Janssen Research & Development *

Clinical Protocol

A Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy

PALOMA-3

Protocol 61186372NSC3004; Phase 3
Version: Amendment 5

JNJ-61186372 (amivantamab) and JNJ-73841937 (lazertinib)

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Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).
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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 5	31 May 2024
Amendment 4	21-Nov-2023
Amendment 3	11-Aug-2023
Amendment 2	27-Oct-2022
Amendment 1	25-Aug-2022
Original Protocol	12-Apr-2022

Amendment 5 (31 May 2024)

Overall Rationale for the Amendment:

To continue providing participants access to study treatment and collect data of clinical relevance/importance while reducing the burden on participants after the primary analysis by adding an long-term extension (LTE) phase to the study.

Changes related to the transition to the European Union (EU)/European Economic Area (EEA) Clinical Trial Regulations (CTR) have also been added to the protocol.

The changes made to the clinical protocol 61186372NSC3004 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.16.

Section Number and Name	Description of Change	Brief Rationale
Title Page	Added text on EU regulation and EU Trial number.	To comply with the EU CTR requirements.
1.1. Synopsis	The Investigational New Drug Application (IND) number, European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) number, and EU Trial number were added.	To comply with the EU CTR requirements.
1.1. Synopsis (Benefit-Risk Assessment) (new section)	A summary of the benefit-risk assessment for the study was added.	To comply with the EU CTR requirements.
1.2. Schema	Updated the study schematic to include the LTE Phase.	To add the LTE Phase to the overall study design.
1.1. Synopsis (Study Design) 4.1.4. Long-term Extension Phase	A description of the LTE Phase was added, with cross-references to the newly added appendix.	To add the LTE Phase to the overall study design.
1.3.1. Schedule of Activities (SoA): Table 1	Added text to the title to indicate that the Schedule of Activities for the LTE Phase is provided in Table 13.	To distinguish the Schedules of Activities in the main study from that in the LTE Phase.
1.3.3. Schedule of Activities for the Long-term Extension Phase	New section added for the study procedures for the LTE Phase.	To add the LTE Phase to the overall study design.
5.4. Screen Failures	Added text related to Interactive Web Response System (IWRS) to align with the sponsor template.	To clarify the use of IWRS.
6.1. Study Treatments Administered	Added a new table categorizing the study treatments as Investigational Medicinal Products (IMPs) or Non-Investigational	To comply with the EU CTR requirements.

	Medicinal Products (NIMPs)/Auxiliary Medicinal Products (AxMPs).	
6.6. Continued Access to Study Treatment After the End of the Study	Text referring to the LTE Phase was added.	For guidance on details related to continued access to study treatment for participants who are still benefiting from study treatment.
10.2.4. Recruitment Strategy	New section added to describe the recruitment strategy.	To comply with the EU CTR requirements.
10.2.14. Record Retention	Added text regarding record retention under EU regulation.	To comply with the EU CTR requirements.
10.15. Appendix 15: Long-term Extension Phase (new appendix)	The study design was modified to include a new study phase (an LTE Phase), whose purpose is to continue providing participants access to study treatment while further reducing the burden on participants.	To provide detailed information on study conduct during the LTE Phase.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

IND: 146319
EudraCT NUMBER: 2022-000525-25

EU TRIAL NUMBER: 2024-512045-16
A Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy.

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (cMET) tyrosine kinase receptor that is being developed for the treatment of solid tumors, including EGFR-mutated non-small cell lung cancer (NSCLC). Amivantamab administered intravenously is conditionally approved by the FDA for patients with EGFR Exon 20ins mutations after treatment with chemotherapy.

In this study subcutaneous amivantamab will be administered as a co-formulation with recombinant human hyaluronidase (rHuPH20). This combination will be designated as amivantamab subcutaneous and co-formulated with recombinant human hyaluronidase (SC-CF) throughout the protocol.

This is a Phase 3, open-label, randomized study to demonstrate the pharmacokinetic noninferiority of amivantamab SC-CF administered via manual injection compared with amivantamab IV, both in combination with lazertinib.

Lazertinib (JNJ-73841937) is an oral, highly potent, third-generation, irreversible EGFR tyrosine kinase inhibitor (TKI) with no demonstrated pharmacokinetic (PK) interaction with amivantamab. It selectively inhibits both activating EGFR mutations (Exon 19del, L858R) and the EGFR T790M resistance mutation while showing mutant-selective activity for EGFR.

BENEFIT-RISK ASSESSMENT

The safety and tolerability of amivantamab and lazertinib in combination has been investigated in several studies.

This study protocol includes elements to mitigate unforeseen safety risks for study participants. In addition to monitoring participants closely for safety throughout the study, an Independent Data Monitoring Committee (IDMC) will be commissioned to review efficacy, safety and tolerability data periodically. Dose modification guidance is also provided to manage toxicities that occur during the study.

Amivantamab, lazertinib, and the combination have each demonstrated activity in patients with locally advanced or metastatic NSCLC with EGFR mutations. Amivantamab, as a monotherapy or in combination with lazertinib, has demonstrated activity in the osimertinib-relapsed setting. It is anticipated that lazertinib will have similar benefits to osimertinib, and that combining the targeted therapies, amivantamab and lazertinib, will be more effective than either targeted monotherapy for the treatment of NSCLC with EGFR Exon 19del or L858R mutations, by delaying or preventing the emergence of resistance to third generation TKI therapy mediated by either the EGFR or cMET pathways.

Taking into account the measures taken to minimize risk to participants of this study, the possible risks identified in association with amivantamab and lazertinib are justified by the anticipated benefits that may be afforded to participants, locally advanced or metastatic NSCLC with EGFR Exon 19del or Exon21 L858R mutations.

OBJECTIVES AND ENDPOINTS

The primary objective is to assess the pharmacokinetic noninferiority of amivantamab SC-CF via manual injection versus amivantamab IV. Key secondary objectives are to assess efficacy (objective response rate [ORR] and progression-free survival [PFS]) and safety of the different administrations.

Exploratory objectives are described in Section 3.

Hypotheses

The primary hypothesis of the study is that amivantamab SC-CF, administered via manual injection at the SC recommended Phase 2 dose (RP2D), exhibits a PK profile that is noninferior to amivantamab administered at the IV recommended dose in participants with locally advanced or metastatic NSCLC with EGFR Exon 19del or Exon 21 L858R mutations whose disease has progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy.

OVERALL DESIGN

Study 61186372NSC3004 (PALOMA-3) is a randomized, open-label, parallel, multicenter, Phase 3 study, which will optimize the administration of amivantamab in participants with EGFR mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy. The study will compare the PK, efficacy, and safety of combining lazertinib with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B).

The study will include Screening (up to 28 days), a Treatment Phase (from randomization until the End of Treatment Visit), and a Follow-up Phase (from End of Treatment Visit until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first).

Participants who continue to benefit from study treatment(s), as determined by their investigator, after completion of the primary analysis may continue to receive access to study treatment(s) within the study by transferring to the long-term extension (LTE) Phase, where only serious adverse event data and the study treatment compliance will be collected. The LTE Phase will continue to provide participants access to study treatment and further reduce protocol-required visit procedures and assessments, after the primary analysis is complete.

The LTE Phase will begin after the primary analysis, and will continue until the discontinuation criteria are met, or until 3 years after local marketing authorization is obtained, whichever occurs first. For transition to the LTE Phase (after the primary analysis), notification from the sponsor will be provided.

NUMBER OF PARTICIPANTS

A target of 400 participants will be enrolled in this study and will be randomized 1:1 between Arms A and B. Randomization will be stratified by brain metastases at baseline (yes vs no), EGFR mutation (L858R vs Exon19del), race (Asian vs non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] vs chemotherapy).

TREATMENT

All participants will receive lazertinib 240 mg orally once daily.

In Cycle 1:

- Amivantamab SC-CF by manual injection, doses at 1,600 mg (2,240 mg if body weight (BW) ≥80 kg) will occur on Days 1, 8, 15, and 22, or
- Amivantamab IV infusion doses at 1,050 mg (1,400 mg if BW ≥80 kg) will occur on Days 1--2 (split dose), 8, 15, and 22.

Starting in Cycle 2, doses will occur on Day 1 and 15 of each 28-day cycle, as one of the following:

- amivantamab SC-CF by manual injection at 1,600 mg (2,240 mg if BW ≥80 kg), or
- amivantamab by IV infusion at 1,050 mg (1,400 mg if BW ≥80 kg)

EFFICACY EVALUATIONS

Disease assessment will be performed using CT, MRI, and other imaging/examination, as applicable, of the chest, abdomen, pelvis, brain, and any other known disease location at Screening, 6 (+1) weeks from randomization, every 6 (±1) weeks for the first 18 months, then every 12 (±1) weeks thereafter until progressive disease (PD). Tumor response will be assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected from participants to assess the serum concentration of amivantamab and the plasma concentration of lazertinib. Samples will be analyzed using a validated method by or under the supervision of the sponsor. Serum and plasma PK samples may be stored for future analysis.

IMMUNOGENICITY EVALUATIONS

Blood samples will be collected to assess the generation of antibodies to amivantamab and to rHuPH20.

EASE OF USE AND SATISFACTION QUESTIONNAIRE

For all participants, health care professionals (HCPs) will evaluate the administration of the therapy with an Ease of Use and Satisfaction Questionnaire.

PATIENT-REPORTED OUTCOMES

Cancer therapy satisfaction in participants will be assessed using the modified Therapy Administration Satisfaction Questionnaire (TASQ).

MEDICAL RESOURCE UTILIZATION

Time and motion studies will evaluate participant chair time, treatment room time, duration of treatment administration, and active HCP time for drug preparation, treatment administration, and post-treatment monitoring.

SAFETY EVALUATIONS

Safety will be assessed by physical examinations, vital signs, electrocardiograms, echocardiograms, ophthalmologic assessments, laboratory tests, AE frequency and severity (by Common Terminology Criteria for Adverse Events (CTCAE) v5.0) monitoring, and concomitant medication use.

BIOMARKER EVALUATIONS

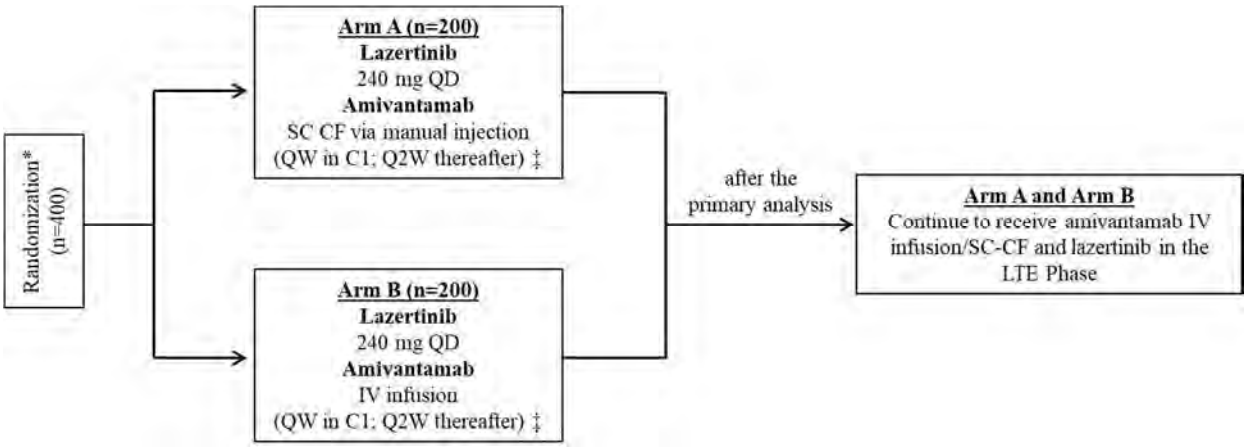
Blood samples collected from participants will undergo circulating tumor deoxyribonucleic acid (ctDNA) analysis by the sponsor to evaluate pretreatment mutational status of EGFR, cMET, and other key oncogenes to characterize the tumor. Blood samples will also be collected for potential analysis of circulating biomarkers (eg, cytokines, growth factors) in samples taken before and after exposure to study treatment(s). Additional biomarkers (eg, DNA, RNA, and protein) relevant to cancer and/or metabolism of study treatments may also be assessed.

STATISTICAL METHODS

The study is designed to establish noninferiority based on the co-primary pharmacokinetic endpoints, C_{trough} of amivantamab (at steady state [Cycle 4 Day 1] for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and $AUC_{D1\text{-}D15}$ in Cycle 2, between amivantamab SC-CF and amivantamab IV. Amivantamab SC-CF will be considered noninferior to IV if the lower bound of the 90% CI for the ratio of the geometric means of C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and $AUC_{D1\text{-}D15}$ in Cycle 2 is at least 80% (noninferiority margin of 20%). The planned 400 participants (200 from Arm A and 200 from Arm B) will provide a power >95% for a one-sided alpha of 0.05 for each of the endpoints. This assumes a true geometric mean ratio of C_{trough} to be 1 and a true geometric mean ratio of the $AUC_{D1\text{-}D15}$ to be 1 between the 2 treatment groups, and a coefficient of variation (CV) of 56% for both endpoints.

1.2. Schema

Figure 1: Schematic Overview of the Study



C#=Cycle #; CF=co-formulation; IV=intravenous; LTE= long-term extension; QD=once daily; QW=once weekly; Q2W=every 2 weeks; SC=subcutaneous.

NOTE: Stratification factors for randomization: brain metastases at baseline (yes vs no), EGFR mutation (L858R vs Exon19del), race (Asian vs non-Asian), last therapy (osimertinib [or another approved 3rd generation EGFR TKI] vs chemotherapy).

‡ Cycle 1 for IV: Days 1-2 (Day 2 applies to IV split dose only), 8, 15, and 22; Cycle 1 for SC: Days 1, 8, 15, and 22; Cycle 2 for all: Days 1, 15

* The 400 participants will be randomized between Arms A and B.

