/oral	
Antihistamine[c]	Diphenhydramine 25 to 50 mg (or equivalent)	IV	
Chemotherapy	Pemetrexed	IV	-
Study Treatment	Amivantamab	IV	-

IV=intravenous.
a. Other agents/dosing can be considered/substituted as per local guidelines for chemotherapy prophylaxis.
b. Pre dose steroids for pemetrexed can be used as per local practice and guidelines. Beginning with Cycle 1 Day 8, optional pre-dose steroids may be administered prior to amivantamab if clinically indicated for participants who experienced an infusion-related reaction on Cycle 1 Day 1 or Cycle 1 Day 2.
c. Required pre-infusion medications for amivantamab.

Post-Infusion Medications

Optional post-infusion medications may be prescribed and continued for up to 48 hours after any infusion if clinically indicated, at the discretion of the investigator (Table 10).

Table 10: Post-Infusion Medications for Amivantamab

Medication	Dose	Route of Administration	Administration Instructions	Cycle/ Day
Optional Post-Infusion Medications[a]				
Glucocorticoid	Dexamethasone 10 mg or comparable corticosteroid	IV or Oral	As clinically indicated	Any
Antihistamine	Diphenhydramine 25 to 50 mg or equivalent	IV or Oral	As clinically indicated	Any
Antipyretic	Paracetamol (acetaminophen) 650 to 1,000 mg	IV or Oral	As clinically indicated	Any
Opiates	Meperidine 25 to 100 mg	IV or Oral	As clinically indicated	Any
Antiemetic	Ondansetron 8 to 16 mg or equivalent	IV	As clinically indicated	Any
	Ondansetron 8 mg or equivalent	Oral		

a. Optional medications can be used prophylactically as clinically indicated. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.

6.6.3. Prohibited or Restricted Medications and Therapies

The following concomitant medications and therapies are prohibited or restricted during the study. The sponsor must be notified in advance, or as soon as possible thereafter, of any instances in which prohibited therapies were administered.

- Any chemotherapy, anti-cancer therapy, or experimental therapy (other than study treatments) is prohibited.
- Radiotherapy to tumor lesions being assessed for tumor response prior to radiographic progression is prohibited.
- Use of live or live attenuated vaccines is prohibited.

- Use of phenytoin, or fosphenytoin with carboplatin is prohibited.
- Nephrotoxic or ototoxic agents should be used cautiously with carboplatin. Concomitant administration of aminoglycosides should be avoided with carboplatin.
- Caution should be exercised when administering pemetrexed concurrently with a nonsteroidal anti-inflammatory drug to a participant whose creatinine clearance is <80 mL/min (exception: low-dose aspirin once daily is permitted during the study).
- Avoid using ibuprofen 2 days before, the day of, and 2 days after administration of pemetrexed, as ibuprofen increases exposure of pemetrexed in patients with creatinine clearance of 45 to 79 mL/min.
- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.

6.7. Dose Delay Guidance

In instances where treatment delay is indicated, treatment with chemotherapy and/or amivantamab may be delayed until recovery of toxicity to a level allowing continuation of therapy. A participant for whom treatment was delayed should be assessed at least weekly to ensure adequate supportive care is being administered and to assess for improvement of toxicity.

Participants must meet retreatment criteria for chemotherapy (as per Section 6.8.1 based on product labeling and as per local regulations and guidelines) or amivantamab (as per Section 6.8.2), in accordance with protocol, prior to redosing with the respective agents.

- Combination Chemotherapy (pemetrexed ± carboplatin): If retreatment criteria are not met for carboplatin and/or pemetrexed, then treatment should be delayed by 1 week at a time. If chemotherapy cannot be administered on the scheduled day, dosing with amivantamab should proceed as planned, if retreatment criteria are met. If chemotherapy is delayed by a week (eg, administered on Day 8 of the cycle) subsequent cycle dosing of amivantamab may be delayed by 1 week to align with the chemotherapy dosing schedule. Alternatively, if chemotherapy is delayed twice (eg, administered on Day 15 of the cycle), then the subsequent cycle dosing of amivantamab can be accelerated by 1 week to align with chemotherapy (see Appendix 9: Dosing Synchronization for Arm A). While some flexibility in the amivantamab dosing schedule is allowed as described above, combination chemotherapy must be dosed at a minimum interval of 21 days (carboplatin administration cannot exceed for more than a total of 4 cycles). In the event chemotherapy administration is delayed beyond 42 days (±3 days) from the last treatment, chemotherapy will be discontinued unless approved by the sponsor.
- Amivantamab: In the event amivantamab dosing on Day 1 of the cycle is delayed, but retreatment criteria for chemotherapy are met, dosing with chemotherapy should continue as planned and subjects should be evaluated weekly for retreatment. If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing. All study treatments will be interrupted in an event of Grade 3 or higher toxicity (exception: for hematologic toxicities, amivantamab will be interrupted only if there is Grade 4 toxicity lasting for >7 days and/or Grade 4 thrombocytopenia associated with bleeding or hospitalization or Grade 4 febrile neutropenia). In the event all treatments must be delayed, subjects should be re-evaluated weekly for retreatment. Redosing with amivantamab may proceed once retreatment criteria are met, whether on Day 8 or Day 15 of

the cycle. The dosing of both chemotherapy and amivantamab may resume on the subsequent cycle once retreatment criteria for pemetrexed ± carboplatin are met, as described above. Discussion with the Medical Monitor should occur prior to restarting protocol treatment.

6.8. Dose Modification

Any dose/dosage adjustment should be overseen by medically qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

6.8.1. Chemotherapy Dose Modification

For chemotherapy dose modification, final treatment decisions should depend on clinical judgment, based on local regulations and labeling. For subjects receiving amivantamab in combination with chemotherapy, decisions on study treatment dose modification should be guided by the safety profile of each drug and the likelihood of causality.

Dose modifications of chemotherapy will be based on the maximum toxicity experienced during a cycle. Treatment should be delayed until the toxicity resolves to Grade ≤1 or the baseline status of the participant.

Participants may have a maximum of 2 dose modifications to each treatment throughout the course of the study for toxicities before the agent should be discontinued. Dose reduction should be based upon the most severe toxicity if multiple toxicities are experienced concurrently.

6.8.1.1. Management of Chemotherapy Toxicities

Given the prevalent use of platinum-based doublet chemotherapy in the treatment of NSCLC, the safety profiles of both carboplatin and pemetrexed are well described. Safety monitoring and dose modifications should therefore follow local regulations and labeling.

In general, participants should undergo laboratory assessments including a complete blood count with platelet counts, as well as an evaluation of liver and kidney function, per the respective approved prescribing information.[2,5] Chemotherapy should be delayed if absolute neutrophil count is <1,500/µL, platelet count is <100,000/µL, or the participant is experiencing non-hematologic toxicity of Grade >2 severity. Table 11 and Table 12 provide additional guidance for dose modification to manage hematologic and non-hematologic toxicities related to chemotherapy based on product labeling. Refer to local labeling for complete information regarding dose adjustment for carboplatin and pemetrexed.[2,5]

Table 11: Guidance for Dose Modifications for Hematologic Chemotherapy Toxicity

Platelets	Absolute Neutrophil Count	Pemetrexed Dosage	Carboplatin Dosage
≥50,000/µL	≥500/µL	100% of previous dose	100% of previous dose
≥50,000/µL	<500/µL	75% of previous dose	75% of previous dose
<50,000/µL without bleeding	(Any)	75% of previous dose	75% of previous dose
<50,000/µL with Grade ≥ 2 bleeding	(Any)	50% of previous dose	50% of previous dose
≥50,000/µL	<1,000/µL + fever ≥38.5°C (101°F)	75% of previous dose	75% of previous dose

Table 12: Guidance for Dose Modifications for Non-Hematologic Chemotherapy Toxicity

	Pemetrexed Dosage	Carboplatin Dosage
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose	100% of previous dose

Pemetrexed therapy should be discontinued if the participant experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed. Refer to local labeling for complete information.

6.8.2. Amivantamab Dose Modification

Refer to Table 13 for guidance on delay and modification of the amivantamab dose based on the toxicity grade of adverse events other than those specified in Section 6.8.2.1, Section 6.8.2.2, Section 6.8.2.3, and Section 6.8.2.4 for rash, infusion-related reaction, liver chemistry abnormalities, and pulmonary toxicity, respectively. When possible, the Medical Monitor should be notified prior to dose modifications.

Table 13: Guidance for Amivantamab Dose Delay and Modification for Toxicities Considered Related to Amivantamab (Other Than Rash, Paronychia, Infusion-Related Reaction, or Pulmonary Toxicity)

Toxicity Grade[a]	Action[b]	Length of Interruption[d]	Dose Modification of Amivantamab after Resolution of Adverse Event[c]
1	None	N/A	Continue at current dose level. Consider supportive care according to local standards as appropriate.
2	None or consider interruption	≤7 days	If interrupted, restart at current dose level.
		>7 days	If interrupted, consider restart at next lower dose level.
3	Interrupt amivantamab	≤7 days	Restart at current dose level.
		>7 days	Restart at next lower dose level.
4	Interrupt amivantamab	≤7 days	Restart at next lower dose level
		>7 days	Consider permanently discontinuing amivantamab. Subjects considered by the investigator and sponsor to be benefiting from treatment may be continued at a lower dose upon satisfactory resolution of the toxicity.

a. Per National Cancer Institute - Common Terminology Criteria for Adverse Events Version 5.0.
b. For all toxicities, consider supportive care according to protocol or local standards (if no protocol guidance provided), as appropriate.
c. Resolution defined as: Grade ≤1 or back to baseline. For hypoalbuminemia, the dose can be resumed without resolution of the event to Grade ≤1 or baseline and based on the Investigator's clinical judgement. For liver enzyme abnormalities requiring interruption of treatment, a discussion should occur with the Medical Monitor before restarting amivantamab.
d. If interruption occurs for more than one cycle contact the Medical Monitor to discuss retreatment.

Guidance for stepwise dose modification of amivantamab is outlined in Table 14.

Table 14: Guidance for Amivantamab Stepwise Dose Reduction

Dose Level	Amivantamab (up to Cycle 2 Day 1)	Amivantamab (Cycle 3+)
0 (starting dose)	1,400 mg (1,750 mg if body weight ≥80 kg)	1,750 mg (2,100 mg if body weight ≥80 kg)
-1	1,050 mg (1,400 mg if body weight ≥80 kg)	1,400 mg (1,750 mg if body weight ≥80 kg)
-2	700 mg (1,050 mg if body weight ≥80 kg)	1,050 mg (1,400 mg if body weight ≥80 kg)
-3	Discontinue	Discontinue

The safety profile of amivantamab is largely distinct from that associated with chemotherapeutic agents. However, overlapping toxicity should be considered in the evaluation of all adverse events. Refer to the local prescribing information for carboplatin and pemetrexed for additional details.[2,5]

If dose reduction of amivantamab is required during dosing with combination chemotherapy, re-escalation of amivantamab to planned dose may be considered in the maintenance setting (when dosed with pemetrexed or as monotherapy). Starting at Cycle 5 Day 1, the dose of amivantamab can be re-escalated to a target dose of 1,750 mg (2,100 mg in participants weighing ≥80 kg) in increments of 350 mg per cycle with pemetrexed, based on tolerability.

The following sections provide additional guidance for the prevention, monitoring, and management of toxicities that have been reported with amivantamab.

6.8.2.1. Rash-Related Adverse Events

The prevention and management of EGFR inhibitor-induced rash-related TEAEs can be conducted in accordance with local institutional guidelines, or according to the Protocol recommendations below.

Prophylaxis Recommendations

The prophylactic regimen can be managed according to local practice and guidelines; however, these should include the following:

- Avoid exposure to sunlight.
- Wear protective clothing (including hat, sunglasses, etc.).
- Use broad-spectrum sunscreen with an SPF of ≥30 and reapply as necessary. UVA light can penetrate glass; therefore, sunscreen should also be worn indoors and in vehicles if exposed to direct sunlight. Recommended active sunscreen ingredients are zinc oxide and/or titanium dioxide.
- Apply alcohol-free emollient cream or ointments (eg, glycerin, cetomacrogol, or ceramide-based cream) or skin moisturizer on dry areas of the body. Topical agents can be applied on a daily basis starting on Day 1, and more often as needed. Ideal time for application is after bathing. Creams and ointments are preferred over gels, lotions and oils.

Reactive Management Recommendations

It is strongly recommended that participants who develop rash/skin toxicities receive evaluations and appropriate management. Consider consultation with a dermatologist, especially if the rash is Grade 3, atypical in appearance or distribution, or does not improve within 2 weeks (for Grade 2 rash).

- Initiate a topical corticosteroid (cream or ointment) twice daily
  - Examples to use for face: betamethasone valerate 0.05%, hydrocortisone valerate 0.2% or desonide 0.05%
  - Examples to use for body: betamethasone valerate 0.1%, triamcinolone acetonide 0.1%

- If not already initiated for prophylaxis, initiate systemic antibiotic (such as doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily), or increase the dosing if already administered.
- If an associated skin infection is suspected, obtain bacterial and fungal cultures followed by adjustment of antibiotic or antifungal therapy, based upon culture and susceptibility determination.
- For reactive management of pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.
- For skin fissures, use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is recommended.
- For xerosis, fragrance-free moisturizing creams or sprays are recommended.
- For desquamation, emollients and mild soap are recommended.
- For paronychia, antiseptic soaks and topical potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended. Refer to Appendix 12: Paronychia.
- After the rash is controlled, consider gradually tapering the antibiotic.
- In case of a Grade 4 rash including severe bullous, blistering, or exfoliating skin condition such as toxic epidermal necrolysis (TEN), study treatment should be discontinued permanently.

A suggested algorithm for stepwise management of rash and paronychia associated with amivantamab is provided in Table 15. Refer to Table 13 and Table 14 for recommended dose adjustment.

Table 15: Suggested Algorithm for Management of Rash and Paronychia

Step	Grade[a]	Management	Amivantamab Dose Adjustment[b,c]
1	1	• Initiate reactive management as above • Reassess after 2 weeks	• Continue current dose of study treatment
2	2	• Initiate reactive management as above • Reassess after 2 weeks	• Continue current dose of study treatment
3	3	• Initiate reactive management as above • Start moderate strength topical corticosteroid[d] and systemic antibiotic as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess after 2 weeks • Consider dermatology consultation and manage rash per recommendation	• Temporarily withhold study treatment until rash improves to ≤Grade 2 • For guidance on withholding study treatment and dose reduction, refer to Table 13 and Table 14

Table 15: Suggested Algorithm for Management of Rash and Paronychia

Step	Grade[a]	Management	Amivantamab Dose Adjustment[b,c]
3	4	• Initiate reactive management as above • Start moderate strength topical corticosteroid[d] and systemic antibiotic as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess after 2 weeks • Consider dermatology consultation and manage rash per recommendation	• Permanently discontinue amivantamab for Grade 4 events
	Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN)	• Consult dermatologist and manage rash per recommendation	• Permanently discontinue amivantamab

a. Grading per National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5.0).
b. If amivantamab must be withheld due to toxicity for 2 consecutive doses, then study treatment cannot be restarted without consultation from the Medical Monitor. Participants considered by the investigator and sponsor to be benefiting from treatment may be continued, potentially at a lower dose upon satisfactory resolution of the toxicity.
c. Resolution defined as: ≤Grade 1 non-hematologic toxicity or back to baseline.
d. For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream.

