

Johnson & Johnson Private Limited

Clinical Protocol

Protocol Title

A Phase 4, Open-Label Study to Evaluate Safety of Amivantamab in Combination With Chemotherapy in Indian Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer With EGFR Exon 19del or Exon21 L858R Mutations After Progression on Osimertinib

Protocol 61186372NSC4018; Phase 4

Version: Amendment 1

JNJ-61186372 (amivantamab)

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Amendment 1	28 April 2026
Original Protocol	10 December 2025

Amendment 1 (28 April 2026)

Overall Rationale for the Amendment: The overall rationale for the amendment is to delete the Cohort A (amivantamab+lazertinib) from the study as per the Indian Health Authority request as the permission for marketing of lazertinib film-coated tablets 80 and 240 mg is not yet granted in India.

The changes made to the clinical protocol 61186372NSC4018 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
Title Page	Study title was updated.	To align with Indian Health Authority request to delete lazertinib-related information from the study as the permission for marketing of lazertinib film-coated tablets 80 and 240 mg is not yet granted in India.
1.2. Schema	Schema was updated to reflect the single arm study design.	
1.3. Schedule of Activities	Following changes were made in SoA table: • A row “Prophylactic Dose of Anticoagulation” was deleted. • Footnote c was deleted and subsequent footnotes were reordered. • Footnote a, d, and m were modified to delete Cohort A related details. • A row in “Study Treatment Administration” was modified to delete Cohort A related information. • Table 1a was deleted and subsequent table was renumbered.	
1.1. Synopsis; 2. Introduction; 2.1. Study Rationale; 2.2. Background	Information related to lazertinib was deleted.	
2.1. Study Rationale	Details of MARIPOSA study were deleted	
2.3. Benefit-risk Assessment	Table 2 was modified and information related to risks associated with lazertinib were deleted.	
1.1. Synopsis; 3. Objectives and Endpoints	Objectives and endpoints related to Cohort A were deleted.	
1.1. Synopsis; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 4.4. End of Study Definition	Overall study design and scientific rationale for study design was modified to depict single arm design, and Cohort A related information was deleted.	
5.1. Inclusion Criteria	Inclusion criterion 2 was deleted.	
5.2. Exclusion Criteria	Exclusion criterion 1 was deleted.	

Section number and Name	Description of Change	Brief Rationale
	Exclusion criterion 15 was modified to delete lazertinib-related information.	
1.1. Synopsis; 6.1 Study Treatments Administered	Cohort A related information was deleted.	
6.2. Preparation/ Handling/Storage/Accountability	Accountability related information for lazertinib was deleted.	
6.5. Study Treatment Compliance	Compliance related information for lazertinib was deleted.	
6.6. Dose Modification; 6.6.1. Dose Modification of Amivantamab; 6.6.2. Dose Modification and Management of Specific Adverse Events	Heading of Section 6.6.1 was updated. Lazertinib dose modification information was deleted. Also, tables containing Cohort A related information were deleted.	
6.7. Continued Access to Study Treatment After the End of the Study; 6.8. Treatment of Overdose	Lazertinib-related details were deleted.	
6.9.2.2. Pre-and Post-Infusion Medications for Amivantamab	Cohort A related information was deleted.	
6.9.3. Prohibited or Restricted Medications and Therapies	Text related to prohibition of strong CYP3A4/5 inducers prior to lazertinib treatment was deleted.	
1.1. Synopsis; 9.1. Statistical Hypotheses; 9.3.1. General Considerations; 9.3.2. Primary Endpoint	Text mentioning “Analysis of 2 cohorts will be done separately” was deleted.	
1.1. Synopsis; 9.5. Sample Size Determination	Text related to sample size determination for Cohort A was deleted. Text related to sample size justification of amivantamab+chemotherapy was updated to include information on COCOON and MARIPOSA-2 studies.	
10.2.6. Storage, Use, Transfer, and Retention of Data and Samples; 10.2.8. Use of Information, Registration of Study and Publication; 10.3.1. Adverse Event Definitions and Classifications; 10.12. Appendix 12: Medications With Potential for QT Interval Prolongation	Lazertinib-related details were deleted.	To align with real-world clinical practice.
5.1. Inclusion Criteria	Criterion 3 was modified to include “Participants who have received 1 to 2 cycles of chemotherapy before starting osimertinib are eligible for this study provided they have not progressed on chemotherapy.”	
5.2. Exclusion Criteria	Criterion 13 was modified to include the text that 1 or 2 cycles of chemotherapy prior to the initiation	

Section number and Name	Description of Change	Brief Rationale
	of osimertinib therapy are allowed if the participant has not progressed on chemotherapy.	
8.4.2.2. Serious Adverse Event	Added timeframe of within 30 days of last dose of study treatment for reporting death events as SAE.	To correct the error as it was missed inadvertently in the original protocol.
10.7. Appendix 7: Liver Event Follow-Up Requirements	Text mentioning blood sample collection for unscheduled pharmacokinetic analysis was deleted.	To correct error as pharmacokinetic analysis is not included in this study and was added inadvertently in the original protocol
Throughout the protocol	Minor grammatical, formatting, language, or spelling changes were made.	Minor errors were noted.

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE	2
TABLE OF CONTENTS	5
LIST OF IN-TEXT TABLES AND FIGURES TABLES	8
ABBREVIATIONS	9
1. PROTOCOL SUMMARY	11
1.1. Synopsis	11
1.2. Schema	15
1.3. Schedule of Activities (SoA).....	16
2. INTRODUCTION.....	19
2.1. Study Rationale	19
2.2. Background	20
2.3. Benefit-risk Assessment.....	21
3. OBJECTIVES AND ENDPOINTS	24
4. STUDY DESIGN	24
4.1. Overall Design.....	24
4.2. Scientific Rationale for Study Design.....	26
4.2.1. Study-specific Ethical Design Considerations	26
4.3. Justification for Dose.....	27
4.4. End of Study Definition.....	27
5. STUDY POPULATION	27
5.1. Inclusion Criteria	27
5.2. Exclusion Criteria	29
5.3. Lifestyle Considerations	33
5.3.1. Activity.....	33
5.4. Screen Failures	33
5.5. Criteria for Temporarily Delaying Enrollment.....	34
6. STUDY TREATMENT AND CONCOMITANT THERAPY	34
6.1. Study Treatments Administered.....	34
6.2. Preparation/Handling/Storage/Accountability	36
6.3. Assignment to Study Treatment.....	37
6.4. Blinding, Masking	37
6.5. Study Treatment Compliance	37
6.6. Dose Modification.....	38
6.6.1. Dose Modification of Amivantamab	38
6.6.2. Dose Modification and Management of Specific Adverse Events	40
6.6.2.1. Infusion-related Reactions.....	40
6.6.2.2. Rash-related Adverse Events.....	42
6.6.2.3. Pruritus	45
6.6.2.4. Paronychia.....	45
6.6.2.5. Oral Mucositis	46
6.6.2.6. Pulmonary Toxicity	47
6.6.2.7. Cardiac Adverse Events	47
6.6.2.8. Liver Chemistry Abnormalities	48
6.6.2.9. Ocular Toxicity	49
6.6.2.10. Diarrhea	49
6.6.2.11. Paresthesia.....	50
6.6.2.12. Venous Thromboembolic Events.....	51
6.6.3. Chemotherapy Dose Modification	51

6.6.3.1.	Management of Chemotherapy Toxicities	51
6.7.	Continued Access to Study Treatment After the End of the Study	52
6.8.	Treatment of Overdose	52
6.9.	Prior and Concomitant Therapy	53
6.9.1.	Recording Prestudy and Concomitant Therapies	53
6.9.2.	Permitted and Required Medications and Therapies	53
6.9.2.1.	Pre- and Post-Infusion Medications for Chemotherapy	53
6.9.2.2.	Pre- and Post-Infusion Medications for Amivantamab	54
6.9.2.3.	Supportive Care	55
6.9.2.4.	Radiotherapy	55
6.9.2.5.	Hormonal Contraception	55
6.9.3.	Prohibited or Restricted Medications and Therapies	56
7.	DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL	57
7.1.	Discontinuation of Study Treatment	57
7.2.	Participant Discontinuation/Withdrawal From the Study	57
7.3.	Lost to Follow up	58
8.	STUDY ASSESSMENTS AND PROCEDURES	58
8.1.	Administrative and General/Baseline Procedures	58
8.2.	Effectiveness Assessments	58
8.2.1.	Symptomatic Progression	59
8.3.	Safety Assessments	59
8.3.1.	Physical Examinations	60
8.3.2.	Vital Signs	60
8.3.3.	Electrocardiograms	60
8.3.4.	Clinical Safety Laboratory Assessments	60
8.3.5.	ECOG Performance Status	61
8.3.6.	Left Ventricular Ejection Fraction	61
8.3.7.	Pregnancy Tests	61
8.4.	Adverse Events, Serious Adverse Events, and Other Safety Reporting	61
8.4.1.	Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	61
8.4.2.	Definitions and Classifications	62
8.4.2.1.	All Adverse Events	62
8.4.2.2.	Serious Adverse Event	62
8.4.3.	Attribution of Causality	63
8.4.4.	Severity Criteria	64
8.4.5.	Special Reporting Situations	64
8.4.6.	Procedures	65
8.4.6.1.	Anticipated Events	65
8.4.6.3.	Adverse Events of Special Interest	65
8.4.7.	Product Quality Complaint Handling	66
8.4.8.	Contacting Sponsor Regarding Safety, Including Product Quality	66
8.5.	Pregnancy and Postpartum Information	67
8.5.1.	Participants Who Become Pregnant During the Trial	67
8.5.2.	Participants Whose Partners Become Pregnant	67
8.6.	Pharmacokinetics	67
8.7.	Pharmacodynamics	67
8.8.	Biomarkers	67
8.9.	Immunogenicity Assessments	67
8.10.	Health Economics OR Medical Resource Utilization and Health Economics	67
9.	STATISTICAL CONSIDERATIONS	67
9.1.	Statistical Hypotheses	68
9.2.	Participant Analysis Sets	68
9.3.	Statistical Analyses	68

9.3.1.	General Considerations	68
9.3.2.	Primary Endpoint	68
9.3.3.	Secondary Endpoints.....	68
9.3.4.	Other Safety Analyses	69
9.4.	Interim Analysis	69
9.5.	Sample Size Determination	69
10.	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	71
10.1.	Appendix 1: Clinical Laboratory Tests	71
10.2.	Appendix 2: Regulatory, Ethical, and Study Oversight Considerations	73
10.2.1.	Regulatory and Ethical Considerations	73
10.2.2.	Financial Disclosure.....	74
10.2.3.	Informed Consent Process	74
10.2.4.	Recruitment Strategy	74
10.2.5.	Data Protection	74
10.2.6.	Storage, Use, Transfer, and Retention of Data and Samples	75
10.2.7.	Committees Structure	75
10.2.8.	Use of Information, Registration of Study and Publication	75
10.2.9.	Data Quality Assurance, Monitoring and Audits	76
10.2.10.	Source Documents and Case Report Form Completion	76
10.2.11.	Study and Site Start and Closure	77
10.3.	Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.....	78
10.3.1.	Adverse Event Definitions and Classifications	78
10.3.2.	Attribution Definitions.....	79
10.3.3.	Severity Criteria	80
10.3.4.	Special Reporting Situations	80
10.3.5.	Procedures	81
10.3.6.	Product Quality Complaint Handling.....	82
10.3.7.	Contacting Sponsor Regarding Safety, Including Product Quality.....	82
10.4.	Appendix 4: Contraceptive and Barrier Guidance	83
10.5.	Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status.....	85
10.6.	Appendix 6: New York Heart Association Criteria	86
10.7.	Appendix 7: Liver Event Follow-Up Requirements	87
10.8.	Appendix 8: Study Conduct During Major Disruptions Due to Disasters and Public Health Emergencies	88
10.9.	Appendix 9: Allowed Recent Second or Prior MalignanciesNot allowed second or prior malignancies:	91
10.10.	Appendix 10: Cytokine Release Syndrome – Severity Grading and Management	92
10.11.	Appendix 11: Formulas for Estimating Glomerular Filtration Rate Using Modified Diet in Renal Disease Formula (in mL/min)	93
10.12.	Appendix 12: Medications With Potential for QT Interval Prolongation	94
10.13.	Appendix 13: Hepatitis B Virus Screening	96
10.14.	Appendix 14: Anticipated Events	97
10.15.	Appendix 15: Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference	99
10.16.	Appendix 16: Protocol Amendment History	101
11.	REFERENCES.....	102
	INVESTIGATOR AGREEMENT	104

LIST OF IN-TEXT TABLES AND FIGURES TABLES

Table 1:	Schedule of Activities	16
Table 2:	Potential Risks	21
Table 3:	Objectives and Endpoints	24
Table 4:	Pre-infusion Medications for Amivantamab	25
Table 5:	Study Treatments Administered	34
Table 6:	Study Treatment Dosing	35
Table 7:	Proactive Dermatologic Regimen	35
Table 8:	Guidance for Amivantamab Stepwise Dose Reduction	38
Table 9:	General Guidance for Withholding Doses for Toxicities Considered Related to Amivantamab, Based on Grade ^a	39
Table 10:	Management of Infusion-related Reactions	41
Table 11:	Suggested Algorithm for Management of Rash	43
Table 12:	Suggested Algorithm for Management of Diarrhea	50
Table 13:	Guidance for Dose Modifications for Hematologic Chemotherapy Toxicity	52
Table 14:	Guidance for Dose Modifications for Non-hematologic Chemotherapy Toxicity	52
Table 15:	Concomitant Medications for Pemetrexed	54
Table 16:	Post-infusion Medications for Amivantamab	55
Table 17:	Adverse Events of Special Interest	66
Table 18:	Analysis Sets	68

FIGURES

Figure 1:	Schematic Overview of the Study	15
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ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under curve
AxMP	Auxiliary Medicinal Product (also known as NIMP)
BID	Twice daily
BUN	Blood urea nitrogen
CDSCO	Central Drugs Standard Control Organization
CD4	Cluster of differentiation 4
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eDC	Electronic data capture
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutated
EOS	End of study
EOT	End of treatment
ESMO	European Society for Medical Oncology
FOIA	Freedom of Information Act
FSH	Follicular-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transferase
HBc	Hepatitis B core antibody
HBs	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILD	Interstitial lung disease

IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous
JEISR	Janssen Electronic Inbound Safety Reporting
LDH	Lactate dehydrogenase
LDR	Legally designated representative
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MCV	Mean corpuscular volume
MET	mesenchymal-epithelial transition
MRI	Magnetic resonance imaging
MUGA	Multiple-Gated Acquisition scan
NA	Not Applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NIMP	Non-Investigational Medicinal Product
NSCLC	Non-small cell lung cancer
NYHA	New York heart association
OD	Once daily
ORR	Objective response rate
OS	Overall survival
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression free survival
PI	Prescribing information
PO	Per oral
PQC	Product quality complaint
QTc	Corrected QT
QTcF	QT Interval Corrected Using Fridericia's Formula
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Respiratory rate
RT	Radiation therapy
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SD	Standard deviation
SoA	Schedule of Activities
SPF	Skin protection factor
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TEN	Toxic epidermal necrolysis
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
VTE	Venous thromboembolic event
WBC	White blood cell

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 4, Open-Label Study to Evaluate Safety of Amivantamab in Combination With Chemotherapy in Indian Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer With EGFR Exon 19del or Exon21 L858R Mutations After Progression on Osimertinib

Regulatory Agency Identifier Number(s): Not Applicable

Amivantamab (JNJ-61186372) is a low fucose, fully human immunoglobulin G1 (IgG1)-based bispecific antibody directed against epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) protooncogene that is being developed for the treatment of solid tumors, including EGFR mutated (EGFRm) non-small cell lung cancer (NSCLC). Amivantamab intravenous (IV) is approved in US Food and Drug Administration (FDA), European Medicines Agency, and other health authorities in EGFRm NSCLC with exon 19del, exon 21 L858R substitution both as first line and second line treatments. Anti-tumor activity, including within central nervous system, has been seen with amivantamab among patients with EGFR-mutated NSCLC who have experienced disease progression on or after osimertinib and chemotherapy.

OBJECTIVES

This study will evaluate the safety profile of amivantamab in combination with chemotherapy in patients with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment in Indian patients (confirmed citizenship of India and residing in India). Overall, in this study, safety of amivantamab in combination with chemotherapy will be assessed in Indian patients with EGFRm NSCLC. The study will also assess the effectiveness of the amivantamab in combination with chemotherapy.

OVERALL DESIGN

Key aspects of the trial design are summarised in table below.

Study Model:	Single arm	Population Type:	Adult patients
Blinding	Open-label	Population Diagnosis or Condition:	Locally advanced or metastatic NSCLC with EGFR exon 19del or exon21 L858R mutations
Study Treatment Assignment Method:	Based on participant disease characteristics and prior anti-cancer therapy	Population Age:	≥18 years of age
Sub-studies	None	Site Distribution:	Multi-site

The end of study is considered as the last scheduled study assessment shown in the schedule of activity (SoA) 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.