1.3. Schedule of Activities (SoA)

Tables reflecting the Schedule of Activities are presented in this section, including sample collection schedules for PK and immunogenicity.

Dose schedules and pretreatment medications are presented in Section 6.1.

1.3.1. Schedule of Activities

Table 1: Schedule of Activities

For Long-Term Extension (LTE) phase, refer to Table 13

	Screening	Treatment (28 days/cycle)																EoT	Follow-up (visit/call[a])
Cycle		1					2							3		4+			
Day	-28 to -1	1	2[b]	8	15	22	1	2	3	4	5	8	15	1	15	1	15	30 days after last dose	Q12W after last dose or PD
Visit Window (days)		0	0	±1	±1	±1	±1	0	0	0	0	±1	±1	±3	±3	±3	±3	+7	±14
Study Procedure																			
In Arm A, amivantamab SC-CF is administered in Cycle 1 on Days 1, 8, 15, and 22 and in subsequent Cycles on Day 1 and 15 of each 28-day cycle. In Arm B, amivantamab IV is administered in Cycle 1 on Days 1-2 (split dose), 8, 15, and 22 and in subsequent Cycles on Day 1 and 15 of each 28-day cycle. Assessments during in-clinic dosing days should be performed prior to administration of study treatment unless otherwise stated. During Cycle 2, if a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule (except disease assessments) should be delayed accordingly to ensure sampling relative to amivantamab dose administration, which would trigger the start of the next cycle. Follow-up assessments will be conducted until the end of study unless the participant has died, is lost to follow up, or has withdrawn consent; see Section 7.2.																		
Screening/ Administrative																			
Informed consent	X																		
Demographics, disease characteristics, medical history	X																		
Inclusion/ exclusion criteria[c]	X	X																	
ECOG performance status	X	X																	
Serology (HIV, HBV, HCV)[d]	X	As clinically indicated.																	
Coagulation	X	As clinically indicated.																	
Urinalysis	X	As clinically indicated.																	
Pregnancy (serum or urine test; FOCBP only)[e]	X	X					X							X		X		X	X (monthly through 7 months after last dose)
Ophthalmologic examination[f]	X	As clinically indicated.																	
Safety Assessments																			
Physical examination[g]	X	As clinically indicated.																	
Vital signs[h]	X	X	X[b]	X	X	X	X						X	X	X	X	X	X	
12-lead ECG[i]	X	As clinically indicated.																	
ECHO or MUGA	X	As clinically indicated.																	
Prophylactic-dose anticoagulation[t]		Recommended during the first 4 months of treatment for participants receiving the combination of amivantamab and lazertinib																	
Clinical Laboratory Tests																			
Hematology, chemistry (<72 hrs predose)	X	X	X[b]	X	X	X	X						X	X	X	X	X	X	
Efficacy Assessments																			
CT/MRI tumor imaging[j]	X	Disease assessment of the chest, abdomen, pelvis, and any other disease location 6 weeks (+1 week) from randomization, every 6 weeks (±1 week) for the first 18 months, then every 12 weeks (±1 week) thereafter. Imaging obtained as part of standard care before signing the ICF, but within 28 days of randomization, may be used for the screening assessment if parameters meet the imaging manual requirements.																	
Brain MRI	X	Expected every 6 weeks if brain mets are present at baseline and being followed as non-target lesions and if no brain mets at baseline, only as clinically indicated.																	

Table 1: Schedule of Activities

For Long-Term Extension (LTE) phase, refer to Table 13

	Screening	Treatment (28 days/cycle)																EoT	Follow-up (visit/call[a])
Cycle		1					2							3		4+			
Day	-28 to -1	1	2[b]	8	15	22	1	2	3	4	5	8	15	1	15	1	15	30 days after last dose	Q12W after last dose or PD
Visit Window (days)		0	0	±1	±1	±1	±1	0	0	0	0	±1	±1	±3	±3	±3	±3	+7	±14
Study Procedure																			
Survival/ disease status																			X
Next anticancer therapy(ies)[k]																			X
Randomization and Study Treatment Administration																			
Randomization[l]		X																	
Amivantamab administration[s,t]		X	X[b]	X	X	X	X						X	X	X	X	X		
Lazertinib administration		On infusion or injection days, lazertinib should be taken more than 15 minutes prior to premedication for amivantamab initiation and then at approximately the same time each day, with or without food.																	
Record lazertinib adherence		X					X							X		X			
PROs																			
Modified TASQ[m]		X	X[b]											X				X	
PGIS[m]		X												X				X	
PGIC[m]				X										X				X	
Medical Resource Utilization																			
Time and motion study[q]		X												X					
Health Care Professional Questionnaire																			
Ease of Use and Satisfaction Questionnaire for all participants (Section 10.11)[r]							X												
Clinical Pharmacology, Biomarkers, and Pharmacogenomics																			
ctDNA blood sample collection[n] (Predose (<-2 hr))		X																X[n]	
Blood samples for exploratory biomarkers (Predose (<-2 hr))		X					X							X		X[u]			
PK and immunogenicity blood sample collection (see Table 2 for details)		X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X[v]	X	X	
Ongoing Participant Review																			
Prior & concomitant medications	X[o]																		
AEs[p]	X																		

Samples will be analyzed and kept within the country/territory in regions where there is such a requirement by applicable laws and regulations.

AE=adverse event; C=cycle; CT=computed tomography; CxDy=Cycle x, Day y; D=day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; hr(s)=hour(s); ICF=informed consent form; IV=intravenous; min=minute(s); MRI=magnetic resonance imaging; MUGA= multigated acquisition; NA=not applicable; PD=disease progression; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic(s); PRO=patient-reported outcome; Q12W=every 12 weeks; SAE=serious adverse event; TASQ=Therapy Administration Satisfaction Questionnaire; FOCBP=females of childbearing potential.

a. Participants for whom there is no safety concern may have telehealth (conducted via phone or video conference) visits.

b. The C1D2 Visit and all of the activities shown for that day only apply to participants randomized to Arm B, ie, those who will receive IV amivantamab split dose over Cycle 1 Day 1 and 2.
c. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. A copy of the initial test report documenting the EGFR mutation must be included in the participant records and a deidentified copy must also be submitted to the sponsor.
d. HIV, HBV and HCV (all participants). HIV viral load and CD4 count for known HIV-positive participants only.
e. Serum test required at Screening; urine test may be used at all other times. Test within 72 hrs before Day 1 of each cycle or monthly, whichever is more frequent.
f. Including slit lamp examination, fundoscopic examination, and visual acuity test. See Section 8.2.6.
g. Symptom-directed PE as clinically indicated of involved organs and other body systems, with clinically significant abnormalities reported as AEs. Record weight on D1 of each cycle. See Section 8.2.1. Evaluate for early signs and symptoms of VTE. Focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed.
h. Heart rate, blood pressure, temperature, and O_2 saturation. See Section 8.2.3. For participants receiving IV amivantamab, collect vital sign measurements ≤30 minutes before amivantamab infusion, at 30-minute intervals (±5 minutes) during each amivantamab infusion, and at the end of the infusion (±5 minutes).
i. Single ECG at Screening. In case of abnormal results, confirm with triplicate ECG. See Section 8.2.4.
j. Continue until PD. For participants who discontinue treatment prior to PD, tumor imaging should continue until PD is documented. If participant begins a new anticancer therapy before PD, obtain tumor imaging before the new therapy. If a participant receives study treatment beyond confirmed documented PD, continue disease assessments as scheduled.
k. Collect information on type of therapy, start date, and stop date.
l. Start study treatment within 3 days of randomization.
m. Complete the PGIS before any tests or procedures. Complete the modified TASQ after study drug administration, and then complete the PGIC.
n. At EoT, blood sample within 30 days of PD; obtain before next anti-cancer therapy. If participant receives study treatment(s) beyond PD, collect additional samples at each post-progression disease assessment. If unable to collect during the disease evaluation visit, the sample may be collected at the next visit prior to subsequent study treatment administration.
o. Record all prescription and over-the-counter treatments administered up to 28 days before randomization through 30 days after the last dose of study treatment (or the start of a subsequent systemic anticancer therapy, if earlier); >30 days after the last dose of study treatment in conjunction with SAEs considered related to study treatment, until resolution of event or start of subsequent anticancer therapy. For participants with Grade 3 or 4 AEs considered related to study drug, record concomitant medications through the end of follow-up of that AE.
p. Continuous from the time ICF is signed through 30 days after last dose of study treatment (or >30 days for an SAE, if considered related to study treatment).
q. Time and motion studies will evaluate participant chair time, treatment room time, duration of treatment administration, and active HCP time for drug preparation, treatment administration, and post-treatment monitoring.
r. The questionnaire is to be filled out once per participant.
s. See Section 6 and the IPPI for study treatment administration instructions. A missed dose is defined as failure to administer study treatment within 1 day of the scheduled dosing date in Cycles 1 and 2, or failure to administer study treatment within 7 days of the scheduled dosing date in Cycle 3 and beyond. If a dose is missed, as defined above, it will not be made up. Administration may resume at the next planned dosing date.
t. Prophylactic-dose anticoagulation is recommended during the first 4 months of treatment. Refer to Section 6.5.3.10 for additional information. Refer to NCCN guidelines Version 1.2022 Cancer-Associated Venous Thromboembolic Disease, Section VTE-B for examples of prophylactic-dose anticoagulants in ambulatory cancer patients.
u. The exploratory biomarker sample is collected only on Day 1 of Cycles 1 to 4. No collection required for subsequent cycles.
v. PK samples are collected on Day 1 of Cycles 5, 7, 9, and 11 (see Table 2).

1.3.2. Collection Times for PK and Immunogenicity Samples

Table 2: Collection Times for PK and Immunogenicity Samples [a]

	Screening	Treatment (28 days/cycle)																EOT
Cycle		1					2							3		4		Cycles 5, 7, 9, 11	30 days after last dose
Day	-28 to -1	1	2	8	15	22	1	2[d]	3[d]	4[d]	5[d]	8[d]	15	1	15	1	15	1	
Visit Window (days)		NA	NA	±1	±1	±1	±1	NA	NA	NA	NA	±1	±1	±3	±3	±3	±3	±3	+7
Study Procedure																			
Lazertinib Plasma PK Samples																			
Lazertinib predose (<-2 hr)		X			X		X							X					
Lazertinib 2 hrs postdose (±15min)		X			X		X												
Lazertinib EOT																			X
Amivantamab Serum PK Samples - Arm B only[b]																			
Preinfusion (<-2 hrs)		X	X	X	X	X	X						X	X	X	X[e]	X	X	X
EOI (+10 min)[c]		X	X				X												
EOI +2 hrs (± 15min)[c]							X												
EOI +6 hrs (± 30min)[c]							X[d]												
EOI +24 hrs (± 1 hr)[c]								X											
EOI +48 hrs (± 2 hr)									X										
EOI+ 72 hrs (± 2 hr)										X									
EOI+ 168 hrs (± 1 day)												X							
Amivantamab Serum PK Samples - Arm A only[b]																			
Predose (<-2 hr)		X		X	X	X	X						X	X	X	X[e]	X	X	X
24 hrs postdose (± 1 hr)								X											
48 hrs postdose (± 2 hr)									X										
72 hrs postdose (± 2 hr)										X									
96 hrs postdose (± 2 hr)											X								
168 hrs postdose (± 1 day)												X							
Amivantamab Serum and rHuPH20 Plasma Immunogenicity Samples[b]																			
Predose (<-2 hr)		X					X							X		X		X	X

Samples will be analyzed and kept within the country/territory in regions where there is such a requirement by applicable laws and regulations.
EOI=end of infusion; EOT=end of treatment; hr(s)=hour(s); min=minute(s); NA=not applicable; PK=pharmacokinetic(s).

a. Sample collection and testing will comply with local regulations.
b. Separate blood draws are not required for amivantamab PK and immunogenicity when collected at the same time point. A separate blood draw is required for rHuPH20 plasma immunogenicity for Arm A participants only.
c. Within 24 hours of study treatment infusion, if the study treatment was infused peripherally, blood samples must be drawn from a vein contralateral to the arm into which Amivantamab was infused.
d. If on-site visit is not possible, the PK draw could be performed outside of the clinic, through a Sponsor-designated home health care vendor, if approved and allowed by local regulations and after requisite consultation with the medical monitor.

e. If Cycle 4 Day 1 dose is delayed or withheld, the amivantamab serum PK sample should be collected on the planned day per protocol. This collection will be considered an unscheduled serum PK sample.

1.3.3. Schedule of Activities for the Long-term Extension Phase

Refer to Table 13 for the study procedures for the LTE Phase.

2. INTRODUCTION

This is a Phase 3, open-label, randomized study to demonstrate the pharmacokinetic noninferiority of amivantamab SC-CF administered via manual injection compared with amivantamab IV. In this study, amivantamab will be administered in combination with orally administered lazertinib. This study will compare amivantamab IV versus amivantamab SC-CF via manual injection.

Amivantamab (JNJ-61186372) is a fully human, low-fucose, IgG1-based bispecific Ab directed against the EGFR and cMET receptor. Amivantamab shows activity against tumors with primary activating EGFR mutations (Exon 19 deletion [Exon 19del], Exon 21 leucine 858 to arginine substitution ([L858R], and Exon 20ins mutations), EGFR resistance mutations (tyrosine 790 to methionine [T790M] or cysteine 797 to serine [C797S] mutations), overexpressed wild type EGFR, and activation of the cMET pathway. Lazertinib is an oral, highly potent, mutant-selective, and irreversible third-generation EGFR TKI that targets both the Exon 19del and the Exon 21 L858R EGFR activating mutations, as well as the T790M resistance mutation. Lazertinib has demonstrated efficacy in participants with EGFR-mutated NSCLC, with activity observed in both systemic and central nervous system lesions, demonstrating its ability to cross the blood-brain barrier. Combining lazertinib, which targets the intracellular EGFR tyrosine kinase site, with amivantamab, which targets the extracellular EGFR ligand-binding domains, has the potential to more potently inhibit the EGFR signaling pathway, attenuate frequent EGFR dependent and independent resistance mechanisms to EGFR TKIs, and induce deeper responses than either agent alone.