Scalp Rash

Atypical scalp rash and associated infection may develop over time with the use of EGFR inhibitors. Treatment options include:

- A topical steroid shampoo (eg, clobetasol 0.05%), or an anti-dandruff shampoo with anti-inflammatory, antibacterial, and antifungal properties (eg, ketoconazole, selenium sulfide [Selsun®], zinc pyrithione [Head and Shoulders®], or Ciclopirox). These shampoos should be used twice/week, massaging into scalp, leaving on for 2-5 minutes, and then rinsing.
- Application of a steroid lotion may also be effective (eg, betamethasone valerate 0.1% lotion, mometasone furoate 0.1% lotion, or betamethasone dipropionate 0.05% lotion).
- Initiation of a systemic antibiotic (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily) may also be used to treat acute scalp infection.

Of note, while wearing hats to avoid sun damage to the scalp is suggested in a prophylactic setting, avoiding any headwear for a participant with established scalp rash is strongly recommended to prevent further spread of the rash.

6.8.2.2. Infusion-Related Reactions

General Guidelines for Infusion-Related Reactions

Infusion-related reactions have been observed during treatment with amivantamab, predominantly with the first exposure on Cycle 1 Day 1. The severity of infusion-related reactions has been variable. Refer to Summary of Data and Guidance for Investigators in the latest version of the IB for amivantamab.[12]

During the amivantamab infusion, participants should be clinically monitored at regular intervals as specified in Table 1 (including an assessment prior to the start of infusion). The monitoring should include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation measurements.

Particularly with the initial dose (Cycle 1, Days 1 and 2), participants should be closely monitored for early signs and symptoms indicative of an acute infusion-related reaction or anaphylaxis. If clinically indicated, even with mild symptoms, the study treatment infusion should be interrupted immediately, as described in the tables below. Trained clinical personnel should be prepared to intervene in the event of infusion-related reactions. Resources necessary for resuscitation (ie, agents such as epinephrine, aerosolized bronchodilator, IV antihistamines, IV corticosteroids; medical equipment such as oxygen, airway management equipment including suction, and a defibrillator) should be readily available.

Prevention of Infusion-Related Reactions

Required prophylaxis for infusion-related reactions is described in Section 6.6.2.2.

Treatment of Infusion-Related Reactions

Participants who experience early symptoms of infusion-related reactions, manifesting as fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypotension or hypertension or other symptoms, should have their amivantamab infusion interrupted, if indicated, and the symptoms managed according to the recommendations provided in Table 16. With the initial dose of amivantamab (Cycle 1, Days 1 and 2), interruption of the infusion should be considered even with mild symptoms to prevent more severe manifestations of infusion-related reaction. All Grade 3 or 4 infusion-related reactions should be reported within 24 hours to the Medical Monitor.

Table 16: Management of Infusion-Related Reactions

Toxicity Grade[a]	Treatment / Study Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction;	Monitor participant as medically indicated until recovery from symptoms. If occurring with initial dose (ie, Cycle 1 Day 1 or 2), consider early infusion interruption to prevent more severe symptoms.	Antihistamine, antipyretic, and glucocorticoid, as per Table 6.
Grade 2 Mild to moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment	**Interrupt infusion** If clinically indicated, start IV fluids; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol (acetaminophen) 650 to 1,000 mg; consider corticosteroids and bronchodilator therapy; monitor participant closely until recovery from symptoms **First interruption for infusion-related reaction: Restart infusion at 50% of the rate at the time of interruption**: if no further evidence of infusion-related reaction after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely. **Second interruption for infusion-related reaction:** Stop and consider discontinuation of further study treatment at that visit; administer diphenhydramine 50 mg IV or equivalent and monitor participant until resolution of symptoms. The amount of study treatment infused must be recorded in the CRF. If continuing administration after the second interruption, restart infusion at 50% of the rate at the time of the second interruption. If no further evidence of infusion-related reaction after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely.	Antihistamine, antipyretic, and glucocorticoid, as per Table 6. Consider meperidine if participant experiences chills and rigors.
Grade 3 or 4 Severe reaction Grade 3: prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: life-threatening; pressor or ventilator support indicated	Stop infusion Start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed (other drugs as appropriate). Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids), as appropriate.	Grade 3: Based on severity of symptoms, consider permanent discontinuation of amivantamab. Discussion with Medical Monitor required before continuing with subsequent dosing. Grade 4: Discontinue further treatment with amivantamab.
General	**Prophylactic medications** (after initial event) may be used as described in Table 6 and Table 10. Appropriate personnel and appropriate resuscitation equipment should be available in or near the infusion room and a physician should be readily available during the infusion of study treatment	

CRF=case report form; IV=intravenous.

a. Per National Cancer Institute - Common Terminology Criteria for Adverse Events Version 5.0

6.8.2.3. Liver Chemistry Abnormalities

Liver chemistry should be monitored according to the Schedule of Activities (Table 1) and study treatment should be withheld for any liver chemistry abnormality of ≥Grade 3 severity (refer to Section 6.7). In addition, if the following criteria are observed, the event should be reported as a serious adverse event to the Sponsor within 24 hours:

a) ALT or AST ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) (or ALT ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured).
   - Exception to the bilirubin elevation is made if the participant has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.

b) ALT or AST >3×ULN (if baseline was normal) with the concurrent appearance of symptoms suggestive of ongoing severe liver injury, such as fatigue, nausea, vomiting (beyond what is anticipated from chemotherapy), right upper quadrant pain or tenderness, fever, rash, and/or new eosinophilia (>5%).

In the event abnormalities of liver function tests require withholding study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. If the liver function test criteria a) above (ALT or AST ≥3×ULN and bilirubin ≥2×ULN [>35% direct bilirubin] [or ALT ≥3×ULN and INR >1.5, if INR measured]) is concurrently met, etiology of the liver chemistry abnormality should be investigated, as described below. If no alternative etiology of liver toxicity is identified, study treatment should be permanently discontinued.

Liver Event Follow-Up Requirements

The following follow-up assessments should be conducted for any participant meeting liver chemistry stopping criteria:

- Monitor liver chemistries (ALT, AST, alkaline phosphatase, bilirubin [including bilirubin fractions], and INR), creatinine phosphokinase, and lactate dehydrogenase, 1 to 2 times per week until resolution, stabilization, or return to participant's baseline values
- Monitor clinical condition closely
- Draw blood samples for unscheduled PK analysis at timepoints when liver chemistry is assessed
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or known hepatotoxins
- Record alcohol use in the CRF
- Check the viral hepatitis serology as appropriate and include:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B core antibody (IgM)
  - Hepatitis C RNA
  - Hepatitis E IgM antibody
  - Cytomegalovirus IgM antibody

  - Epstein-Barr viral capsid antigen IgM antibody (or equivalent test)
- Assess anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies
- Conduct liver imaging (ultrasound, magnetic resonance [MRI], or CT) to evaluate liver disease
- Refer to a specialist as appropriate

Rechallenge Criteria

Resumption of study treatment(s) may be considered if all the following criteria are met:

- Hy's Law has been excluded.
- A reversible underlying cause not associated with study treatment(s) (eg, other hepatobiliary disorder such as cholelithiasis, etc, alcohol use, or concomitant medication) is clearly identified and agreed upon in consultation with the Medical Monitor.
- Liver chemistry abnormalities have resolved, or values have returned to baseline.

6.8.2.4. Pulmonary Toxicity

The etiology of any clinically significant change in respiratory status and/or non-oncogenic radiological appearance suggestive of lung inflammation (eg, ground glass opacities) should be investigated in accordance with local practice/guidelines to rule out early ILD/pneumonitis. The recommended evaluations include:

- Detailed focused history reviewing respiratory status and exercise tolerance.
- Focused physical exam including full assessment of vital signs (with pulse oximetry).
- Unscheduled radiological assessment, including chest x-ray or CT scan, to rule out pneumonitis and to investigate other causes such as pneumonia, pulmonary embolus, or worsening pulmonary disease.

Documentation of ILD/pneumonitis of any grade should prompt withholding study treatments and contacting the Medical Monitor. For symptomatic pneumonitis (Grade 2 and above), treatment with steroids should be initiated in addition to withholding of study treatment. Confirmation of ILD/pneumonitis of any grade should prompt discontinuation of all study treatment and should be reported as a serious adverse event (see Section 8.3.1). Pertinent radiological images and reports should be submitted to the Sponsor.

6.9. Treatment of Overdose

There are no data on overdose from studies of amivantamab.

In the event of an overdose of a study treatment, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for adverse event/serious adverse event and laboratory abnormalities.

- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study treatment
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study treatment
- The participant becomes pregnant (refer to Appendix 4: Contraceptive and Barrier Guidance).
- Noncompliance with study treatment administration
- Documented radiographic (RECIST v1.1) disease progression by BICR (except during the OLE and LTE phases, during which investigator assessment will be used), unless treatment beyond disease progression has been approved by the Medical Monitor. Discontinuation for disease progression based on local assessment prior to BICR confirmation should be discussed with the Medical Monitor.
- General or specific changes in the participant’s condition that render the participant unacceptable for further treatment in the judgment of the investigator
- The participant receives concurrent (nonprotocol) anticancer treatment

If a participant discontinues study treatment for any reason before the end of the treatment period, then the end of treatment assessments should be obtained and Follow-up Visits should continue after study treatment is discontinued. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant. Additional participants will not be entered.

Continuation of study treatment after BICR confirmed disease progression may be allowed in accordance with local practice, after approval from the Medical Monitor, if the investigator believes the participant is deriving clinical benefit.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- The sponsor discontinues the study

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant (eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members).

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Table 1) summarizes the frequency and timing of measurements applicable to this study.

The total blood volume to be collected from each participant will be approximately 300 mL for a participant in Arm A who receives study treatment for 11 cycles in the main study, and approximately 350 mL for a participant in Arm B who receives study treatment for 7 cycles in the main study and amivantamab monotherapy for 6 cycles after crossover.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF and laboratory requisition form.

Refer to the Schedule of Activities (Table 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Clinical Protocol
- IB for amivantamab
- IPPI and SIPPM
- Laboratory manual and kits
- Electronic data capture (eDC) Manual
- IWRS manual
- Imaging Manual
- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0
- RECIST guidelines, Version 1.1
- Sample master ICF
- Wallet cards
- Study treatment (amivantamab will be supplied centrally; depending on region, chemotherapy may be either centrally or locally sourced)
- Ancillary supplies (as needed)
- Tablets (for PRO collection)

8.1. Efficacy Assessments

8.1.1. Disease Assessments

Disease assessments will be performed as scheduled according to the Schedule of Activities (Table 1), regardless of any dose modifications. More frequent radiologic assessments are allowed if clinically indicated.

CT scan of the chest (including the supraclavicular region), abdomen, pelvis, and any other disease location(s) should be performed with an IV contrast agent. Participants not able to undergo CT scans with IV contrast (eg, due to allergy or renal insufficiency) may have non-contrast CT of the thorax and MRI of the abdomen and pelvis with IV contrast at baseline and during the study if approved by the Sponsor. Contraindications to the CT scan with IV contrast that develop post-baseline should be discussed with the Medical Monitor.

The baseline disease assessments should be performed as close as possible to the start of treatment, but no more than 28 days prior to randomization. Subsequent assessments should be performed at 6 weeks (+1 week) after randomization, then every 6 weeks (±1 week) for the first 18 months and then every 12 weeks (±1 week), until objective radiographic disease progression by BICR. In the OLE/LTE Phase, disease assessments should continue until objective radiographic disease progression by investigator assessment by RECIST v1.1. If an assessment is performed outside of the scheduled visit and the participant has not progressed, every attempt should be made to perform the subsequent assessment at their scheduled visit timepoint. Any other site at which new disease is suspected should also be imaged.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to nontarget lesions or the appearance of a new lesion, continue treatment until the next scheduled assessment (or sooner if clinically indicated) and reassess the participant's status. If the repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression. To achieve "unequivocal progression" on the basis of nontarget lesions, there must be an overall substantial worsening in nontarget lesions such that, even in the presence of stable disease or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression.

In the event an Investigator suspects progression, they should submit scans with a request for confirmation of progression to the BICR. The BICR will confirm if radiographic progression is observed at the suspected imaging assessment. Investigators should consider BICR non-PD assessments when making discontinuation decisions and can continue with study treatment until BICR confirmed disease progression. However, Investigators may use discretion, based on clinical benefit and other factors, to retain a participant on study despite BICR confirmation. In the OLE/LTE Phase, treatment decisions will be made based on investigator assessment by RECIST v1.1.

MRI can be used to evaluate sites of disease that cannot be adequately imaged using CT. Identical methodology (CT scan with contrast agent or MRI) should be used for disease assessment at

baseline and throughout the course of the study to characterize each identified and reported lesion to document disease status. Techniques other than CT or MRI may be used based upon investigator's judgment, local standard of care, and RECIST v1.1 guidelines for the use of these alternative techniques. For example, bone scintigraphy may be used to identify bone lesions at screening or new bone lesions during treatment, but bone lesions will not be considered target lesions. Sites will be required to retain digital copies of radiologic images (eg, x-ray, CT, MRI) used for disease assessments for potential independent review.

Participants will have MRI of the brain at screening, with subsequent definitive treatment of identified active lesions before starting study treatment (see Section 5.1). For patients who are intolerant to brain MRI, alternative imaging modality can be considered for screening after discussion with the Medical Monitor. Brain MRI is not required with every subsequent disease assessment and should be performed according to local guidelines and practice.

All imaging assessments including unscheduled visit scans should be collected on an ongoing basis and sent to a Janssen-appointed Clinical Research Organization for independent central analyses. RECIST v1.1 criteria will be used to assess participant response to treatment: complete response, partial response, stable disease, progressive disease, or unevaluable.

If symptomatic deterioration (on the basis of global deterioration of health status) is recorded as the basis for determining disease progression, then the clinical findings used to make the determination must be specified in the CRF and documented in the source documents. Every effort should be made to document radiographic progression even after discontinuation of treatment for symptomatic deterioration, but prior to subsequent therapy, if possible.