TREATMENT GROUPS AND DURATION

Approximately 40 participants with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment will be assigned to amivantamab (1400 mg for body weight <80 kg once weekly for the first 4 weeks followed by 1750 mg every 3 weeks starting at Week 7 onwards, similarly for body weight $\geq$ 80 kg, 1750 mg by IV infusion once weekly for the first 4 weeks followed by 2100 mg once every 3 weeks) in combination with carboplatin and pemetrexed.

Total study duration for each participant will be approximately 8 months. The study will include a Screening Phase (28 days), a Treatment Phase (6 months), and a Follow-up Phase (1 month). In the treatment phase, participants will receive study treatment for 8 cycles (21 days each cycle), until one of the treatment discontinuation conditions is met, withdrawal of consent for study participation, death or whichever occurs first. Dose modifications and interruptions of the assigned study treatment are allowed in case of treatment-related toxicity as defined in the protocol. Study participants receiving amivantamab until 8 cycles during the treatment phase may continue to receive amivantamab, if in the opinion of their treating physician the participants continue to derive clinical benefit from continued treatment or have not progressed clinically. These participants will be provided treatment as per recommendation from treating physicians. Amivantamab will be provided from local commercial supply through local distribution channel. Such participants will not be monitored after end of follow-up phase.

Participants will be monitored throughout the study period for the adverse events (AEs)/serious adverse events (SAEs) reporting.

Description of Treatments**Study Treatment administered**

Treatment Name	Amivantamab IV	Carboplatin-pemetrexed Chemotherapy
Dose Formulation	Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial	Carboplatin ^a Pemetrexed ^a
Dosage Levels	-1400 mg for body weight <80 kg, weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 -1750 mg every 3 weeks starting at Week 7 onwards -1750 mg for body weight ≥80 kg IV, weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 -2100 mg every 3 weeks starting at Week 7 onwards	Carboplatin: every 3 weeks for first 4 cycles, AUC5 Pemetrexed: every 3 weeks, 500 mg/m²
Route of Administration	IV infusion	IV infusion
Use	Treatment	Background Intervention

a. Formulation available in India will be used.

All participants in this study will receive enhanced dermatological management as prophylaxis comprising of:

- Oral doxycycline or minocycline 100 mg twice daily (BID) for 12 weeks (to be continued beyond 12 weeks if clinically indicated or at investigator's discretion)
- Clindamycin 1% lotion on scalp once daily (OD) starting at Week 13 or at the end of tetracycline treatment as per investigator discretion
- Chlorhexidine 4% solution used to wash hands and feet OD up to end of treatment (EOT)
- Noncomedogenic ceramide-based skin moisturizer on face and whole body (except scalp) OD

All participants in this study will also receive infusion-related reaction (IRR) prophylaxis as per the SKIPPirr regimen for first infusion of amivantamab and pre-infusion medications (eg. dexamethasone, diphenhydramine, paracetamol/acetaminophen).

STATISTICAL METHODS

The study targets to include total 40 participants.

Sample size calculation is based on probability of observing at least one clinical interest AE including SAE, AE leading to treatment discontinuation, dermatological event, venous thromboembolic event (VTE) and IRR. Assuming that the true clinical interest AE rate is as low as 15%, with a total of 40 participants at least one expected AE will be observed with a probability of >99%.

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variance, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages.

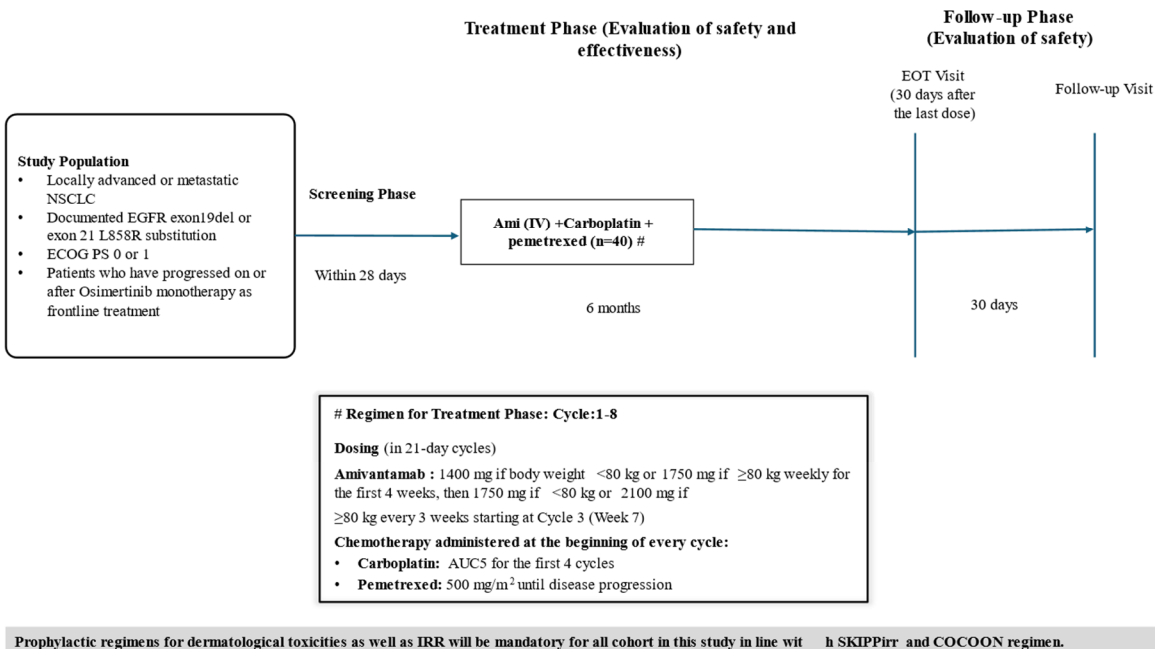
The rates of overall treatment-emergent adverse events (TEAEs), SAEs, and special interest AEs, with their 95% confidence intervals (CIs) will be provided. Summaries, listings, datasets, or participant narratives may be provided, as appropriate for those participants who die, experience an adverse event of special interest (AESI), discontinue treatment due to an AE, or experience a severe, or a SAE.

Objective response rate (ORR) will be tabulated together with its 2-sided 95% exact CI. In addition, the number and percentage of participants in each response category (complete response, partial response, stable disease, progressive disease, or unevaluable) will be tabulated. For the calculation of ORR, those participants who are not evaluable for response will be listed as such and considered as non-responders.

In this study, no interim analysis is planned.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities

Study Phase	Screening Phase	Treatment Phase ^a (6 Months)									End of Treatment Visit ^b	Follow-up Phase (Call)
Cycle (C)	-28 to -1	C1					C2		C3 ^{a+}		1 month after the last dose	1 month after EOT
Cycle Day		1	2	8	15	22 ^c	1	15	1	15		
Visit Window (Days)		-	-	±1	±1	±1	±3	±3	±3	±3	+7	±3
STUDY PROCEDURES (Perform assessments on dosing days before study treatment administration, unless otherwise stated)												
Screening Assessments - If an assessment was performed as part of the participant’s routine clinical evaluation and not specifically for this study, it need not be repeated after signed informed consent has been obtained provided the assessments fulfil the study requirements. Results of the screening assessments must be reviewed by the investigator prior to enrollment. Participants who fail screening may be rescreened if their condition changes but must sign a new ICF.												
Informed Consent	X											
Demography	X											
Medical History	X											
Disease Characteristics	X											
Serology (HIV, HBsAg, and HCV)	X	As clinically indicated										
Inclusion/Exclusion Criteria	X											
ECOG Performance Status	X	X ^c	As clinically indicated							X		
Hematology/Serum Chemistry	X	X ^c		X (prior to each dose of study treatment administration) ^d						X		
Pregnancy Test	X	X ^{c,e}					X		X		X	
Previous and Concomitant Medications	X	X ^f										
Coagulation	X	As clinically indicated										
Urinalysis	X	As clinically indicated										

Safety Assessments												
Vital Signs (HR, BP, Temp, RR, O2 saturation) ^g	X	X (at each dose of study treatment administration) ^d								X		
Physical Examination ^h (height [at screening], full exam & weight [at screening and Day 1 of each cycle], and symptom directed exam (all visits) ⁱ	X	X ^c	X (prior to each dose of study treatment administration) ^d								X	
12 Lead ECG	X ^j	X ^c	As clinically indicated									
ECHO/MUGA	X	As clinically indicated										
Adverse Event (serious or non-serious)	X										X	
Dermatological Prophylaxis		X (as per COCOON regimen)										
Effectiveness Assessments												
CT/PET Tumor Staging	X ^k	As clinically indicated								X		
MRI Brain	X ^k	As clinically indicated								X		
Symptomatic Progression Event		X (collect continuously until Follow-up)										
Survival/Disease Status										X	X	
Study Treatment Administration ^l												
Pre-infusion Medications		X										
Study Treatment Administration (21 days cycle)		X ^m										
Biomarker Evaluation												
Tumor Biopsy ⁿ	X											

- Treatment phase will include 8 treatment cycles (21 days/cycle).
- With the exception of the EOT pregnancy test for participants of childbearing potential, which must occur at least 30 days after the last dose of study treatment, EOT procedures may be conducted before completion of 30 days after last dose of study treatment if new anti-cancer therapy is to be initiated.
- If performed within 72 hours before the first dose of study treatment, then the assessment does not need to be repeated at Cycle 1 Day 1.

- d. When chemotherapy and amivantamab are administered on different days, perform assessments before each study treatment if period between pre-chemo and pre-amivantamab is expected to be >72 hours.
- e. A serum pregnancy test is required at Screening and within 72 hours of first dose of study treatment (Cycle 1). A serum or urine pregnancy test is required at first dose of subsequent treatment cycles. A final pregnancy test will be performed at the EoT.
- f. Record medications through 30 days after the last dose of study treatment administration; >30 days after last dose of study treatment in conjunction with SAEs considered related to study treatment; until resolution of event or start of subsequent therapy. For participants, with Grade 3 or 4 AEs considered related to study treatment, record concomitant medications through end of follow-up of that AE.
- g. Vital signs measurement to be performed per the site-specific protocol and as per the investigator's discretion.
- h. Within 72 hours of Day 1 of each cycle and at end of treatment, symptom directed PE of involved organs and other body systems will be performed.
- i. Evaluate for signs and symptoms of VTE events. A focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed.
- j. Triplicate ECG will be performed at Screening.
- k. Imaging obtained as part of standard of care before signing the ICF, but within 28 days of enrollment, may be used for the screening assessment.
- l. Refer to Section 6.6 for details on dose modifications.
- m. Detailed study treatment administration is presented in [Table 1a](#).
- n. Biopsy at screening would be performed locally at the site laboratory or site preferred laboratory if there is no confirmed diagnosis or biopsy report at the time of screening.

Table 1a Study Treatment Administration (21-day cycle)

Study Phase	Treatment Phase (6 months)							
	Cycles 1 to 8							
Cycle (C)	C1				C2	C3	C4	C5+
Cycle Day	1	2	8	15	1	1	1	1
Pre-infusion medications prior to each Amivantamab and chemotherapy administration ^a	X	X	X	X	X	X	X	X
Amivantamab Infusion (split dose on C1D1 and C1D2) ^b	X	X	X	X	X	X	X	X
Pemetrexed Administration	X				X	X	X	X
Carboplatin Administration ^c	X				X	X	X	

- a. Dexamethasone (8 mg) PO BID (16 mg daily) on Cycle 1 Day -2, -1, and 1 dose of dexamethasone (20 mg) IV approximately 1 hour prior to the start of the infusion of IV amivantamab on C1D1. For the timings and further details on other pre-medications for chemotherapy and amivantamab, refer to Section 6.9.2.1 and Section 6.9.2.2, respectively.
- b. Amivantamab will be administered once weekly for the first 4 weeks followed by once every 3 weeks. Refer to [Table 6](#) for dosing details.
- c. Carboplatin to be administered only for the first 4 cycles (ie, C1 to C4).

2. INTRODUCTION

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against EGFR and MET protooncogene.

The current study will evaluate the safety profile of amivantamab IV in combination with chemotherapy in patients with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment. This study is being conducted as a post-marketing commitment to the Indian Health Authority.

For the most comprehensive nonclinical and clinical information regarding amivantamab refer to the current approved local PI. For further information regarding carboplatin and pemetrexed, refer to the local PI for each product.

The term “study treatment” throughout the protocol, refers to study drugs as defined in Section 6.1.

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 "patient".

2.1. Study Rationale

The third-generation tyrosine kinase inhibitor (EGFR TKI), osimertinib, is indicated for the first- and second-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. While osimertinib represents a significant advance over earlier EGFR TKIs, almost all patients eventually relapse ([Ettinger 2022](#); [ESMO 2020](#)). Hence, there is an unmet need to improve first-line therapy to extend PFS beyond the median of 19 months observed with osimertinib ([Soria 2018](#); [Ramalingam 2020](#)). The emergence of resistance is also a problem that renders treatment with osimertinib ineffective and currently, there are no targeted therapies approved in osimertinib-relapsed disease, despite evidence that many patients have disease that continues to be dependent on signaling through either EGFR and/or MET pathways. Standard of care, therefore, remains platinum-based doublet chemotherapy, such as carboplatin and pemetrexed. The ORR associated with this therapy, as determined in Phase 3 studies of similar populations, has been approximately 30%, with a median PFS of 4 to 5 months. Therefore, treatment options for patients with EGFR-mutated NSCLC are limited after first-line or second-line osimertinib, and there is a high unmet need for additional therapeutics that further control tumor growth before non-targeted therapies are used ([Passaro 2021](#)).

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against EGFR and MET tyrosine kinase receptors that is being developed for the treatment of solid tumors, including EGFR-mutated NSCLC. In the MARIPOSA-2 trial, PFS and key secondary endpoints, such as objective response rate, duration of response, and intracranial PFS, were significantly improved with amivantamab and chemotherapy combination compared with chemotherapy alone in patients with EGFR-mutated advanced NSCLC with disease progression on or after osimertinib. In both these studies, amivantamab based regimens are associated with a tolerable and manageable safety profile with low rates of treatment discontinuation. The adverse

events with amivantamab, either in combination with lazertinib or chemotherapy were consistent with AEs seen with EGFR or MET inhibition or seen with chemotherapy (Cho 2020; Passaro 2024).

India has been a part of MARIPOSA-2 global clinical trials for amivantamab based regimen with 26 patients being enrolled. Based on the results of the global clinical trial as well as on the basis of participation of India in global clinical trial, the Health Authority has provided a conditional approval for amivantamab in combination with chemotherapy in the second-line setting following progression on osimertinib with a post approval commitment to conduct Phase 4. The Indian Health Authority during the deliberation for MARIPOSA-2 data observed that the safety data of amivantamab based regimens in these settings is limited for Indian patients in the global Phase 3 trials thus highlighting the need for generation of additional safety data in Indian patients (SEC recommendations 2025a,b). Since this would be a post-marketing study, the data obtained will help reaffirm the safety profile of amivantamab in combination with chemotherapy in Indian patients with that of overall global Phase 3 trial MARIPOSA-2 (amivantamab in combination with platinum-based chemotherapy).

2.2. Background

Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer worldwide. It is the fourth most common cancer in India and is the second most common cancer in Indian males and seventh most common cancer in females (IARC 2025). The age standardized rate for lung cancer incidence in India is 5.8 per 1,00,00 population amounting to 8,1748 new cases a year (Noronha 2024). The estimated age-standardized 5-year survival for lung cancer in India (2010 to 2014) was 3.7% (95% CI: 1.6–5.7), as compared to the USA at 21.2% (95% CI: 21.1–21.3) (Bi 2024).

NSCLC is the most common subtype of lung cancer in India constituting approximately 90% of cases. Mutations in the EGFR are major oncogenic driver mutations in patients with NSCLC. In the recent past, there has been significant advancement in the understanding of the underlying biology of NSCLC, including the identification of multiple “driver” mutations that can result in a constitutive activation of pro-growth signaling pathways. The incidence of EGFR mutations in NSCLC patients ranges from 23% to 30% as reported in large cohort studies from India (Chougule 2013; Chougule 2023; Kate 2019).

Overall, in-frame deletions in exon 19 and the exon 21-point mutation L858R represent 85% to 90% of all EGFR mutations in NSCLC and are conventionally referred to as the common EGFR mutations (Ramalingam 2020).

The third-generation EGFR TKI, osimertinib, is indicated for the first- and second-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. Compared with first- and second-generation EGFR TKIs, third-generation EGFR TKIs provide better efficacy benefits in general and may penetrate the blood-brain barrier better and more effectively treat brain metastasis, which occurs in approximately 10% to 20% of patients with treatment naïve EGFR-mutated NSCLC (Reungwetwattana 2018). With its demonstrated activity against the EGFR T790M+ resistance mutation, as well as brain metastases, it was hypothesized that osimertinib as a first-line treatment would delay emergence of T790M-mediated resistance,

as well as relapse within the CNS, resulting in improved disease control ([Reungwetwattana 2018](#)). The FLAURA study compared the third-generation EGFR TKI osimertinib versus a standard EGFR TKI (gefitinib or erlotinib) as first-line therapy for patients with metastatic NSCLC and exon 19del or exon 21 L858R mutations and demonstrated a statistically significant improvement in PFS and OS for participants randomized to osimertinib treatment. In patients receiving osimertinib versus a first-generation EGFR TKI, median PFS was 18.9 versus 10.2 months, respectively, with a HR of 0.46; and median OS was 38.6 versus 31.8 months, respectively, with a HR of 0.80. This significant improvement in median PFS with osimertinib treatment was not associated with an improved ORR, suggesting the majority of benefit may have been derived from activity of osimertinib against the T790M+ resistance mutation and improved activity within the CNS ([Soria 2018](#)).