For the most comprehensive nonclinical and clinical information regarding the combination of lazertinib with either amivantamab as monotherapy or in combination with chemotherapy, refer to the latest version of the IBs for amivantamab and lazertinib.

The term “study treatment” throughout the protocol, refers to amivantamab (JNJ-61186372) and/or lazertinib (JNJ-73841937) as defined in Section 6.1, Study Treatments Administered.

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.

2.1. Study Rationale

One of the most common side effects associated with amivantamab are IRRs, which were experienced by 64% of participants receiving amivantamab IV. The vast majority (97%) of IRRs occurred during the first infusion, with a median time to onset of 56 minutes. To mitigate the risk of IRRs, the initial dose of amivantamab is preceded by glucocorticoid premedication and is administered at reduced infusion rates, which requires splitting of the first dose over 2 days. Subsequent infusions within Cycle 1 occur at an increased rate, with maintenance doses (starting Cycle 2) administered over 2-hour infusions. These mitigations, which increase the time a patient spends in clinic, present a significant opportunity to improve both patient and health care provider experience with amivantamab.

To simplify amivantamab administration and reduce dose times, a new formulation of amivantamab, amivantamab SC-CF, is being developed in the ongoing Phase 1 PALOMA study for subcutaneous administration. This formulation has the potential to enhance both the patient and physician experience with amivantamab by providing easier and accelerated administration via manual injection.

This study is focused on participants with NSCLC with Exon 19 deletions and Exon 21 L858R mutations in EGFR who have progressed on or after both a third generation TKI and platinum based chemotherapy. Amivantamab in combination with lazertinib has demonstrated clinical activity in this patient population (Shu 2021). The rationale for conducting this study in this setting is based on 2 factors. First, previously-treated NSCLCs harboring an EGFR Exon 19del or Exon 21 L858R mutation represents a large patient population with profound unmet medical needs. Second, in order to identify the impact of changing amivantamab from an IV administration to a SC route of administration, the ideal clinical setting is one where amivantamab is anticipated to be the major contributor to the observed anti-tumor activity. Among patients who have already experienced disease progression on the third generation EGFR TKI osimertinib (or another approved 3rd generation EGFR TKI), it is unlikely that the third-generation EGFR TKI lazertinib alone would have significant activity. Therefore, the ORR in this setting more closely reflects the clinical activity of amivantamab and is therefore the most appropriate clinical setting to demonstrate the non-inferiority of amivantamab SC versus amivantamab IV combinations. The pharmacokinetic results of this study are not expected to be affected by the line of therapy or combinations with agents that do not affect the pharmacokinetic profile of amivantamab. As a result, the results from this trial can potentially provide supportive data supporting future administration of amivantamab subcutaneous regimens.

2.2. Background

2.2.1. Non-small Cell Lung Cancer

Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer. Over the past decade, there has been significant advancement in the understanding of the underlying biology of NSCLC, including the identification of multiple “driver” mutations that can result in a constitutive activation of pro-growth signaling pathways. The most prevalent of these driver mutations considered actionable are those that result in the activation of EGFR, which are identified in approximately 15% of Western patients (Pao 2011) and in up to 40% to 50% of Asian patients (Jänne 2006).

The most frequently identified EGFR mutations, the Exon 19del and Exon 21 L858R point mutation, are identified in 80% to 85% of participants with activating EGFR mutations. The FLAURA study established the EGFR TKI osimertinib as the preferred front-line therapy for patients with metastatic NSCLC and Exon 19del or L858R mutations (Soria 2018).

Despite improved initial disease control, almost all patients treated with osimertinib will relapse, and there are no approved targeted therapies for the treatment of these patients. Notably, the most common mechanisms of resistance to osimertinib are based in the EGFR (EGFR amplification,

C797S mutation, and others) and cMET (cMET amplification, cMET Exon 14 skipping mutations, and others) genes. A targeted therapy with activity against both EGFR and cMET might be particularly relevant in this setting. Once emergence of resistance renders treatment with osimertinib ineffective, National Comprehensive Cancer Network (NCCN) treatment guidelines for advanced or metastatic NSCLC recommend platinum-based chemotherapy, such as carboplatin and pemetrexed, as the next line of therapy (NCCN 2021). The overall response rate (ORR) associated with this therapy, as determined in Phase 3 studies of similar populations, has been approximately 30%, with the median PFS of 4.4 months to 5.4 months (Mok 2017, Soria 2015). After disease progression on platinum-based chemotherapy, treatment options are quite limited. The standard of care is single agent chemotherapy with an ORR of 14% (Garon, 2014). 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 targeted therapies that further control the growth of tumors reliant on aberrant EGFR and/or cMET.

2.2.2. Amivantamab (JNJ-61186372)

2.2.2.1. Amivantamab IV

Amivantamab IV has been granted conditional approval by the FDA, EMA, and other health authorities for patients with EGFR Exon 20ins mutations whose disease has progressed on or after platinum-based chemotherapy. Unlike EGFR TKIs, which bind to the intracellular portion of the EGFR, amivantamab is a bispecific antibody that targets the extracellular domain of both EGFR and cMET, the 2 pathways most frequently involved in tumor resistance to EGFR TKIs.

Amivantamab has a manageable safety profile, consistent with inhibition of EGFR and cMET pathways. In Study 61186372EDI1001, as of 17 Jan 2022, the most common TEAEs (ie, frequency ≥20%) in participants (N=518) treated at the recommended dose were IRRs (67%), paronychia (43%), rash (36%) dermatitis acneiform (35%) hypoalbuminemia (30%), constipation (23%), nausea (23%) peripheral oedema (21%), stomatitis (20%), and dyspnea (20%). Nearly all IRRs occurred during the first infusion (Cycle 1 Day 1) and did not recur with subsequent infusions. TEAEs of Grade ≥3 severity were reported in 240 (46.3%) participants, with 98 (18.9%) of these participants experiencing TEAEs of Grade ≥3 severity reported as related to amivantamab by the investigator. The most common treatment-related TEAEs with Grade ≥3 severity (occurring in ≥1% of participants) were IRR (2.5%), paronychia (1.9%), dermatitis acneiform, (1.7%), rash (1.5%), hypoalbuminemia (1.2%), and oedema peripheral (1.0%). There was no consistent pattern of treatment-related TEAEs of Grade ≥3 severity; only IRRs were reported in 2.5% of participants. (See Section 2.2.4 for additional details regarding Study 61186372EDI1001.)

Background information on the combination of amivantamab IV and lazertinib that is relevant to this study is provided in Section 2.2.4. For clinical information regarding the combination of lazertinib with either amivantamab IV as monotherapy or in combination with chemotherapy, refer to the latest version of the IB for amivantamab and for lazertinib..

2.2.2.2. Amivantamab SC-CF

The 61186372NSC1003 (PALOMA) study was initiated to evaluate the safety and effectiveness of amivantamab SC in participants with advanced solid malignancies. In this dose escalation study, amivantamab SC was administered to participants with a solid malignancy who were deemed by the investigators to possibly benefit from treatment with an EGFR- or cMET-directed therapy, with and without co-formulation with recombinant human hyaluronidase (rHuPH20), the active ingredient of the commercial product Hylenex® recombinant (hyaluronidase human injection). Hylenex®, which was approved for use in the United States in December 2005, is also approved in combination with multiple protein therapeutics for SC administration in the United States and European Union, such as HyQvia (Immune globulin infusion 10% [human] with recombinant human hyaluronidase), as well as anticancer medications such as Herceptin® SC (trastuzumab), MabThera® SC (rituximab), Rituxan Hycela® SC (rituximab), and subcutaneous Darzalex (Darzalex Faspro® in the US [daratumumab]).

Study 61186372NSC1003 is an open-label, non-randomized, multicenter, Phase 1b, 3-part study evaluating the PK, safety, and antitumor activity of amivantamab SC in participants with advanced solid malignancies using different formulations (low concentration and high concentration formulations of amivantamab SC, with and without rHuPH20). Part 1 consists of 2 cohorts (approximately 8 participants per cohort), with participants receiving amivantamab SC at the same concentration and dose used for amivantamab IV (50 mg/mL, 1,050 mg/1,400 mg), with (Cohort 1a) or without (Cohort 1b) rHuPH20. In Part 2, participants receive the same doses of amivantamab utilizing a high concentration formulation (160 mg/mL) with (Cohort 2a) or without (Cohort 2b) rHuPH20. Additional dose levels in Part 2 are being evaluated to confirm the proposed SC recommended Phase 2 dose (RP2D). Part 3 will evaluate the safety and PK of high concentration amivantamab SC at the RP2D from Part 2 in combination with lazertinib.

In Study 61186372NSC1003, the co-formulation of high concentration amivantamab with rHuPH20 (ie, amivantamab SC-CF) shortened the needed injection time to approximately 5 minutes, with a bioavailability (BA) estimated to be 65% and was selected for further development. The RP2D for NSC3004 will be 1,600 mg for participants with a BW <80 kg and 2,240 mg for participants with a BW ≥80 kg. This dose is currently undergoing confirmation in Study 61186372NSC1003. At the 9 February 2022 SET meeting, the safety of the modeled RP2D of 1600/2240 mg was confirmed in 4 participants, and expansion of the cohort was initiated. In total, 37 participants have been treated with amivantamab -SC at any dose. At the 1600/2240 mg dose in Study 61186372NSC1003, no DLTs and no new safety signals were identified and subsequent evaluation of safety, PK and PD among 25 subjects in this cohort at the 25 July 2022 SET meeting confirmed 1600/2240 mg as the SC Q2W RP2D. Refer to Section 4.3.2 for additional details regarding the justification for the amivantamab SC-CF dose used in this study.

2.2.3. Lazertinib (JNJ-73841937)

Lazertinib (JNJ-73841937) is an oral, highly potent, third-generation, irreversible EGFR TKI with no demonstrated PK interaction with amivantamab. Like osimertinib, it selectively inhibits both activating EGFR mutations (Exon 19del, L858R) and the EGFR T790M resistance mutation while showing mutant-selective activity for EGFR. Lazertinib has demonstrated efficacy in patients with

EGFR-mutated NSCLC, with activity observed in both systemic and central nervous system lesions, demonstrating its ability to cross the blood-brain barrier. Lazertinib received approval from the Ministry of Food and Drug Safety in South Korea for use in patients with advanced EGFR T790M+ NSCLC. Lazertinib monotherapy is being further evaluated as front-line treatment for patients with NSCLC, EGFR-activating mutations Exon 19del and Exon 21 L858R (YH25448-301).

Lazertinib was tested in a Phase 1/2 study (73841937NSC2001; YH25448-201) in which 181 participants were enrolled with EGFR-mutated advanced NSCLC that progressed following prior therapy with an EGFR TKI. In dose escalation, clinical activity was observed in each dose cohort, from 20 mg through the highest dose cohort of 320 mg, with no dose-limiting toxicities, and no maximum tolerated dose was identified. The RP2D of lazertinib was determined to be 240 mg PO once daily. At the recommended dose of 240 mg, the response rate of lazertinib in the T790M+ TKI-relapsed population was 58%, with a median PFS of 11.0 months (refer to the lazertinib IB). In participants with measurable brain metastasis at baseline (n=22), the intracranial ORR of lazertinib at any dose was 55%, indicating effective blood-brain barrier penetration, with intracranial responses observed in participants beginning at the 40 mg dose level (Kim 2020).

Lazertinib was well tolerated across all doses (dose range 20 to 320 mg) in 228 participants who were evaluable for safety (Ahn 2019; refer to lazertinib IB). The most commonly reported TEAEs (any grade) were rash (32%), pruritus (30%), diarrhea (24%), paresthesia (23%), constipation (22%), and decreased appetite (21%). Grade 3 or 4 events were observed in 29% of participants. Drug-related serious TEAEs were reported in 8 participants (4%). TEAEs leading to dose reduction or drug discontinuation were observed in 10% and 7% of participants, respectively. Overall, the incidence and severity of adverse events seen in this study were similar to those of osimertinib in the Phase 1 AURA study (Jänne 2015). Importantly, cardiac safety assessment in these participants has shown that lazertinib has no clinically relevant effect on QT interval or left ventricular ejection fraction (LVEF) (Ahn 2019). In summary, the currently available safety and efficacy profile of lazertinib appears similar to that of osimertinib as a second-line therapy. A Phase 3 trial evaluating lazertinib as a first-line monotherapy for participants with metastatic disease bearing Exon 19del or Exon 21 L858R substitution EGFR mutations is underway (NCT04487080).

2.2.4. Amivantamab IV and Lazertinib Combination Therapy

As a third-generation EGFR-TKI targeting activating EGFR mutations, lazertinib has a mechanism of action complementary to amivantamab. The mechanisms of action of amivantamab and lazertinib suggest potential improvement in clinical outcomes through the combination of these 2 agents. By expanding coverage against additional EGFR TKI resistance mutations (eg, C797S and cMET amplification), the combination of amivantamab with lazertinib is hypothesized to delay the development of disease resistance, thereby prolonging disease control beyond that observed with a third-generation TKI alone. In addition, the complementary mechanisms of action of amivantamab combined with anti-EGFR TKI therapy, which targets both the extracellular ligand binding domain and the intracellular active site, respectively, has the potential to more potently inhibit the EGFR pathway than either agent alone.