For participants who discontinue study treatment due to toxicity or a reason other than objective progressive disease by BICR, tumor assessments should be continued per schedule until radiographic progressive disease is documented and confirmed by BICR. In the OLE/LTE Phase, radiographic disease progression will be by investigator assessment by RECIST v1.1). Following disease progression, these participants should continue to be followed up for survival every 12 weeks as outlined in the Schedule of Activities (Table 1). Additional follow-up calls may be made in the 2 weeks (14 days) before data cutoff to assess participant survival less than 12 weeks after the previous assessment.

If a participant is treated beyond documented disease progression, disease assessments will continue as scheduled and the investigator and the Medical Monitor will review clinical benefit after each disease assessment.

8.1.2. Symptomatic Progression

Symptoms, attribution, and related interventions will be recorded in the eCRF at the times specified in the Schedule of Activities. If symptomatic progression is not reported prior to treatment discontinuation, continued assessment of the symptoms is required during the follow up period even after subsequent therapy is initiated.

8.1.3. Patient-Reported Outcomes

PRO measures will be collected at the times specified in the Schedule of Activities (Table 1). All PROs should be administered prior to other assessments. The PRO instrument will be provided in the local language in accordance with local guidelines. The PRO instrument must be available for regulators and for IRB/IRC submissions, therefore the PRO instrument or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol. The PRO and adverse event data will not be reconciled with one another.

The PRO instruments in this study are:

- The EuroQol five dimensional descriptive system (5 level version) (EQ-5D-5L) is a validated tool to measure health status and health utility, including mobility, self-care, usual activities, pain, discomfort, and anxiety/depression.[10]
- The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) assesses functioning domains and common cancer symptoms with recall in the past week.[15]
- Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function (short-form) is used to characterize and better understand overall health, level of physical disability, and general well-being. Physical function is a foundation for commonly used general and cancer-specific PRO measures.

8.2. Safety Assessments

Details regarding the Data Monitoring Committee are provided in Committees Structure in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.2.1. Physical Examinations

The Screening physical examination will include, at a minimum, the participant's height, weight, and general appearance and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. On Day 1 of each cycle, directed physical examinations of involved organs and other body systems, as indicated, will be performed and participant body weight will be obtained using a calibrated scale.

8.2.2. Vital Signs

Vital sign measurements will include the following assessments and be obtained as indicated in the Schedule of Activities (Table 1).

- Temperature
- Heart rate
- Respiratory rate
- Oxygen saturation
- Blood pressure

Blood pressure and pulse/heart rate measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

During the collection of electrocardiograms (ECGs), participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

Collection of ECGs will be obtained as indicated in the Schedule of Activities (Table 1). At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but approximately 2 minutes apart. A copy of triplicate ECGs on Cycle 1 Day 1 and Cycle 3 Day 1 will be sent to a central reader. If the Screening ECG is performed in triplicate within 72 hours before the first dose of study treatment, the assessment does not need to be repeated at Cycle 1 Day 1 (and a copy of these triplicate ECGs can be sent to a central reader in lieu of Cycle 1 Day 1). Refer to the ECG Manual for additional details.

The clinical investigator will review the printout, including ECG morphology, for immediate management, and will enter the results in the eCRF. Clinically significant abnormalities noted at Screening should be included in the medical history.

8.2.4. ECOG Performance Status

ECOG performance status score will be determined during the Screening Phase and at time points listed in the Schedule of Activities (Table 1). Any decline in ECOG performance status score should be reported as an adverse event.

8.2.5. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, coagulation, and a urine sample for urinalysis will be collected as noted in Appendix 7: Clinical Laboratory Tests at the times listed in the Schedule of Activities (Table 1). The investigator must review the laboratory results, document

this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents. At the start of each new cycle, the investigator must confirm that participants meet treatment criteria.

More frequent clinical laboratory tests may be performed as indicated by the overall clinical condition of the participant or abnormalities that warrant more frequent monitoring.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies including adverse events, serious adverse events, and product quality complaints (PQC) are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on adverse events, serious adverse events, and PQC can be found in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last scheduled study-related procedure, which may include contact for follow-up of safety. Please refer to Table 1 for more details.

Serious Adverse Events

All serious adverse events, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the serious adverse event form. A serious adverse event spontaneously reported to the investigator more than 30 days after the last dose of study treatment must also be reported using a serious adverse event form, if the investigator considers the event to be related to study treatment. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and

follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local (at the infusion site) and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the adverse event, serious adverse event, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, the serious adverse events listed in Appendix 8: Anticipated Events will be considered anticipated events.

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis

indicates that the anticipated event occurs more frequently in the treatment group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the serious adverse event reporting form. Any participant who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study treatment on sperm is unknown, pregnancies in partners of male participants included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

Progression of disease should not be considered nor should be reported as an adverse event (or serious adverse event). However, signs and symptoms of disease progression or clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

8.3.7. Adverse Events of Special Interest

Adverse events of special interest for this study include pneumonitis/ILD, rash, and IRR. Additional information may be collected to more fully describe these events. Confirmed cases of pneumonitis/ILD (regardless of grade) should be reported as serious adverse events (see Section 8.3.1). All Grade 3 or 4 IRRs should be reported within 24 hours to the Medical Monitor. Events of rash should follow standard reporting guidelines.

8.4. Pharmacokinetics

Blood samples will be used to evaluate the PK of amivantamab in Arm A. Serum collected for PK may additionally be used to evaluate exposure-response relationships for safety or efficacy that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

Blood samples will be collected from participants in Arm A for the evaluation of PK of amivantamab at the designated time points according to the Schedule of Activities (Table 2). The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Blood collected for PK may additionally be used to identify circulating metabolites and/or evaluate safety or efficacy aspects that address concerns arising during or after the study period.

Pharmacokinetic analysis of serum concentration data for amivantamab will be performed. Serum concentrations and PK parameters will be listed and summarized by sampling interval. Pharmacokinetic serum concentration-time data from this study will be analyzed using a population PK approach. The data collected from this study may also be combined with similar data from other studies to perform population PK and assess the relationship between PK or immunogenicity and selected safety and efficacy endpoints. Details will be provided in a population PK and exposure-response analysis plan and results of the analysis will be presented in a separate report.

8.4.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of amivantamab using a validated, specific, and sensitive method by or under the supervision of the sponsor. In addition, serum PK samples may be stored for future analysis of other co-administered treatments, protein binding, and the metabolite profile.

8.5. Biomarkers

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. A minimum of 10 slides (up to 15 when available) or equivalent material from formalin-fixed and paraffin-embedded (FFPE) tissue block must be provided. Slides cut from FFPE blocks of resections or biopsies are recommended not be older than 27 months; FFPE blocks are not recommended to exceed 5 years of age and FNA cell blocks are not recommended be older than 4 months. If the tissue sample is archival, it must have been obtained at or after diagnosis of locally advanced or metastatic NSCLC. Please refer to the laboratory manual.

Screening blood samples collected from all participants will undergo ctDNA analysis by the sponsor to evaluate pre-treatment mutational status of EGFR, MET, and other key oncogenes to characterize the tumor. Tumor tissue will undergo genetic analysis to provide additional characterization of the tumor. 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 specified in Table 1 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.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study treatment(s) or diseases being investigated.

8.6. Immunogenicity Assessments

Serum samples will be collected for immunogenicity assessments of amivantamab (anti-drug antibodies to amivantamab) from all participants in Arm A at the time points outlined in Table 2. The detection and characterization of antibodies to amivantamab will be performed using a validated assay method by or under the supervision of the sponsor. All serum samples collected for detection of antibodies to amivantamab will also be evaluated for amivantamab serum concentration to enable interpretation of the immunogenicity data. Other analyses may be performed to characterize immunogenicity.

Serum samples will be screened for antibodies binding to amivantamab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of

antibodies to amivantamab and/or further characterize the immunogenicity of amivantamab. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to amivantamab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to amivantamab will also be evaluated for amivantamab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment(s). Samples may be stored up to 15 years (or according to local regulations) following the last participant’s last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to amivantamab.

8.7. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

9.1. Statistical Hypotheses

The statistical hypothesis is that amivantamab and chemotherapy combination therapy will reduce the risk of either progression or death compared with standard of care combination chemotherapy in patients with locally advanced or metastatic NSCLC characterized by Exon 20ins mutations.

9.2. Sample Size Determination

A total of 200 PFS events will provide approximately 90% power to detect a hazard ratio (HR) of 0.625 that corresponds to at least 3-month improvement in the median PFS (5 months for chemotherapy and 8 months for the combination of amivantamab with chemotherapy) with a log-rank test (two-sided alpha=0.05). The total sample size needed for the study is approximately 300 participants (150 per group). The sample size calculation has taken into consideration an annual dropout rate of 5%.

Assuming a 15-month recruitment period, 200 PFS events are expected to occur approximately 18 months after the first participant is randomized in the study.

9.3. Populations for Analyses Sets

For purposes of analysis, the following populations are defined:

Table 17: Populations for Analyses Sets

Population	Description
Full Analysis Set	All randomized participants, classified according to their assigned treatment arm regardless of the actual treatment received.
Safety	Randomized participants who receive at least 1 dose of study treatment.
Pharmacokinetics	Randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline concentration measurement.[a]
Patient-Reported Outcomes	Randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline patient-reported outcome measurement.
Biomarkers	Randomized participants who receive at least 1 dose of study treatment, have at least 1 disease assessment, and have at least 1 biomarker measurement.

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

The Full Analysis Set will be used to summarize the study population and characteristics, as well as efficacy data; the Safety Population will be used to summarize the safety data, unless otherwise specified.

9.4. Statistical Analyses

The Statistical Analysis Plan, which will be finalized prior to database lock for the primary analysis, will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

All tests will be conducted at a 2-sided alpha level of 0.05, and 95% CI will be provided, unless stated otherwise. All efficacy endpoints will be analyzed using the Full Analysis Set. The Kaplan-Meier product limit method and a stratified Cox model will be used to estimate the time-to-event variables and to obtain the HR along with the associated confidence intervals. Unless otherwise specified, a log-rank test stratified by ECOG performance status (0 or 1), history of brain metastases (yes or no), and prior EGFR TKI use (yes or no) will be used to test the treatment effect for time-to-event variables; response rate variables will be evaluated using Cochran Mantel Haenszel test stratified by the randomization stratification factors; Continuous variables will be analyzed using an analysis of covariate (ANCOVA) model, with treatment group and randomization stratification factors as fixed effects and baseline value as a covariate.

9.4.2. Primary Endpoint

9.4.2.1. Progression-Free Survival by Blinded Independent Central Review

The primary efficacy endpoint is PFS, 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) in the absence of progression, whichever comes first. Participants who have not progressed or have not

died at the time of analysis will be censored at the time of the latest date of their last evaluable RECIST v1.1 assessment. If the participant progresses or dies after 2 or more consecutive missed disease assessments, the participant will be censored at the time of the last evaluable RECIST v1.1 assessment. If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline.

The primary efficacy endpoint will be analyzed in the Full Analysis Set based on randomized treatment group and strata at randomization. A log rank test will 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. The hazard ratio for PFS will be calculated, along with its 95% confidence intervals, from a stratified Cox model using the same stratification factors as for the log-rank test.

9.4.3. Secondary Endpoints

9.4.3.1. Objective Response Rate

Objective response rate (ORR) is defined as the percentage of participants with best response of complete response or partial response, as defined by RECIST v1.1. Complete response is defined as disappearance of all target lesions and non-target lesions present at baseline (with the exception of lymph nodes, which must be <10 mm to be considered non-pathological) and new lesions since baseline. Partial response is defined as a decrease of 30% or more from baseline in the sum of diameters of the target lesions, with no evidence of progression, and non-target lesions are at least stable with no evidence of new lesions.

Participants who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. However, any complete response or partial response which occurred after a further anticancer therapy was received will not be included in numerator of the ORR calculation (where the Full Analysis Set will be the denominator).

Objective response will be analyzed 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). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence intervals.

9.4.3.2. Duration of Response

Duration of response (DoR) is defined as the time from the date of first documented response (complete response or partial response) until the date of documented progression or death, whichever comes first. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then his/her duration of response will use the PFS censoring time. The analysis of DoR will be stratified by the same covariates as the primary analysis. DoR in responding participants will be summarized and the number of responding participants with a duration of response (>6, >9, >12, and >15 months) will be presented by treatment group. A Kaplan-Meier plot and median DoR with

95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented by treatment group.

9.4.3.3. Overall Survival

Overall survival (OS) is defined as the time from the date of randomization until the date of death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive. OS will be analyzed using the same methodology and model as for the analysis of PFS provided there are sufficient events available for a meaningful analysis.

The analysis of OS will be conducted at 2 time points:

- At the time of the primary analysis of PFS, when approximately 85 deaths overall are anticipated. Based on the O'Brien Fleming alpha spending approach, a 2-sided alpha of 0.0008 will be allocated to the interim analysis.
- Approximately 48 months after the first participant is randomized, when approximately 210 deaths overall are anticipated. The final analysis will be conducted at a 2-sided alpha of 0.0498.

To control the overall type I error rate for the hypotheses testing of primary and secondary endpoints strongly at 5%, a sequential testing strategy will be used. If the testing for the primary endpoint of PFS is statistically significant, key secondary endpoints including ORR and OS will be sequentially tested, each with an overall 2-sided alpha of 0.05. Details of the hierarchical testing procedure will be specified in the Statistical Analysis Plan.

9.4.3.4. Time to Subsequent Therapy

Time to subsequent therapy (TST) is defined as the time from the date of randomization to the start date of the subsequent anti-cancer therapy following study treatment discontinuation, or death. Participants not starting subsequent therapy and still alive will be censored at last time known to be alive. The TST will be analyzed using the same method as the analysis of PFS. Summary statistics will be produced for time on first subsequent anti-cancer treatment, by treatment group.

9.4.3.5. Progression-free Survival After First Subsequent Therapy

Progression-free survival after first subsequent therapy (PFS2) is defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the primary variable PFS or death after starting the next line of treatment. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression (ie, censored at the last progression assessment date if the patient has not had a second progression or death). PFS2 will be analyzed using the same method as the analysis of PFS.

9.4.3.6. Time to Symptomatic Progression

Time to symptomatic progression (TTSP) is 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 requires either a change in anticancer treatment and/or clinical intervention to manage symptoms. The TTSP for a participant who does not experience any of these events will be censored on the date on which the participant was last known to be event-free. The TTSP will be analyzed using the similar methods as the analysis of PFS.

9.4.4. Exploratory Endpoints

Analyses of exploratory (clinical) endpoints will be described in the Statistical Analysis Plan.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population. Baseline for all laboratory evaluations, vital signs, and ECG measurements will be defined as the last evaluation done before the first study treatment administration.

An IDMC will be established as noted in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. The frequency of IDMC meetings will be described in the charter.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any adverse event occurring at or after the initial administration of study treatment through the day of last dose plus 30 days or until the start of subsequent anticancer therapy, if earlier, is considered to be treatment emergent. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study treatment group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-study treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the participant during the study will be provided as shift tables.