Despite improved initial disease control with osimertinib front-line therapy, all patients treated with osimertinib will relapse. Once emergence of resistance renders treatment with osimertinib ineffective, there are no targeted therapies approved in osimertinib-relapsed disease. Evidence suggests that signaling through either EGFR and/or MET pathways may lead to resistance mechanism. Standard of care, therefore, remains platinum- based doublet chemotherapy, such as carboplatin and pemetrexed. The ORR associated with this therapy, as determined in Phase 3 studies of similar populations, have been approximately 30%, with a median PFS of 4 to 5 months. Therefore, treatment options for patients with EGFR-mutated NSCLC are limited after front-line or second-line osimertinib, and there is a high unmet need for additional therapeutics that further control tumor growth before non-targeted therapies are used ([Leonetti 2019](#); [Mok 2017](#)).

This study will evaluate the safety profile of amivantamab IV in combination with chemotherapy in patients with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment.

2.3. Benefit-risk Assessment

More detailed information about the known and expected benefits and risks of amivantamab may be found in the current approved local PI. Information about the benefits and risks of carboplatin and pemetrexed may be found in the respective local PIs.

The potential risks for study participation and mitigation strategies are presented in [Table 2](#).

Table 2: Potential Risks

Potential Risks of Clinical Significance	Rationale for Risk	Mitigation Strategy
Risks Due to Study Treatments (Amivantamab)		
Infusion-related Reactions: Most signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, and vomiting	IRRs have been commonly observed with amivantamab treatment (61% of participants). The majority of these IRRs (93% events) are Grade 1 or 2. Refer to Amivantamab IB Section 5 for further information.	Prophylactic guidance is provided in Section 6.9.2.2. Instructions for management of IRRs are provided in Section 6.6.2.1. Participants will be monitored closely for early signs and symptoms indicative of an acute IRR, particularly on C1D1.

Dermatologic Toxicity: Rash (including dermatitis acneiform), pruritus, dry skin, paronychia, and oral mucositis.	Rash (including dermatitis acneiform), pruritus, and dry skin occurred in participants treated with amivantamab. Most cases were Grade 1 or 2, with Grade 3 or 4 events occurring in 15.5% of participants. Rash leading to amivantamab discontinuation occurred in 2.9% of participants. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in participants treated with amivantamab. Most events were Grade 1 or 2, with Grade 3 or 4 nail toxicity occurring in 6.3% of participants.	Prophylactic treatment to reduce the risk and severity of rash-related events and management guidance is described in Section 6.6.2.2. Site-directed physical exam is required prior to every amivantamab injection. General sun protective measures are recommended. Reactive management guidance for pruritus and paronychia is provided in Sections 6.6.2.3 and 6.6.2.4, respectively.
Pulmonary Toxicity: ILD or ILD-like adverse reactions (eg, pneumonitis)	ILD or ILD-like adverse reactions (eg, pneumonitis) occurred in 2.7% of participants treated with amivantamab, including 0.1% fatal events.	Participants with active or prior medical history of ILD/pneumonitis are excluded from participating in the study per Exclusion criterion 5. Respiratory status will be assessed at each visit as part of physical examination. The protocol also provides detailed recommendations and guidelines for pulmonary toxicities (Section 6.6.2.6).
VTE Events	VTE events, including DVT and pulmonary embolism (PE) reported in 36% patients, predominantly in the first 4 months of therapy including 0.5% fatal events in participants receiving amivantamab with lazertinib.	The protocol provides detailed recommendations and guidelines for VTE events described in Section 6.6.2.12.
Eye Disorders: Keratitis and other symptoms including dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperemia, conjunctival hyperemia, blepharitis, and uveitis.	Eye disorders, including keratitis (1.6%), occurred in participants treated with amivantamab. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperemia, conjunctival hyperemia, blepharitis, and uveitis. Most events were Grade 1 or 2.	Refer to Section 6.6.2.9 for more details on ocular toxicity management.
Embryo-fetal toxicity	Amivantamab may cause fetal toxicity.	Participants who are breast feeding, pregnant, or planning to get pregnant while enrolled in study are excluded from the study per Exclusion criterion 10. Participants with reproductive potential are recommended to follow effective contraceptive methods (Appendix 4: Contraceptive and Barrier Guidance).
Other events (diarrhea, paresthesia, and liver chemistry abnormality)	These events are very common with amivantamab treatment.	Detailed dose modification and management guidance of liver chemistry abnormality, diarrhea,

		and paresthesia are provided in Sections 6.6.2.8, 6.6.2.10, and 6.6.2.11, respectively.
Risks Due to Chemotherapy		
Hematologic Toxicity	Hematologic toxicities are associated with chemotherapy	Monitoring participants for chemotherapy-related toxicities and laboratory assessments are recommended. Detailed prophylactic and management guidance are provided in Sections 6.9.2.1 and 6.6.3, respectively.
Risks Due to Other Causes		
Risks due to Dermatologic Management: Oral Antibiotics- Doxycycline/minocycline	Treatment with oral doxycycline can result in photosensitivity. Rare cases of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, a life-threatening adverse drug reaction that presents with generalized rash, fever, and internal organ involvement have been reported with oral minocycline.	Sun avoidance will be recommended to all participants as part of the standard of care dermatologic management.
Topical antibiotics- Clindamycin: Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis)	Symptoms have been reported with the use of topical and systemic clindamycin.	Participants will be monitored for AEs throughout the study.

In addition to the possible risks outlined in above table, unforeseen safety risks associated with the study treatments are possible.

Potential risks of study treatments are addressed via judicious inclusion/exclusion criteria, frequent study visits to allow for close monitoring of patient safety, guidelines for participant management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed description of allowed and prohibited concomitant medications, dose modification guidance, prophylactic regimens, supportive care medications, and comprehensive medical monitoring of data by the sponsor during the conduct of the study.

The potential benefits for a study participant could be:

- Study treatment administration: Amivantamab has undergone extensive nonclinical and clinical development and has established favorable benefit-risk profile. The favorable profile has resulted in regulatory approval and the study treatment is marketed in many regions across globe.
- Medical evaluations/assessments associated with study procedures (eg, physical examination, ECG, and laboratory test).

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with are justified by the anticipated benefits that may be afforded to participants with locally or advanced metastatic non-small cell lung cancer with EGFR exon 19del or exon 21 L858R mutations.

3. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate safety of amivantamab in combination with chemotherapy in patients with EGFRm NSCLC with exon 19del or exon 21 L858R substitution whose disease progressed on or after osimertinib monotherapy	Cumulative AE profile which includes TEAEs (Serious and non-serious TEAEs, and TEAEs of special interest) observed
Secondary	
To evaluate effectiveness of amivantamab in combination with chemotherapy in patients with EGFRm NSCLC with exon 19del or exon 21 L858R substitution whose disease progressed on or after osimertinib monotherapy	ORR at 6 months

HYPOTHESIS

This is a post-approval commitment study mandated by the Health Authority (CDSCO) in India with descriptive purpose and hence, only descriptive statistical analyses will be performed. No formal hypothesis testing will be specified.

4. STUDY DESIGN

4.1. Overall Design

This is a prospective, Phase 4, single arm, open-label, multicenter, interventional study in Indian patients (confirmed citizenship of India and residing in India) with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment. This study is being conducted as a regulatory requirement to evaluate the safety of amivantamab in combination with chemotherapy.

Approximately 40 participants with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment will be assigned to amivantamab (1400 mg for body weight <80 kg once weekly for the first 4 weeks followed by 1750 mg every 3 weeks starting at Week 7 onwards, similarly for body weight ≥80 kg, 1750 mg by IV infusion once weekly for the first 4 weeks followed by 2100 mg once every 3 weeks) in combination with carboplatin and pemetrexed.

All participants in this study will receive enhanced dermatological management as prophylaxis comprising of:

- Oral doxycycline or minocycline 100 mg BID for 12 weeks (to be continued beyond 12 weeks if clinically indicated or at investigator's discretion)
- Clindamycin 1% lotion on scalp OD starting at Week 13 or at the end of tetracycline treatment as per investigator discretion
- Chlorhexidine 4% solution used to wash hands and feet OD up to EOT
- Noncomedogenic ceramide-based skin moisturizer on face and whole body (except scalp) OD

All participants in this study will receive IRR prophylaxis as per the SKIPPirr regimen for first infusion of amivantamab ([Spira 2025](#)) and pre-infusion medications:

Two days before the first infusion:

- Oral dexamethasone
- During the 2 days prior to the initial amivantamab infusion, participants should receive 8 mg dexamethasone orally, BID. On the day of the initial infusion (Week 1, Day 1), participants should receive 8 mg dexamethasone orally, one hour prior to infusion in addition to IV dexamethasone to further reduce the risk of IRR.

Day of infusion:

- Prior to initial infusion of amivantamab (Week 1, Days 1 and 2), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs. For subsequent doses antihistamines and antipyretics should be administered. Administration of antiemetics is as per investigator's discretion.

Table 4: Pre-infusion Medications for Amivantamab

Medication	Dose	Route of Administration	Dosing Window Prior to Amivantamab Administration
Antihistamine^a	Diphenhydramine (25 to 50 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic	Paracetamol/Acetaminophen (650 to 1000 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid^b	Dexamethasone (20 mg) or equivalent	IV	60 to 120 minutes
Glucocorticoid^c	Dexamethasone (10 mg) or equivalent	IV	45 to 60 minutes

a. Required at all doses.

b. Required at initial dose (Week 1, Day 1).

c. Required at second dose (Week 1, Day 2); optional for subsequent doses.

Total study duration for each participant will be approximately 8 months. The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. In the treatment phase, participants will receive study treatment for 8 cycles (21 days each cycle), until one of the treatment discontinuation conditions is met, withdrawal of consent for study participation, death or whichever occurs first. Study treatment may be withheld, and dosages may be modified, as needed to manage AEs. If toxicity results in withholding or discontinuing 1 study treatment, then it may be possible to continue the other study treatment(s). Study participants receiving amivantamab until 8 cycles during the treatment phase may continue to receive amivantamab, if in the opinion of their treating physician the participants continue to derive clinical benefit from continued treatment or have not progressed clinically. These participants will be provided treatment as per recommendation from treating physicians. Amivantamab will be provided from local commercial

supply through local distribution channel. Such participants will not be monitored after end of follow-up phase.

Participants will be monitored throughout the study period for the AEs/SAEs reporting.

4.2. Scientific Rationale for Study Design

This is a prospective, Phase 4, single arm, open-label, multicenter, interventional study being conducted as a regulatory requirement to evaluate the safety of amivantamab in combination with chemotherapy in Indian patients with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment. The prospective Phase 4 study design facilitates collection of a sufficient quantity of defined variables, where available in clinical practice, to address the study objectives.

Eligibility Criteria for Inclusion in the Study

The eligibility criteria for enrollment in the study are aligned with approved indication by Indian Health Authority.

Dose Selection for the Study

The dose of each study treatment in this study is aligned with previously conducted clinical trials and current approved local PI.

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 this information and provide their consent voluntarily will be enrolled. If applicable, the LDR must sign the ICF. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and patient preferences.

The primary ethical concern is that the total blood volume to be collected 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 care.

As per recommendation from CDSCO in India, this Phase 4 study is planned with the aim to assess the safety of amivantamab in combination with platinum-based chemotherapy in Indian participants as a post-marketing requirement. Based on the established safety profile of amivantamab and time to onset of most relevant AEs of amivantamab, prospective study with 6 months of treatment duration is considered adequate to characterize the safety profile of amivantamab in Indian participants with locally advanced or metastatic NSCLC with EGFR

exon 19del or exon 21 L858R mutations who have disease progression on or after osimertinib monotherapy as frontline treatment.

4.3. Justification for Dose

The justification for dose of study treatment is included in Section 4.2.

4.4. End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the SoA 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.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

Participants who prematurely discontinue study intervention for any reason before completion of 8 treatment cycles will be considered to have completed the study once all assessments scheduled for the post-treatment follow-up visit are performed at the time of discontinuation, or as soon as possible. For these participants, the last study visit will be the follow-up visit 30 days after the EOT visit.

5. STUDY POPULATION

5.1. Inclusion Criteria

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

Age

1. At the time of informed consent, be ≥ 18 years of age
2. Criterion deleted per Amendment 1

Type of Participant and Disease Characteristics

3. Criterion modified per Amendment 1

3.1 Participant must have histologically or cytologically confirmed, locally advanced or metastatic NSCLC not amenable to curative therapy including surgical resection or chemoradiation and previously determined exon 19del or exon 21 L858R substitution, detected by a certified local laboratory with the biopsy being obtained at or after the diagnosis of advanced disease and must have progressed on or after osimertinib monotherapy as the first-line treatment. Participants who have received 1 to 2 cycles of chemotherapy before starting osimertinib are eligible for this study provided they have not progressed on chemotherapy. (Note: Results from liquid or tissue biopsy are acceptable. A copy of the test report documenting the EGFR mutation must be included in the participant records.)

Participants who received either neoadjuvant and/or adjuvant treatment are eligible if progression to locally advanced or metastatic disease occurred at least 12 months after the last dose of such therapy and then the participant progressed on or after osimertinib in the locally advanced or metastatic setting.

Treatment with osimertinib must be discontinued at least 8 days (4 half-lives) prior to enrollment (ie, last dose no later than Day -8).

Type of Participant and Disease Characteristic(s)

4. Any toxicities from prior anticancer therapy must have resolved to CTCAE Version 5.0 Grade 1 or baseline level.

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

- a) Hemoglobin ≥ 10 g/dL
- b) Absolute neutrophil count $\geq 1.5 \times 10^9/L$, without use of G-CSF within 10 days prior to the date of the test
- c) Platelets $\geq 75 \times 10^9/L$
- d) ALT and AST $\leq 3 \times ULN$
- e) Total bilirubin $\leq 1.5 \times ULN$ if no liver metastasis, or $\leq 3 \times ULN$ in the presence of liver metastasis (participants with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits)
- f) Creatinine clearance > 45 mL/min as measured or calculated by Cockcroft-Gault formula

6. Participant must have ECOG status of 0 or 1

7. A participant with definitively, locally treated brain metastases must be clinically stable and asymptomatic, with or without low-dose corticosteroid treatment (≤ 10 mg prednisone or equivalent), for at least 14 days prior to enrollment

Sex and Contraceptive/Barrier Requirements

8. While on study treatment and for 6 months after the last dose of study treatment, a participant must:

- a) Not breastfeed or be pregnant
- b) Not donate gametes (ie, eggs or sperm) or freeze for future use for the purposes of assisted reproduction
- c) Wear an external condom
- d) If of childbearing potential,
 - have a negative highly sensitive (eg, beta-human chorionic gonadotropin) pregnancy test at screening and within 72 hours of the first dose of study treatment and agree to further pregnancy tests,
 - practice at least 1 highly effective method of contraception; if oral contraceptives are used, a barrier method of contraception must also be used
- e) If a partner of a participant capable of producing sperm is of childbearing potential, the partner must practice a highly effective method of contraception unless the participant is vasectomized

See [Appendix 4: Contraceptive and Barrier Guidance](#) for details.

Informed Consent

9. Must provide informed consent as will be described in [Appendix 2: Regulatory, Ethical, and Study Oversight Considerations](#).

10. Participant must be willing and able to adhere to the lifestyle restrictions specified in the 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 deleted per Amendment 1

Medical Conditions

2. Participant has active brain metastases not definitively treated with local therapy
3. Participant has an active or past medical history of leptomeningeal disease
4. Participant has uncontrolled tumor-related pain (symptomatic lesions amenable to palliative radiotherapy [eg, bone metastases or metastases causing nerve impingement] should be treated 14 days prior to randomization)
5. Participant has an active or past medical history of ILD/pneumonitis, including drug-induced or radiation ILD/pneumonitis.
6. Participant has an uncontrolled illness, including but not limited to:

- a) Uncontrolled diabetes
 - b) Ongoing or active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week prior to starting study treatment] or diagnosed or suspected viral infection).
 - c) Active bleeding diathesis
 - d) Impaired oxygenation requiring continuous oxygen supplementation
 - e) Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of study treatment
 - f) Psychiatric illness, social situation, or any other circumstances that would limit compliance with study requirements
 - g) Any ophthalmologic condition that is either clinically unstable or requires treatment
7. Participant has known small cell transformation
8. Participant has an active malignancy other than the disease being treated under study.