The combination of amivantamab and lazertinib was first explored in the ongoing Phase 1 Study 61186372EDI1001 (CHRYSALIS) (Cho 2020). The combination of amivantamab and lazertinib demonstrated an ORR of 100% (95% CI, 83%-100%) among participants with treatment-naïve EGFR Exon 19 del or L858R NSCLC, and 36% (95% CI, 22%-51%) in participants with osimertinib-relapsed but chemotherapy-naïve EGFR Exon 19 del or L858R NSCLC.

The safety profile of the combination, as assessed in the 91 total participants with a 6 months median follow up, was tolerable with the majority of toxicities being Grade 1 or 2 in severity (11% of participants reported a treatment-related TEAE of at least Grade 3 severity), and 6% of participants reporting a TEAE leading to discontinuation of either one or both drugs. The most common TEAEs (ie, occurring in ≥20% of participants) were rash (85%), IRR (65%), paronychia (53%), hypoalbuminemia (37%), stomatitis (33%), nausea (28%), ALT increased (21%), paresthesia (20%), and decreased appetite (20%) (Bauml 2021).

The activity of amivantamab and lazertinib is being explored further in the ongoing Phase 1/1b Study 73841937NSC1001 (CHRYSALIS-2). In a cohort of 80 participants with EGFR Exon 19del or L8585R disease who had experienced disease progression on osimertinib and platinum doublet chemotherapy, the combination of amivantamab and lazertinib demonstrated an ORR of 41% (95% CI, 24%-61%) and a clinical benefit rate of 69%. No new safety signals were identified (Shu 2021).

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of amivantamab and lazertinib may be found in the IB for each product.

2.3.1. Risks for Study Participation

Risks of amivantamab - lazertinib

As clinical data are limited, unforeseen safety risks associated with the study treatments are possible. The safety and tolerability of amivantamab IV and lazertinib in combination was demonstrated in the Study 61186372EDI1001 and is being further explored in Study 73841937NSC1001 (Section 2.2.2.1 and Section 2.2.4) and 73841937NSC3003. The safety and tolerability of amivantamab SC-CF monotherapy has been investigated, and evaluation of amivantamab SC-CF in combination with lazertinib is planned, in Study 61186372NSC1003 (Section 2.2.2.2).

Table 3: Mitigation Strategies for Possible Risks Associated with amivantamab and lazertinib

Possible Risk	Mitigation Strategies
IRR and local administration-related reactions	Mandatory predose medications (Section 6.8.2.1), detailed prophylactic and reactive management guidance in protocol (Section 6.5).
Rash-related AEs, paronychia, oral mucositis	Detailed prophylactic and/or reactive management guidance in protocol (Section 6.5).

Possible Risk	Mitigation Strategies
Pulmonary toxicity	
Liver chemistry abnormalities	
Cardiac AEs	
Diarrhea	
VTE	

In addition to the possible risks outlined in Table 3, unforeseen safety risks associated with the study treatments are possible. While clinical experience with amivantamab IV plus lazertinib in Studies 61186372EDI1001, 73841937NSC1001, and 73841937NSC3003 suggests that this combination is safe, in order to mitigate risks for study participants, this study protocol specifies that an Independent Data Monitoring Committee (IDMC) will be commissioned to review efficacy, safety, and tolerability data at regular intervals.

2.3.2. Benefits for Study Participation

Amivantamab in combination with lazertinib has demonstrated activity in the osimertinib-relapsed setting (Section 2.2.4). It has been demonstrated that patients having EGFR-mutated NSCLC and have experienced PD on or after treatment with both osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy may receive clinical benefit from the combination of amivantamab with lazertinib.

Participants will receive medical care, monitoring, and management of their disease by the study site team.

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures taken to minimize risk to participants of this study, the possible risks identified for the combination of lazertinib with either amivantamab IV or amivantamab SC-CF via manual injection are justified by the anticipated benefits that may be afforded to participants with locally advanced or metastatic NSCLC and EGFR Exon 19del or Exon 21 L858R mutations who have progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy.

At the 20 July 2022 IDMC review of unblinded safety and efficacy data from another ongoing study of amivantamab and lazertinib combination therapy (73841937NSC3003), the IDMC confirmed a favorable benefit-risk assessment and therefore recommended continuation of the study. The IDMC also recommended that additional measures be taken to mitigate an observed increase in venous thromboembolic (VTE) events for the combination that was primarily evident within the first 4 months of initiating therapy. Notably, based on the VTE search strategy used at

the time of IDMC review, no Grade 5 VTEs were identified, and only 1 participant discontinued study treatment due to VTE events.

VTE -related changes implemented during protocol Amendment 1 for this study are intended to 1) provide guidance to increase awareness of the potential increased incidence of VTE events during the first 4 months of treatment with the amivantamab and lazertinib combination, 2) describe measures to increase monitoring for these VTE events, 3) increase data collection related to all VTE events to better understand these events and their potential relatedness to study drugs, and 4) recommend prophylactic anticoagulation during the first 4 months of combination therapy. These measures are being implemented in each study of amivantamab and lazertinib combination therapy to further optimize the benefit-risk balance for participants.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the noninferiority of amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B)	• C_{trough} of amivantamab: o at steady state (Cycle 4 Day 1) for all regions other than EU and others accepting Cycle 2 Day 1 o pre-dose on Cycle 2 Day 1 for EU and any applicable region • AUC_{D1-D15} in Cycle 2
Secondary	
To assess the efficacy of amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B)	• ORR • PFS • DoR • TTR
To assess the safety of amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B)	• Incidence and severity of adverse events and clinical laboratory abnormalities • Incidence and severity of IRR
To assess amivantamab pharmacokinetics and immunogenicity to amivantamab or rHuPH20 in participants treated with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B).	• C_{trough} of amivantamab: o pre-dose on Cycle 2 Day 1 for regions other than EU and others accepting Cycle 2 Day 1 o at steady state Cycle 4 Day 1 for EU and any applicable region • Model-predicted AUC_{D1-D15} in Cycle 4 • The presence of anti-amivantamab antibodies and anti-rHuPH20 antibodies
To assess cancer therapy satisfaction in participants treated with amivantamab SC-CF administered via manual injection (ArmA) versus amivantamab IV (Arm B)	• Modified TASQ • Change from baseline assessed over time
Time and motion analysis in participants treated with amivantamab SC-CF administered via manual injection (ArmA) versus amivantamab IV (Arm B)	• Participant chair time • Participant time in treatment room • Duration of treatment administration • Active HCP time for drug preparation, treatment administration, and post-treatment monitoring.
Exploratory	
To explore additional measures of efficacy of amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B)	• Overall survival
To explore potential mechanisms of resistance to amivantamab and lazertinib	• Characterization of tumor genetics by NGS of ctDNA
To further explore cancer therapy satisfaction in participants treated with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B)	• PGIS, PGIC
To explore the relationship between PK or immunogenicity and selected endpoints (including but not limited to efficacy, safety, and/or patient-reported outcomes)	• Serum amivantamab and plasma lazertinib concentrations, and serum anti-amivantamab antibodies

AUC=area under the concentration-time curve; CF=co-formulation; C_{max}=maximum plasma/serum concentration; C_{trough}=plasma/serum concentration immediately prior the next study treatment administration; D=day ; DoR=duration of response; HCP=health care professional; IV=intravenous(ly);; ORR=objective response rate; PFS=progression-free survival; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of

Severity; PK=pharmacokinetic(s); rHuPH20=recombinant human hyaluronidase; SC=subcutaneous(ly); TASQ=Therapy Administration Satisfaction Questionnaire; TTR=time to response.

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

HYPOTHESIS

The primary hypothesis of the study is that amivantamab SC-CF, administered via manual injection at the RP2D, is noninferior to amivantamab IV in participants with locally advanced or metastatic NSCLC with EGFR Exon 19del or Exon 21 L858R mutations whose disease has progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy.

4. STUDY DESIGN

4.1. Overall Design

Study 61186372NSC3004 (PALOMA-3) is a randomized, open-label, parallel, multicenter, Phase 3 study, which will optimize the administration of amivantamab in participants with EGFR mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy. The study will compare the PK, efficacy, and safety of combining lazertinib with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B).

Approximately 400 participants will be enrolled in this study. Participants will be stratified by brain metastases at baseline (yes versus no), EGFR mutation (L858R versus Exon 19del), race (Asian versus non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] versus chemotherapy).

The Schema is shown above (Figure 1). The study will include Screening (Section 4.1.1), a Treatment Phase (Section 4.1.2), and a Follow-up Phase (Section 4.1.3).

The study will aim to enroll a participant population that is geographically reflective of the overall incidence/prevalence of this disease. Enrollment of study participants in a given country may continue beyond the global enrollment period defined to reach the overall planned sample size, to ensure adequate representation in the study.

A target of 400 participants will be enrolled in this study and will be randomized 1:1 between Arms A and B. An IDMC will be commissioned for this study. Refer to Committees Structure in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations for details.

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

Note: For clarity this protocol uses arm names ‘A’ and ‘B’, however in other documents and systems these may be referred to as ‘A1’ and ‘B1’ as these were already in place at the time of this Global Amendment 2 to remove Part 2 of the study

4.1.1. Screening

The informed consent form (ICF) must be signed before the first study-related activity is conducted. Screening procedures must be completed within 28 days before randomization.

All information required for randomization purposes must be available at the time of randomization, including all screening assessments per the applicable Schedule of Activities (Table 1) and documentation to support mutation status. In addition, results of the Cycle 1 Day 1 assessments such as ECOG performance status, ECG, laboratory values, pregnancy test (as applicable), and symptom-directed physical exam should be available and reviewed by the Investigator prior to randomization. See the Schedule of Activities for details on completion of assessments within 72 hours prior to the first dose of study treatment.

4.1.2. Treatment Phase

The Treatment Phase will begin at randomization, with first treatment on Cycle 1 Day 1 to occur within 72 hours and continue in 28-day cycles until the End of Treatment visit, approximately 30 days after the last dose of study treatment. Study treatment will continue until documented clinical or radiographic (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 [Appendix 8]) disease progression or until the participant meets another criterion for discontinuation of study treatment (Section 7.1). Participants will be stratified based on the presence or history of brain metastases at baseline (yes vs no), EGFR mutation (L858R vs Exon19del), race (Asian vs non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] vs chemotherapy) and assigned randomly in a 1:1 ratio into 1 of 2 treatment arms as follows:

Arm A:

- Lazertinib 240 mg orally once daily
- Amivantamab SC-CF by manual injection into the abdomen in 28-day cycles:
  - 1,600 mg (2,240 mg if BW ≥80 kg) on Cycle 1 Days 1, 8, 15, and 22
  - 1,600 mg (2,240 mg if BW ≥80 kg) on Day 1 and 15 of each subsequent 28-day cycle, starting on Cycle 2

Arm B:

- Lazertinib 240 mg orally once daily
- Amivantamab by IV infusion in 28-day cycles:
  - 1,050 mg (1,400 mg if BW ≥80 kg) on Cycle 1 Days 1-2 (split dose), 8, 15, and 22
  - 1,050 mg (1,400 mg if BW ≥80 kg) on Days 1 and 15 of each subsequent 28-day cycle, starting on Cycle 2

Disease assessments will occur within 28 days before randomization to the start of treatment (baseline screening scans), 6 weeks (+1 week) after randomization, every 6 weeks (±1 week) for the first 18 months and every 12 weeks (±1 week) thereafter, until radiographic disease progression

is confirmed. Timing of disease assessments is relative to randomization, regardless of when study treatment is administered.

At study visits during the Treatment Phase, participants will undergo safety evaluations, including physical examinations and assessment of TEAEs, vital signs, concomitant medication usage, and clinical laboratory parameters. Participants will complete questionnaires for PROs at selected visits. Participants will also have blood samples drawn for assessment of PK parameters, immunogenicity, and biomarker evaluations at selected visits. Medical resource utilization data associated with medical encounters will be collected by HCPs for all participants throughout the study.

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

4.1.3. Follow-up Phase

For participants who discontinue treatment prior to disease progression, tumor imaging should continue as scheduled (see Schedule of Activities) until disease progression is documented, if clinically feasible. Participants who discontinue study treatment for any reason will be followed in the Follow-up Phase after last study treatment until disease progression or death, whichever comes first. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the electronic case report form (eCRF). Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations).

4.1.4. Long-term Extension Phase

Participants who continue to benefit from study treatment(s), as determined by their investigator, after completion of the primary analysis may continue to receive access to study treatment(s) within the study by transferring to the LTE Phase, where only serious adverse event data and the study treatment compliance data will be collected. The LTE Phase will continue to provide participants access to study treatment and further reduce protocol-required visit procedures and assessments, and burden on participants after the primary analysis is complete.

The LTE Phase (see details provided in Section 10.15 [Appendix 15]) will begin after the primary analysis, and will continue until the discontinuation criteria described in Section 7.1 are met, or until 3 years after local marketing authorization is obtained, whichever occurs first. For transition to the LTE Phase (after primary analysis), notification from the sponsor will be provided.

4.2. Scientific Rationale for Study Design

Control, Study Phase/Periods, Treatment Groups

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

Clinical Pharmacology Assessments

Blood samples will be analyzed for serum amivantamab and plasma lazertinib concentrations and estimation of PK parameters. PK noninferiority of amivantamab SC-CF administrated via manual injection versus amivantamab IV will be assessed using C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and $AUC_{D1\text{-}D15}$ in Cycle 2. A population PK model will be developed as a means to derive the individual participant's exposure, for determination of participant covariates that influence the PK of amivantamab. Exposure-response analysis may be conducted. Sample collection and testing will comply with local regulations.

ctDNA Collection

Circulating tumor deoxyribonucleic acid (ctDNA) will be collected to identify co-occurring EGFR mutations, cMET alterations, and mutations in other key oncogenes to characterize the tumor to explain interindividual variability in clinical outcomes, or to identify population subgroups that respond differently to a treatment. The ctDNA samples may be used to explore the potential to predict clinical benefit, relapse, and/or identify mechanisms of resistance to assigned therapy, and to enable the development of safer, more effective, and ultimately individualized therapies. Sample collection and testing will comply with local regulations.