Electrocardiogram

The effects of study treatment on cardiovascular variables will be evaluated by descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values at each scheduled timepoint (the predose ECG at Cycle 1 Day 1 will be used as baseline) in ECG parameters including heart rate, QRS axis, and intervals for PR, QT, QRS, RR, and QTcF. Frequency tabulations of the abnormalities will be made. Moreover, the data collected from this study may also be combined with similar data from other studies to perform exposure-QTcF analysis.

Vital Signs

Vital signs including weight, temperature, pulse/heart rate, respiratory rate, blood pressure (systolic and diastolic), and oxygen saturation will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.6. Other Analyses

Pharmacokinetic Analyses

Participants with at least one measurable PK and relevant date and time of the sample will be included in the analysis set. For participants randomized to the combination of amivantamab and chemotherapy, all serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or Statistical Analysis Software (SAS) dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the CSR.

Individual PK parameters will be estimated by inspection of the concentration-time profiles. Based on the individual serum concentration-time data, using the actual sampling times, the following PK parameters of amivantamab will be determined.

- C_{eoi}: end of infusion serum concentration
- $C_{eoi,ss}$: end of infusion serum concentration at steady state
- C_{trough}: serum concentration immediately prior the next study treatment administration
- $C_{trough,ss}$: serum concentration immediately prior the next study treatment administration at steady state

In addition, population PK analysis of serum concentration-time data of amivantamab will be performed using nonlinear mixed-effects modeling (NONMEM) and may be combined with similar data from other studies, with the aim of providing estimates of PK parameters or metrics of systemic exposure. Model-derived plasma concentrations or metrics of exposure parameters (eg, C_{max} or AUC) may be subjected to further analyses to explore PK correlation between exposure and relevant safety and efficacy endpoints or biomarkers.

Biomarkers Analyses

Each baseline tumor status will be evaluated by both tumor and ctDNA NGS to characterize potential mechanisms of resistance to amivantamab in combination with chemotherapy.

The association of biomarker-positivity (eg, EGFR mutation status, circulating biomarkers) with clinical response or time-to-event endpoints will be assessed using statistical methods appropriate for each endpoint (eg, analysis of variance, categorical, or survival models). Correlation of baseline biomarker expression levels with clinical response or relevant time to-event endpoints will be performed to identify responsive (or resistant) subgroups.

Assessment of additional genes or biomarkers (DNA, RNA, or protein) relevant to lung or other cancers and assessment of the mechanism of action or metabolism of study treatments may also be performed in blood and tissue samples collected on study to better understand mechanisms of response or resistance to study treatments. Alterations in blood characteristics may be evaluated for correlation with response to study treatments, tumor burden, and disease progression as data warrant.

Immunogenicity Analyses

The incidence of antibodies to amivantamab will be summarized for all participants who receive at least 1 dose of amivantamab and have appropriate samples for detection of antibodies to amivantamab (ie, participants with at least 1 sample obtained after their first dose of amivantamab).

A listing of participants who are positive for antibodies to amivantamab will be provided. The maximum titers of antibodies to amivantamab will be summarized for participants who are positive for antibodies to amivantamab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Exposure-Response Analyses

The exposure-response relationship between amivantamab (eg, derived AUC or trough concentrations) and key efficacy (eg, PFS and OS) and safety parameters (eg, skin rash), will be explored graphically, as data allow. In addition, the relationship may be characterized using an exposure-response or logistic regression model. Details will be provided in an analysis plan and detailed results may be reported separately from the CSR.

Patient-Reported Outcomes Analyses

Results for EORTC-QLQ-C30 and Patient Reported Outcomes Measurement Information System – Physical Function (PROMIS-PF) will be summarized for randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline measurement (Table 17).

Time to worsening in EORTC-QLQ-C30 total score and individual scales will be analyzed using a Kaplan-Meier method and stratified Cox proportional-hazard model. Additional analysis may be done, if appropriate. Analysis details will be included in the Statistical Analysis Plan.

The PROMIS-PF data will be summarized descriptively by treatment group and study visit. Each multi-item scale and individual item will be summarized using count and percent.

9.5. Interim Analysis

Not applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
ALT	alanine aminotransferase
Anti-HCV	hepatitis C virus antibody
ART	anti-retroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC 5	area under the concentration-time curve 5 mg/mL per minute
AxMP	auxiliary medicinal product
BICR	blinded independent central review
CI	confidence interval
C_{max}	maximum serum concentration
CRF	case report form
CSR	clinical study report
CT	computerized tomography
CTR	Clinical Trial Regulations
ctDNA	circulating tumor deoxyribonucleic acid
C_{trough}	serum concentration immediately prior the next study treatment administration
DBL	database lock
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQol five-dimensional descriptive system (5-level version)
ESMO	European Society for Medical Oncology
EU	European Union
Exon 20ins	Exon 20 insertion
FDA	Food and Drug Administration
FFPE	formalin-fixed and paraffin-embedded
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	interactive web response system
LTE	long-term extension
mAb	monoclonal antibody
MET	mesenchymal-epithelial transition
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
NIMP	non-investigational medicinal product
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OLE	open-label extension
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic(s)
PQC	product quality complaint
PRO	patient reported outcomes
PROMIS-PF	Patient-Reported Outcomes Measurement Information System – Physical Function
Q3W	every 3 weeks
QTcF	corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	RR interval
SAC	Safety Assessment Committee
SIPPM	Site Investigational Product and Procedures Manual
SMT	safety management team
SPF	skin protection factor

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTSP	time to symptomatic progression
ULN	upper limit of normal
US	United States

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study treatment to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study treatment
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.2.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.2.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study

physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the participant's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

When prior consent of the participant is not possible and the participant's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

10.2.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant (or his or her legally acceptable representative) includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests

concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand amivantamab, to understand the disease under investigation, to understand differential study treatment responders, and to develop tests/assays related to amivantamab and NSCLC. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal from the Use of Research Samples).

10.2.6. Committees Structure

Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor data on an ongoing basis. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data, at intervals that will be described in the charter. After the review, the IDMC will make recommendations regarding the continuation of the study.

Safety Evaluation Team (SET)

If a Safety Run-in phase is conducted, the SET will oversee safety evaluation during this part of the study. The SET will monitor all available treatment-emergent data from the Safety Run-in on an ongoing basis to ensure the continued safety of participants. The SET will be responsible for making a formal determination of whether the study will proceed to the randomization, based on the DLT rules. The Sponsor's study-responsible physician will chair the SET. Other Sponsor membership will include a clinical scientist, statistician, clinical pharmacologist, and additional

staff, as appropriate. Investigators who have enrolled participants in the Safety Run-in phase will also participate in the SET. The SET will meet approximately monthly during the Safety Run-in phase and as necessary during the remainder of the study. Documentation of meeting outcomes will be maintained by the Sponsor in the Trial Master File. Decisions with the potential to affect participant safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and regulatory authorities as appropriate.

10.2.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding amivantamab, or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish the goals of this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of amivantamab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.2.8. Data Quality Assurance

Data Quality Assurance/Quality Control

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

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.2.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.2.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; study treatment receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or another equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical

study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

10.2.11. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.2.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a

regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.2.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.2.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization except for the following
  - Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
  - Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
  - For convenience the investigator may choose to hospitalize the participant for the duration of the study treatment period.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For amivantamab, expectedness of an adverse event will be determined by whether or not it is listed in the IB.

10.3.2. Attribution Definitions

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator. The following selection should be used to assess all adverse events.

Related

There is a reasonable causal relationship between study treatment administration and the adverse event. Related events would include probably and possibly related events.

Not Related

There is not a reasonable causal relationship between study treatment administration and the adverse event. Not related events would include doubtfully related events.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.3.3. Severity Criteria

An assessment of severity grade will be made by the investigator according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 using the following categorical descriptors:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to adverse event.

10.3.4. Special Reporting Situations

Safety events of interest on a sponsor study treatment in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study treatment
- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study treatment from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

10.3.5. Procedures

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number

- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the participant for the duration of the study treatment period.

Progression of disease should not be recorded as an adverse event (or serious adverse event). However, signs and symptoms of disease progression or of clinical sequelae resulting from disease progression/lack of efficacy that are determined by the investigator to be of clinical significance should be reported per the usual reporting requirements.

10.3.6. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.3.7. Product Quality Complaint Handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

  If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] –oral –intravaginal –transdermal –injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] –oral –injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) The study treatment may interact with hormonal contraception, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study treatment.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

Female participants who become pregnant during the study will be withdrawn from the study treatment and followed for safety (Section 8.3.5).

10.5. Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Eastern Cooperative Oncology Group, Robert Comis M.D, Group Chair (Oken, 1982).[19]

10.6. Appendix 6: New York Heart Association Criteria

The following table presents the New York Heart Association classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Classification of Functional Capacity and Objective Assessment. Available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp Accessed 18 March 2019.

10.7. Appendix 7: Clinical Laboratory Tests

The following tests will be performed by the local laboratory according to the Schedule of Activities (Table 1) during the main study, and according to Table 22 during the OLE Phase:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hemoglobin Platelet count Mean corpuscular volume (MCV)	Absolute neutrophil count White blood cell (WBC) count with differential
Clinical Chemistry	**At Each Assessment (Including Screening)** Alkaline phosphatase Creatinine AST ALT Creatinine clearance (Cockcroft-Gault formula) Gamma-glutamyl transferase (GGT) Bilirubin (total, direct, indirect) Lactic acid dehydrogenase Albumin Magnesium Phosphorus Sodium Potassium Calcium	**Additional Tests at Screening only** Total protein Blood urea nitrogen (BUN) Blood glucose
Coagulation	Prothrombin time (PT) Activated partial thromboplastin time (APTT)	International normalized ratio (INR)
Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase (if available)	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria
Serology	Anti-HIV antibody HBsAg, hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (Participants with a history of HBV are also required to have HBV DNA quantification) Anti-HCV antibody (Participants with a history of HCV are required to have HCV RNA quantification)	

10.8. Appendix 8: Anticipated Events

An anticipated event is an adverse event (serious or nonserious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. For the purposes of this study, the following events will be considered anticipated events:

Assessment of anticipated events will be stopped after the OLE Phase has started.

Constitutional
Dehydration
Sepsis
Weakness/asthenia
Fatigue
Fever/pyrexia
Weight loss
Failure to thrive
Decreased appetite/Anorexia
General physical health deterioration (decline in ECOG status to 3 or 4)

Respiratory
Pneumonia
Upper respiratory infection
Lower lung infection
Hypoxia
Dyspnea
Bronchitis
Emphysema
COPD exacerbation
Malignant pleural effusion
Cough
Empyema
Pulmonary emboli
Respiratory failure
Pneumothorax
Hemoptysis
Radiation pneumonitis

Cardiovascular
Superior vena cava syndrome
Pericardial effusion
Cardiac tamponade (associated with pericardial metastasis)
Myocardial infarction
Stroke

Gastrointestinal
Dysphagia
Esophageal obstruction
Intestinal obstruction
Bleeding ulcers
Diverticulitis

Musculoskeletal (associated with metastatic or advanced disease)
Pain
Fracture (pathologic fracture)

Hematologic
Thromboembolic events – deep vein thromboses, pulmonary emboli
Anemia

Neurologic (associated with metastatic or advanced disease)
Cranial nerve palsies
Weakness of upper, lower extremities
Confusion
Mental status changes
Seizures
Unstable gait

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 10.3.1. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 10.3.1. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) per applicable clinical trial legislation to Health Authorities and IRB/IECs (Note: Japan will not identify anticipated events for the Health Authorities). If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/IECs. If an interim analysis of

trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

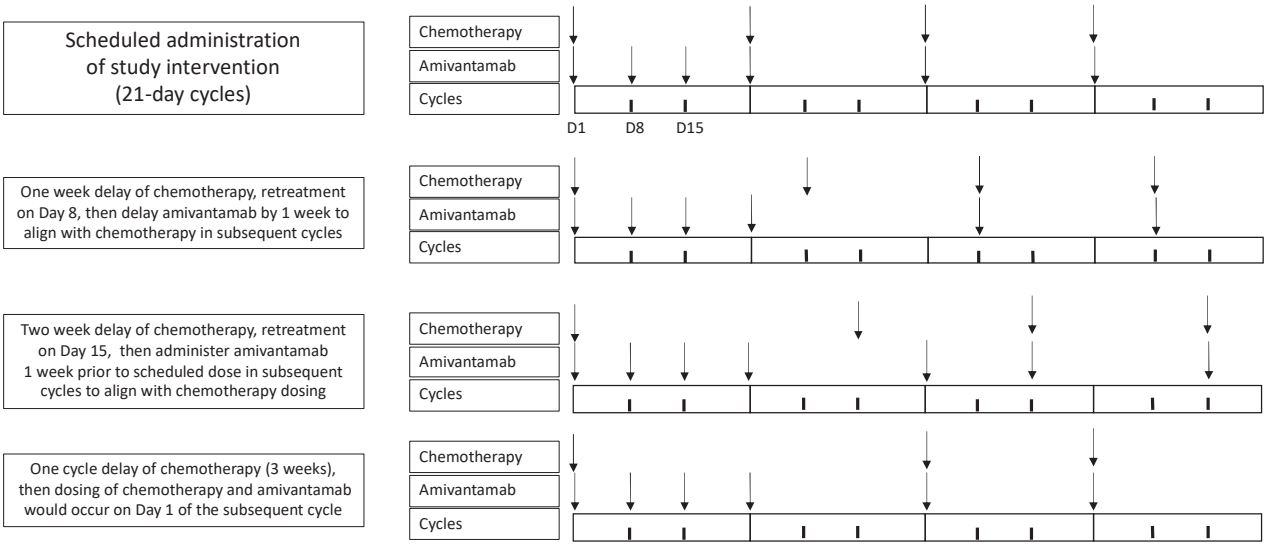
Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study treatment based on a review of the aggregate data by arm.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

10.9. Appendix 9: Dosing Synchronization for Arm A



10.10. Appendix 10: Safety Run-in

The safety of amivantamab in combination with carboplatin and pemetrexed is being investigated in the ongoing Phase 1 Study (61186372EDI1001), in parallel to Phase 3 study development, and will be confirmed prior to enrollment of participants in this Phase 3 study. If regulatory or health authorities request region-specific safety experience for amivantamab in combination with carboplatin-pemetrexed, an optional Safety Run-in may be performed prior to enrollment of participants in the randomized Phase 3 portion of the study in that region/country.

In the Safety Run-in, approximately 6-12 participants of the target population will be dosed with the carboplatin-pemetrexed-amivantamab combination, and safety experience will be summarized using descriptive statistics. These participants will be in addition to the approximately 300 participants in the main study.