The only allowed exceptions are:

- a) Non-muscle invasive bladder cancer 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 active cardiovascular disease including, but not limited to:

- a) A medical history of deep vein thrombosis or pulmonary embolism within 1 month prior to enrollment or any of the following within 6 months prior to enrollment: 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
 - b) Prolonged corrected QT interval by Fridericia's (QTcF >470 msec), clinically significant cardiac arrhythmia (eg, atrial fibrillation with uncontrolled rate) or abnormalities in conduction or morphology of ECG (eg, complete left bundle branch block, third- or second-degree heart block, PR interval >250 msec), or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator)
 - c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medications known to prolong QT interval or induce Torsades de Pointes
 - d) Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg
 - e) CHF, defined as NYHA class III-IV or hospitalization for CHF (any NYHA class; refer to [Appendix 6: New York Heart Association Criteria](#)) within 6 months of randomization.
 - f) An active or past medical history of pericarditis, pericardial effusion, or myocarditis
 - g) Baseline LVEF below the LLN as assessed by screening ECHO or MUGA scan
- 10 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
- 11 Participant plans to father a child while enrolled in this study or within 6 months after the last dose of study treatment
- 12 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

Prior/Concomitant Therapy

- 13 Criterion modified per Amendment 1

13.1 Participant has received any prior systemic treatment for locally advanced or metastatic disease (adjuvant or neoadjuvant therapy is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease)

Participants who have received 1 to 2 cycles of chemotherapy before starting osimertinib and have not progressed on it and participants progressed on or after osimertinib in the locally advanced or metastatic setting are allowed.

- 14 Participant is currently receiving medications or herbal supplements known to be potent CYP3A4/5 inhibitors or inducers and is unable to stop use for an appropriate washout period prior to enrollment

15 Criterion modified per Amendment 1

15.1 Participant has known allergy, hypersensitivity, or intolerance to the excipients used in formulation of amivantamab, carboplatin, pemetrexed

16 Participant received radiotherapy for palliative treatment of NSCLC less than 14 days prior to enrollment

Prior/Concurrent Clinical Study Experience

17 Participant has received an investigational medication within 12 months before enrollment or is currently enrolled in an investigational study

Diagnostic Assessments

18 Participant has at Screening: Positive hepatitis B (HBV) surface antigen (HBsAg) (For more details refer [Appendix 13: Hepatitis B Virus Screening](#))

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 DNA (viral load) below the lower limit of quantification, per local testing

19 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 (HCV) antibody (anti-HCV)

Note: Participants with a prior history of HCV who have completed antiviral treatment and have subsequently documented HCV RNA below the lower limit of quantification per local testing are eligible.

20. Participant has received a live or live attenuated vaccine within 4 weeks before enrollment

21. a. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if:

- Has a history of successful treatment, defined as being negative for HCV RNA obtained at least 12 weeks after completing antiviral treatment and has a negative HCV RNA at screening; OR
- Has a negative HCV RNA test result obtained at least 12 weeks prior to screening and at screening.

b. Other clinically active liver disease of infectious origin.

22. Participant is known to be positive for HIV with 1 or more of the following:

- a) Not receiving highly active ART
- b) Had a change in ART within 6 months of the start of screening
- c) Receiving ART that may interfere with study treatment (consult sponsor for review of medication prior to enrollment)
- d) CD4 count <350 at screening
- e) AIDS-defining opportunistic infection within 6 months of start of screening

- f) Not agreeing to start ART and be on ART > 4 weeks plus having HIV viral load
- g) < 400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled).

23 Participant had major surgery (eg, requiring general anesthesia), excluding placement of vascular access or tumor biopsy, or had significant traumatic injury within 4 weeks before signing the ICF, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. 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 intervention is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Protocol Section 5.4 will describe options for retesting. The required source documentation to support meeting the enrollment criteria will be noted in Protocol [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 study to be eligible for participation:

1. Refer to Section 6.9.3 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).

5.3.1. Activity

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 SPF ≥ 30 (refer to Section 6.6.2.2).

5.4. Screen Failures

Individuals who do not meet all inclusion and exclusion criteria for participation in this study (and is thus a screen failure) may be rescreened. Participants who are determined to be eligible for the study after their condition changes must sign a new ICF and a new participant number will be assigned.

Mandatory Participant/Subject Identification and Enrollment Log Form

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. 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.

Participant/Subject Screening Log Form

The investigator agrees to complete a participant/subject screening log tracking patients from prescreening (as applicable) to enrollment, to record reasons why screened patients were not enrolled, and to identify those patients that did not meet the eligibility criteria, to permit better understanding of participant population and enrollment at the site by the sponsor. This study will not use an RTSM system (eg interactive web response system).

5.5. Criteria for Temporarily Delaying Enrollment

Not applicable.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatments Administered

Approximately 40 participants will be assigned to amivantamab (1400 mg for body weight <80 kg once weekly for the first 4 weeks followed by 1750 mg every 3 weeks starting at Week 7 onwards, similarly for body weight ≥80 kg, 1750 mg by IV infusion once weekly for the first 4 weeks followed by 2100 mg once every 3 weeks) in combination with carboplatin and pemetrexed.

Table 5: Study Treatments Administered

Treatment Name	Amivantamab IV	Carboplatin-pemetrexed Chemotherapy
Dose Formulation	Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial	Carboplatin ^a Pemetrexed ^a
Unit Dose Strengths	350 mg/7 mL	Carboplatin: AUC 5 Pemetrexed: 500 mg/m ²
Dosage Levels ^b	-1400 mg for body weight <80 kg, once weekly (total of 4 doses) from Weeks 1 to 4 - Week 1 - split infusion on Day 1 and Day 2 - Weeks 2 to 4 - infusion on Day 1 -1750 mg every 3 weeks starting at Week 7 onwards -1750 mg for body weight ≥80 kg IV, once weekly (total of 4 doses) from Weeks 1 to 4 - Week 1 - split infusion on Day 1 and Day 2 - Weeks 2 to 4 - infusion on Day 1 -2100 mg every 3 weeks starting at Week 7 onwards	Carboplatin: every 3 weeks for first 4 cycles Pemetrexed: every 3 weeks
Route of Administration	IV infusion	IV infusion
Use	Treatment	Background intervention

Treatment Name	Amivantamab IV	Carboplatin-pemetrexed Chemotherapy
Investigational Medicinal Product (IMP)	Yes	No
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	Yes

- a. Formulation available in India will be used.
b. For cycle and day wise details regarding dosage level please refer to [Table 6](#).

Table 6: Study Treatment Dosing

Cycle	Study Treatment	Days	Dosage
Cycle 1	Pemetrexed	Day 1	500 mg/m ²
	Carboplatin	Day 1	AUC 5
	Amivantamab	Day 1 (split dose 1)	350 mg (regardless of body weight)
		Day 2 (split dose 2)	1,050 mg (<80 kg)/1400 mg (≥80 kg)
		Day 8 and Day 15	1400 mg (<80 kg), 1750 mg (≥80 kg)
Cycle 2	Pemetrexed	Day 1	500 mg/m ²
	Carboplatin		AUC 5
	Amivantamab		1400 mg (<80 kg), 1750 mg (≥80 kg)
Cycle 3 and Cycle 4	Pemetrexed	Day 1	500 mg/m ²
	Carboplatin		AUC 5
	Amivantamab		1750 mg (<80 kg), 2100 mg (≥80 kg)
Cycle 5 onwards	Pemetrexed	Day 1	500 mg/m ²
	Amivantamab		1750 mg (<80 kg), 2100 mg (≥80 kg)

Table 7: Proactive Dermatologic Regimen

Treatment Name	Doxycycline or Minocycline	Clindamycin 1% Lotion	Chlorhexidine 4% Solution	Noncomedogenic Ceramide-based Skin Moisturizer
Dose Formulation	Tablets or capsules	Topical lotion	Topical solution	NA
Unit Dose Strength	50 mg, 100 mg	1%	4%	NA
Dosage Levels and Frequency	100 mg BID for 12 weeks to be continued beyond 12 weeks if clinically indicated or at investigator's discretion	Once daily starting at Week 13 or at the end of tetracycline treatment as per investigator discretion. Sufficient	Sufficient quantity to cover, and as per dosing instructions until EOT	Sufficient quantity to cover, and as per dosing instructions

Treatment Name	Doxycycline or Minocycline	Clindamycin 1% Lotion	Chlorhexidine 4% Solution	Noncomedogenic Ceramide-based Skin Moisturizer
		quantity to cover and as per dosing instructions		
Route of Administration	Take the drug with food to avoid gastric irritation. Administration of adequate amounts of fluid along with capsule or tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. Do not crush.	Apply to clean scalp and massage in OD	Once daily during showering, gently rub the chlorhexidine and hands and feet including nailbeds for 30 seconds and let it suds on the skin for 1 minute. Rinse off completely.	Wash hands thoroughly. Apply a generous amount of moisturizer to the skin. Rub the moisturizer in gently until it is absorbed. Apply moisturizer to all areas of skin including face, neck, hands, and feet (except scalp) daily after showering. Apply moisturizer more often if skin is dry or if in a dry climate.
Use	Non-experimental	Non-experimental	Non-experimental	Non-experimental
IMP	No	No	No	NA
NIMP	No	No	No	NA
Cosmetic Product	No	No	No	Yes

*Specific treatments may be provided according to investigator's choice and availability.

6.2. Preparation/Handling/Storage/Accountability

Study treatment must 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 in the study.

Refer to the study materials, such as pharmacy manuals or, if applicable, to the PI, for all guidance on study treatment preparation, handling, storage and disposal. The investigator is responsible for ensuring that all study treatment received at the site is inventoried, accounted for throughout the study, stored and disposed of according to the sponsor's instructions, in accordance with the protocol, study manuals and as indicated on the container label.

Preparation/Handling/Storage

All study treatment must be stored at controlled temperatures according to the requirements on the label. Amivantamab must be protected from light prior to use. For additional guidance on study treatment preparation, handling, and storage, refer to the current approved local PI for amivantamab, and carboplatin and pemetrexed.

Accountability

The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. For amivantamab, the study treatment administered to the participant must be documented on the treatment accountability form. All study treatments 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 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 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 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. Returned study treatment must not be dispensed again, even to the same participant. Whenever a participant brings his or her study treatment to the study site for pill count, this is not seen as a return of supplies. 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 site investigational product and procedures manual.

6.3. Assignment to Study Treatment

Randomization will not be used in this study. Participants at each site who meet eligibility criteria will be assigned to treatment group by health care provider and treated as per the protocol.

6.4. Blinding, Masking

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

6.5. Study Treatment Compliance

Study treatments should be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms. 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. Study treatments provided by the sponsor may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Pre-infusion Medications

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

Amivantamab

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). The dispensing of amivantamab to the participant must be documented on the treatment accountability form.

Chemotherapy (Carboplatin and Pemetrexed)

Carboplatin and pemetrexed will be administered as IV infusions by qualified study-site personnel according to local guidelines and/or product labeling, and the details of each administration will be recorded in the source documents and eCRF (including date, start, and stop times of the IV infusion, and volume infused).

6.6. Dose Modification

Any dose adjustment must be overseen by medically qualified study site personnel (principal or sub-investigator unless an immediate safety risk appears to be present). In case a dose modification is necessary, the study treatment will be administered in accordance with dose modification guidelines mentioned in Section 6.6.1 to Section 6.6.3.

Based on clinical experience with the study treatments, the anticipated toxicities of amivantamab are expected to be distinct from those associated with chemotherapy. Anti-EGFR toxicities are likely to be associated with amivantamab whereas hematologic toxicities are expected to be most likely associated with chemotherapy.

6.6.1. Dose Modification of Amivantamab

Decisions regarding dose modification of the amivantamab should be guided by the observed toxicity, the safety profile, the likelihood of causality, as well its potential contribution to any observed clinical benefit.

Refer to Table 9 for guidance on dose modification based on the toxicity grade of AEs other than those specified in Section 6.6.2, with dose reductions of amivantamab conducted according to Table 8. In the case of a second occurrence of the same Grade 4 toxicity, permanently discontinue amivantamab, if investigator considers the event related to amivantamab.

Table 8: Guidance for Amivantamab Stepwise Dose Reduction

Dose ^a	1 st Dose Reduction	2 nd Dose Reduction	3 rd Dose Modification
1050 mg	700 mg	350 mg	Discontinue
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

a. Dose at which the adverse reaction occurred.

Table 9: General Guidance for Withholding Doses for Toxicities Considered Related to Amivantamab, Based on Grade^a

Grade ^b	Action ^c	Dose Modification After Resolution of Toxicity ^d
1	None	Continue amivantamab at current dose level.
2	None, or consider withholding amivantamab	Restart study treatment at current dose level.
3	Withhold amivantamab	If Grade 3 adverse reaction improves to Grade 0-2 after withholding study treatment for up to 3 weeks, study treatment may be restarted at the same dose or a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. If Grade 3 adverse reaction does not improve to Grade 0-2 after withholding study treatment for up to 3 weeks, permanently discontinue amivantamab.
4	Withhold amivantamab	If Grade 4 adverse reaction improves to Grade 0-2 after withholding study treatment for up to 3 weeks, study treatment may be restarted at a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. If Grade 4 adverse reaction does not improve to Grade 0-2 after withholding study treatment for up to 3 weeks, permanently discontinue amivantamab. If Grade 4 adverse reaction reoccurs, permanently discontinue amivantamab, if investigator considers the event related to the study treatment.

- For rash related events, see [Table 11](#).
- Per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0.
- For all toxicities, consider supportive care according to protocol as appropriate.
- Resolution defined as: $\leq$ Grade 1 or back to baseline status for the participant (except for rash, oral mucositis, or paronychia, which should recover to $\leq$ Grade 2 or baseline).

Re-escalation of amivantamab after a prior dose reduction is allowed if determined to be in the best interest of the participant.

6.6.2. Dose Modification and Management of Specific Adverse Events

6.6.2.1. Infusion-related Reactions

General Guidelines for Infusion-related Reactions

Infusion-related reactions have been commonly observed during treatment with amivantamab, predominantly with the first exposure on Cycle 1 Day 1, and typically within the first 90 minutes of the infusion. The majority of IRRs are Grade 1 or 2 (Section 2.3). Refer to guidelines mentioned in current approved PI of amivantamab. The guidelines described here relate to the safe administration of amivantamab during initial dosing.

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

Particularly with the initial dose (Cycle 1, Day 1 and Day 2), participants should be educated on 1) the likelihood of experiencing an IRR with the initial dose, 2) the symptoms to anticipate (which include chills, dyspnea, chest discomfort, fever, flushing, among others), 3) that they should alert nursing staff if they experience these symptoms, and 4) that the experience of an IRR will not preclude further therapy with amivantamab. Participants must be monitored closely for early signs and symptoms indicative of an acute IRR. Even with mild symptoms, the study treatment infusion should be interrupted immediately, as described in the tables below, to prevent more serious grade IRRs from occurring. Trained clinical personnel should be prepared to intervene in the event of IRRs. 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) must be readily available.

Prevention of Infusion-related Reactions

Required prophylaxis for IRRs is described in Section 6.9.2.2.

Treatment of Infusion-related Reactions

Participants who experience early symptoms of IRRs, manifesting, but not limited to, as fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypo- or hypertension or other symptoms, must have their amivantamab infusion interrupted, if indicated, and the symptoms managed according to the recommendations provided in Table 10. With the initial dose of amivantamab (Cycle 1, Days 1 and 2), interrupting the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR. All Grade 3 or 4 IRRs should be reported within 24 hours to the Medical Monitor. The start and end time and grade of each IRR symptom as well as the overall IRR should be reported in the eCRF.

Table 10: Management of Infusion-related Reactions

Toxicity Grade*	Treatment	Premedication at Subsequent Dosing or Other Action to be Taken
Grade 1 Mild reaction	Monitor participant as medically indicated until recovery from symptoms. If occurring with initial dose (ie, Cycle 1 Day 1 or Day 2), consider early infusion interruption to prevent more severe symptoms. If infusion is interrupted, follow the guidance for Grade 2 interruptions.	Antihistamine, antipyretic, and glucocorticoid, as per Table 4
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; antiemetic and supplemental oxygen; monitor participant closely until recovery from symptoms First interruption for IRR: Restart infusion at 50% of the rate at the time of interruption: if no further evidence of IRR after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely. Infusion rate escalation may resume per the current approved local PI, after the infusion has been administered for at least 30 minutes at 100% of the infusion rate used at the time of dose interruption.	Antihistamine, antipyretic, and glucocorticoid, as per Table 4 Consider meperidine if participant experiences chills and rigors.
	Second interruption for IRR: 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 eCRF. 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 IRR after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely. Infusion rate escalation may resume per the current approved local PI, after the infusion has been administered for at least 30 minutes at 100% of the infusion rate used at the time of dose interruption.	
Grade 3 Severe reaction that is 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)	Stop infusion Start IV saline infusion; recommend bronchodilators, supplemental oxygen; epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10000 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). Participants 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	Based on severity of symptoms, consider permanent discontinuation of amivantamab. Consultation with Medical Monitor required before continuing with subsequent dosing.

Toxicity Grade*	Treatment	Premedication at Subsequent Dosing or Other Action to be Taken
	treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids), as appropriate.	
Grade 4 Life-threatening; pressor or ventilator support indicated	Same as for Grade 3	Amivantamab treatment must be permanently discontinued.

*Per NCI-CTCAE Version 5.0.

6.6.2.2. 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 recommendations below.