4.2.1. Study-Specific Ethical Design Considerations

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

Thorough scientific evaluation of any treatment before marketing authorization is an ethical and regulatory requirement. As the benefits and risks of combining lazertinib with amivantamab IV or amivantamab SC-CF via manual injection in this study population are not fully known, this study will evaluate safety and clinical activity. Participants will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit. The IDMC will review evolving safety data from this study, as well as efficacy data as appropriate. Based on the observed activity of both amivantamab and lazertinib in this setting, there is adequate justification

for evaluating these drugs in combination for the treatment of NSCLC in participants who are eligible for this study.

All participants will undergo regular disease assessments to monitor their underlying disease. Prior EGFR testing in accordance with site standard of care, obtained at or after the diagnosis of locally advanced or metastatic NSCLC and before signing informed consent will be used to document EGFR mutation status.

As with all clinical studies, there are risks associated with venipuncture and multiple blood sample collection. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacology of the study treatment. This minimizes the number of venipunctures and the total volume of blood collected from each participant during the study. The total blood volume 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 blood donation standards of the American Red Cross (American Red Cross 2022) and the World Health Organisation (WHO 2012).

4.3. Justification for Dose

4.3.1. Amivantamab IV Dose

The recommended dose of 1050 mg for BW <80 kg and 1400 mg for BW ≥80 kg, once weekly for the first 4 weeks and every 2 weeks thereafter on a 28-day cycle for amivantamab was established based on the totality of PK, PD, safety, and efficacy data obtained in the ongoing Phase 1 Study 61186372EDI1001. Amivantamab was generally well tolerated in a Phase 1 study up to the dose of 1750 mg, with no DLTs reported during dose escalation and no MTD identified. This dose of 1050/1400 mg every 2 weeks was subsequently approved for patients with NSCLC characterized by EGFR Exon20ins mutation after progression on chemotherapy by the FDA, EMA and other health authorities. The safety and tolerability of amivantamab IV at this same dose combined with lazertinib was demonstrated in the Study 61186372EDI1001 and is being further explored in Study 73841937NSC1001 (Section 2.2.2.1 and Section 2.2.4) and 73841937NSC3003.

4.3.2. Amivantamab SC-CF Dose

The SC Q2W RP2D for amivantamab SC-CF (160 mg/mL co-formulated with rHuPH20) in the current Study 61186372NSC3004 was determined to be 1,600 mg for participants with a BW <80 kg and 2,240 mg for participants with a BW ≥80 kg (Section 2.2.2.2).

The proposed recommended dosing regimens for SC amivantamab are selected to ensure that the resulting exposures are similar to those observed with the IV recommended dose regimens. Bioavailability was estimated by comparing the observed AUC following SC dosing (cohorts with and without rHuPH20 formulations) to the corresponding observed AUC following IV dosing. The SC cohorts were dosed at the IV recommended dose (1050 mg for participants with a BW <80 kg and 1400 mg for participants with a BW ≥80 kg). At this dose, saturation of soluble free EGFR and cMET was achieved after the first SC dose. Following the first dose in Cycle 2 (after the weekly induction dosing in Cycle 1), the mean (CV%, n) area under the concentration time curves

$(AUC)_{C2D1\text{-}C2D15}$ were 95,416 µg×h/mL (45.4%, 7) and 75,378 µg×h/mL (27.0%, 5) for cohorts from 160mg/ml with and without rHuPH20, respectively. Based on these results and supported by preliminary compartmental PK modeling, the estimated bioavailability was 65% with rHuPH20.

Emerging data from Study 61186372NSC1003 indicates a lower incidence of IRRs (18.7% overall and 0 Grade ≥3) than previously reported with amivantamab IV (65.9% overall and 2.3% Grade ≥3). As a result of the reduced incidence and severity of IRRs, the study demonstrated the feasibility of a single-day infusion of amivantamab SC for the first dose.

4.3.3. Lazertinib Dose

Lazertinib 240 mg QD is the approved dose for lazertinib monotherapy in Korea based on previous single agent studies in participants with NSCLC. Lazertinib 240 mg QD is designated as the RP2D in this combination study. Preliminary PK data in Study 61186372EDI1001 demonstrated a lack of drug-drug interaction between amivantamab IV and lazertinib, as the PK profile of both amivantamab IV and lazertinib was consistent when administered as monotherapies and in combination. To date, lazertinib 240 mg has been combined with amivantamab at the recommended dose in 890 participants.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as 12 months after the last participant has been randomized. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

The sponsor will make every effort to ensure that participants benefiting from treatment with amivantamab will be able to continue receiving treatment after the end of the study. For participants ongoing at the time of completion of the study and who are eligible for a continued access program (post study access or other open-label extension study under a different/separate protocol), the end of study for that participant is defined as the end of treatment visit.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant (1) died while on study, or (2) was on study at the time of end-of-study. Participants who prematurely discontinue study treatment for any reason other than death before completion of the randomized treatment phase will not be considered to have completed the study..

5. STUDY POPULATION

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

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor

representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

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

5.1. Inclusion Criteria

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

1. Be ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of informed consent.

2. Have histologically or cytologically confirmed, advanced or metastatic NSCLC, characterized by either EGFR Exon 19del or Exon 21 L858R mutation by an FDA-approved or other validated test of either ctDNA or tumor tissue in a CLIA certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US). A copy of the initial test report documenting the EGFR mutation must be included in the participant records and a deidentified copy must also be submitted to the sponsor.

3. Criterion modified per Amendment 1
   3.1 Have progressed on or after osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy (irrespective of order).
   - The 3rd generation EGFR TKI must have been administered as the first EGFR TKI for metastatic disease or as the second TKI after prior treatment with first- or second-generation EGFR TKI in participants with metastatic EGFR T790M mutation positive NSCLC.
   - Participants who decline or are otherwise ineligible for chemotherapy may be enrolled after discussion with the medical monitor.
   - Any adjuvant or neoadjuvant treatment, whether with a 3rd generation EGFR TKI or platinum-based chemotherapy, would count towards the prior treatment requirement if the participant experienced disease progression within 6 months of the last dose.

4. Have at least 1 measurable lesion, according to RECIST v1.1. If the only target lesion has been previously irradiated, it must show signs of disease progression since radiation was completed.

5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Section 10.10).

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

   - Hemoglobin ≥9 g/dL

- Absolute neutrophil count $\geq 1.5\times10^9$/L, without use of granulocyte colony stimulating factor within 10 days prior to the date of the test
- Platelets $\geq 75\times10^9$/L
- ALT and AST ≤3×ULN if no demonstrable liver metastases or ≤5xULN in the presence of liver metastases.
- Total bilirubin:
  - ≤1.5×ULN if no demonstrated liver metastasis
  - ≤3×ULN in the presence of liver metastasis
  - ≤3×ULN for those participants with known Gilbert's syndrome with conjugated [direct] bilirubin <1.5xULN
- Creatinine clearance >50 mL/min as measured or calculated by MDRD (Appendix 12: Formulas for Estimating Glomerular Filtration Rate Using Modified Diet in Renal Disease Formula (in mL/min))

7. Human immunodeficiency virus-positive participants are eligible if they meet all of the following:

   a. No detectable viral load (ie, <50 copies/mL) at screening

   b. CD4+ count >300 cells/mm3 at screening

   c. No acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of screening

   d. Receiving HAART. Any changes in HAART due to resistance/progression should occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.

   Note: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment).

8. Any toxicities from prior anticancer therapy must have resolved to CTCAE Version 5.0 Grade 1 or baseline level (except for alopecia [any grade], Grade ≤2 peripheral neuropathy, and Grade ≤2 hypothyroidism stable on hormone replacement).

9. A female participant of childbearing potential must have a negative serum pregnancy test at screening and must agree to further serum or urine pregnancy tests within 72 hours of the first dose, during the study, and for 7 months after the last dose of study treatment.

10. A female participant must be either of the following (as defined in Appendix 5: Contraceptive and Barrier Guidance):

    a. Not of childbearing potential, or

b. Of childbearing potential and practicing at least 1 highly effective method of contraception (details in Appendix 5: Contraceptive and Barrier Guidance) throughout the study and through 7 months after the last dose of study treatment.

Note: If a female participant becomes of childbearing potential after the start of the study, the female participant must comply with (b.).

11. A female participant must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 7 months after receiving the last dose of study treatment. Female participants should consider preservation of eggs prior to study treatment as anti-cancer treatments may impair fertility.

12. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 7 months after receiving the last dose of study treatment.

    If partner is a female of childbearing potential, the male participant must use condom and the partner must also be practicing a highly effective method of contraception (see Appendix 5: Contraceptive and Barrier Guidance). A male participant who is vasectomized must still use a condom, but the partner is not required to use contraception.

13. A male participant must agree not to donate sperm for the purposes of reproduction during the study and for 7 months after receiving the last dose of study treatment. Male participants should consider preservation of sperm prior to study treatment as anti-cancer treatments may impair fertility.

14. Must sign an ICF (or their legally acceptable representative must sign if allowed per local regulation) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

15. Be willing and able to adhere to the lifestyle restrictions specified in this protocol.

16. Criterion moved from Exclusion Criteria to Inclusion Criteria per Amendment 2

    A female participant must agree not to be pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 7 months after the last dose of study treatment.

5.2. Exclusion Criteria

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

1. Participant has received cytotoxic, investigational, or targeted therapies beyond one regimen of platinum-based chemotherapy and EGFR inhibitors, as allowed in Inclusion criterion 3.

2. Participant has a history of uncontrolled illness, including but not limited to the following:

   - Uncontrolled diabetes
   - 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).
   - Active bleeding diathesis
   - 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
   - Psychiatric illness or any other circumstances (including social circumstances) that would limit compliance with study requirements
   - Any ophthalmologic condition that is clinically unstable

3. Participant has received radiotherapy for palliative purposes less than 7 days prior to randomization.

4. Participant has symptomatic or progressive brain metastases. Participants with treated metastases that are clinically stable and asymptomatic for at least 2 weeks and who are off or receiving low-dose corticosteroid treatment (≤10 mg prednisone or equivalent) for at least 2 weeks prior to randomization are eligible.

5. Participant has leptomeningeal disease, or participant has spinal cord compression not definitively treated with surgery or radiation.

6. Participant has uncontrolled tumor-related pain. Symptomatic lesions amenable to palliative radiotherapy (eg, bone metastases, or metastases causing nerve impingement) should be treated more than 7 days prior to the randomization.

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

8. Have a prior or concurrent second malignancy (other than the disease under study) which natural history or treatment is likely to interfere with any study endpoints of safety or the efficacy of the study treatment(s) (see Appendix 13: Allowed Recent Second or Prior Malignancies for details).

9. Participant has a history of hypersensitivity to any of the excipients of amivantamab, lazertinib, or to rHuPH20.

10. Criterion modified per Amendment 3

10.1 Participant has a history of clinically significant cardiovascular disease including, but not limited to, the following:

- Diagnosis of deep vein thrombosis or pulmonary embolism within 1 month prior to the first dose of study treatment, or any of the following within 6 months prior to the first dose of study treatment: 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.
- Participant has a significant genetic predisposition to venous thromboembolic (VTE) events such as Factor V Leiden.
- Participant has a prior history of VTE and is not on appropriate therapeutic anticoagulation as per NCCN or local guidelines.
- Prolonged QTcF interval >480 msec or clinically significant cardiac arrhythmia or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate).
- Uncontrolled (persistent) hypertension: systolic blood pressure >160 mmHg; diastolic blood pressure >100 mmHg
- Congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III-IV (see Appendix 9: New York Heart Association Criteria) or Hospitalization for CHF (any NYHA class) within 6 months of randomization
- Pericarditis/clinically significant pericardial effusion
- Myocarditis

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

12. Participant has at Screening any of the following:

- Seropositive for hepatitis B: defined by a positive test for hepatitis B surface antigen [HBsAg]. Participants with resolved infection (ie, participants who are HBsAg negative with antibodies to total hepatitis B core antigen [anti-HBc] with or without the presence of hepatitis B surface antibody [anti-HBs]) must be screened using real-time polymerase chain reaction (RT-PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by RT-PCR.

- Positive hepatitis C antibody test result at screening or within 3 months prior to starting study treatment.

  NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained.

- Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

  NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

- Other clinically active infectious liver disease.

13. Participant has received a live or live attenuated vaccine within 3 months before randomization. The seasonal influenza vaccine and non-live vaccines against COVID-19 are not exclusionary.

14. Criterion modified per Amendment 1

    14.1 Participant is currently receiving medications or herbal supplements known to be potent CYP3A4/5 inducers and is unable to stop use for an appropriate washout period prior to randomization.

15. Participant previously enrolled in the Sponsor's studies 73841937NSC3003 (NCT04487080) or 61186372NSC3002 (NCT04988295).

16. Criterion added per Amendment 1

    16.1 Criterion moved to Inclusion Criterion 16 per Amendment 2

NOTE: Investigators must ensure that all study enrollment procedures have been completed during the screening period and eligibility confirmed on the date of, and prior to, randomization. If a participant's clinical status changes/declines during the screening period, eligibility must be reconfirmed prior to randomization. The required source documentation to support meeting the enrollment criteria is noted in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. If the participant's last treatment was osimertinib (or another approved 3rd generation EGFR TKI), this must be discontinued at least 8 days prior to first dose of study drug

(ie, last dose no later than Study Day -8). If the participant's last treatment contained chemotherapy, the last dose of treatment must be no later than 2 weeks or 4 half-lives prior to study treatment, whichever is longer. For agents such as immunotherapy with a long half-life, the maximum required time since last dose is 6 weeks.