The Safety Run-in will use the study inclusion (Section 5.1) and exclusion (Section 5.2) criteria from the main study, with the following exceptions:

1) The Safety Run-in will not be limited to participants with an Exon 20ins activating mutation. Participants in the Safety Run-in can have histologically or cytologically confirmed, locally advanced or metastatic, NSCLC with any previously documented primary EGFR or MET activating mutation.

2) Participants in the Safety Run-in may have received prior systemic therapy. Participants who have received prior EGFR TKI or MET therapy must have a washout period of 2 weeks or 5 half-lives, whichever is longer, before the first administration of study treatment. For agents with long half-lives, the maximum required time since last dose is 4 weeks. Toxicities from previous TKI therapies should have resolved to baseline levels or to Grade 1 or less.

Pemetrexed, carboplatin, and amivantamab for the Safety Run-in will be dosed and administered as described in Section 6.

Collection times for PK and immunogenicity samples in the Safety Run-in are shown in Table 2. Tumor biopsies are not required for participants in the Safety Run-in; other activities in the Safety Run-in will be conducted as listed in the Schedule of Activities (Table 1).

10.11. Appendix 11: Optional Crossover After Disease Progression to Second-Line Amivantamab Monotherapy (Arm B Only)

A participant who was randomized into the Arm B (platinum-based doublet chemotherapy) may cross over to amivantamab monotherapy after disease progression, as confirmed by blinded independent central review (BICR) (see Figure 1). A participant crossing over to second-line amivantamab monotherapy will be re-screened to ensure eligibility is met to receive amivantamab.

For study conduct/information after the study has transitioned to the OLE Phase, please refer to Section 10.14.

STUDY DESIGN

This phase of the study will not be randomized or controlled. All participants in the Crossover Phase will receive amivantamab in 21-day cycles as follows:

- 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

Crossover participants must 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.

Other treatment related procedures are described in Table 20.

STUDY POPULATION

Crossover Eligibility Criteria

Each potential participant must satisfy all the following criteria to be enrolled in the crossover:

1. Prior study randomization to Arm B, with subsequent disease progression after treatment with carboplatin-pemetrexed, and confirmation of disease progression by BICR.
2. No intervening systemic anti-cancer therapy or investigational therapy following discontinuation of assigned Arm B study treatment.
3. 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.
4. Participant must have signed ICF for crossover section of the study.
5. Participant must have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
6. Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion or platelet transfusion within 7 days prior to the date of the test.
   - Hemoglobin ≥10 g/dL
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, without any prior use of G-CSF
   - Platelets $\geq 100 \times 10^9$/L

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3×ULN
- Total bilirubin ≤1.5×ULN (participants with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits)
- Creatinine clearance >50 mL/min as measured or calculated by Cockcroft-Gault formula

7. Participant must have no untreated CNS metastases (a participant with definitively, locally treated metastasis who is clinically stable and asymptomatic for at least 2 weeks off corticosteroid treatment before enrollment will be eligible).
8. Participant must have no ongoing or active bacterial infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week before the first dose of amivantamab]), symptomatic viral infection, or any other clinically significant infection.
9. Criterion added per Amendment 1:
10. Patients must not have a medical history of ILD/pneumonitis.
11. Furthermore, subjects should meet eligibility criteria required for protection against reproductive risks: inclusion criteria 8, 9, 10, 11, and 12 (see Section 5.1) and exclusion criteria 18 and 19 (see Section 5.2).

STUDY TREATMENT

Follow the guidance in Section 6 for study treatment, with the following modifications:

- Amivantamab will be administered at the dosage described above in STUDY DESIGN
- No chemotherapy will be administered in this portion of the study.

Refer to Table 18 and Table 19 for preinfusion and post-infusion medications, respectively.

Table 18: Preinfusion Medications for Amivantamab

Medication	Dose	Route of Administration	Recommended Dosing Window
Glucocorticoid	Cycle 1 Day 1: dexamethasone 20 mg or methylprednisolone 80 mg	IV	Start 45-60 minutes before amivantamab infusion
	Cycle 1 Day 2: dexamethasone 10 mg or methylprednisolone 40 mg (or equivalent)		
	All other doses[a]: dexamethasone 10 mg or methylprednisolone 40 mg (or equivalent)		
Antipyretic	Paracetamol (acetaminophen) 650 to 1,000 mg (or equivalent)	IV/oral	For IV preparation start 15-30 minutes before amivantamab infusion. For oral preparation start 30-60 mins before amivantamab dose.
Antihistamine	Diphenhydramine 25 to 50 mg (or equivalent)	IV/oral	

IV=intravenous.

a. Pre-dose steroids are mandatory for Cycle 1 Day 1 and Cycle 1 Day 2 and optional for other doses. Beginning with Cycle 1 Day 8, optional pre-dose steroids may be administered prior to amivantamab if clinically indicated for participants who experienced an infusion-related reaction on Cycle 1 Day 1 or Cycle 1 Day 2.

Table 19: Post-Infusion Medications for Amivantamab

Medication	Dose	Route of Administration	Administration Instructions	Cycle/ Day
Optional Post-Infusion Medications[a]				
Glucocorticoid	Dexamethasone 10 mg (or equivalent)	IV or Oral	As clinically indicated	Any
Antihistamine	Diphenhydramine 25 to 50 mg (or equivalent)	IV or Oral	As clinically indicated	Any
Antipyretic	Paracetamol (acetaminophen) 650 to 1,000 mg	IV or Oral	As clinically indicated	Any
Opiates	Meperidine 25 to 100 mg	IV or Oral	As clinically indicated	Any
Antiemetic	Ondansetron 8 to 16 mg (or equivalent)	IV	As clinically indicated	Any
	Ondansetron 8 mg (or equivalent)	Oral		

IV=intravenous.

a. Optional medications can be used prophylactically as clinically indicated. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.

- The participant will be weighed again at the Screening visit for the crossover; this weight will be used for the dosage of amivantamab.
- Amivantamab treatment delays: Amivantamab treatment may be delayed until recovery from toxicity to a level allowing continuation of therapy. A participant for whom a cycle was delayed should be assessed at least weekly for resolution of toxicity. Starting in Cycle 2, if 2 or more consecutive doses of amivantamab monotherapy are missed, then the participant should discontinue the study treatment. However, amivantamab may be restarted after missing 2 consecutive doses if there is clear clinical benefit and only after approval by the Medical Monitor. In this situation, adjustments to the study treatment dose and infusion administration procedures may be necessary. If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing.
- Follow the general guidance for amivantamab dose modification and toxicity management in Section 6.8.2.

DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Follow the guidance in Section 7 for discontinuation of study treatment and participant discontinuation or withdrawal. Additionally, study treatment must be discontinued for documented radiographic disease progression as per RECIST v1.1 unless treatment beyond disease progression is approved by the Medical Monitor.

CROSSOVER ASSESSMENTS AND PROCEDURES

Participants receiving crossover amivantamab monotherapy will follow the assessments and procedures described in the main study protocol, with the modifications described in this appendix. For assessments/procedures after the study has transitioned to the OLE Phase, please refer to Section 10.14.

- Screening procedures need to be completed within 28 days of the first dose of amivantamab.
- All procedures and assessments completed at the time of withdrawal from the main study may be used as appropriate for the start of the Crossover Phase of the study, if done within 28 days.
- Baseline tumor imaging must be performed within 28 days before the first dose of amivantamab monotherapy. The tumor image that was used to determine progressive disease in the main study can be used as the baseline image for the Crossover phase if:
  - The tumor image was collected within 28 days before the first dose of amivantamab monotherapy.
  - No study treatment was administered between the imaging and the first dose of amivantamab monotherapy.

As summarized in Table 20, follow the guidance in Section 8 for study assessments and procedures, with the following modifications:

- Efficacy assessments (Section 8.1): conduct disease assessments at 6 weeks (+1 week) relative to Cycle 1 Day 1 of amivantamab monotherapy, every 6 weeks (±1 week) for the first 18 months, then every 12 weeks (±1 week), with brain MRI as clinically indicated.
- Patient-reported outcomes (Section 8.1.3): assess PROs every 12 weeks for 1 year, starting from the date of first disease progression.
- Safety assessments (Section 8.2) and adverse events (Section 8.3): see Table 20.
- Pharmacokinetics (Section 8.4) and immunogenicity (Section 8.6): collect blood samples for PK and immunogenicity as summarized in Table 21.
- Biomarkers (Section 8.5): ctDNA and tumor biopsy (if clinically feasible) will be collected at the End of Treatment Visit.

STATISTICAL CONSIDERATIONS

Data from the crossover Phase will be summarized descriptively. Endpoints to be analyzed include overall response rate, duration of response, and safety. Other statistical considerations for this phase of the study will be specified in the Statistical Analysis Plan.

Table 20: Optional Crossover to Second-Line Amivantamab Monotherapy: Schedule of Activities for Study Assessments/Procedures (Crossover Section of Main Study Only)

Study Phase		Second-Line Treatment (21 Days/Cycle)					End of Treatment	Follow-up (Visit/Call)	
Cycle		Cycle 1				Cycles 2+	30 Days After		
Cycle Day	Screening	1	2	8	15	1	Last Dose*	Q12W	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±3	+7	±14	Notes
STUDY PROCEDURES Treatment cycles are 21 days in duration. In Cycle 1, amivantamab is administered on Days 1, 2, 8, and 15. In all subsequent cycles, amivantamab is administered once every 3 weeks on Day 1 of each 21-day cycle. Assessments during in-clinic dosing days should be performed prior to administration of study treatment unless otherwise stated. Investigator must confirm that the participant meets treatment criteria before administration of study treatment. *End of Treatment visit should occur 30 days after the last dose or before starting the next anti-cancer treatment, whichever occurs first. In Follow-up phase, collect data until the end of study unless the participant has died, is lost to follow-up, or has withdrawn consent.									
Screening Assessments									
Informed consent	X								Must be signed before the first study-related procedure in Second-Line Treatment Phase.
Inclusion/exclusion criteria	X								Confirm all criteria are met before participant enters Second-Line Treatment Phase.
Disease characteristics	X								
ECOG performance status	X	X				X	X		
Pregnancy test (serum or urine)	X	X	As clinically indicated, according to local regulation requirements, or following the local practice of the center						Women of child-bearing potential only. Required at Screening and within 72 hours before the first dose of amivantamab. If local regulations mandate pregnancy testing before administration of amivantamab, the test should be completed within 72 hours before Day 1 of each cycle or monthly, whichever is more frequent.
Coagulation	X								
Urinalysis	X								
12-lead ECG	X								At Screening, then as clinically indicated (triplicate if clinically significant).
Hematology/chemistry (up to 72 hours predose)	X	X		X	X	X	X		Laboratory assessments are listed in Appendix 7. Results of the screening assessments must be reviewed by the Investigator prior to enrollment; laboratory assessments must be reviewed by the Investigator prior to infusion of amivantamab. Report clinically significant abnormalities as adverse events.
Efficacy Assessments									
CT/MRI tumor imaging	X	6 weeks (+1 week) from first dose of amivantamab monotherapy, then every 6 weeks (±1 week) for the first 18 months, then every 12 weeks (±1 week) afterward							Use same method throughout study (Section 8.1). Continue until second disease progression. If a participant is treated beyond documented second disease progression, continue disease assessments as scheduled and review clinical benefit with the Medical Monitor after each disease assessment.
Brain MRI	X	As clinically indicated							
Symptomatic progression events	X								Collect continuously from crossover Screening (including during the Follow-up Phase)
Survival/disease status								X	
Subsequent anticancer therapy								X	Collect information on type of therapy, treatment start date, and treatment stop date.
Safety Assessments (predose, except as noted)									
Vital signs	X	X	X	X	X	X	X		Heart rate, BP, respiratory rate, temperature, and O_2 saturation ≤30 min before amivantamab infusion, 30-min intervals (±5 minutes) during each amivantamab infusion, and at end of infusion (+5 minutes).

Table 20: Optional Crossover to Second-Line Amivantamab Monotherapy: Schedule of Activities for Study Assessments/Procedures (Crossover Section of Main Study Only)

Study Phase		Second-Line Treatment (21 Days/Cycle)					End of Treatment	Follow-up (Visit/Call)	
Cycle		Cycle 1				Cycles 2+	30 Days After		
Cycle Day	Screening	1	2	8	15	1	Last Dose*	Q12W	
Visit Window (Days)	-28 to -1	-	-	±1	±1	±3	+7	±14	Notes
Physical examination	X	X				X	X		Screening will include, at a minimum, weight, general appearance, and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. On Day 1 of each cycle, directed physical examination of involved organs and other body systems will be performed as indicated. Report clinically significant abnormalities as adverse events.
Adverse events	Continuous from the time ICF is signed through 30 days after the last dose of study treatment (or >30 days, if considered related to study treatment)								
Prior and concomitant medications	X								Record all prescription and over-the-counter treatments administered through 30 days after the last dose of study treatment (or the start of a subsequent systemic anti-cancer therapy, if earlier). For participants with Grade 3 or 4 adverse events considered related to amivantamab, or adverse events considered related to amivantamab occurring after 30 days following the last dose, record concomitant medications through the end of follow-up.
Study Treatment									
Amivantamab		X	X	X	X	X			If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing. If the first dose in Cycle 2 or beyond is delayed, then the next dose of amivantamab will be based on the previous dose of amivantamab .
Preinfusion Medications									
Preinfusion medications		X	X	X	X	X			See Table 18. Record all preinfusion medications.
Patient-Reported Outcomes (predose on dosing days)									
EQ-5D-5L, EORTC-QLQ-C30, PROMIS-PF		Every 12 weeks starting C1D1							On C1D1, the Patient-Reported Outcomes data can be collected 24 hours before the first dose. Record every 12 weeks until end of study treatment or for 1 year after first disease progression, whichever is longer.
Biomarkers									
Tumor biopsy							X		Post-progression, obtain biopsy within 30 days of disease progression, if clinically feasible, before the next anti-cancer therapy. Provide a minimum of 10 slides (up to 15 when available) or equivalent material.
ctDNA (predose) blood sample							X		

BP=blood pressure; CT=computerized tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol 5-dimensional descriptive system (5-level version); h=hours; ICF=informed consent form; min=minutes; MRI=magnetic resonance imaging; O_2=oxygen; PROMIS-PF=Patient-Reported Outcomes Measurement Information System – Physical Function; Q12W=every 12 weeks.