Mandatory Prophylaxis

The prophylactic regimen can be managed according to local practice and guidelines; however, it 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. Ultraviolet A 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. These 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.
- Alcohol-based (eg, gel formulations) topical agents such as steroids, antibiotics, or hand sanitizers can dry the skin and should be avoided.
- A proactive approach is recommended, given the anticipated increase in anti-EGFR activity:
 - These participants should have prescriptions (preferably already filled) for topical antibiotics, oral antibiotics, and topical steroids at the time of initial dosing, to minimize any delay in reactive management once rash is observed.
 - Antibiotic therapy will be initiated on Cycle 1 Day 1 and continuing antibiotic therapy for the first 8 weeks: a topical antibiotic (clindamycin, mupirocin, or fusidic acid) on sun-exposed skin, or an oral antibiotic (such as doxycycline 100 mg OD, minocycline 100 mg OD, or cephalexin 500 mg OD), or both.
 - A topical corticosteroid of medium to low potency BID on the face and chest (such as alclometasone 0.05% or desonide 0.05% cream) may also be considered.

Reactive Management Recommendations

It is strongly recommended that participants who develop rash/skin toxicities receive evaluations for management on the specific AE.

- 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).
- Consultation with a dermatologist is required if the rash is Grade 4.
- Initiate a topical corticosteroid (cream or ointment) BID.
 - 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 BID, minocycline 100 mg BID, or cephalexin 500 mg BID), 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, see Section 6.6.2.3.
- 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.
- After the rash is controlled, consider gradually tapering the antibiotic.

A suggested algorithm for stepwise management of rash is provided in [Table 11](#).

Table 11: Suggested Algorithm for Management of Rash

Grade ^a	Management	Dose Adjustment
1	• Initiate reactive management as above • Reassess weekly	Continue current dose(s) of study treatment
2	• Initiate reactive management as above • Reassess weekly	Continue current dose(s) of study treatment. <i>or</i> If intolerable, consider withholding amivantamab. Upon satisfactory resolution, restart on Day 8 or Day 15 of the current cycle or Day 1 of next cycle at either the same or a reduced dose (see Table 8) for amivantamab dose reduction guidance.
3	• Initiate reactive management as above • Start moderate strength topical corticosteroids^b and systemic antibiotics as	Withhold amivantamab until rash improves to ≤Grade 2. If Grade 3 adverse reaction improves to Grade 0-2 after withholding amivantamab for up to 3 weeks, restart amivantamab at the same dose or a reduced

Grade ^a	Management	Dose Adjustment
	above, plus systemic prednisone (0.5 mg/kg) for 7 days - Consider low doses of acitretin or isotretinoin (20-30 mg/day) - Reassess weekly - Consider dermatology consultation and manage rash per recommendation	dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. If Grade 3 adverse reaction does not improve to Grade 0-2 after withholding amivantamab for up to 3 weeks, permanently discontinued amivantamab.
4	- Initiate reactive management as above - Start moderate strength topical corticosteroids^b and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days - Consider low doses of acitretin or isotretinoin (20-30 mg/day) - Reassess weekly - Consult dermatologist and manage rash per recommendation	Permanently discontinue all study treatments (amivantamab, pemetrexed, and carboplatin).
Severe bullous, blistering, or exfoliating skin conditions including TEN	Consult dermatologist and manage rash per recommendation	Permanently discontinue all study treatments (amivantamab, pemetrexed, and carboplatin).

a. Grading per NCI-CTCAE Version 5.0.

b. For eg, 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 BID, minocycline 100 mg BID) 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.

6.6.2.3. Pruritus

Reactive Management Recommendations (Fischer 2013)

Grade 1 pruritus:

- Apply topical low to moderate strength steroid cream (eg, hydrocortisone 2.5%, desonide 0.05%, or betamethasone valerate 0.05%), topical calcineurin inhibitor (eg, tacrolimus or pimecrolimus), or topical antipruritic containing numbing agent (eg, pramoxine) and menthol.

Grade 2 pruritus:

- Apply topical moderate to high strength steroid cream (eg, betamethasone valerate 0.1%, triamcinolone acetate 0.1%) or topical antipruritic containing numbing agent (eg, pramoxine) and menthol.
- Initiate an oral antipruritic (eg, cetirizine, fexofenadine, rupatadine, bilastine) one dose BID. If still pruritic after 2-5 days, may increase to double dose BID.

Grade 3 pruritus:

- Initiate an oral antipruritic (as above for Grade 2 pruritus).
- Initiate oral pregabalin or gabapentin.
- Initiate an oral corticosteroid (eg, prednisone 0.5-1.0 mg/kg/day or equivalent for 5 days).

6.6.2.4. 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 participant 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 BID: 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) BID.

- Apply a topical steroid ointment (eg, betamethasone valerate 0.1% or clobetasol) or topical calcineurin inhibitor (eg, tacrolimus 0.1%) BID. 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) BID.
- Initiate oral antibiotic for at least 14 days (eg, doxycycline 100 mg BID, minocycline 100 mg BID, or cephalexin 500 mg BID).
- Consult a dermatologist or podiatrist.

6.6.2.5. Oral Mucositis

Mucositis is a well-recognized toxicity associated with anti-EGFR therapeutics and may be mild/moderate and localized (Grades 1-2) or severe and widespread ($\geq$ Grade 3). As a result, there are recommendations that should be followed to prevent or minimize participant discomfort associated with this toxicity. Prophylaxis should occur according to local institutional practice and guidelines, and should include the following:

Prophylaxis Recommendations

- Use good oral hygiene, dentition review and referral to an oral hygienist if necessary.
- Use a soft toothbrush.
- Use mild-flavored toothpastes.
- Use saline-peroxide or salt and soda mouthwashes 3 or 4 times per day.
- Use water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth).
- Avoid spicy, acidic, hard, and hot food and beverages.

Reactive Management Guidelines

- Asymptomatic or mild symptoms: topical steroid (dexamethasone 0.5/mL elixir) and lidocaine 2% to 5% jelly or solution (swish and spit) 4 times per day.
- Co-trimoxazole lozenges can be used to prevent secondary candida infection.
- In cases of moderate to severe pain:
- Compounded mouthwash (eg, “magic mouthwash”) including an antifungal, steroid, antihistamine, anesthetic, and/or antacid/mucosal coating agent as per local practice and guidelines.
- Dexamethasone solution 3.3 mg/5 mL swish and spit 4 times per day, and lidocaine jelly 2% to 5% or solution 4 times per day.

6.6.2.6. Pulmonary Toxicity

Patients with NSCLC are at risk of multiple AEs affecting pulmonary function, including disease progression, pulmonary embolus, infectious pneumonias, and more rarely, drug-related ILD/pneumonitis. Participant respiratory status should be assessed at every visit; any clinically significant change in respiratory status should prompt immediate investigation into the etiology in accordance with local practice/guidelines to institute appropriate treatments and to rule out early ILD/pneumonitis. If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pulmonary AE is observed, including ILD/pneumonitis, all study treatments, including carboplatin and pemetrexed, should be withheld, and appropriate treatment/management should be promptly initiated.

The following evaluations are recommended in order to exclude alternative etiologies such as lymphangitic carcinomatosis, pulmonary embolism, infection, allergy, and cardiogenic edema:

- 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 (high-resolution CT is preferred).
- Infectious evaluation, including blood and sputum cultures, atypical pneumonia panels, and SARS-CoV-2 testing, if indicated.
- Hematology and other laboratory tests, including serum albumin levels.
- Referral to pulmonologist for evaluation, including bronchoscopy with biopsy, cell counts, and cultures as feasible.
- Evaluation of cardiac function, if indicated.

Where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered, and study treatment permanently discontinued. Study treatment should not be restarted until pneumonitis/ILD is ruled out. For participants with symptomatic pneumonitis (Grade 2 or above), treatment with steroids should be initiated per local guidelines, in addition to withholding of study treatment.

Confirmation of ILD/pneumonitis of any grade should prompt discontinuation of all study treatments and should be reported as a SAE. In the absence of a diagnosis of ILD/pneumonitis, study treatment may be restarted after discussion with Medical Monitor.

6.6.2.7. Cardiac Adverse Events

Newly diagnosed or suspected changes in cardiac status, including QTcF prolongation or change in LVEF, should prompt additional investigations, including referral to cardiologists as per local practice or guidelines.

QTcF Prolongation

- Check the quality of ECG recording and check for electrolyte abnormalities (eg, potassium, calcium, magnesium); correct as needed.

- QTc prolongation of >60 msec from baseline, or absolute value of >500 msec:
- For QTcF prolongation >60 msec from baseline, or absolute value >500 msec (from a manual ECG read), medications should be reviewed to rule out new or existing concomitant medications with potential for QT prolongation (see [Appendix 12: Medications With Potential for QT Interval Prolongation](#)), and these should be discontinued, if possible, with action reported in eCRF.
- Check for electrolyte abnormalities and correct as needed (eg, potassium, calcium, magnesium).
- If QTcF prolongation is confirmed and potentially attributable to study treatments, then all study treatments, including carboplatin and pemetrexed, should be withheld.
- Retreatment, at a reduced dose, should only occur once QTc interval is ≤ 480 msec, as measured by repeat triplicate ECG, or recovery to baseline is documented. If retreatment is indicated, amivantamab should be reduced by 1 dose level each (see [Table 8](#)).
- Treat as per local standard of care in consultation with a cardiologist.
- QTc interval prolongation with signs/symptoms of life-threatening arrhythmia, including but not limited to the following: documented episode of ventricular tachycardia, ventricular fibrillation, complete heart block (Grade III atrioventricular block) or second-degree atrioventricular block Mobitz type II, QTc >500 msec at repeated ECG measurements, after dose adjustment was performed:
- Permanently discontinue study treatment.

Change in LVEF

- Absolute LVEF decline of >10% and absolute LVEF value below the LLN:
- For participants experiencing absolute decline of LVEF of >10% from baseline and absolute LVEF percentage below LLN, the decline should first be confirmed by having the 2 assessments read, and measurements confirmed, by the same cardiologist.
- Confirmed drops in LVEF assessments should prompt withholding study treatment, referral to a cardiologist for further evaluation, and consultation with the Medical Monitor; repeat LVEF assessment within at least 2 weeks to monitor status.
- Symptomatic CHF:
- Permanently discontinue all study treatments, including carboplatin and pemetrexed.

6.6.2.8. Liver Chemistry Abnormalities

Liver chemistry threshold stopping criteria have been established to provide safety to the participants and to better assess the etiology of a liver event. Liver chemistry should be monitored according to the Schedule of Activities and study treatment should be withheld for any liver chemistry abnormality of $\geq$ Grade 3 severity (refer to Section [6.6.1](#)). In addition, if the following

criteria are observed, then study treatment should be withheld, and the event should be reported as an SAE to the sponsor within 24 hours:

- ALT or AST $\geq 3 \times$ ULN (if baseline was normal; $\geq 3 \times$ baseline if baseline was abnormal) and bilirubin $\geq 2 \times$ ULN (if baseline was normal; $\geq 2 \times$ baseline if baseline was abnormal) ($>35\%$ direct bilirubin). Exception to the bilirubin elevation is made if the participant has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.
- ALT or AST $\geq 3 \times$ ULN (if baseline was normal; $\geq 3 \times$ baseline if baseline was abnormal) and international normalized ratio (INR) >1.5 if INR is measured.
- ALT or AST $\geq 3 \times$ ULN (if baseline was normal; $\geq 3 \times$ baseline if baseline was abnormal) with the concomitant appearance of worsening symptoms attributable to drug induced liver injury, such as the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or new onset 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. Etiology of the liver chemistry abnormality should be investigated, as described in [Appendix 7: Liver Event Follow-Up Requirements](#). If no alternative etiology of liver toxicity is identified, all study treatments, including carboplatin and pemetrexed, should be permanently discontinued.

6.6.2.9. Ocular Toxicity

Ophthalmologic complications are infrequently observed with anti-EGFR therapeutics. In the case of signs or symptoms associated with ophthalmologic toxicity, including change in vision (including change in acuity or visual distortion), eye inflammation, lacrimation, light sensitivity, or eye pain, among others, the participant should be referred for ophthalmologic assessment. Participants should be advised of the increased risk for eye toxicity associated with anti-EGFR therapeutics with the use of contact lenses.

6.6.2.10. Diarrhea

If participants experience diarrhea, they should be encouraged to drink 8 to 10 large glasses (total volume of 2 L) of clear liquids per day while on study to maintain adequate hydration. Maintenance of electrolyte balance using electrolyte containing drinks, broth, and clear juices should be considered. If an infectious cause of the diarrhea is suspected, perform stool testing and administer antibiotic therapy (avoiding strong CYP3A4 inhibitors, when possible) as appropriate.

General dietary measures to limit impact of diarrhea include the following:

- Stop all lactose-containing products in participants with evidence of lactose intolerance
- Eat frequent small meals if experiencing increased frequency of stools
- Consider low-fat regimen enriched with bananas, rice, applesauce, and toast

Diarrhea management guidelines are shown in [Table 12](#).

Table 12: Suggested Algorithm for Management of Diarrhea

Grade	Management	Study Treatment
1	- Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). - Fluid intake of at least 2 L as described above.	Continue study treatment(s).
2	- Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours), or consider diphenoxylate and atropine formulations. - Fluid intake of at least 2 L as described above. Monitor participant closely and consider intravenous hydration.	- If not improved to $\leq$Grade 1 within 24 hours despite use of loperamide, hold amivantamab treatment until $\leq$Grade 1. - If diarrhea of $>$Grade 1 recurs after initial improvement, consider reduction of amivantamab dose by one dose level
3	- Oral therapy with diphenoxylate and atropine formulations, or tincture of opium. - Fluid intake of at least 2 L should be maintained as described above, intravenously if necessary. - Consider use of octreotide 100-150 μg subcutaneously BID with escalation to 500 μg 3 times daily. - Consider hospitalization if does not improve to $\leq$Grade 2 within 24 hours, or in presence of fever, abdominal pain, etc.	- Hold amivantamab. Upon resolution to $\leq$Grade 1, resume amivantamab on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle. - Consider reducing dose by 1 level.
4	Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leukocytosis, marked dehydration, etc.	Hold amivantamab until $\leq$Grade 1. Upon resolution to $\leq$Grade 1, resume amivantamab at a reduced dose on Day 8 or Day 15 of the current cycle or Day 1 of the next cycle.

6.6.2.11. Paresthesia

If a participant experiences paresthesia, contributing medical conditions should first be considered and optimally managed. For example:

- Vitamin or mineral deficiency (eg, Vitamin B1 [thiamine], B6 [pyridoxine], B12 [cobalamin], B9 [folate], Vit E, Copper) should be corrected
- Diabetes should be optimally managed
- General safety measures are recommended to protect against injury, infection etc.

The following symptomatic management guidance is provided in the event the paresthesia is considered related to study treatment:

- Grade 1: Nutraceutical/non-pharmacologic interventions may be considered (ie, vitamin supplementation including vitamins B1, B6, B9, B12, E, glutamine, alpha-lipoic acid, glutathione, calcium/magnesium, copper). Topical therapy (eg, capsaicin) may be considered.
- Grade 2: Duloxetine, pregabalin, or gabapentin are recommended. Titrate dose for efficacy and tolerability. Adding tricyclic or selective serotonin reuptake inhibitor antidepressant may be considered. Opioids (tramadol or strong opioids) may be considered. Neurologic consultation if symptoms persist on medication.

- Grade 3: Neurologic consultation. Duloxetine, pregabalin, or gabapentin are recommended. Titrate dose for efficacy and tolerability. Adding tricyclic or selective serotonin reuptake inhibitor antidepressant may be considered. Opioids (tramadol or strong opioids) may be considered.

Refer to [Table 8](#) and [Table 9](#) for recommended dose adjustment.

6.6.2.12. Venous Thromboembolic Events

Participants with NSCLC are at risk of developing complications, including VTE events. Investigators should closely monitor all participants for signs and symptoms of VTE events, specifically pulmonary embolism and deep vein thrombosis, throughout the duration of the study. Physical examinations (see Section [8.3.1](#)) should include focus on signs and symptoms of VTE events, including upper- or lower-extremity swelling and discoloration. There should be a low threshold to perform additional diagnostic testing (eg, CT angiogram or lower-extremity ultrasound) for VTE events beyond the scheduled disease evaluations. For participants that have experienced VTE, if symptoms persist or in case of worsening VTE, further imaging studies (which may include doppler studies) should be performed to assess the resolution of the event with corrective measures, as per the treating physician's discretion.

If a VTE event is diagnosed, the participant should be treated with treatment-dose anticoagulation as per local guidelines. Vitamin K antagonists are not recommended because of numerous drug interactions. For VTE events associated with clinical instability (eg, respiratory failure or cardiac dysfunction) in participants receiving amivantamab, study treatment should be held until the participant recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator.

Refer to [Table 8](#) and [Table 9](#) for recommended dose adjustment for any adverse events.

6.6.3. Chemotherapy Dose Modification

Dose modifications of chemotherapy should be based on the maximum toxicity experienced during a cycle. Treatment should be delayed until the toxicity resolves to $\leq$ Grade 1 or the baseline status of the participant. Final treatment decisions should depend on clinical judgment, based on local regulations and labeling. Decisions on study treatment dose modification should be guided by the safety profile of each drug and the likelihood of causality.

Dose modifications will be based on the maximum toxicity experienced during a cycle. Participants may have a maximum of 2 dose modifications to each treatment throughout 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. Do not re-escalate chemotherapy dosing after a prior dose reduction.