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

4. Participants must 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. Participants must agree to avoid unnecessary exposure to sunlight and use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥30.

5. Carry a "wallet study card" with pertinent information about the study for the duration of study participation.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

This study does use interactive web response system (IWRS). During the screening and enrollment, the investigator did not generate screening and enrollment logs directly from IWRS.

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants who are determined to be eligible for the study after their condition changes must sign a new ICF prior to re-screening.

5.5. Criteria for Temporarily Delaying Randomization

Not applicable.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatments Administered

Study treatment administration must be captured in the source documents and the eCRF. Study site personnel will instruct participants on how to store study treatment for at-home (lazertinib only) use as indicated for this protocol.

Amivantamab and lazertinib will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for amivantamab and the IB for lazertinib for lists of excipients.

Refer to the Investigational Product Preparation Instructions (IPPI) or Site Investigational Product Procedures Manual (SIPPM) for additional guidance on preparation, handling, and storage of study treatments.

For a definition of study treatment overdose, refer to Section 6.7, Treatment of Overdose.

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Products (IMPs)</td><td>amivantamab, lazertinib

Authorization Status in the EU:
<table><tr><td>Authorized</td><td>Amivantamab IV</td></tr><tr><td>Unauthorized</td><td>Amivantamab SC, lazertinib</td></tr></table>
Used not in accordance with Marketing Authorization: amivantamab</td></tr>
<tr><td>Non-investigational Medicinal Products (NIMPs)/Auxiliary Medicinal Products (AxMPs)</td><td>Not applicable</td></tr>
</table>

Description of Treatments

Arm Name	All Arms	Arms A	Arm B
Treatment Name	Lazertinib	Amivantamab SC-CF	Amivantamab IV
Type	Drug	Drug	Drug
Dose Formulation	Oval, yellow, film-coated tablet	25R vial	7 mL vial
Unit Dose Strength(s)	80 mg	1600 or 2240 mg/vial with concentration of 160 mg/mL co-formulated with rHuPH20	350 mg/vial with concentration of 50 mg/mL; IV infusion will be prepared at the site in ~250 mL diluent
Dosage Level(s)	240 mg once daily	Up to Cycle 2 Day 1: once weekly 1600 mg (2240 mg if BW is ≥80 kg) Cycles 2+: 1600 mg (2240 mg if BW is ≥80 kg) on Day 1 and 15 of each 28-day cycle	Up to Cycle 2 Day 1: once weekly (with the first dose split over Days 1-2): 1050 mg (1400 mg if BW is ≥80 kg) Cycles 2+: 1050 mg (1400 mg if BW is ≥80 kg) on Day 1 and 15 of each 28-day cycle
Route of Administration	oral	other: subcutaneous by manual injection	IV infusion
Use	Experimental	Experimental	Experimental
Investigational Medicinal Product (IMP)	Yes	Yes	Yes
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	No	No	No
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	Will be provided in a 93-count bottle	pre-filled vials of either 1600 mg or 2240 mg amivantamab at 160 mg/mL co-formulated with rHuPH20	pre-filled vials of 350 mg at 50 mg/mL
	Child resistant packaging	Not in child resistant packaging	Not in child resistant packaging

Arm Name	All Arms	Arms A	Arm B
Delivery Instructions	Self-administered with or without food; first 2 doses (cycle 1, Day 1 and 2), should be taken in the clinic (on visit days), more than 15 minutes prior to initiation of premedication for amivantamab. The tablets should be swallowed intact with water ad libitum and taken around the same time each day, approximately 24 hours apart, if possible.	Per Investigational Product Preparation and Administration Instructions.	Per Investigational Product Preparation and Administration Instructions.
Current/Former Name(s) or Alias(es)	JNJ-73841937; YH25448	JNJ-61186372	JNJ-61186372

6.1.1. Scheduled Dosage and Timing

Administration of study treatment should begin within 3 days of randomization. On days when multiple study drugs are dosed together, the order of medications should be as follows: 1) lazertinib, 2) predose medications required with amivantamab; 3) amivantamab. Refer to Table 7 for predose medications required with amivantamab.

6.1.2. Amivantamab SC-CF by Manual Injection (Arm A)

Amivantamab SC-CF will be manufactured and provided for this study under the responsibility of the sponsor. Refer to the amivantamab IB for a list of excipients.

In Arm A, amivantamab SC-CF will be delivered by means of a manual injection into the abdomen. Doses will be administered at alternating locations on the abdomen in the periumbilical area. Refer to the IPPI for details regarding the needle gauge, angle, and depth. The dosage of amivantamab SC-CF will be based on the participant's BW at screening. The dose remains based on BW at screening regardless of subsequent changes in BW during the course of treatment. Qualified site personnel will administer amivantamab as a manual injection in 28-day cycles as follows:

- 1,600 mg (2,240 mg if BW ≥80 kg) on Cycle 1 Days 1, 8, 15, and 22
- 1,600 mg (2,240 mg if BW ≥80 kg) on Day 1 and 15 of each 28-day cycle, starting on Cycle 2

The actual start and end times of each injection should be accurately recorded.

6.1.3. Amivantamab IV (Arm B)

Amivantamab IV will be manufactured and provided for this study under the responsibility of the sponsor. Refer to the amivantamab IB for a list of excipients.

The dosage of amivantamab IV will be based on the participant's BW at screening. The dose remains based on BW at screening regardless of subsequent changes in BW during the course of treatment. Qualified site personnel will administer amivantamab as an IV infusion in 28-day cycles as follows:

- 1,050 mg (1,400 mg if BW ≥80 kg) on Cycle 1 Days 1-2 (split dose), 8, 15, and 22
- 1,050 mg (1,400 mg if BW ≥80 kg) on Days 1 and 15 of each 28-day cycle, starting on Cycle 2

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

Infusion durations that exceed the planned length of time due to IV bag overfill, minor equipment calibration factors, and/or participant factors not under the control of administering personnel will not be considered protocol deviations. The actual start and end times of each infusion and infusion rate(s) should be accurately recorded.

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

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

6.1.4. Lazertinib

Lazertinib for oral administration is an 80 mg oval, yellow, film-coated tablet. Refer to the IB for a list of excipients. Participants will self-administer lazertinib as an oral therapy, with an initial dosage of 240 mg (3 tablets) once daily. Lazertinib tablets can be administered with or without food. Lazertinib should be dosed at the study site on Day 1 of each cycle. Lazertinib should be taken at approximately the same time each day, approximately 24 hours apart, if possible. If a participant misses a scheduled dose, it is acceptable to take the dose within a window of 12 hours. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and the participant should be instructed to take the next dose at the next scheduled time. If a participant vomits after taking lazertinib, the participant should not make up for this dose but should take the next scheduled dose. The time of vomiting should be captured in the source document.

6.2. Preparation/Handling/Storage/Accountability

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 IPPI/SIPPM.

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 treatment will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study treatment containers.

For lazertinib, the dispensing of study treatment to the participant, and the return of study treatment from the participant (if applicable), must be documented on the treatment accountability form. Participants, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study treatment.

Amivantamab treatment must be handled in strict accordance with the protocol and as indicated on 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, must be disposed of immediately in a safe manner and therefore will not be retained for treatment accountability purposes.

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 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 SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by brain metastases at baseline (yes vs no), EGFR mutation (L858R vs Exon19del), race (Asian vs non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] vs chemotherapy). The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

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

6.4. 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 drugs 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.

Predose Medications

Administration of predose medications will be documented in the source documents and eCRF.

Lazertinib

The dispensing of lazertinib to the participant and the return of lazertinib from the participant must be documented on the treatment accountability form. Participants, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing lazertinib. Study-site personnel must not combine contents of the lazertinib containers.

Amivantamab

Amivantamab will be administered as an IV infusion or SC manual injection by qualified study site personnel, and the details of each administration will be recorded in the eCRF. Dispensing of all study treatment must also be recorded in the participant's source documents.

6.5. Dose Modification

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

Guidance on dose modification is provided in Sections 6.5.2 and 6.5.3. Refer to Table 4, Table 5, and Table 6 for guidance on delay and modification of the amivantamab dose or lazertinib dose based on the toxicity grade of AEs other than those specified in Section 6.5.3. When possible, the medical monitor should be notified prior to dose modifications.

Changes to amivantamab and/or lazertinib dosing (including dose interruptions, change in dose, or change in infusion rate) and the reason for the change, must be recorded in the CRF. For a dose interruption, the duration of the interruption is to be recorded.

6.5.1. Dose Delay Guidance

In instances where study treatment delay is indicated, treatment with amivantamab and/or lazertinib may be delayed until recovery of toxicity to a level allowing continuation of therapy. A participant for whom treatment was delayed should be assessed at least weekly to ensure adequate supportive care is being administered and to assess for improvement of toxicity. Participants must meet retreatment criteria for amivantamab and/or lazertinib (as per Section 6.5.2), in accordance with protocol, prior to redosing.

For VTE events associated with clinical instability (eg, respiratory failure or cardiac dysfunction) in participants receiving the combination of amivantamab and lazertinib, study treatment should be held until the participant recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator.

6.5.2. Dose Modification of Amivantamab and Lazertinib

Decisions regarding dose modification of amivantamab and lazertinib should be guided by the observed toxicity, the safety profile of each drug, the likelihood of causality to each agent, as well as each agent's potential contribution to any observed clinical benefit.

For toxicities associated with EGFR inhibition that require treatment modification, and which can therefore be attributed to either drug, modification should be instituted for lazertinib prior to modification of amivantamab dosing.

If a participant experiences a CTCAE Grade 3 or higher and/or unacceptable toxicity (any grade) that the investigator considers to be specifically associated with EGFR inhibition, then dosing with lazertinib should be interrupted immediately and supportive therapy administered as required in accordance with local practice/guidelines. The participant should be reassessed at next scheduled amivantamab dose (Day 1 of the next cycle), for resolution of symptoms and need for amivantamab dosing modifications (delay or dose modification). For the majority of clinically significant toxicities withholding doses and dose modifications should occur per the guidelines described in Table 4 below, with the following additional considerations:

- In instances of intolerable toxicity, study treatment should be withheld and may be restarted upon resolution of the intolerable toxicity to ≤Grade 1 or baseline status (except for rash, oral mucositis, or paronychia, which should recover to ≤Grade 2 or baseline).
- If amivantamab is withheld for 2 consecutive doses for any reason, consult with the Medical Monitor before restarting amivantamab to discuss plans for dose.
- While recommendations in Table 4 are provided as guidelines to toxicity management with the combination, investigators should exercise their clinical judgement, taking into account the nature of the toxicity, each agent's potential contribution to the toxicity, as well as each agent's potential contribution to any observed clinical benefit. For guidance around specific adverse events, see Section 6.5.3.

Table 4: Guidance for Withholding Doses for Toxicities Based on Grade

Grade[a]	Action[b,c]	Dose Modification After Resolution of Toxicity[d]
1	None	Continue both agents at current dose level; consider supportive care according to local standards as appropriate
2	None, or consider withholding lazertinib (unless the experienced toxicity is strongly suspected to be related to amivantamab alone, in which case amivantamab should be withheld).	If amivantamab is withheld <21 days, restart study treatment at current dose level. If lazertinib is withheld, restart on Day 1 of next cycle at a reduced dose.
3 or 4	Withhold lazertinib and if not resolved by next scheduled dose, hold amivantamab.	Grade 3: If Grade 3 adverse event improves to Grade 0-2 after withholding study drugs for up to 3 weeks, then upon resolution: - Restart lazertinib at a reduced dose on Day 1 of next cycle. Restart amivantamab at current dose level or consider dose reduction on Day 8, Day 15, or Day 22 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 drugs for up to 3 weeks, permanently discontinue lazertinib, amivantamab, or both Grade 4: If Grade 4 adverse reaction improves to Grade 0-2 after withholding study drugs for up to 3 weeks, then upon resolution: Restart lazertinib at a reduced dose on Day 1 of next cycle. Restart amivantamab at a reduced dose on Day 8, Day 15, or Day 22 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 drugs for up to 3 weeks, permanently discontinue lazertinib, amivantamab, or both.

a. Per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0.
b. For all toxicities, consider supportive care according to protocol as appropriate.
c. For toxicities related to EGFR inhibition, lazertinib should be held first.
d. Resolution defined as: Grade ≤1 or back to baseline status for the participant (except for rash, oral mucositis, or paronychia, which should recover to ≤Grade 2 or baseline).
For VTE events associated with clinical instability (eg, respiratory failure or cardiac dysfunction) in participants receiving the combination of amivantamab and lazertinib, study treatment should be held until the patient recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator.

Amivantamab and Lazertinib Dose Reduction

If a participant experiences an EGFR TKI-related toxicity requiring dose reduction after withholding study treatment and resolution, then the dose of lazertinib should be preferentially reduced, as outlined in Table 5 below, unless the experienced toxicity is strongly suspected to be related to amivantamab alone (refer to respective IBs), in which case the dose of amivantamab should be reduced according to Table 6.

Given the potential for increased anti-EGFR activity on this study, accelerated (ie, proactive) dose reductions are allowed if toxicity is encountered. Upon resolution of the toxicity, or with improved control with supportive measures, the dose of the reduced therapy dose may be increased on Day 1 of the next cycle.