Table 21: Collection Times for Pharmacokinetics and Immunogenicity Samples Among Participants Receiving Second-Line Amivantamab Monotherapy (Crossover Section of Main Study Only)

Study Phase	Treatment				End of Treatment
Cycle	Cycle 1		Cycle 2	Cycles 3, 5, 7, 9, 11, and 13	30 Days After Last Dose
Cycle Day	1	2	1[a]	1[a]	-
Dosing Visit Window (days)	-	-	±1	±3	+7
Pharmacokinetic Samples[c]					
Preinfusion (0-2 hr before planned amivantamab)	X	X	X	X	
End of infusion (0-15 min after amivantamab)	X	X	X	X	
At End of Treatment Visit					X
Immunogenicity Samples[c]					
Preinfusion (0-2 hr before planned amivantamab)	X		X	X	
At End of Treatment Visit					X

a. At any dose starting with Cycle 2 Day 1: If a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule should be delayed accordingly to ensure sampling relative to amivantamab dose administration.
b. Separate blood draws are not required for amivantamab PK and immunogenicity when collected at the same time point.

10.12. Appendix 12: Paronychia

Paronychia is a well-recognized toxicity associated with anti-EGFR therapeutics. As a result, there are recommendations that should be followed to prevent or minimize patient discomfort associated with this toxicity.

Prophylaxis Recommendations

- Avoid skin irritants.
- Cushion affected areas.
- Wear gloves and comfortable shoes.
- Apply moisturizer to nails.

Reactive Management Recommendations

Grade 1 paronychia:

- Use antimicrobial soaks once or twice daily: warm bowl of water + 5 mL of bleach (sodium hypochlorite) or vinegar (DO NOT USE BOTH TOGETHER); soak for 5 minutes, rinse, pat dry, and then apply either emollient or topical treatments below.
- Apply topical antiseptic (povidone-iodine 10% solution) twice daily.
- Apply a topical steroid ointment (eg, betamethasone valerate 0.1% or clobetasol) or topical calcineurin inhibitor (eg, tacrolimus 0.1%) twice daily. If using topical steroid, once resolved, switch to topical calcineurin inhibitor daily or decrease to twice per week to maintain.

Grade 2 or 3 paronychia:

- In addition to the guidance for Grade 1 paronychia above:
  - Apply topical antibiotic/antifungal agent (eg, mupirocin, fusidic acid, clotrimazole, or miconazole) twice daily.
  - Initiate oral antibiotic for at least 14 days (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily).
  - Consult a dermatologist or podiatrist.

For dose modifications in the event of paronychia, please refer to Table 15.

10.13. Appendix 13: Guidance on Study Conduct During a COVID-19 Pandemic

It is recognized that a Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; and changes in hospital or clinic procedures required to address the COVID-19 challenge, including study site personnel being reassigned to critical tasks. The guidance herein is applicable until the clinical site returns to pre-pandemic operational capacity and practices.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is at risk, study intervention will be discontinued, and study follow-up will be conducted as outlined in the protocol.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Study drug interruptions, discontinuations of study interventions, changes in study visit schedules, missed visits/assessments, and/or participant discontinuations may lead to missing data, including data related to protocol-specified procedures, and will be captured in the clinical trial management system for protocol deviations and documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of a COVID-19 pandemic will be summarized in the clinical study report.

Consent/Screening

- Consenting of subjects for study screening including the crossover portion of the study can be performed remotely by telephone or video conferencing. Re-consenting of active subjects due to new safety information or updated study design should also be assessed for its feasibility to be conducted remotely.

- All screening procedures and assessments must be conducted per protocol at the investigative site.

- During screening of participants, the investigator should evaluate the feasibility of participants returning for scheduled dosing visits per protocol based on history of potential COVID-19 exposure and local travel restrictions. If the situation suggests that this is not possible, the participant may be screen failed and re-screened when conditions improve.

- COVID-19 screening procedures that may be mandated by local healthcare systems do not need to be reported as an amendment to the protocol even if done during clinical study visits.

- As SARS-CoV-2 represents a new infectious agent, and COVID-19 a new clinical syndrome, it is unclear how infection with this virus will impact the benefit/risk assessment with regards to JNJ-61186372 and/or chemotherapy treatment, particularly given its association with the risk of severe viral pneumonia. As per the study exclusion criteria, participants with active infection, including viral illnesses such as COVID-19, should be excluded from study participation.

Study Treatment

Study treatment with amivantamab and/or chemotherapy (carboplatin and/or pemetrexed), should continue to be administered at the investigative site in accordance with the protocol. Potential interruptions to therapy should be assessed on a case by case basis and include consideration of potential impact on participant's safety. If doses are missed or delayed due to COVID-19 related circumstances, these deviations should be noted in the appropriate CRF page, as "missed or delayed due to COVID-19". The sponsor's Medical Monitor should be alerted to any anticipated interruption in Amivantamab, carboplatin, and/or pemetrexed.

Study treatment should be held for all participants with suspected (symptomatic) or documented SARS-CoV-2 positive disease, until recovery from all infection-related symptoms, and documented to be negative for SARS-CoV-2. Given the unmet medical need of this study population, and the unknown impact of prior COVID-19 infection on the risk of study treatment, re-initiation of study treatments should be evaluated with the Medical Monitor on a case-by-case basis, taking into account the severity of the COVID-19 related symptoms, and the observed clinical benefit from study treatment. Please report the event to the sponsor, following usual Adverse Event reporting requirements.

COVID-19 vaccination

The amivantamab safety management team (SMT) evaluated available COVID-19 vaccines for study participants. The study excludes subjects who have received live or live attenuated vaccines in the past 3 months and such vaccines are also prohibited while on study treatment. Based on this evaluation, the SMT has concluded that the administration of any COVID-19 vaccine that is not live or live attenuated is permitted in accordance with local guidelines and practice.

Treatment and Follow-up Visits

All study visits and assessments specified in the Schedule of Activities including key efficacy endpoint assessments should be followed in accordance to the protocol, unless COVID-19 related staffing shortages, site policies, or travel restrictions render these infeasible. In such cases, the following modifications may be implemented:

- If study imaging procedures cannot be performed at the active clinical study site, participants will be permitted to use other local imaging facilities (eg, at hospitals that are

not the active study site). In these cases, digital copies should be made available to the investigator for submission to the central imaging vendor.

Safety evaluations (eg, laboratory assessments) may be conducted at certified testing and triage facilities or at other local hospitals. Records for these evaluations must be available for the investigator to review prior to dosing and copies of the results should be included in the participant's study chart as a source document.

Telemedicine/ Teleconferencing/Videoconferencing:

If the subject is doing well and has no safety concerns, scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually (eg, conducted via phone or computer), where feasible, or delayed until such time which access is determined to be appropriate by the Investigator and Sponsor. At each telephone or telemedicine contact:

- Review of new, and follow-up of existing, adverse events and concomitant medications between regularly scheduled on-site visits (eg, weekly assessments of adverse events leading to treatment delay, as described in Section 6.7).
- The subject can complete any scheduled patient-reported outcome (PRO) assessments.
- Review of body systems and collection of general health status (to be followed up with in-person examination if indicated) prior to dosing days, if consistent with site's typical practice.
- Study assessments requiring investigator judgement should be conducted by the investigator.

Home Health Care

Blood sample collection may be done at the participant's home by mobile study personnel (ie, nurse or mobile phlebotomist) or at a commercial laboratory (eg, LabCorp). Other programs may be implemented with approval from the sponsor, such as Home Health Care Visits for study assessments and procedures (eg, physical exam), where feasible and permissible by local policy and regulations. Study treatment with Amivantamab and/ or chemotherapy will only be administered at the study site and will not be administered at Home Health Care Visits.

Flexibility for all protocol-required assessments will be provided on a case-by-case basis, and with agreement between the Sponsor and Investigator. However, every effort should be made to adhere to protocol-specified assessments, including follow-up, if it is in the best interest of the subject.

For regions significantly impacted by a COVID-19 pandemic, the investigator and sponsor may explore the possibility of transferring participants to nearby, less impacted, study sites (if warranted) on either a temporary or permanent basis. The sponsor should be informed of any decisions related to the transfer of participants to other study sites prior to their transfer

Monitoring Visits

When on-site monitoring by the sponsor is not feasible due to changes in hospital or clinic's visitation policies, the sponsor's site monitor will contact the study site to schedule remote visits. In such cases, on-site monitoring visits will resume when feasible, with increased frequency to address the source data verification backlog.

Even with staffing limitations during this COVID-19 pandemic, all routine operations related to clinical trials should be well-documented and archived as part of standard process. When conditions permit, all parties involved in this clinical trial should communicate relevant information in a timely manner so that all relevant parties remain sufficiently informed to take any necessary measures in a timely manner.

10.14. Appendix 14: Open-label Extension Phase

The purpose of the OLE Phase is to continue providing participants access to study treatment and collect data of clinical relevance/importance while reducing the burden on participants after the primary analysis. Data collected during this phase will be limited to those procedures and assessments specified in Table 22.

The OLE Phase will begin after approval of Amendment 3 by health authorities of countries in which this study is still being conducted at the time of transition, and by study site ECs/IRBs.

During the OLE Phase:

- Participants in Arm A (amivantamab plus chemotherapy) will continue to receive the study treatment they are currently receiving at the time of transition to the OLE Phase and until the discontinuation criteria described in Section 7.1 are met, or until the end of the OLE Phase and/or transition to the LTE Phase.
- Participants in Arm B (chemotherapy) will continue to receive the study treatment they are currently receiving at the time of transition to the OLE Phase and until the discontinuation criteria described in Section 7.1 are met, or until the end of the OLE Phase and/or transition to the LTE Phase. Participants who discontinue chemotherapy in Arm B for any reason, including investigator-assessed disease progression, have not started subsequent therapy, and satisfy the eligibility criteria described in Section 10.14.1 will be allowed to cross over to start receiving amivantamab monotherapy. If a participant in Arm B does not meet these eligibility criteria, the participant will enter the Follow-up phase.
- Participants in the optional crossover to second-line amivantamab monotherapy will continue to receive amivantamab monotherapy until the discontinuation criteria described in Section 7.1 are met, or until the end of the OLE Phase and/or transition to the LTE Phase.
- Participants who have already ended study treatment altogether and are in the Follow-up Phase in the main study will continue to be in Follow-up as specified in the Schedule of Activities for the OLE Phase (Table 22).

10.14.1. Eligibility Criteria to Cross Over to Second-Line Amivantamab Monotherapy (Arm B Only) Within the OLE Phase

Each participant in Arm B who is identified as a candidate for crossover to amivantamab monotherapy must satisfy all of the following eligibility criteria below within 28 days prior to initiating amivantamab monotherapy.

1. Prior study randomization to Arm B, with subsequent disease progression after treatment with carboplatin-pemetrexed, and confirmation of disease progression by investigator assessment by RECIST v1.1.
2. No intervening systemic anti-cancer therapy or investigational therapy following discontinuation of assigned Arm B study treatment.
3. 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 treatment.

4. Participant must have signed an ICF for the crossover.
5. Participant must have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
6. Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion or platelet transfusion within 7 days prior to the date of the test.
   - Hemoglobin ≥10 g/dL
   - Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L, without any prior use of G-CSF
   - Platelets $\geq 100\times10^9$/L
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3×ULN
   - Total bilirubin ≤1.5×ULN (participants with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits)
   - Creatinine clearance >50 mL/min as measured or calculated by Cockcroft-Gault formula
7. Participant must have no untreated CNS metastases (a participant with definitively, locally treated metastasis who is clinically stable and asymptomatic for at least 2 weeks off corticosteroid treatment before enrollment will be eligible).
8. Participant must have no ongoing or active bacterial infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week before the first dose of amivantamab]), symptomatic viral infection, or any other clinically significant infection.
9. Participants must not have a medical history of ILD/pneumonitis.
10. A female participant of childbearing potential must have a negative serum or urine test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.
11. A female participant must be (as defined in Appendix 4: Contraceptive and Barrier Guidance) either of the following:
    c. Not of childbearing potential
    d. Of childbearing potential and practicing 2 methods of contraception, including 1 highly effective, user independent method. Examples of highly effective methods of contraception are located in Appendix 4: Contraceptive and Barrier Guidance.

    Participant must agree to continue contraception throughout the study and through 6 months after the last dose of study treatment.

    Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) the woman must begin 2 methods of birth control, as described above.
12. A female participant must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study treatment.
13. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 6 months after receiving

the last dose of study treatment. If the participant is vasectomized, he must still use a condom (with or without spermicide) for prevention of passage of exposure through ejaculation, but his female partner is not required to use contraception.

A male participant who is sexually active with a woman of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository and his partner must also be practicing a highly effective method of contraception (ie, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]).

14. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study treatment.
15. Participant is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment.
16. Participant plans to father a child while enrolled in this study or within 6 months after the last dose of study treatment.

Participants who satisfy the eligibility criteria above will receive amivantamab monotherapy, with treatment beginning with Cycle X+1, where X is the last cycle that the participant completed during the OLE Phase.

10.14.2. Study Treatment Administration

Study treatment should be continued as specified in Section 6. Participants in Arm B who cross over to amivantamab monotherapy should follow study treatment as specified in Section 10.11 (Appendix 11).

10.14.3. Study Procedures

All participants in the OLE Phase should follow the Schedule of Activities for the OLE Phase (Table 22).

Laboratory tests should be conducted by a local laboratory as specified in the Schedule of Activities for the OLE Phase (Table 22). The investigator should review the laboratory report, document this review, and record only clinically relevant changes in the adverse event eCRF. Additional follow-up monitoring as specified in the Schedule of Activities in Table 22 should be performed. Pregnancy reporting should continue as described in Section 8.3.5. A positive pregnancy test should be reported via the adverse event/serious adverse event process (see Section 8.3.5 and Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

After notification from the sponsor to the site that final analysis for overall survival is complete, participants on study treatment in the OLE Phase will be provided the option to transfer to the LTE Phase (see Section 10.15 [Appendix 15]).

During the OLE Phase, data for the following study assessments will be collected.