6.6.3.1. 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 be monitored for chemotherapy-related toxicities and 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. Chemotherapy should be delayed if absolute neutrophil count is $<1,500/\mu\text{L}$, platelet count is $<100,000/\mu\text{L}$, or the participant is experiencing non-hematologic toxicity of $>\text{Grade } 2$ severity. All participants who experience hematologic toxicities while on treatment are recommended to receive colony stimulating factors as per international guidelines (eg, MGF-3 and TGF-1 from the NCCN Guidelines for Hematopoietic Growth Factors as an example). [Table 13](#) and [Table 14](#) 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.

Table 13: Guidance for Dose Modifications for Hematologic Chemotherapy Toxicity

Platelets (Nadir)	Absolute Neutrophil Count (Nadir)	Pemetrexed Dosage	Carboplatin Dosage
$\geq 50,000/\mu\text{L}$	$\geq 500/\mu\text{L}$	100% of previous dose	100% of previous dose
$\geq 50,000/\mu\text{L}$	$< 500/\mu\text{L}$	75% of previous dose	75% of previous dose
$< 50,000/\mu\text{L}$ without bleeding	Any	75% of previous dose	75% of previous dose
$< 50,000/\mu\text{L}$ with $\geq \text{Grade } 2$ bleeding	Any	50% of previous dose	50% of previous dose
$\geq 50,000/\mu\text{L}$	$< 1,000/\mu\text{L}$ + fever $\geq 38.5^\circ\text{C}$ (101°F)	75% of previous dose	75% of previous dose

Table 14: 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.

6.7. Continued Access to Study Treatment After the End of the Study

At the end of their participation in the study, participants who are benefiting from the study treatment (amivantamab), as determined by their investigator, will be able to receive continued access as per recommendation from treating physician. Amivantamab will be provided from local commercial supply through local distribution channel. Such participants will not be monitored after end of follow-up phase.

6.8. Treatment of Overdose

There are no data on overdose from studies of amivantamab (refer to IB).

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

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study treatment must be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until can no longer be detected systemically.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.9. Prior and Concomitant Therapy

6.9.1. Recording Prestudy and Concomitant Therapies

Prestudy therapies administered up to 30 days before first dose of study treatment must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study treatment to 30 days after the last dose of study treatment. Concomitant therapies must also be recorded beyond 30 days only in conjunction with SAEs and Grade 3 or 4 AEs considered related to study treatment, until resolution of event or start of subsequent therapy.

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 eCRF. Recorded information will include a description of the type of therapy, dates of use, dose regimen, route of administration, and indication. 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.

6.9.2. Permitted and Required Medications and Therapies

6.9.2.1. Pre- and Post-Infusion Medications for Chemotherapy

Corticosteroids, folic acid, and vitamin B12 will be administered concomitantly with pemetrexed (Table 15), according to local prescribing information or per standard local practice.

Table 15: Concomitant Medications for Pemetrexed

Medication	Dose	Timing
Corticosteroid	Dexamethasone 4 mg orally BID 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 prior to and including 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 BID dose can be skipped on Cycle 1 Day 1 and Day 2, at the discretion of the investigator since IV dexamethasone is administered as a medication for amivantamab on those days per [Table 4](#).
- 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 PI, local practice guidelines, or as clinically indicated. Permitted prophylactic medications 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 Cycle 1 Day 1.
- G-CSFs should not be used prophylactically during screening. Use of prophylactic colony stimulating factors may be considered after first dose as per local guidelines or prescribing information.

Concomitant medications for the symptomatic treatment of related toxicities (Grade 1 to 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.

6.9.2.2. 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 4](#).

On days when multiple study treatments are dosed together, the order of medications should be as follows:

- a) Pre-infusion medications for chemotherapy (eg, antiemetic, antihistamine, glucocorticoid) per local guidelines or site practice
- b) Pemetrexed per label/site practice
- c) Carboplatin (up to a maximum of 4 cycles) per label/site practice
- d) Pre-infusion medications for amivantamab (per [Table 4](#)), to commence after completion carboplatin infusion. Note: Participants should receive the required pre-medications, but if the medications are already administered prior to chemotherapy, administration does not

need to be repeated prior to initiation of the amivantamab infusion if dose was administered within the recommended window.

e) 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 16](#)).

Table 16: 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.

6.9.2.3. Supportive Care

Supportive care and other medications that are considered necessary for the participant's well-being may be given at the discretion of the investigator.

6.9.2.4. Radiotherapy

Localized, limited radiotherapy of short duration (eg, 5 days or less) for palliative purposes of nontarget lesions may be permitted, but only after consultation with the Medical Monitor. Study treatment interruption is not required but is allowed as per investigator discretion. Radiotherapy should be scheduled for the weeks between scheduled doses of amivantamab.

6.9.2.5. Hormonal Contraception

Participants using hormonal contraceptives as a means of birth control must continue to use the same hormonal contraceptives throughout the study and through 6 months after the last dose of study treatment.

6.9.3. Prohibited or Restricted Medications and Therapies

Prohibited Medications and Therapies

The following concomitant medications and therapies are prohibited until the EOT visit. The sponsor must be notified as soon as possible of any instances in which prohibited therapies were administered.

- Any chemotherapy, anticancer therapy, or experimental therapy (other than study treatments) for the treatment of NSCLC is prohibited.
- Radiotherapy to a target lesion is prohibited.
- Use of live or live attenuated vaccines is prohibited until at least 90 days after the last dose of study treatment.
- Use of phenytoin or fosphenytoin with carboplatin is prohibited.
- Prescription and over the counter medications, herbal supplements or ingestion of foods with known potent inducer effects on CYP3A4/5 activity (For a list of such medications, refer [US FDA 2023](#)). Appropriate medical judgment is required, if any of the strong CYP3A4/5 inducer medications should be utilized, if clinically indicated, for the treatment of AEs. Please contact the local pharmacist or Medical Monitor with any questions.

Restricted Medications and Therapies

The following concomitant medications and therapies are restricted until the EOT visit and should be avoided, when possible, or used with caution.

- Use caution with co-administration of medicines that prolong QT interval (see [Appendix 12: Medications With Potential for QT Interval Prolongation](#)). If there are no other alternative medications that can be used, limit treatment duration when possible. Please contact the local pharmacist or Medical Monitor with any questions.
- Avoid concomitant use of CYP3A4/5 substrate drugs and medications known to be strong inhibitors of CYP3A4/5 (For a list of such medications, refer [US FDA 2023](#)). If no other alternatives exist monitor participants more closely for adverse reactions. Please contact the local pharmacist or Medical Monitor with any questions.
- Medications that are substrates of P-glycoprotein, multi-drug resistance protein 4, Breast Cancer Resistance Protein, and Organic Cation Transporter 1 should be used with caution. (For a list of such medications, refer [US FDA 2023](#)). Please contact the local pharmacist or Medical Monitor with any questions.
- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.
- Nephrotoxic or ototoxic agents should be used cautiously with carboplatin. Nephrotoxic drugs should also be used cautiously with pemetrexed. 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 OD is permitted during the study). Ibuprofen should be avoided from 2 days before until 2 days after administration of pemetrexed.

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
- Investigator decision (as they believe it is in the best interest of the participant to discontinue study treatment)
- The participant becomes pregnant
- Noncompliance with study treatment administration or procedure requirements as judged by the investigator
- Radiographic disease progression by investigator using RECIST v1.1 (**Exception:** Continuation of study treatment after disease progression may be allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believes the participant is deriving clinical benefit. In general, this implies the absence of significant worsening of clinical symptoms or signs of disease progression, including clinically significant worsening of laboratory abnormalities, deterioration in ECOG performance status, or rapid progression at critical anatomical sites which may require urgent alternative medical intervention.)
- Disease progression that, at the discretion of the treating investigator, requires the initiation of a new systemic anti-cancer treatment.
- The participant experiences a Grade 4 rash, severe bullous, blistering, or exfoliating skin conditions including TEN.

If a participant discontinues study treatment for any reason before the end of the treatment period, then the end-of-treatment assessments must be obtained and scheduled assessments off study treatment should be continued. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant. Additional participants will not be entered.

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
- Start of subsequent therapy

When a participant withdraws consent as described on the ICF by the participant, further data collection will be limited to what the participant agreed to. In such case, the investigator must discuss the different types for alternative follow-up, should the participant be agreeable to this. Details regarding these alternative contacts must be properly documented in source records including responses from participants.

7.3. Lost to Follow up

To reduce the chances of a participant being deemed lost to follow up, attempts should be made prior to study entry to obtain contact information from each participant, eg, 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 the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site, despite all reasonable efforts documented in the participant's medical records. Reasonable effort includes, where possible, 3 telephone calls, emails or messaging apps, a certified letter to the participant's last known mailing address, or local equivalent methods.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General/Baseline Procedures

Overview

The SoA summarizes the frequency and timing of all assessments applicable to this study. The total blood volume to be collected from each participant will be approximately 150 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. This total blood volume is considered to be acceptable based upon the recommendations by the Dana Farber/Harvard Cancer Center Guidance, which indicates a maximum of 10.5 mL/kg (52 kg person) or 550 mL, whichever is smaller, over any 8-week period.

Sample Collection and Handling

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

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

8.2. Effectiveness Assessments

The effectiveness objective is to assess the ORR at 6 months.

Assessments (for timing, see SoA [Table 1](#)) include: radiological imaging using CT/PET scan.

RECIST v1.1 criteria (for details refer to [Appendix 15: Response Evaluation Criteria in Solid Tumors \(RECIST\) Quick Reference](#)) will be used by investigator to assess participant response to treatment: complete response, partial response, stable disease, progressive disease, or unevaluable.

Disease assessments will include the chest, abdomen, and pelvis, and any other disease location(s). Baseline disease assessments should be performed no more than 28 days prior to enrollment. If an imaging 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. Refer to the latest Imaging Site manual.

Radiological assessments will be performed at screening and at EOT, in between if needed based upon investigator's discretion. Additional assessments will be performed during treatment period per investigator's discretion. Identical methodology (CT/PET scan) 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/PET scan may be used, based upon investigator judgment, local standard of care, and RECIST v1.1 guidelines for the use of these alternative techniques.

Brain MRI (or brain CT scan if MRI is medically prohibited) will be performed at screening, EOT visit, and at investigator's discretion during treatment phase.

All participants who discontinue study treatment for any reason should have the EOT assessments continue to be followed up in accordance with the follow-up phase.

If symptomatic deterioration (on the basis of global deterioration of health status) is recorded as the basis for discontinuation of study treatment, then the clinical findings used to make the determination must be specified in the eCRF 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.

If a participant is treated beyond Investigator-confirmed disease progression, disease assessments will continue according to the SoA.

Survival and disease status will be assessed at EOT and during follow-up period.

8.2.1. Symptomatic Progression

Symptoms, attribution, and related treatments will be recorded on the eCRF at the times specified in the SoA ([Table 1](#)). If symptomatic progression is not reported prior to treatment discontinuation, continued assessment is required during the follow-up period, even after subsequent therapy is initiated.

8.3. Safety Assessments

Timing of safety assessments is specified in the SoA, [Table 1](#).

Adverse events will be reported and followed by the investigator as specified in [Section 8.4](#) and [Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: 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 eCRF.

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 SoA.

8.3.1. Physical Examinations

The screening physical examination will include, at a minimum, the participant's height, weight, general appearance and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.

At all visits, participants should be questioned for skin and eye symptoms with directed physical examinations conducted as appropriate and specialty referral as indicated. In addition, participants should similarly be questioned for signs and symptoms of VTE events, and a focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed, particularly during the first 4 months of assigned therapy. Any changes from baseline should prompt consideration for further diagnostic evaluation, including unscheduled CT exam or lower-extremity Doppler evaluation.

On Day 1 of each cycle and at the EOT 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.

8.3.2. Vital Signs

Temperature, pulse/heart rate, RR, oxygen saturation, and blood pressure will be assessed. Pulse/heart rate measurements will be assessed in a seated position with an automated device; if not available manual techniques are allowed. Pulse/heart rate and blood pressure measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.3.3. Electrocardiograms

During the collection of 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 SoA ([Table 1](#)). For triplicate ECGs at Screening and other times if clinically indicated, 3 individual ECG tracings should be obtained as closely as possible in succession, approximately 2 minutes apart. The clinical investigator will review the ECG, including ECG morphology, for immediate management. The results will be entered into the eCRF. Abnormalities noted at screening should be included in the medical history.

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, coagulation, serology and a random urine sample for urinalysis will be collected as noted in [Appendix 1: Clinical Laboratory Tests](#) at times specified

in the SoA (Section 1.3). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.3.5. ECOG Performance Status

ECOG performance status score (refer to [Appendix 5: Eastern Cooperative Oncology Group \(ECOG\) Performance Status](#)) will be determined during the Screening Phase and at time points listed in the SoA ([Table 1](#)). Any decline in ECOG performance status score should be reported as an AE.

8.3.6. Left Ventricular Ejection Fraction

During the Screening Phase, each participant will undergo a baseline LVEF assessment performed locally by cardiac ECHO or MUGA scan in order to demonstrate eligibility (ie, a LVEF within the normal range). Participants will undergo postbaseline LVEF assessments, as clinically indicated.

8.3.7. Pregnancy Tests

For participants of childbearing potential, a negative serum pregnancy test is required at Screening and within 72 hours before the first dose of study treatment (ie, prior to Cycle 1). A serum or urine pregnancy test is required within 72 hours before the first dose of each subsequent treatment cycle and at the EOT visit. Additional serum or urine pregnancy tests may be performed as determined necessary by the investigator, or as required by local regulation, to establish the absence of pregnancy at any time during participation in the study.

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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQCs, from clinical studies are crucial for the protection of study participants *and patients*, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures to ensure appropriate safety reporting; and this study is *to 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 LDR).

For study treatment that meets the definition of a combination product, malfunctions or deficiencies of a device constituent will be reported as a PQC.

The sponsor assumes responsibility for appropriate reporting of the Safety Information, including SAEs, SUSARs, to the Regulatory Authorities/IECs/IRBs in each respective country/territory, as applicable.

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

All AEs and special reporting situations, whether serious or non-serious, regardless of the investigator-attributed causal relationship with study treatment or study mandated procedures,

must be recorded using medical terminology in the source document and on the appropriate pages of the eCRF and appropriate forms. 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 eCRF their opinion concerning the relationship of the AE to study therapy (see [Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting](#)). All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained.

All AEs, special reporting situations and SAEs that occur until 30 days after study treatment discontinuation or until starting new subsequent anticancer therapy, whichever is earlier, must be reported and recorded on the appropriate pages in the eCRF or on specific forms.

Information regarding SAEs (initial and any follow up) will be transmitted to the sponsor/CRO immediately, but no later than 24 hours of their knowledge of the event, using the study specific SAE Form with the complete (eg, causality, narrative) information available in the medical records that has been already assessed by a study site physician, and transmitted via eCRF through JEISR.

8.4.2. Definitions and Classifications

8.4.2.1. All Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding from a diagnostic procedure or laboratory assay), symptom, or disease that is new in onset or aggravated in severity or frequency from baseline and temporally associated with the use of such product (as defined by ICH).

The investigator is obligated to take all necessary steps to elucidate the nature and causality of the AE as fully as possible.

8.4.2.2. Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- **Results in death**

The cause of death of a participant in a study (within 30 days of the last dose of study treatment), whether or not the event is expected or associated with the study treatment, is considered an SAE. However, death attributed to progression of disease should not be considered an AE or SAE. For details, see [Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting](#).

- 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:
 - Hospitalization attributed to progression of disease; for details, see Section 8.4.6.2.
 - Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility, convenience for participant)
 - Surgery or procedure planned before entry into the study (must be documented in the eCRF). (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.)
- 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 indicating suicidal ideation or behavior
- Is a Hy's law Case (defined by the occurrence of ALT or AST $\geq 3 \times$ ULN, ALP $< 2 \times$ ULN together with Total bilirubin $\geq 2 \times$ ULN or INR > 1.5 [if measured] with no alternate etiology). A confirmed Hy's Law as well as a possible Hy's law Case must be reported as SAE.
- Is

Medically	Important
Exercise medical judgment to decide on reporting as SAE of other 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 outcomes listed above.	

SAE recording and reporting

All SAEs that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves, stabilizes or 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, or participant is lost to follow-up)

8.4.3. Attribution of Causality

The causal relationship between study treatment administration and the AE is assessed by the Investigator and documented in the Medical Records. This assessment must consider factors such as characteristics of participant and event, temporal relationship, pharmacologic plausibility and confounding clinical factors. Data on challenge can help the assessment (did the event improve

when the study treatment was withdrawn in the absence of any other intervention and what happened when participant re-started the study treatment). The following must be used for all AEs:

- **Related:** There is a reasonable causal relationship.
- **Not Related:** There is not a reasonable causal relationship.

8.4.4. Severity Criteria

An assessment of severity grade will be made by the investigator according to the NCI-CTCAE (Version 5.0). Any AE or SAE not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard grades as follows:

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

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Notes: A semi-colon indicates 'or' within the description of the grade.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

8.4.5. Special Reporting Situations

Safety events of interest pertaining to the study treatment in this study that require expedited reporting and may trigger safety evaluation include, but are not limited to:

- Overdose of study treatment
- Suspected abuse/misuse of study treatment
- Accidental or occupational exposure to study treatment
- Exposure to study treatment from breastfeeding
- Any failure of expected pharmacologic action (ie, lack of effect if used according to the local label) or any unexpected therapeutic benefit, to be reported as a PQC for the marketed product(s)

- 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)
- Reporting of participant pregnancy or participant partner(s) pregnancy

Participant-specific special reporting situations must be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the eCRF. Reporting should occur as for other AE and SAE (Section 8.4.1).