Table 5: Guidance for Lazertinib Stepwise Dose Reduction

Dose Level	Lazertinib (any cycle)
0 (starting dose)	240 mg
-1	160 mg
-2	80 mg
-3	Discontinue

Table 6: Guidance for Amivantamab Stepwise Dose Reduction

Dose Level	Amivantamab IV	Amivantamab SC-CF
0 (starting dose)	1,050 mg (1,400 mg if BW ≥80 kg)	1600 mg (2240 mg if BW ≥80 kg)
-1	700 mg (1,050 mg if BW ≥80 kg)	1050 mg (1600 mg if BW ≥80 kg)
-2	350 mg (700 mg if BW ≥80 kg)	700 mg (1050 mg if BW ≥80 kg)
-3	Discontinue	Discontinue

6.5.3. Dose Modification and Management of Specific Adverse Events

6.5.3.1. Infusion-Related Reactions and Local Administration-Related Reactions

General Guidelines for Infusion-Related Reactions

Infusion-related reactions have been commonly observed during treatment with amivantamab IV, 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 2.2.2.1). Refer to Summary of Data and Guidance for Investigators in the current version of the IB for amivantamab. The guidelines described here relate to the safe administration of amivantamab (IV and SC-CF) during initial dosing.

During the amivantamab infusions, participants should be clinically monitored at regular intervals as specified in the Schedule of Activities (including an assessment prior to the start of infusion). The monitoring should include heart rate, blood pressure, temperature, and oxygen saturation measurements. For Cycle 1 Day 1 only, participants in Arm A will remain at the site for at least 4 hours after the amivantamab injection for observation. For participants in Arm B, the 4-hour infusion time is considered adequate for observation; no additional observation time is needed.

Particularly with the initial dose (Cycle 1, Day 1 and Day 2 in case of split dose), 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 generally preclude further therapy with amivantamab. Participants must be monitored closely for early signs and symptoms indicative of an acute IRR. Even with

mild symptoms, any ongoing 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: Predose Medications

Required predose medications and optional predose medications for amivantamab are summarized in Table 7. Required predose medications are 1 each of an antihistamine and antipyretic on all dose days, as well as a glucocorticoid on Cycle 1 Day 1 and, for amivantamab IV only, on Cycle 1 Day 2.

Table 7: Predose Medications for Amivantamab (all arms)

Required Predose Medications[a, b]				
Medication (select one from each category)	Dose	Route of Administration	Approximate Dosing Window Prior to Study Drug Administration	Cycle/Day
Glucocorticoid	Dexamethasone (10 mg) or methylprednisolone (40 mg) or equivalent	IV or Oral	45 to 60 minutes for IV At least 60 minutes for oral	C1D1 C1D2 (amivantamab IV only)
Antihistamine	Diphenhydramine (25 to 50 mg) or chlorphenamine (10 mg) or equivalent	IV	15 to 30 minutes	All
	Diphenhydramine (25 to 50 mg) or equivalent	Oral	30 to 60 minutes	
Antipyretic	Paracetamol/acetaminophen (650 to 1000 mg) or equivalent	IV	15 to 30 minutes	All
		Oral	30 to 60 minutes	
Optional Predose Medications[a,b]				
Medication	Dose	Route of Administration	Approximate Dosing Window Prior to Study Drug Administration	Cycle/Day
Glucocorticoid[c]	Dexamethasone (10 mg) or methylprednisolone (40 mg)	IV	45 to 60 minutes	C1D8 and beyond
		Oral	60 to 90 minutes	
H_2 -antagonist	Ranitidine (50 mg) or equivalent	IV	15 to 30 minutes	Any
Antiemetic	Ondansetron (16 mg) or equivalent	IV	15 to 30 minutes	Any
	Ondansetron (8 mg) or equivalent	Oral	15 to 30 minutes	

CxDy=Cycle x, Day y; IV=intravenous.

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

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

c) Beginning with Cycle 1 Day 8, optional predose steroids may be administered prior to amivantamab if clinically indicated for participants who experienced an IRR on C1D1 or C1D2.

Prevention of Infusion-Related Reactions: Postdose Medications

Optional postdose medications may be prescribed and continued for up to 48 hours after any dose if clinically indicated, at the discretion of the investigator (Table 8).

Table 8: Postdose Medications for Amivantamab (all arms)

Medication	Dose	Route of Administration	Administration Instructions	Cycle/ Day
Optional Postdose 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.

Treatment of Infusion-Related Reactions

Participants who experience early symptoms of IRRs, manifesting 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 9. With the initial dose of amivantamab (Cycle 1, Day 1 for Arm A and Cycle 1, Days 1 and 2 for Arm B), 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.

Management of Local Administration Related Reactions

Local administration related reactions are considered a potential risk of subcutaneous administration. Subcutaneous administration of amivantamab in abdominal subcutaneous tissue was associated with LARRs, such as induration and erythema, in some participants. Local administration related reactions should be managed per institutional standards. The prophylactic and reactive management recommendations for LARRs are the same as those of infusion-related reactions (as described above).

Table 9: Management of Infusion-related Reactions

Toxicity Grade[a]	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction	Monitor participant as medically indicated until recovery from symptoms. If occurring with initial dose (ie, Cycle 1 Day 1 or Day 2), consider early infusion interruption to prevent more severe symptoms.	Antihistamine, antipyretic, and glucocorticoid.
Grade 2 Moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment	**Interrupt infusion, if ongoing** If clinically indicated, start IV fluids; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol (acetaminophen) 650 to 1000 mg; consider corticosteroids and bronchodilator therapy; 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 IPPI schedule, after the infusion has been administered for at least 30 minutes at 100% of the infusion rate used at the time of dose interruption. **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 IPPI schedule, 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. Consider meperidine if participant experiences chills and rigors.

Table 9: Management of Infusion-related Reactions

Toxicity Grade[a]	Treatment	Premedication at Subsequent Dosing
Grade 3 or 4 Grade 3: severe reaction, prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: life-threatening; pressor or ventilator support indicated	**Stop infusion, if ongoing** 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 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed (other drugs as appropriate). Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids), as appropriate.	Based on severity of symptoms, consider permanent discontinuation of study treatment. Consultation with Medical Monitor required before continuing with subsequent dosing.

eCRF=electronic case report form; IPPI=Investigational Product Preparation Instructions; IRR=infusion-related reaction; IV=intravenous.

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

6.5.3.2. 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.

Prophylaxis Recommendations

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. UVA light can penetrate glass; therefore, sunscreen should also be worn indoors and in vehicles if exposed to direct sunlight. Recommended active sunscreen ingredients are zinc oxide and/or titanium dioxide.
- Apply alcohol-free emollient cream or ointments (eg, glycerin, cetomacrogol, or ceramide-based cream) or skin moisturizer on dry areas of the body. 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.
  - Strongly consider initiating antibiotic therapy on Cycle 1 Day 1 and continuing antibiotic therapy for the first 8 weeks: either a topical antibiotic (clindamycin, mupirocin, or fusidic acid) on sun-exposed skin, or an oral antibiotic (such as doxycycline 100 mg once daily, minocycline 100 mg once daily, or cephalexin 500 mg once daily).
  - A topical corticosteroid of medium to low potency twice daily 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).
- Initiate a topical corticosteroid (cream or ointment) twice daily
  - Examples to use for face: betamethasone valerate 0.05%, hydrocortisone valerate 0.2% or desonide 0.05%
  - Examples to use for body: betamethasone valerate 0.1%, triamcinolone acetonide 0.1%
- If not already initiated for prophylaxis, initiate systemic antibiotic (such as doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily), or increase the dosing if already administered.
- If an associated skin infection is suspected, obtain bacterial and fungal cultures followed by adjustment of antibiotic or antifungal therapy, based upon culture and susceptibility determination.
- For skin fissures, use of Monsel's solution (ferric subsulfate solution), silver nitrate, zinc oxide cream, or cyanoacrylate sealant 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 10.

Table 10: Suggested Algorithm for Management of Rash

Grade[a]	Management	Dose Adjustment
1	• Initiate reactive management as above • Reassess after 2 weeks	Continue current dose(s) of amivantamab and lazertinib
2	• Initiate reactive management as above • Reassess after 2 weeks	Continue current dose(s) of amivantamab and lazertinib. Refer to the dose modification guidance for further instructions.
3	• Initiate reactive management as above • Start moderate strength topical corticosteroids[c] 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 after 2 weeks • Consider dermatology consultation and manage rash per recommendation	Temporarily withhold lazertinib until rash improves to Grade ≤2 (If rash does not improve by the next scheduled amivantamab dose, then amivantamab administration should be held as well until the rash improves to Grade ≤2)[b]. Refer to the dose modification guidance for further instructions
4	• Initiate reactive management as above • Start moderate strength topical corticosteroids[c] 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 after 2 weeks • Consider dermatology consultation and manage rash per recommendation	Permanently discontinue amivantamab and hold lazertinib. Consider restarting lazertinib per investigator assessment of causality, once resolved.
Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN)	• Consult dermatologist and manage rash per recommendation	Permanently discontinue amivantamab and hold lazertinib. Consider restarting lazertinib per investigator assessment of causality, once resolved.

a. Grading per National Cancer Institute - Common Terminology Criteria for Adverse Events (Version 5.0).
b. If amivantamab must be withheld due to toxicity for ≥21 days, the study treatment cannot be restarted without consultation from the medical monitor. Participants considered by the investigator and sponsor to be benefiting from treatment may be continued, potentially at a lower dose upon satisfactory resolution of the toxicity.
c. For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream.

6.5.3.3. Suspected Pulmonary Toxicity

Participants 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, including a change in radiographic lung images, 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 adverse event is observed, including ILD/pneumonitis, study treatments 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, SARS-CoV-2 testing, and broader viral panels 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

Documentation of ILD/pneumonitis of any grade should prompt withholding study treatment and contacting the Medical Monitor. Pertinent radiological images and reports should be submitted to the Sponsor. For symptomatic participants with pneumonitis (Grade 2 and above), treatment with steroids should be initiated per local guidelines, in addition to withholding of study treatment. Study treatment/s should be discontinued upon confirmation of ILD/pneumonitis. In the absence of a diagnosis of ILD/pneumonitis, study treatment may be restarted.

6.5.3.4. 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 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.

- QTcF 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, 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 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, lazertinib and amivantamab should be reduced by 1 dose level each (see Table 5).
  - 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

- Drug-related absolute LVEF decline of >10% from baseline 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 at least 2 weeks after initial assessment to monitor status.
- Symptomatic CHF:
  - Permanently discontinue all study treatments.

6.5.3.5. 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 ≥Grade 3 severity (refer to Section 6.5.2). In addition, if the following

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

a) ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) and bilirubin ≥2×ULN (if baseline was normal; ≥2×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.

b) ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) and INR >1.5 if INR is measured.

c) ALT or AST ≥3×ULN (if baseline was normal; ≥3×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 to 3 days and until abnormal values resolve/return to baseline. Etiology of the liver chemistry abnormality should be investigated, as described in Appendix 7. If no alternative etiology of liver toxicity is identified, all study treatments should be permanently discontinued.

6.5.3.6. 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 twice daily. If still pruritic after 2-5 days, may increase to double dose twice daily.

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).

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

Grade 2 or 3 paronychia:

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

6.5.3.8. 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 (≥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%-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%-5% or solution 4 times per day.

6.5.3.9. Diarrhea

Reactive Management Recommendations

If participants experience diarrhea, they should be encouraged to drink 8 to 10 large glasses (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 CYP3A4/5 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 11.

Table 11: 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 ≤Grade 1 within 24 hours despite use of loperamide, hold treatment until ≤Grade 1. • If diarrhea of >Grade 1 recurs after initial improvement, consider reduction by one dose level (see Table 5 and Table 6).
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 twice daily with escalation to 500 µg 3 times daily. • Consider hospitalization if does not improve to ≤Grade 2 within 24 hours, or in presence of fever, abdominal pain, etc.	• Withhold study treatment(s). Upon resolution to ≤Grade 1, resume study treatment(s) with consideration of reduction by 1 dose level see Table 5 and Table 6).
4	• Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of investigator for fever, leukocytosis, marked dehydration, etc.	• Hold study treatment until ≤Grade 1. Mandatory dose reduction by 1 dose level (see Table 5 and Table 6).

6.5.3.10. Venous Thromboembolic Events

Patients with NSCLC are at risk of developing complications, including VTE events. Investigators should closely monitor 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 8.2.1) should include focus on 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.

All study participants are recommended to receive prophylactic-dose anticoagulation as per local guidelines during the first 4 months of combination therapy. Vitamin K antagonists are not recommended due to numerous drug interactions. The benefit-risk assessment for participants to tolerate prophylactic-dose anticoagulation is at the discretion of the treating investigator. Notably,

prophylactic-dose anticoagulation has been found to be safe and effective in multiple prior studies (Carrier 2019, Rutjes 2020, NCCN Guidelines Version 1.2022).

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 the combination of amivantamab and lazertinib, study treatment should be held until the patient recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator.

In the case of a recurrent VTE whilst on therapeutic anticoagulation therapy, the combination of amivantamab and lazertinib should be permanently discontinued. Participants may continue to receive treatment with either amivantamab or lazertinib (but not both) at the discretion of the treating physician.

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

The sponsor will make every effort to ensure that participants benefiting from treatment with amivantamab will be able to continue receiving treatment after the end of the study; see details for the LTE Phase (Section 10.15 [Appendix 15]) and Section 4.1.4.

6.7. Treatment of Overdose

There are no data on overdose from studies of amivantamab or lazertinib (refer to IB for each agent). 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 should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Concomitant Therapy

6.8.1. Recording Prestudy and Concomitant Therapies

Prestudy therapies administered up to 28 days before randomization must be recorded. Concomitant therapies must be recorded throughout the study beginning with randomization to 30 days after the last dose of study treatment or start of subsequent anticancer therapy, whichever is first. Concomitant therapies should also be recorded beyond 30 days only in conjunction with SAEs and Grade 3 or Grade 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, exercise regimens, or other specific categories of interest) different from the study treatment must be

recorded in the eCRF. 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.

6.8.2. Permitted and Required Medications and Therapies

6.8.2.1. Pre- and Post-dose Medications for Amivantamab

See Section 6.5.3.1.

6.8.2.2. Supportive Care

Concomitant medications for the symptomatic treatment of related toxicities (Grades 1 through 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.