- Dosing, including pre-infusion and post-infusion medications
- Investigator-assessed disease assessment by RECIST v1.1
- Survival data

- TTSP (until final OS analysis)
- TTST
- PROs (predose on dosing days): EQ-5D-5L, EORT-QLQ-C30, PROMIS-PF (for 1 year after disease progression, reducing the data collection frequency from every 3 months to every 6 months)
- All adverse events (including serious adverse events and adverse events of special interest)
- Concomitant medications (for safety), clinical laboratory assessments (for safety), subsequent treatment

Table 22: Schedule of Activities for Study Assessments/Procedures in the Open-label Extension Phase

Study Phase	Screening (Arm B crossover only)	Treatment (21 Days/Cycle)					End of Treatment	Follow-up (Visit/Call)	Notes
Cycle		Cycle 1				Cycles 2+	30 Days After Last Dose*	Q12W	
Cycle Day		1	2	8	15	1			
Visit Window (Days)	-28 to -1	-	-	±1	±1	±3	+7	±14	
STUDY PROCEDURES Treatment cycles are 21 days in duration. In Cycle 1, amivantamab is administered on Days 1, 2, 8, and 15. In all subsequent cycles, amivantamab is administered once every 3 weeks on Day 1 of each 21-day cycle. Assessments during in-clinic dosing days should be performed prior to administration of study treatment unless otherwise stated. Investigator must confirm that the participant meets treatment criteria before administration of study treatment. *End of Treatment visit should occur 30 days after the last dose or before starting the next anti-cancer treatment, whichever occurs first. In Follow-up phase, collect data until the end of study unless the participant has died, is lost to follow-up, or has withdrawn consent.									
Screening Assessments									
Informed consent	X (all participants)								Must be signed before the first study-related procedure in the OLE Phase.
Inclusion/exclusion criteria	X								Confirm all criteria are met before participant enters crossover in the OLE Phase (see Section 10.14.1).
ECOG performance status	X								
Pregnancy test (serum or urine)	X	As clinically indicated, according to local regulation requirements, or following the local practice of the center.							Women of child-bearing potential only. Required at Screening and within 72 hours before the first dose of amivantamab. If local regulations mandate pregnancy testing before administration of amivantamab, the test should be completed within 72 hours before Day 1 of each cycle or monthly, whichever is more frequent. Pregnancy reporting should continue as described in Section 8.3.5. A positive pregnancy test should be reported via the AE/SAE process (see Section 8.3 5 and Appendix 3).
Coagulation	X								
Urinalysis	X								
12-lead ECG	X								At Screening, then as clinically indicated (triplicate if clinically significant).
Hematology/chemistry (up to 72 hours predose)	X	X		X	X	X	X		Laboratory assessments are listed in Appendix 7. Laboratory assessments must be reviewed by the Investigator prior to the infusion of amivantamab. Report only clinically significant abnormalities as an adverse event in the eCRF.
Efficacy Assessments									
CT/MRI tumor imaging	X	6 weeks (+1 week) from first dose of amivantamab monotherapy, then every 6 weeks (±1 week) for the first 18 months, then every 12 weeks (±1 week) afterward							Use same method throughout study (Section 8.1). Continue until disease progression per investigator assessment by RECIST v1.1. If a participant is treated beyond documented disease progression, continue disease assessments as scheduled and review clinical benefit with the Medical Monitor after each disease assessment.
Brain MRI	X	As clinically indicated							
Symptomatic progression events	X								Collect continuously from randomization (including during the Follow-up Phase)
Survival/disease status								X	
Subsequent anticancer therapy								X	Collect information on type of therapy, treatment start date, and treatment stop date.
Safety Assessments (predose, except as noted) – vital signs and physical exam must be conducted as specified; however, they will be recorded in the eCRF only if associated with an Adverse Event									
Vital signs	X	X	X	X	X	X	X		Heart rate, BP, respiratory rate, temperature, and O_2 saturation

Table 22: Schedule of Activities for Study Assessments/Procedures in the Open-label Extension Phase

Study Phase	Screening (Arm B crossover only)	Treatment (21 Days/Cycle)					End of Treatment	Follow-up (Visit/Call)	Notes
Cycle		Cycle 1				Cycles 2+	30 Days After Last Dose*	Q12W	
Cycle Day		1	2	8	15	1			
Visit Window (Days)	-28 to -1	-	-	±1	±1	±3	+7	±14	
Physical examination	X	X				X	X		Screening will include, at a minimum, weight, general appearance, and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.
Adverse events	Continuous from the time ICF is signed through 30 days after the last dose of study treatment (or >30 days, if considered related to study treatment)								
Prior and concomitant medications	X								Record all prescription and over-the-counter treatments administered through 30 days after the last dose of study treatment (or the start of a subsequent systemic anti-cancer therapy, if earlier). For participants with Grade 3 or 4 adverse events considered related to amivantamab, or adverse events considered related to amivantamab occurring after 30 days following the last dose, record concomitant medications through the end of follow-up.
Patient-Reported Outcomes (predose on dosing days)									
EQ-5D-5L, EORTC-QLQ-C30, PROMIS-PF		X				C3, 5, 7, 9, etc	X	Every 6 months	On C1D1, the Patient-Reported Outcomes data can be collected 24 hours before the first dose. Continue in Follow-up phase for 1 year, regardless of whether subsequent therapy has been started.
Study Treatment									
Amivantamab (Arm A and crossover)		X	X	X	X	X			If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing. If the first dose in Cycle 2 or beyond is delayed, then the next dose of amivantamab will be based on the previous dose of amivantamab .
Pemetrexed administration (Arm A/B)		X				X			
Preinfusion Medications									
Preinfusion medications		X	X	X	X	X			See Table 18. Record all preinfusion medications.

AE=adverse event; BP=blood pressure; CT=computerized tomography; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; MRI=magnetic resonance imaging; O_2=oxygen; OLE=open-label extension; Q12W=every 12 weeks.

10.15. Appendix 15: Long-term Extension Phase

The purpose of the LTE Phase is to continue providing participants access to study treatment while further reducing the burden on participants after the final analysis for overall survival is complete. Investigators should monitor and assess the participants for disease status (response, progression, survival) and safety according to routine standard practice and local label requirements. The LTE Phase will begin after the final analysis for overall survival and will continue until the discontinuation criteria described in Section 7.1 are met, or until 2 years after local marketing authorization is obtained for the studied indication, whichever occurs first. After prior notification from the sponsor. participants still in the study after the OLE Phase will be provided the option to transfer to the LTE Phase.

Data collection will be limited to serious adverse events, which will be reported on the appropriate serious adverse event form and recorded by the sponsor in the Global Medical Safety database. Pregnancy reporting should continue as described in Section 8.2.5. Other safety and efficacy data will not be collected during the LTE Phase. No analyses other than routine periodic safety reviews encompassing reported serious adverse events are planned for the LTE Phase.

Participants who had discontinued study treatment and are in the Follow-up Phase, or participants who elect not to enter the LTE Phase will be discontinued from the study upon the start of the LTE Phase.

Participants entering the LTE Phase will continue to receive the study treatment they were receiving at the time of transfer to the LTE Phase. The sponsor will continue to provide study drugs until the discontinuation criteria described in Section 7.1 are met, or until 2 years after local marketing authorization is obtained for the studied indication, whichever occurs first. Study treatment dispensation and accountability will be performed via IWRS.

10.15.1. Eligibility Criteria

All participants still in the OLE Phase are eligible to transfer to the LTE Phase.

Participants who discontinue chemotherapy in Arm B for any reason, including investigator-assessed disease progression, have not started subsequent therapy, and satisfy the eligibility criteria described in Section 10.14.1 will be allowed to cross over to start receiving amivantamab monotherapy.

Each participant in Arm B who is identified as a candidate for crossover to amivantamab monotherapy must satisfy all of the eligibility criteria in Section 10.14.1 within 28 days prior to initiating amivantamab monotherapy. If a participant in Arm B does not meet these eligibility criteria, the participant will enter the Follow-up phase.

Participants who satisfy the eligibility criteria will receive amivantamab monotherapy, with treatment beginning with Cycle X+1, where X is the last cycle that the participant completed during the LTE Phase.

10.15.2. Study Treatment Administration

Study treatment should be continued as specified in Section 6. Participants in Arm B who cross over to amivantamab monotherapy should follow study treatment as specified in Section 10.11 (Appendix 11).

10.15.3. Study Procedures

All participants in the LTE Phase should follow the Schedule of Activities for the LTE Phase (Table 23).

Participants in the LTE Phase should be followed up for disease assessment and safety per the local practice and following the local label(s). No efficacy data will be collected; only serious adverse events will be collected via the serious adverse event form per the serious adverse event process. Pregnancy reporting should continue as described in Section 8.2.5. A positive pregnancy test should be documented in the subject file/source notes. Other procedures and safety assessments may be performed per local practice.

No data will be collected in the eCRF during the LTE Phase. However, assessments performed should continue to be documented in the subject file/source notes.

Table 23: Schedule of Activities for Study Assessments/Procedures in the Long-term Extension Phase

Study Phase	Screening (Arm B crossover only)	Treatment (21 Days/Cycle)					End of Treatment	Follow-up (Visit/Call)	Notes
Cycle		Cycle 1				Cycles 2+	30 Days After Last Dose*	Q12W	
Cycle Day		1	2	8	15	1			
Visit Window (Days)	-28 to -1	-	-	±1	±1	±3	+7	±14	
STUDY PROCEDURES Treatment cycles are 21 days in duration. In Cycle 1, amivantamab is administered on Days 1, 2, 8, and 15. In all subsequent cycles, amivantamab is administered once every 3 weeks on Day 1 of each 21-day cycle. Assessments during in-clinic dosing days should be performed prior to administration of study treatment unless otherwise stated. Investigator must confirm that the participant meets treatment criteria before administration of study treatment. *End of Treatment visit should occur 30 days after the last dose or before starting the next anti-cancer treatment, whichever occurs first. In Follow-up phase, collect data until the end of study unless the participant has died, is lost to follow-up, or has withdrawn consent.									
Screening Assessments									
Informed consent	X (All subjects)								Must be signed before the first study-related procedure in the LTE Phase.
Inclusion/exclusion criteria	X								Confirm all criteria are met before participant enters crossover in the LTE Phase (see Section 10.15.1).
Pregnancy test (serum or urine)	X	As clinically indicated, according to local regulation requirements, or following the local practice of the center							Women of child-bearing potential only. Required at Screening and within 72 hours before the first dose of amivantamab. If local regulations mandate pregnancy testing before administration of amivantamab, the test should be completed within 72 hours before Day 1 of each cycle or monthly, whichever is more frequent. Pregnancy reporting should continue as described in Section 8.2.5 A positive pregnancy test should be documented in the subject file/source notes.
Safety and Efficacy Assessments (predose, except as noted)									
Safety and Efficacy Assessments	X								All participants continuing in the LTE Phase should be followed up for disease assessment and safety per the local practice and following the local label(s).
Adverse events (SAEs only)	Continuous from the time ICF is signed through 30 days after the last dose of study treatment (or >30 days, if considered related to study treatment)								
Study Treatment									
Amivantamab (Arm A and crossover)		X	X	X	X	X			If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing. If the first dose in Cycle 2 or beyond is delayed, then the next dose of amivantamab will be based on the previous dose of amivantamab .
Pemetrexed administration (Arm A/B)		X				X			
Preinfusion Medications									
Preinfusion medications		X	X	X	X	X			See Table 18. Record all preinfusion medications.

LTE=long-term extension; Q12W=every 12 weeks; SAE=serious adverse event.

10.16. Appendix 16: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 2 (12 August 2022)

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

When changes are provided verbatim, deleted text is shown as strikethrough, and added text is shown as bold font.

Section Number and Name	Description of Change(s)	Brief Rationale
Section 1.3: Schedule of Activities	CT/MRI tumor imaging row; notes section, text added to say: Use same method throughout study (Section 8.1). Continue until disease **progression by BICR.** Added text to Subsequent anticancer therapy, Notes, column: Collect information on type of therapy, treatment start date, and treatment stop date, **objective disease response and progression** Added the full term for BICR in Table 1 footnote.	To clarify imaging assessments. To clarify assessments in the follow up phase To define the full term of abbreviation mentioned in Table 1.
Section 4.1.3 Follow up Phase	Added Note: Note: For participants who discontinue prior to disease progression by BICR, tumor imaging should continue per schedule of activities.	To clarify assessments in the follow up phase
Section 6.8.2.1: Rash-Related Adverse Events	Bullet point added: • In case of a Grade 4 rash including severe bullous, blistering, or exfoliating skin condition such as toxic epidermal necrolysis (TEN), study treatment should be discontinued permanently. Text was added for Grade 4 event management and for management of severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN) in Table 15: Suggested Algorithm for Management of Rash and Paronychia. Cross reference to Table 13 and Table 14 added for recommended dose adjustment.	Description of action in the event of TEN required by Health Authority.
Section 7.1: Discontinuation of Study Treatment	Added text: Documented radiographic (RECIST, Version 1.1) disease progression **by BICR**, unless treatment beyond disease progression has been approved by the Medical Monitor**. Discontinuation for disease progression based on local assessment prior to BICR confirmation should be discussed with the Medical Monitor** Continuation of study treatment after **BICR confirmed** disease progression may be allowed in accordance with local practice, after approval from the Medical Monitor, if the investigator believes the participant is deriving clinical benefit.	To clarify steps beyond disease progression.

Section 8.1.1: Disease Assessments	Text added: Subsequent assessments should be performed at 6 weeks (+1 week) after randomization, then every 6 weeks (±1 week) for the first 18 months and then every 12 weeks (±1 week), until objective radiographic disease progression **by BICR**. Also added: Investigators should consider BICR non-PD assessments when making discontinuation decisions **and can continue with study treatment until BICR confirmed disease progression**. Also added: For participants who discontinue study treatment due to toxicity or a reason other than objective progressive disease **by BICR**, tumor assessments should be continued per schedule until radiographic progressive disease is documented **and confirmed by BICR**	To clarify imaging assessments.
Section 8.1.2 Symptomatic Progression	Text added: Symptoms, attribution, and related interventions will be recorded in the eCRF at the times specified in the Schedule of Activities. **If symptomatic progression is not reported prior to treatment discontinuation, continued assessment of the symptoms is required during the follow up period even after subsequent therapy is initiated.**	To clarify assessments for symptomatic progression.
Section 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Cross-reference to Table 1 added.	To provide cross-reference to extra detail.
10.7:.Appendix 7: Clinical Laboratory Tests	Text added: Leukocyte esterase **(if available)**	To allow flexibility at site.
Appendix 11: Optional Crossover After Disease Progression to Second-Line Amivantamab Monotherapy (Arm B Only)	Table 18: Preinfusion Medications for Amivantamab: Timing of preinfusion medications has been updated. Route of administration of antihistamines has also been updated. Text added to Discontinuation Of Study Treatment And Participant Discontinuation/Withdrawal subsection: Follow the guidance in Section 7 for discontinuation of study treatment and participant discontinuation or withdrawal. **Additionally, study treatment must be discontinued for documented radiographic disease progression as per RECIST v1.1 unless treatment beyond disease progression is approved by the Medical Monitor.**	To be consistent with pre-infusion medication guidelines throughout the study. To clarify discontinuation of crossover subjects.

Amendment 1 (20 May 2021)

Overall Rationale for the Amendment: To provide clarifications to the current protocol and to provide the latest combination therapy data from the Phase 1 Study 61186372EDI1001. When changes are provided verbatim, deleted text is shown as strikethrough, and added text is shown as bold font.