8.4.6. Procedures

8.4.6.1. Anticipated Events

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, anticipated events will be periodically analyzed as specified in [Appendix 14: Anticipated Events](#).

8.4.6.2. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Progression of disease and signs and symptoms which do not meet the criteria of SAE reporting, that are part of the natural course of the disease under study, should not be considered or reported as a (serious) adverse event to the sponsor.

- Progression of disease: document on the appropriate eCRF form (eg, Disease Progression form)
- Death due to disease progression: document on the appropriate eCRF form (eg, Death form).
 - Death of a study participant, irrespective of its cause ie, progressive disease will be reported to the CDSCO as per provisions of the New Drugs and Clinical Trial Rules, 2019 during the trial.
- Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure should be documented on the appropriate eCRF form (eg, Symptomatic Progression Form).
- Of note, for the rare case of (accelerated) progression of disease induced by the study treatment: report this accelerated progression or its specific signs/symptoms as drug-related AE per the usual reporting requirements.

8.4.6.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid

communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation to characterize and understand it. Depending on the nature of the event, expedited reporting by the study sponsor to other parties (eg, regulators) might be warranted.

The communication requirements for AESIs are detailed in the table below. Any AESI should be followed until recovery.

Table 17: Adverse Events of Special Interest

Adverse Event of Special Interest	Guidance
IRR	All Grade 3 or 4 IRRs should be reported within 24 hours to the medical monitor. See Section 6.6.2.1 for monitoring and management guidelines.
Rash ^a	All Grade 3 and 4 rash should be reported within 24 hours to the medical monitor. See Sections 6.6.2.2, 6.6.2.3, and 6.6.2.4 for monitoring and management guidelines.
VTE	All Grade 3 and 4 VTEs should be reported within 24 hours to the medical monitor. See Section 6.6.2.12 for monitoring and management guidelines.
Pneumonitis/ILD	Confirmed cases of pneumonitis/ILD (regardless of grade) should be reported as SAEs (see Section 8.4.1).

^a The term “Rash” includes dermatologic adverse events of interest which is a group of events: rash, dermatitis, paronychia, skin fissures, acne, erythema, skin exfoliation, skin lesion, skin irritation, and eczema.

8.4.7. Product Quality Complaint Handling

Definition

A 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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and effectiveness of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

8.4.8. Contacting Sponsor Regarding Safety, Including Product Quality

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

8.5. Pregnancy and Postpartum Information

8.5.1. Participants Who Become Pregnant During the Trial

Pregnancy testing must be performed as specified in the SoA. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Any participant who becomes pregnant during the study must discontinue further study treatment.

8.5.2. Participants Whose Partners Become Pregnant

All initial reports must be made to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Outcome of the reported pregnancy and any postnatal sequelae in the infant will be required. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported as SAEs.

8.6. Pharmacokinetics

Not applicable.

8.7. Pharmacodynamics

Not applicable.

8.8. Biomarkers

Sample collection and testing will comply with local regulations.

Additional Collections

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

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under its authority. A general description of the statistical methods to be used is outlined below; for more detail see the SAP, which should be finalized prior to database lock.

9.1. Statistical Hypotheses

This is a post-approval commitment study mandated by the CDSCO in India to evaluate the safety data of amivantamab with descriptive purpose and hence, no formal statistical hypothesis is prespecified. The rates of TEAE, SAE, and clinical interest AE and their 95% CIs will be provided.

9.2. Participant Analysis Sets

For purposes of analysis, safety and efficacy analyses will be performed on safety analysis set. The following analysis sets are defined:

Table 18: Analysis Sets

Analysis Sets	Description
Screened	All participants who sign the ICF
Enrolled	All participants who sign the ICF and are not screen failures
Safety	All participants who received at least 1 dose of study treatment

9.3. Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. The SAP will include a more technical and detailed description of the statistical analyses described in this section.

9.3.1. General Considerations

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variance, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages.

9.3.2. Primary Endpoint

The primary endpoint is the rates of TEAEs, based on safety analysis set.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA. TEAEs are AEs with onset during the treatment phase or that are a consequence of a preexisting condition that has worsened since the first dose of study treatment through the day of last dose plus 30 days or prior to the start of subsequent anticancer therapy, whichever is earlier, or any AE that is considered treatment-related regardless of the start date of the event. All reported TEAEs will be included in the analysis.

Data will be summarized using descriptive statistics. The rates of overall TEAEs, SAEs and special interest AEs, with their 95% CIs will be provided.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate for those participants who die, experience an AESI, discontinue treatment due to an AE, or experience a severe, or a SAE.

9.3.3. Secondary Endpoints

The secondary endpoint is used for efficacy analysis. The definition of secondary endpoint is as following:

- **Objective response rate (ORR)** is defined as the proportion of participants who have a PR or better according to the RECIST v1.1 criteria.

ORR rate will be based on safety analysis set.

ORR will be tabulated together with its 2-sided 95% exact CI. In addition, the number and percentage of participants in each response category (complete response, partial response, stable disease, progressive disease, or unevaluable) will be tabulated. For the calculation of ORR, those participants who are not evaluable for response will be listed as such and considered as non-responders.

9.3.4. Other Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics, analyses of frequency tabulations and change from baseline results will be specified in the SAP. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. 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-treatment cross-tabulations [with classes for below, within, and above normal ranges]). Toxicity grade during treatment will be used according to NCI-CTCAE Version 5.0. Change from baseline to the worst toxicity grade experienced by the participant during the study will be provided as shift tables. A listing of participants with abnormal laboratory results will be provided as defined in the SAP.

Vital Signs

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

Physical Examinations

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

9.4. Interim Analysis

In this study, no interim analysis is planned.

9.5. Sample Size Determination

Sample size calculation is based on the probability of observing at least one clinical interest AE given the certain sample size.

There is no direct data source with the use of prophylaxis regimen referred from the available studies. In MARIPOSA-2 study, rash rate in the first 4 months was 38.5%. Leveraging the findings that the rate would drop by 50% in global Phase 2 study COCOON which evaluated the impact of enhanced versus standard dermatologic management among patients with locally advanced or metastatic EGFR mutated NSCLC treated first line with amivanatamab+lazertinib, the rash rate in amivantamab+chemotherapy cohort with allowed prophylaxis regimen is assumed as 19%. For infusion-related reaction, the rate would be assumed to drop to 20% similar with dexamethasone 8 mg as prophylaxis regimen in the SKIPPirr study which prevented infusion related reactions associated with amivantamab among post-osimertinib advanced or metastatic EGFR-mutated NSCLC, with a median duration of treatment of 4.2 months. Additionally, the rates in MARIPOSA-2 study with a median duration of ACP arm of 6.3 months including serious TEAE (32.3%), related serious TEAE (23.1%), and AE leading to discontinuation (18%) are assumed to be similar with prophylaxis approach. Based on the consideration above, assuming that the true clinical interest AE rate is as low as 15%, with a total of 40 participants, at least one expected AE will be observed with a probability of >99%.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Clinical Laboratory Tests

The following tests will be performed according to the SoA by the local laboratory.

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	• Platelet count • Hemoglobin • White Blood Cell (WBC) count • Absolute Neutrophil count (ANC) • Mean corpuscular volume (MCV) Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.	
Clinical Chemistry	At all visits specified in SoA • Sodium • Potassium • Magnesium • Calcium • Creatinine • AST/SGOT • ALT/SGPT • GGT • ALP • Total bilirubin^a • Albumin • LDH	Tests at Screening only • Total Protein • Blood urea nitrogen (BUN) • Blood glucose
Routine Urinalysis ^b	<u>Dipstick</u> Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	<u>Sediment (if dipstick result is abnormal) by flow cytometry or microscopy</u> White blood cells Bacteria

Laboratory Assessments	Parameters
	If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. In the microscopic examination, observations other than the presence of WBC may also be reported by the laboratory. Dipstick and flow cytometric analysis of the urine samples will be performed in parallel, ie, in the same sample at the same time. Leukocyte esterase will be determined using dipstick. WBCs will be measured using flow cytometry. Crystals, casts, and bacteria will only be reported if they are present.
Other Laboratory Tests	• Serum/Urine pregnancy testing (for participants of childbearing potential only) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Coagulation^c (PT, aPTT, and INR)

- At screening, direct and indirect bilirubin can be performed at the discretion of the treating physician. During the treatment period, if total bilirubin is normal, direct and indirect bilirubin is not required. If total bilirubin is abnormal, then direct or indirect bilirubin is required.
- If urinalysis reveals bacteria and leukocytes (positive nitrite, leukocyte esterase) or an infection is otherwise suspected, a urine culture must be done to rule out a urinary tract infection prior to randomization.
- INR and aPTT are required. PT may be omitted if not routinely performed by the clinical laboratory.

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

10.2.1. Regulatory and Ethical Considerations

- **The investigator is responsible** for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country- or territory-specific requirements.
- **Regulatory Approval/Notification:** This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.
- **Protocol Amendments:** No modification to this protocol will occur without a formal amendment issued by the sponsor and signed and dated by the investigator. Amendments can't be implemented without prior approval by IEC/IRB and relevant competent authority, except to eliminate immediate hazards to the participants (promptly submit amendment to the IEC/IRB and relevant competent authority). Documentation of amendment approvals must be provided to the sponsor.
- **Departure from the Protocol:** In situations where a departure from the protocol is unavoidable during the study, the investigator or delegate will contact the appropriate sponsor representative listed in the Contact Information page(s) to discuss the situation and agree on an appropriate course of action prior to such departure, except in emergency situations. The departure and its rationale must be recorded in source documents and be reflected in the eCRF data.
- **Required Prestudy Documentation:** Documentation that must be provided to the sponsor before shipment of study treatment to the study site are specified in the appropriate documents such as the Clinical Trial Agreement. Additional documentation might need to be provided prior to enrolment of the first participant.
- **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 all documents as required by local regulations. Required documents are specified in the appropriate documents such as the Clinical Trial Agreement. This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, which should be submitted promptly, 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 dated approval, with clear identification of the IEC/IRB and the documents approved. During the study the investigator (or sponsor where required) will send documents and updates to the IEC/IRB for their review and approval, where appropriate, as specified in the appropriate documents such as the Clinical Trial Agreement.

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.

- Other Ethical Considerations:

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

10.2.2. Financial Disclosure

During the study and for 1 year after completion of the study, investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations. Refer to appropriate documents such as the Clinical Trial Agreement for details.

10.2.3. Informed Consent Process

Each participant or an LDR must give consent according to local requirements after the nature of the study has been fully explained and a response to all questions regarding the study was given. The ICF(s) must be signed before any study-related activity.

The consent must be appropriately recorded by means of either the participant's or their LDR's personally dated signature; the authorized person obtaining the consent must also sign the ICF. After consent, a copy of the ICF must be given to the participant. The medical records must include a statement that consent was obtained as required.

If the participant or LDR is unable to read or write, an impartial witness must be present for the entire process and must personally date and sign the ICF after the oral consent of the participant or LDR is obtained.

Rescreened participants must sign a new ICF and will then be assigned new participant numbers.

Where local regulations require, a separate ICF may be used for the specific component(s), such as DNA analysis, of the study.

When applicable, during the study, participants must be re-consented to the most current version of the ICF(s).

10.2.4. Recruitment Strategy

In this Phase 4 study, potential participants will be identified by the investigators from their regular practice and database of patients in follow-up.

10.2.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant data that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects, including notification to appropriate authorities in accordance with applicable law.

10.2.6. Storage, Use, Transfer, and Retention of Data and Samples

- Study samples will be coded (or anonymized) at all times in accordance with the informed consent; no personal identifiers will be used.
- Investigator and study site will only store, use, transfer and retain data and (optional) study samples, in accordance with the informed consent, applicable law, and any written agreement with sponsor. Other than what is specified in this written agreement with sponsor, study site and investigator shall not conduct or facilitate any research not required by the protocol (i) on participants, or (ii) on samples or data collected from study participants during the study, if the research relates to amivantamab.
- Sponsor may store, use, transfer or retain the data and (optional) study samples, for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.
- The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer disks or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated or discontinued.
- If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.2.7. Committees Structure

There will be no DMC planned for this study.

10.2.8. Use of Information, Registration of Study and Publication

- All information, including but not limited to information regarding amivantamab, supplied by the sponsor to the study site or investigator and not previously published, and any data generated as a result of this study, are considered confidential and the sole property of the sponsor. Study site and investigator shall not use nor disclose this information except as needed for the conduct of the study, and then only on like terms of confidentiality and non-use.
- Study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between sponsor and study site or investigator.
- The Sponsor will register the study and publish the study results in compliance with applicable law. The disclosure of the study results will be performed after the end of study. The sponsor will generally support publication of multicenter studies only in their entirety.
- Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.

10.2.9. Data Quality Assurance, Monitoring and Audits

- Data quality will be ensured by selection of qualified investigators and study sites, review of protocol procedures and guidelines for eCRF completion with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor. Review and verification of eCRF data may occur, as appropriate.
- Written instructions will be provided for collection, handling, storage, and shipment of samples.
- The sponsor will use monitoring techniques such as remote, or on-site monitoring to monitor this study as frequently as necessary. It is expected that during remote contacts, study site personnel will be available to provide an update on the study.
- Representatives of the sponsor's clinical quality assurance department may conduct an on-site compliance visit to verify that the study is in compliance with regulatory guidelines and company policy. Study site personnel must be available for consultation. These audits will require access to all study records, including source documents. Participant privacy must, however, be respected.
- Similar compliance visit 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 must immediately notify the sponsor if they were contacted concerning such inspection.

10.2.10. Source Documents and Case Report Form Completion

- For each participant, the sponsor provides eCRFs in electronic format for recording, in English, of all data relating to the study by the investigator or authorized study site personnel. Worksheets, which are considered part of participant's source documents, may be used for the capture of some data to facilitate completion of the eCRF. The eCRF must be completed as soon as possible after a participant visit. The investigator must verify that all data entries in the eCRF are accurate and make corrections as appropriate. Study-specific data will be transmitted in a secure manner to the sponsor. If necessary, queries will be generated in the eDC tool.
- Source documents, on paper to be filed or using any eSource system to be maintained at the study site, provide evidence for the existence of the participant and substantiate the integrity of all study data collected, with at minimum the level of detail as commonly recorded at the study site.
- The author of an entry in the source documents must be identifiable.
- Specific details required as source data for the study and source data collection methods will be reviewed with the study staff before the study and will be described in the monitoring guidelines (or other equivalent document). This will include the list of any data recorded directly into the eCRF that will be considered source data.

10.2.11. Study and Site Start and Closure

Study Start Date is defined as the date the first participant is screened.

Study/Site 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.

10.3. Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE 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 on Harmonisation [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 AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.4.1, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU 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
- 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. This also includes the situation when treatment-invoked signs and symptoms of disease progression are determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease.

Note: Events that do not qualify as AEs cannot be reported as SAEs, even if seriousness conditions are met. This in particular is the case for events due to disease progression.

Expected signs or symptoms of disease progression should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

If a serious and unexpected AE 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 Suspected Unexpected Serious Adverse Reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

10.3.2. Attribution Definitions

Assessment of Causality

The causal relationship to study treatment is determined by the Investigator and documented in the Medical Records.

The assessment of causality must consider the following factors:

- Temporal relationship
- Clinical characteristics of event
- Pharmacological plausibility
- Confounding risk factors:
 - Concomitant medication
 - Underlying/concurrent disease
 - Family/social history
- Challenge:
 - De-challenge: Did the reaction improve when the investigational product was withdrawn, in the absence of any other treatment?
 - Re-challenge: What happens if participant is re-challenged with investigational product?
- Other considerations: Participant characteristics and past medical history, and quality of information

The following selection must be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE. Related events include those that are probably and possibly related events.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE. Not related events include those that are doubtfully related events.

10.3.3. Severity Criteria

Adverse event severity is a clinical determination of the intensity of an AE. The severity assessment for an AE or serious AE should be completed using the NCI-CTCAE, Version 5.0. Any AE or SAE not listed in the NCI-CTCAE, Version 5.0 will be graded according to the investigator clinical judgment by using the standard grades as follows:

- 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^a
- 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^b
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

^a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Self-care ADL refers to bathing; dressing and undressing; feeding self; using the toilet; taking medications; and not bedridden.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

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
- Reporting of participant pregnancy or participant partner(s) pregnancy

Participant-specific special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.3.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE 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 SAEs that have not resolved by the end of SAE reporting period, or that have not resolved upon the participant’s discontinuation from 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)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (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 eCRF). 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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the treatment period.

10.3.6. Product Quality Complaint Handling

Definition

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, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

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.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.3.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study 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 (Section 5.1). In case a pregnancy occurs while on study treatment, pregnancy information will be collected and reported as noted in Section 8.4.5.

Definitions

Participants of Childbearing Potential

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

Participants 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 FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or 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 participants on HRT, the participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish to continue HRT during the study.