Section Number and Name	Description of Changes(s)[a]	Brief Rationale
1.1 Synopsis	Addition of the text in bold **The combination of amivantamab with chemotherapy in participants with EGFR mutated NSCLC is also being evaluated in this study. As of 20 October 2020, 16 patients have been dosed with the combination amivantamab and chemotherapy (carboplatin and pemetrexed). Preliminary safety analysis of the combination is consistent with the monotherapy experience of amivantamab and chemotherapy alone. Preliminary pharmacokinetic (PK) data suggests no impact of chemotherapy on amivantamab exposure**.	Presentation of the latest combination therapy data from Phase 1 Study 61186372EDI1001.
Figure 1: Schematic Overview of the Study Design	Corrected to show that the crossover dosing is from Cycle 3 Day 1 onwards	Clarification.
Table 1: Schedule of Activities for Study Assessments/ Procedures	Serology note updated: HIV antibody, ~~HBV, HCV,~~ HBsAg, HBsAb, HBcAb, anti-HCV antibody, HBV viral load (if needed) and HCV viral load (if needed). Hematology/chemistry note updated: **Hematology/chemistry schedule on C1D8 and C1D15 applies to both Arm A and Arm B**. Vital signs note updated: **Vital signs on C1D2 are not required for Arm B as no C1D2 visit is required**. Amivantamab administration (Arm A only) note updated: ~~Any missed scheduled doses should be discussed with the Medical Monitor prior to redosing. If a dose is delayed in Cycle 2 or beyond, then the dates of all subsequent doses must be maintained as originally scheduled based on first dose of Cycle 1.~~ **See Section 6.2.1 for guidance if changes are required to scheduled doses of amivantamab.** Patient-Reported Outcomes note updated: **On C1D1, the Patient-Reported Outcomes data can be collected 24 hours before the first dose.**	Clarification.
2.2.1. Clinical Studies of Amivantamab	Addition of the text in bold **Updated efficacy and safety data of amivantamab monotherapy in patients with EGFR Exon 20ins NSCLC were recently presented at the International Association for the Study of Lung Cancer (IASLC) 2021 World Conference.[26] Results remain consistent with the previous experience with amivantamab. These updated data are also available in IB Version 5.0.[12]**	Addition of the latest monotherapy data and reference.
2.2.3 Rationale for Amivantamab Chemotherapy Combination	Addition of the text in bold **As of 20 October 2020, 16 patients have been dosed with the combination amivantamab and chemotherapy (carboplatin and pemetrexed) in the ongoing Phase 1 study CHRYSALIS (61186372EDI1001). Preliminary safety analysis of the combination is consistent with the monotherapy experience of amivantamab and chemotherapy alone. Preliminary PK data suggests no impact of chemotherapy on amivantamab exposure. Please refer to the IB (Version 5.0) for additional information.[12]**	Presentation of the latest combination therapy data from Phase 1 Study 61186372EDI1001.

2.3.1. Risks for Study Participation	Addition of the text in bold The safety of amivantamab in combination with carboplatin and pemetrexed is being investigated in a Phase 1 study (61186372EDI1001) **and results from this cohort have been updated in the IB.**[12] An Independent Data Monitoring Committee (IDMC) will review safety and tolerability data periodically (refer to Appendix 2: Regulatory, Ethical, and Study Oversight Considerations). The IDMC ~~will~~ **has** review**ed** safety results for amivantamab in combination with carboplatin and pemetrexed in the ongoing Phase 1 study prior to enrollment of participants in this Phase 3 study. In addition, an early IDMC meeting **is planned**~~may occur~~ after approximately 20 participants have been randomized and treated for 2 cycles with the protocol treatment for additional review of the safety with this combination.	Presentation of the latest combination therapy data from Phase 1 Study 61186372EDI1001.
4.3.2. Amivantamab and Chemotherapy Combination Dose Rationale	Addition of the text in bold: **In the ongoing Phase 1 Study 61186372EDI1001, Cycle 1 PK data suggest no impact of chemotherapy on amivantamab exposure. Preliminary trough concentration comparisons suggest that higher doses of amivantamab given every 3 weeks (Q3W; 21-day cycle), are similar to the recommended dose for monotherapy given every 2 weeks (28-day cycle). Please refer to IB Version 5.0 for further information**.[12]	Presentation of the latest combination therapy data from Phase 1 Study 61186372EDI1001.
5.1. Inclusion Criteria	Updates to inclusion criterion 9: **Criterion modified per Amendment 1:** **9.1.** A female participant must be (as defined in Appendix 4: Contraceptive and Barrier Guidance) either of the following: a. Not of childbearing potential Of childbearing potential and • ~~practicing true abstinence during the entire period of the study, including up to 6 months after the last dose of study treatment is given;~~ • ~~have a sole partner who is vasectomized;~~ ~~or~~ practicing 2 ~~highly effective~~ methods of contraception, including 1 **highly effective,** user independent method. Examples of highly effective methods of contraception are located in Appendix 4: Contraceptive and Barrier Guidance. Participant must agree to continue contraception throughout the study and through 6 months after the last dose of study treatment. Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) the woman must begin 2 ~~highly effective~~ methods of birth control, as described above.	To comply with the requirements of the 2020 Clinical Trials Facilitation Group Contraception Guidance.

5.2. Exclusion Criteria	Exclusion criterion 1, addition of the text in bold: **Criterion modified per Amendment 1:** **1.1.** Participant has received any prior systemic treatment for locally advanced or metastatic disease, with the following exceptions: • Prior adjuvant or neoadjuvant platinum-based doublet chemotherapy is allowed, if completed at least 12 months prior to signing the study ICF. • Localized radiotherapy to the lung must be completed at least 6 months prior to randomization. Palliative radiation to other sites must be completed at least 7 days prior to randomization. ~~See Section 8.1 for information regarding irradiated target lesions.~~ • Prior monotherapy with an approved EGFR TKI (**ie** gefitinib, erlotinib, afatinib, **dacomitinib,** or osimertinib) as non-standard first-line therapy for the treatment of locally advanced or metastatic disease is allowed, if: 1) treatment duration did not exceed 8 weeks; 2) lack of disease response was documented (radiographically) by an increase in tumor burden **(a copy of the computerized tomography [CT] report showing increase in tumor burden from baseline should be submitted);** Exclusion criterion 2, addition of the text in bold: **Criterion modified per Amendment 1:** **2.1.** Participant has evidence of synchronous NSCLC **disease (as suggested by genetic characterization or radiographic appearance).** ~~with an EGFR mutation other than EGFR Exon 20ins.~~ Exclusion criterion 8, addition of the text in bold: **Criterion modified per Amendment 1:** **8.1.** Participant has an active malignancy (ie, **ongoing,** progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. Exclusion criterion 11, addition of the text in bold: **Criterion modified per Amendment 1:** **11.1.** Participant is known to be positive for human immunodeficiency virus (HIV) **and meets one of the following criteria:** Note updated, addition of the text in bold: NOTE: Investigators ~~should~~ must ensure that all study enrollment ~~criteria~~ **procedures** have been ~~met at screening~~ **completed during the screening period and the subject continues to meet eligibility at the time of randomization, is clinically stable and is expected to initiate therapy within 72 hours of randomization**. ~~If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 describes options for retesting.~~	Clarification.

6.2.1 Scheduled Dosage and Timing	Addition of the text in bold: **If amivantamab treatment is delayed from Cycle 1 Day 1 to Day 2 and Cycle 1 Day 2 to Day 3, appropriate premedications should be administered before amivantamab infusion. Please refer to Table 6 for premedications required with amivantamab**. […] **Amivantamab should typically be administered Q3W but if amivantamab dosing needs to align with a delayed dose of chemotherapy then it can be administered at an interval between 2 and 4 weeks (see Appendix 9: Dosing Synchronization for Arm A). Any missed scheduled doses should be discussed with the Medical Monitor prior to redosing. If a dose is delayed on Cycle 1 Day 8 and/or Cycle 1 Day 15 it will not be made up. If a dose is delayed in Cycle 2 or beyond, then the dates of the subsequent doses will be scheduled based on the timing of the previous dose of amivantamab. If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing.**	Clarification.
6.2.3 Amivantamab	Deletion of the following text: ~~The minimum infusion time will be 120 minutes.~~	To ensure that investigators refer to the IPPI for information describing the stability and administration of amivantamab.
6.3 Preparation/Handling/ Storage/ Accountability	Addition of the text in bold: Preparation/Handling/Storage **The instructions below on study treatment preparation, handling, and storage apply only to amivantamab and/or centrally sourced chemotherapy. For locally sourced chemotherapy, please follow the instructions on the local package insert**. Accountability **The instructions below on study treatment apply only to amivantamab and/or centrally sourced chemotherapy. For locally sourced chemotherapy, please follow the instructions on the local package insert**.	Clarification.
6.5 Study Treatment Compliance	Addition of the text in bold: **The instructions below on study treatment compliance apply only to amivantamab and/or centrally sourced chemotherapy. For locally sourced chemotherapy, please follow the instructions on the local package insert.**	Clarification.
6.6.2.2. Pre- and Post-Infusion Medications for Amivantamab	Table 7 updated: **Fosprepitant**/Aprepitant ~~150 mg~~	Clarification.
6.7. Dose Delay Guidance	Addition of the text in bold: Combination Chemotherapy (pemetrexed ± carboplatin): […]While some flexibility in the amivantamab dosing schedule is allowed as described above, combination chemotherapy must be dosed at a minimum interval of 21 days **(carboplatin administration cannot exceed for more than a total of 4 cycles)**~~for a total of 4 cycles~~. Amivantamab: **In the event amivantamab dosing on Day 1 of the cycle is delayed, but retreatment criteria for chemotherapy are met, dosing with chemotherapy should continue as planned and subjects should be evaluated weekly for retreatment. If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing**. ~~In the event chemotherapy dosing on Day 1 of the cycle is delayed, but retreatment criteria for amivantamab are met, dosing with amivantamab should continue as planned. As discussed above, if chemotherapy dosing subsequently occurs on Day 8 or Day 15 of the cycle, the next dose of amivantamab can be aligned with chemotherapy dosing in the subsequent cycle.~~	Clarification.

6.8.2. Amivantamab Dose Modification	Addition of the text in bold: Table 13: Guidance for Amivantamab Dose Delay and Modification for Toxicities **Considered Related to Amivantamab** (Other Than Rash, **Paronychia**, Infusion-Related Reaction, ~~Liver Toxicity,~~ or Pulmonary Toxicity). Footnote c edited: Resolution defined as: Grade ≤1 ~~non hematologic toxicity~~ or back to baseline. **For hypoalbuminemia, the dose can be resumed without resolution of the event to Grade ≤1 or baseline and based on the Investigator's clinical judgement. For liver enzyme abnormalities requiring interruption of treatment, a discussion should occur with the Medical Monitor before restarting amivantamab.** Table 15: Suggested Algorithm for Management of Rash **and Paronychia.**	Clarification.
6.8.2.3. Liver Chemistry Abnormalities	Clarification added in bold: b. ALT or AST >3×ULN **(if baseline was normal)** with the concurrent appearance of **symptoms suggestive of ongoing severe liver injury, such as** fatigue, nausea, vomiting **(beyond what is anticipated from chemotherapy),** right upper quadrant pain or tenderness, fever, rash, and/or **new** eosinophilia (>5%). In the event abnormalities of liver function tests require withholding study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. **If the liver function test criteria a) above (ALT or AST ≥3×ULN and bilirubin ≥2×ULN [>35% direct bilirubin] [or ALT ≥3×ULN and INR >1.5, if INR measured]) is concurrently met, e**tiology of the liver chemistry abnormality should be investigated, as described below. If no alternative etiology of liver toxicity is identified, study treatment should be permanently discontinued.	Clarification.
8. STUDY ASSESSMENTS AND PROCEDURES	Clarification added in bold: Study treatment **(amivantamab will be supplied centrally; depending on region, chemotherapy may be either centrally or locally sourced)**	Clarification.
8.1.1. Disease Assessments	Addition of the text in bold Participants will have MRI of the brain at screening, with subsequent definitive treatment of identified active lesions before starting study treatment (see Section 5.1). **For patients who are intolerant to brain MRI, alternative imaging modality can be considered for screening after discussion with the Medical Monitor.**	Clarification.
8.2.3. Electrocardiograms	Section updated: During the collection of electrocardiograms (ECGs), participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. ~~If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.~~ Collection of ECGs will be obtained as indicated in the Schedule of Activities (Table 1). At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but approximately 2 minutes apart. A copy of triplicate ECGs on Cycle 1 Day 1 and Cycle 3 Day 1 will be sent to a central reader. **If the Screening ECG is performed in triplicate within 72 hours before the first dose of study treatment, the assessment does not need to be repeated at Cycle 1 Day 1 (and a copy of these triplicate ECGs can be sent to a central reader in lieu of Cycle 1 Day 1).**	Clarification.

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting; Section 10.3.2	Addition of the text in bold Related There is a reasonable causal relationship between study treatment administration and the AE. **Related events would include probably and possibly related events.** Not Related There is not a reasonable causal relationship between study treatment administration and the AE. **Not related events would include doubtfully related events.**	Clarification.
Appendix 7: Clinical Laboratory Tests, Protocol-Required Safety Laboratory Assessments	Protocol-required safety laboratory assessments updated to include the following clinical chemistry at each assessment (not just at Screening): magnesium, phosphorus, sodium, potassium, calcium. Blood glucose added as an additional test at Screening only	Clarification.
Appendix 11: Optional Crossover After Disease Progression to Second Line Amivantamab Monotherapy (Arm B Only) Crossover Eligibility Criteria	Addition of the text in bold **9. Criterion added per Amendment 1:** **Patients must not have a medical history of ILD/pneumonitis.** Study treatment clarified: **If amivantamab is delayed for ≥6 weeks from the last dose, a discussion should occur with the Medical Monitor prior to redosing.** Table 20: Updated to reflect the updates made to Table 1 (Schedule of Assessments).	Addition of the crossover eligibility criterion and study treatment clarified.
Appendix 12: Paronychia, Reactive Management Recommendations	Addition of the text in bold **For dose modifications in the event of paronychia, please refer to Table 15.**	Clarification.
Appendix 13: Guidance on Study Conduct During a COVID-19 Pandemic	Addition of the text in bold **COVID-19 vaccination** **The amivantamab safety management team (SMT) evaluated available COVID-19 vaccines for study participants. The study excludes subjects who have received live or live attenuated vaccines in the past 3 months and such vaccines are also prohibited while on study treatment. Based on this evaluation, the SMT has concluded that the administration of any COVID-19 vaccine that is not live or live attenuated is permitted in accordance with local guidelines and practice.**	Instructional text was updated for clarification.
Appendix 14: Protocol Amendment History	The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.	Updated to include Protocol Amendment 1.
References	Addition of the following references: Investigator's Brochure: JNJ-61186372 Edition 5. Janssen Research & Development, LLC (08 March 2021). Park et al, 2020. Sabari, J. et al. 2021.	To align with changes made in the Protocol Amendment 1.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

[a] Text added during Amendment 1 is shown in bold font, text removed since the original protocol is shown in strikethrough.

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INVESTIGATOR AGREEMENT

JNJ-61186372 (amivantamab) Clinical Protocol 61186372NSC3001 Amendment 3

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 07 August 2023