- **permanent absence of reproductive potential (for the purpose of this study)**

- Has undergone a procedure that precludes reproductive potential.
- Has a congenital abnormality that precludes reproductive potential.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant becomes sexually active where pregnancy can occur), a 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 participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

If applicable, study participants should be counselled about donation and cryopreservation of gametes prior to starting study treatment.

Examples of Contraceptives

EXAMPLES OF HIGHLY EFFECTIVE METHODS OF CONTRACEPTIVES^a:
USER INDEPENDENT Highly Effective Methods^a
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)

• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner (<i>vasectomized or due to medical cause</i>) (<i>Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.</i>)
USER DEPENDENT Highly Effective Methods^a
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b: oral, injectable, transdermal or intravaginal
• Progestogen-only hormone contraception associated with inhibition of ovulation^b: oral or injectable
• Sexual abstinence from intercourse where pregnancy could occur (<i>Sexual abstinence is considered a highly effective method only if defined as refraining from sexual intercourse where the possibility of pregnancy exists during the entire period of risk associated with exposure to the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.</i>)
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of $\geq 1\%$ per year)^a
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Condom with or without spermicide (don't use multiple condoms together because of risk for failure due to friction)
• Cap, diaphragm, or sponge with spermicide
• A combination of external condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a. Highly Effective Methods have a failure rate of $<1\%$ per year when used consistently and correctly. 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. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study treatment. A participant using oral contraceptives must use an additional contraceptive method.

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

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](#)).

10.6. Appendix 6: New York Heart Association Criteria

The following table presents the NYHA 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 <https://professional.heart.org/en/guidelines-and-statements/classification>. Assessed on 27 October 2025.

10.7. Appendix 7: 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
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or known hepatotoxins
- Record alcohol use in the eCRF
- 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, 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, 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.

10.8. Appendix 8: Study Conduct During Major Disruptions Due to Disasters and Public Health Emergencies

It is recognized that major disruptions may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

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 travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study treatment will be followed.

If, as a result of the major disruption scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatments and withdrawal from the study should be documented with the prefix "Major Disruption-related" in the eCRF.

NATURAL DISASTER/MAJOR DISRUPTION (eg, regional crisis): 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. Modifications made to the study conduct as a result of the major disruption should be summarized in the clinical study report.

PANDEMIC (eg, COVID-19): If the participant has tested positive for the pandemic related disease the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study treatment, performing study assessments, and follow-up. Modifications made to the study conduct as a result of the pandemic (eg, COVID-19) should be summarized in the clinical study report.

Consent/Screening

- Consenting of participants for study screening can be performed remotely by telephone or video conferencing per local policies and regulations. Re-consenting of active participants due to new safety information or updated study design should also be assessed for its feasibility to be conducted remotely per local policies and regulations.

- 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 exposure to a pandemic (eg, COVID-19) and local travel restrictions due to a natural disaster or major disruption. the situation suggests that this is not possible, the participant may be screen failed and rescreened when conditions improve.
- Screening procedures to a pandemic (eg, COVID-19) 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 study treatment, particularly given its association with the risk of severe viral pneumonia. Per the study exclusion criteria, participants with active infection should be excluded from study participation.
- Study Treatment
- Study treatment 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 natural disaster, major disruption or pandemic-related circumstances, these deviations should be noted in the appropriate eCRF page, as "missed or delayed due to natural disaster/major disruption/pandemic", as applicable. The sponsor's medical monitor should be alerted to any anticipated interruption in study treatment.
- 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. The latest official guidance (eg, United States Food and Drug Administration, American Society of Clinical Oncology, European Society of Medical Oncology) should be followed and treatment decisions should be made in consultation with the medical monitor. 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. Report the event to the sponsor, following usual AE reporting requirements.

Note: Administration of non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed before or during this study.

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 with the protocol, unless natural disaster, major disruption, or pandemic (eg, 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).
- 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 participant 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 when 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 AEs and concomitant medications between regularly scheduled on-site visits (eg, weekly assessments of AEs leading to treatment delay).
- 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 judgment should be conducted by the investigator.

Monitoring Visits

When on-site monitoring by the sponsor is not feasible due to changes in hospital or clinic 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 a natural disaster, major disruption, or 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.

10.9. Appendix 9: Allowed Recent Second or Prior MalignanciesNot allowed second or prior malignancies:

- i. Any ongoing myelodysplastic syndrome or B-cell malignancy (other than multiple myeloma)
- ii. Any history of malignancy, other than multiple myeloma, which is considered at high risk of recurrence requiring systemic therapy

Allowed Recent Second or Prior Malignancies

- i. Any malignancy that was not progressing nor requiring treatment change in the last 12 months and not considered at high risk of recurrence requiring systemic therapy.
- ii. Malignancies treated within the last 12 months and considered at very low risk for recurrence:
 - a) Non-muscle invasive bladder cancer (solitary Ta-PUNLMP or low-grade, <3 cm, no CIS).
 - b) Skin cancer (non-melanoma or melanoma).
 - c) Non-invasive cervical cancer.
 - d) Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, localized breast cancer and receiving antihormonal agents.
 - e) Localized prostate cancer (M0, N0) with a Gleason Score $\leq 7a$, treated locally only (RP/RT/focal treatment).
- iii. Other malignancy that is considered at minimal risk of recurrence.

In the event of any questions, consult with the sponsor's medical monitor prior to enrolling a participant.

10.10. Appendix 10: Cytokine Release Syndrome – Severity Grading and Management

ASTCT CRS Consensus Grading				
CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever^a	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
	With			
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
	And/Or ^b			
Hypoxia	None	Requiring low-flow nasal cannula ^c or blow-by	Requiring high-flow nasal cannula ^c , facemask, nonbreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BIPAP, intubation, and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading

- Fever is defined as temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In participants who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
- CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C , hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.
- Low-flow nasal cannula is defined as oxygen delivered at $\leq 6\text{L/minute}$. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at $>6\text{L/minute}$.

Source: (Lee 2019)

High-dose Vasopressors ^b	
Pressor	Dose
Norepinephrine monotherapy	$\geq 20\text{ }\mu\text{g/min}$
Dopamine monotherapy	$\geq 10\text{ }\mu\text{g/kg/min}$
Phenylephrine monotherapy	$\geq 200\text{ }\mu\text{g/min}$
Epinephrine monotherapy	$\geq 10\text{ }\mu\text{g/min}$
If on vasopressin	Vasopressin + norepinephrine equivalent of $\geq 10\text{ }\mu\text{g/min}^{\text{a}}$
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of $\geq 20\text{ }\mu\text{g/min}^{\text{a}}$

- VASST Trial vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine ($\mu\text{g/min}$)] + [dopamine ($\mu\text{g/kg/min}$) $\div 2$] + [epinephrine ($\mu\text{g/min}$)] + [phenylephrine ($\mu\text{g/min}$) $\div 10$]
- All doses are required for ≥ 3 hours.

Source: (Lee 2014)

10.11. Appendix 11: Formulas for Estimating Glomerular Filtration Rate Using Modified Diet in Renal Disease Formula (in mL/min)

For standardized serum creatinine (S_{Cr}) in **mg/dL**, the estimated glomerular filtration rate (eGFR) in **mL/min** is:

$$eGFR = 175 \times S_{Cr} (mg/dL)^{-1.154} \times age (years)^{-0.203} \times 1.212_{if \text{ black}} \times 0.742_{if \text{ female}} \times \frac{BSA (m^2)}{1.73}$$

Body surface area (BSA) is estimated based on height and weight ([Mosteller 1987](#)):

$$BSA (m^2) = \sqrt{\frac{height (cm) \times weight (kg)}{3600}}$$

If creatinine levels are given in $\mu\text{mol/L}$, the equation above can be used after converting the creatinine level to mg/dL:

$$creatinine (mg/dL) = \frac{creatinine (\mu\text{mol/L})}{88.4}$$

Alternatively, for standardized serum creatinine (S_{Cr}) in **$\mu\text{mol/L}$** , the eGFR in **mL/min** is:

$$eGFR = 30849 \times S_{Cr} (\mu\text{mol/L})^{-1.154} \times age (years)^{-0.203} \times 1.212_{if \text{ black}} \times 0.742_{if \text{ female}} \times \frac{BSA (m^2)}{1.73}$$

NOTES:

- Renal clearance of a drug is proportional to individual GFR (expressed in **mL/min**) and not BSA-standardized GFR ($\text{mL/min}/1.73\text{m}^2$).
- The formulas above for the calculation of eGFR are based on MDRD ([Levey 2006](#)) but have been adapted to estimate GFR in **mL/min** ([FDA 2020](#)).
- Serum creatinine values must be standardized: creatinine assay calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure (this is the case for most assays).

10.12. Appendix 12: Medications With Potential for QT Interval Prolongation

Although amivantamab has not shown liability for QT prolongation, the following drugs are known to or may possibly prolong QT interval or induce Torsades de Pointes and should be used with caution for any participant in this study. This list is not meant to be exhaustive, and similar restrictions should be applied to other drugs known to prolong QT interval or induce Torsades de Pointes. Appropriate medical judgment is required.

Medications known to prolong QT interval or induce Torsades de Pointes
anagrelide, ciprofloxacin, clarithromycin, cocaine (only medical use), domperidone, droperidol, erythromycin, ibutilide, levofloxacin, ondansetron, papaverine HCl (intra- coronary), procainamide, quinidine, sulpiride, sultopride, terlipressin, thioridazine
chlorpromazine, cilostazol, disopyramide, dofetilide, dronedarone, ibogaine, levosulpiride, moxifloxacin, sotalol
citalopram, escitalopram, flecainide, fluconazole, levomepromazine (ethotrimeprazine), roxithromycin, sevoflurane
methadone, pimozide, terodiline
azithromycin, donepezil, propofol
halofantrine, pentamidine
haloperidol
amiodarone, chloroquine

Medications that may prolong QT interval or induce Torsades de pointes

apomorphine, benperidol, clotiapine, dexmedetomidine, dolasetron, eliglustat, encorafenib, gemifloxacin, granisetron, hydrocodone-ER, isradipine, melperone, nicardipine, ofloxacin, oxytocin, perflutren lipid microspheres, pilsicainide, primaquine phosphate, prothipendyl, risperidone, saquinavir, telavancin, tetrabenazine, tiapride, tolterodine, tramadol, tropisetron, vardenafil
alfuzosin, clozapine, cyamemazine (cyamemazine), deutetrabenazine, dextromethorphan/quinidine, ezogabine (retigabine), lacidipine, lopinavir/ritonavir, mifepristone, moexipril/HCTZ, pasireotide, perphenazine, promethazine, telithromycin, venlafaxine
asenapine, atomoxetine, betrixaban, felbamate, imipramine (melipramine), ketanserin, nortriptyline, paliperidone, pipamperone, trimipramine, valbenazine, zotepine, zuclopenthixol (oral)
buprenorphine, delamanid, desipramine, iloperidone, lithium, maprotiline, mirabegron, mirtazapine, palonosetron, rilpivirine, tacrolimus, tizanidine
aripiprazole, clomipramine, efavirenz, memantine
artemether/lumefantrine, sertindole
fingolimod, flupentixol, pimavanserin
zuclopenthixol (IM injection)
artenimol/piperaquine
clofazimine
nusinersen
bedaquiline

10.13. Appendix 13: Hepatitis B Virus Screening

The following hepatitis B virus screening guide is to be used to determine participant eligibility (see Section 5.2) for the study:

- Individuals who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) **are eligible** for this protocol.
- Individuals who test **negative** for surface antigen (HBsAg-) and **positive** for core antibody (anti-HBc+) **and either positive or negative** for surface antibody (anti-HBs+ or anti-HBs-) **must undergo further testing for the presence of HBV DNA.**
 - If the HBV DNA test is **negative**, the participant is eligible for this protocol. However, testing for the presence of HBV DNA should be performed every 3 months in addition to the ALT/AST laboratories according to the SoA while receiving study treatment until EOT. HBV DNA should be continued every 3 months along with ALT/AST monthly in the follow up period, if one exists, up to 12 months or before the start of new anticancer treatment. If there is evidence of HBV reactivation, hold study treatment, if applicable, and initiate treatment for HBV infection as appropriate per institutional guidance.
 - If the HBV DNA test is **positive**, the individual is **NOT eligible** for this protocol. In the event the HBV DNA test cannot be performed, the individual is **NOT eligible** for this protocol.
- Individuals who test **positive only** for **surface antibody** (anti-HBs+) and have a known history of prior HBV vaccination **are eligible** for this protocol.
- Individuals who test **positive** for surface antigen (HBsAg+) **are NOT eligible** for this protocol, regardless of the results of other hepatitis B tests.

Eligibility Based on Hepatitis B Virus Test Results				
Hepatitis B test result				
Action	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)	Hepatitis B core antibody (anti-HBc total)	Hepatitis B DNA
Exclude	positive	negative <i>or</i> positive	negative <i>or</i> positive	NA
	negative	negative <i>or</i> positive	positive	positive
Include	negative	negative	negative	NA
	negative	negative <i>or</i> positive	positive	negative
	negative	positive	negative	NA

NA: Not applicable or no need to test. A negative test (or antibodies/DNA below the level of quantification) is denoted as “negative”; a positive test (or presence of antibodies/DNA above laboratory thresholds) is denoted as “positive”.

Modified from source: <https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf>. Accessed 11 March 2020.

10.14. Appendix 14: Anticipated Events

Definition of an Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs, independent of exposure to study treatment, as a consequence of (a) the underlying disease or condition under investigation, (b) characteristics of the study population (eg, age), or (c) the background treatment regimen.

Analysis and Reporting of Anticipated Events

All AEs and SAEs will be recorded and reported by the investigator to the sponsor as described in [Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting](#).

Anticipated Events for the Study

The below list includes adverse events that are commonly anticipated for the disease stage, study population and background treatment, for which the Sponsor does not plan to report individual cases, regardless of the assessment of causality. This list is limited to those events for which an individual occurrence, or even an aggregate incidence consistent with the background rate in the study population, is inconsequential in the developing safety profile of the study treatment.

For the purposes of this study, the following events will be considered anticipated events:

Constitutional	Cardiovascular
Dehydration	Superior vena cava syndrome
Sepsis	Pericardial effusion
Weakness/asthenia	Cardiac tamponade (associated with pericardial metastasis)
Fatigue	Myocardial infarction
Fever/pyrexia	Stroke
Weight loss	
Failure to thrive	Gastrointestinal
Decreased appetite/anorexia	Dysphagia
General physical health deterioration	Esophageal obstruction
	Intestinal obstruction
Respiratory	Bleeding ulcers
Pneumonia	Diverticulitis
Upper respiratory infection	
Lower lung infection	Musculoskeletal (associated with metastatic or advanced disease)
Hypoxia	Pain
Dyspnea	Fracture (pathologic fracture)
Bronchitis	

Emphysema	Hematologic
Chronic obstructive pulmonary disease exacerbation	Thromboembolic events – deep vein thromboses, pulmonary emboli
Malignant pleural effusion	Anemia
Cough	Neurologic (associated with metastatic or advanced disease)
Empyema	Cranial nerve palsies
Pulmonary emboli	Weakness of upper, lower extremities
Respiratory failure	Confusion
Pneumothorax	Mental status changes
Hemoptysis	Seizures
Radiation pneumonitis	Unstable gait
	Spinal cord compression

10.15. Appendix 15: Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

	RECIST 1.1
Measurable Tumor Burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥10 mm in longest diameter (LD) and 2X the slice thickness for extranodal lesions. ≥15 mm in short axis diameter (SAD) for nodal lesions. ≥10 mm in LD for clinical lesions (must be measured using electronic calipers). ≥20 mm in LD for chest x-ray (if clearly defined and surrounded by aerated lung); CT is preferable. Ultrasound (US) cannot be used to measure lesions.
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SAD. To be measurable, nodal lesions must be ≥15 mm in SAD. Nodal lesions with SAD >10 mm and <15 mm are non-measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.
Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emission therapy (PET) or plain films are non-measurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Non-cystic lesions are preferable.
Lesions with Prior Local Treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy.
Too Small To Measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions That Split or Coalesce	If extranodal target lesions fragment, the LDs of the fragmented portions are added to calculate the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of Complete Response (CR)	CR requires the disappearance of all extranodal lesions, the regression of all nodal lesions to <10 mm SAD and the normalization of tumor marker level.
Definition of Progressive Disease (PD)	PD is assessed if the sum of the diameters has increased by ≥20% and ≥5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.
Assessment of New Lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (ie, 'new' bone lesions may be healing or flare of pre-existing lesions). If on is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET:(-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to preexisting lesion on CT that is not progressing; not PD.

Recurrence of Lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall Response	One overall response table integrates target, non-target and new lesions and another table integrates non-target and new lesions for the assessment of subjects without measurable disease.
Confirmation of Response	Confirmation of PR/CR is ONLY required for non-randomized trials where response is the primary endpoint. In these trials, subsequent confirmation of PR with one interim timepoint of SD is acceptable.

Source: ([Eisenhauer 2009](#)).

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.

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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): Dr. Nishita ShahInstitution: Johnson & Johnson Private LimitedSignature: electronic signature appended at the end of the protocol Date: _____

(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.