6.8.2.3. Radiotherapy

Localized, limited radiotherapy of short duration for palliative purposes of nontarget lesions may be permitted, but only after consultation with the Medical Monitor.

6.8.3. Prohibited or Restricted Medications and Therapies

Prohibited Medications and Therapies

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

- Any chemotherapy or systemic anticancer therapy, approved or experimental, other than study treatments, except as allowed by Exclusion criterion #8.
- Radiotherapy to target lesions prior to disease progression.
- Use of live or live attenuated vaccines. (Except for live or live attenuated vaccines, vaccination is allowed per local guidelines including annual influenza and inactivated SARS-CoV-2 vaccines; see also stand-alone appendix.)
- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.
- Prescription and over the counter medications, herbal supplements and/or ingestion of foods with known potent inducer effects on CYP3A4/5 activity (For some examples see: US FDA. Drug development and drug interactions: Table of Substrates, Inhibitors and Inducers 2022). Strong inducers of CYP3A4/5 are prohibited and should be discontinued for an appropriate period (at least 4 elimination half-lives) before starting study treatment. 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 End of Treatment visit and should be avoided, when possible, or used with caution:

- Avoid concomitant use of CYP3A4/5 substrate drugs and medications known to be strong inhibitors of CYP3A4/5 (For some examples see: US FDA. Drug development and drug interactions: Table of Substrates, Inhibitors and Inducers 2022). 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-gp, MRP4, BCRP, and OCT1 should be used with caution (For some examples see: US FDA. Drug development and drug interactions: Table of Substrates, Inhibitors and Inducers 2022). Please contact the local pharmacist or Medical Monitor with any questions.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

A participant's study treatment must be discontinued if any of the following apply:

- The participant withdraws consent to receive study treatment
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study treatment
- The participant becomes pregnant
- Noncompliance with study drug administration or procedure requirements as judged by the investigator
- Radiographic disease progression using RECIST (Version 1.1) (**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.)

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

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

Withdrawal of Consent

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

7.2.1. Withdrawal From the Use of Research Samples

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

7.3. Lost to Follow-up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedules of Activities summarize the frequency and timing of measurements applicable to this study.

The modified TASQ should be completed after study drug administration. PGIS should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses, when possible.

The total blood volume to be collected from each participant depends upon the duration of participation and the required blood volume for local laboratory assessments. Through the first 5 cycles of treatment and the End of Treatment visit, the total amount of blood drawn from each

participant in this study is anticipated to be approximately 376 mL. Depending on country/territory-specific regulations, the total blood volume may vary.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If Cycle 4 Day 1 dose is delayed or withheld, the amivantamab serum PK sample should be collected on the planned day per protocol. This collection will be considered an unscheduled serum PK sample. Refer to the Schedules of Activities for the timing and frequency of all sample collections. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Sample collection and testing will comply with local regulations.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Study protocol (and any amendments)
- IB for amivantamab
- IB for lazertinib
- IPPI and SIPPM; amivantamab SC-CF IPPI
- PQC reporting form
- Laboratory manual and kits
- eCRF completion guidelines
- IWRS Manual
- eDC Manual
- Imaging Manual
- NCI CTCAE Version 5.0
- RECIST guidelines, Version 1.1
- PRO questionnaires and PRO completion guidelines
- Tablet (for PRO collection)
- Sample ICF
- Wallet cards
- Study treatment

8.1. Efficacy Assessments

Disease assessment will be performed using CT, MRI, and other imaging/examination, as applicable, of the chest, abdomen, pelvis, brain, and any other disease location at Screening, 6 (+1) weeks from randomization, every 6 (±1) weeks for the first 18 months, then every 12 (±1) weeks thereafter until PD. Repeat brain imaging will be performed every 6 weeks if brain mets are present at baseline and being followed as non-target lesions and if there are no brain mets at baseline then perform as clinically indicated. For participants who discontinue treatment prior to PD, tumor imaging should continue until PD is documented. If participant begins a new anticancer therapy before PD, tumor imaging should be obtained before the new therapy. If a participant receives study treatment beyond confirmed documented PD, continue disease assessments as scheduled. Tumor response evaluation will be assessed by the investigator according to RECIST v1.1. Further details are provided in the Imaging Manual.

8.1.1. Patient-Reported Outcomes

Patient-reported outcomes measures will be collected at the times specified in the Schedule of Activities. The PRO instrument will be provided in the local language in accordance with local guidelines. The PRO instrument must be available for regulators and for IRB/IRC submissions, therefore the PRO instrument or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol. The PRO and AE data will not be reconciled with one another.

The modified TASQ (Appendix 14) is an 11-item questionnaire measuring the impact of each mode of treatment administration on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. Example questions include, “How satisfied or dissatisfied were you with the SC injection/IV infusion?”, “How much pain did you experience at the site of the SC injection/IV site?”, and “How convenient is it for you to get your SC injection/IV infusion?” The modified TASQ-IV will be completed by participants in Arm B and the modified TASQ-SC by participants in Arm A. The modified TASQ should be completed after the study drug administration.

The TASQ was derived from the Rituxan Administration Satisfaction Questionnaire (RASQ). Modification addresses the administration site of amivantamab. TASQ is designed for an adult population to measure the impact of the mode of treatment administration on 5 domains, including 9 items: Physical Impact (3 items), Psychological Impact (1 item), Impact on Activities of Daily Living (1 item), Convenience (2 items), and Satisfaction (2 items). Recall/Observation period is based on participants most recent SC injection/IV infusion (Theodore-Oklota, 2016).

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) are single-item questionnaires that provide an anchor-based comparison for the TASQ. The PGIC will not be administered at the first visit because it captures change.

The PGIS should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses, when possible.

8.2. Safety Assessments

Independent Data Monitoring Committee

Details regarding the IDMC are provided in Committees Structure in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. The frequency of IDMC meetings will be described in the IDMC charter. A first IDMC meeting will be held after the first 20 participants complete 2 cycles of treatment. AEs will be reported and followed by the investigator as specified in Section 8.3 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 Schedule of Activities.

Medical history, including but not limited to, all ongoing relevant and clinically significant comorbidities according to NCI-CTCAE Version 5.0, including severity grade will be recorded during screening.

8.2.1. Physical Examinations

A complete physical examination will be conducted at screening. Symptom-directed physical examinations will be conducted thereafter. Clinically significant postbaseline abnormalities should be reported as AEs.

Participants should be questioned for skin and eye symptoms at all visits 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, directed physical examinations of involved organs and other body systems, as indicated, will be performed and participant BW will be obtained.

8.2.2. ECOG Performance Status

Assessment of ECOG status should be part of regular ongoing clinical monitoring of patients. Decline in ECOG performance status score (refer to Appendix 10: Eastern Cooperative Oncology Group (ECOG) Performance Status) should be reported as an AE.

8.2.3. Vital Signs

Vital sign measurements will include the following assessments:

- Temperature
- Heart rate
- Oxygen saturation
- Blood pressure

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

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

For participants receiving IV amivantamab, collect vital sign measurements ≤30 minutes before amivantamab infusion, at 30-minute intervals (±5 minutes) during each amivantamab infusion, and at the end of the infusion (±5 minutes).

8.2.4. 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 single ECG recording, the procedures should be performed in the following order: single ECG(s), vital signs, blood draw.

Clinically significant abnormal results should be confirmed by triplicate ECG assessments.

At each time point at which triplicate ECGs are required, 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.

8.2.5. LVEF measurements by echocardiography (ECHO) or Multigated Acquisition (MUGA) scan

During the Screening Phase each participant will undergo a baseline LVEF assessment performed locally by cardiac echocardiogram or MUGA scan to demonstrate eligibility (ie, a LVEF within the normal range).

8.2.6. Ophthalmologic Assessment

An ophthalmologic assessment, including slit lamp examination, fundoscopic examination, and visual acuity test will be performed at screening and should be repeated if a participant experiences any visual symptoms (including blurring of vision), with additional tests if clinically indicated.

Clinically significant findings noted at screening should be included in the medical history, and not as an AE. After screening, any clinically significant findings, including those confirmed by the ophthalmologist, must be reported as an AE. Photographs, especially of anterior eye, should be performed to record any clinically significant findings. These photographs should be available for review by the Medical Monitor if necessary. Ophthalmology examination results should be recorded in the eCRF.

8.2.7. Pregnancy Testing

For women of childbearing potential, a negative serum pregnancy test is required at screening. A negative serum or urine pregnancy test is required within 72 hours before Day 1 of each cycle, at the EOT Visit, monthly during treatment and through 7 months after the last dose of study treatment. At other times, a serum or urine pregnancy test should be performed as clinically indicated, according to local regulation requirements, or following the local practice of the study site.

8.2.8. Clinical Safety Laboratory Assessments

Clinical laboratory assessments will be performed locally. Blood samples for serum chemistry, hematology, coagulation, and a urine sample for urinalysis as noted in Appendix 6: Clinical Laboratory Tests will be collected at the times listed in the Schedules of Activities. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. The laboratory reports must be filed with the source documents. At the start of each new cycle, the investigator must confirm that participants meet treatment criteria.

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

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study. Further details on AEs, SAEs, and PQCs can be found 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.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after last dose of study treatment (or >30 days for an SAE, if considered related to study treatment).

Serious Adverse Events

All SAEs as well as PQC occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 24 hours of their knowledge of the event.

SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

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

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

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

Adverse events and the special reporting situation of pregnancy will be followed by the investigator as specified 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.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

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 are discussed in Appendix 4: Anticipated Events.

8.3.5. Pregnancy

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

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, and any postnatal sequelae in the infant will be required.

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

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

Expected progression of disease, which is part of the natural course of the disease under study, should not be considered or reported as an adverse event (or serious adverse event).

However, if determined by the investigator to be more likely related to the study treatment, protocol design, or protocol procedures than being expected from the underlying disease, the treatment-invoked progression (ie the treatment-invoked signs/symptoms of such progression) should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications 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).

Death that is attributed by the Investigator explicitly to progression of disease should not be considered nor reported as an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment, protocol design, or protocol procedures than being expected from the underlying disease, the treatment-invoked death due to progression should be reported

per the usual reporting requirements (refer to Adverse Event Definitions and Classifications 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).

Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form). Signs or symptoms of disease progression that are of clinical significance, such as, but not limited to, spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure should be documented on the appropriate eCRF forms (eg, the Clinical Progression form).

8.3.7. Adverse Events of Special Interest

AEs of special interest are pneumonitis/ILD, rash, IRR, LARR and VTE. Additional information will be collected for these events. Refer to the monitoring and management guidelines for these events in Section 6.5.3. Confirmed cases of pneumonitis/ILD (regardless of grade) should be reported as SAEs (see Section 8.3.1). All Grade 3 or 4 IRRs should be reported within 24 hours to the Medical Monitor (ie, via email). Events of rash and VTE should follow standard reporting guidelines.

8.4. Pharmacokinetic and Immunogenicity Assessments

8.4.1. Evaluations

Blood samples to assess the serum concentration (PK) of amivantamab, the plasma concentration of lazertinib (PK), and the generation of antibodies to amivantamab (immunogenicity) will be obtained from all participants according to Section 1.3.2.

Plasma samples will also be collected to evaluate the immunogenicity of rHuPH20 according to Section 1.3.2.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual. Samples collected for determining serum concentrations/immunogenicity of amivantamab or immunogenicity of rHuPH20 in this study may be retained to address questions about drug characteristics that may arise at a later time point.

Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.4.2. Analytical Procedures

Serum and plasma samples will be analyzed to determine concentrations of amivantamab and lazertinib, respectively, using a validated method by or under the supervision of the sponsor. In addition, serum and plasma PK samples may be stored for future analysis.

The detection and characterization of antibodies to amivantamab and rHuPH20 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to amivantamab will also be evaluated for amivantamab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug(s). Samples may be stored up to 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to amivantamab and rHuPH20.

8.4.3. Pharmacokinetic Parameters and Evaluations

The PK assessments are defined as follows:

- C_{trough} Observed concentration immediately prior to the next drug administration
- $AUC_{(D1\text{-}D15)}$ Area under the concentration time curve from Day 1 to Day 15

The primary PK endpoints are C_{trough} (at steady state in Cycle 4 Day 1 for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) prior to administration of Cycle 2 Day 1 dose and $AUC_{D1\text{-}D15}$ at Cycle 2. The secondary endpoint, model-predicted $AUC_{D1\text{-}D15}$ at Cycle 4, will be estimated based on the Population PK modeling. The details and the results of the Population PK modeling and simulation will be presented in a separate report.

The incidence of anti-amivantamab antibodies will be summarized for all participants who receive a dose of amivantamab and have appropriate samples for detection of antibodies to amivantamab. The prevalence and incidence of anti-rHuPH20 antibodies will be summarized for all participants who receive a dose of amivantamab co-formulated with rHuPH20 and have appropriate samples for detection of anti-rHuPH20 antibodies.

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

8.5. Pharmacogenomics

Pharmacogenomics are not evaluated in this study.

8.6. Biomarkers

Blood Samples

Baseline blood samples collected from all participants may undergo ctDNA analysis by the sponsor to evaluate pretreatment mutational status of EGFR, cMET, and other key oncogenes to characterize the tumor. Additional blood samples will be collected during the study and may be evaluated for ctDNA to assess changes in the levels or types of genetic alterations observed over time, and to monitor for the emergence of potential markers of resistance to the study therapy. Blood samples will also be collected at the time points specified in the Schedule of Activities and

may be analyzed to investigate circulating factors, eg cytokines, associated with response to treatment.

Analysis

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

Additional Collections

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

8.7. Medical Resource Utilization and Health Economics

Time and motion studies will evaluate participant chair time, treatment room time, duration of treatment administration, and active HCP time for drug preparation, treatment administration, and post-treatment monitoring.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

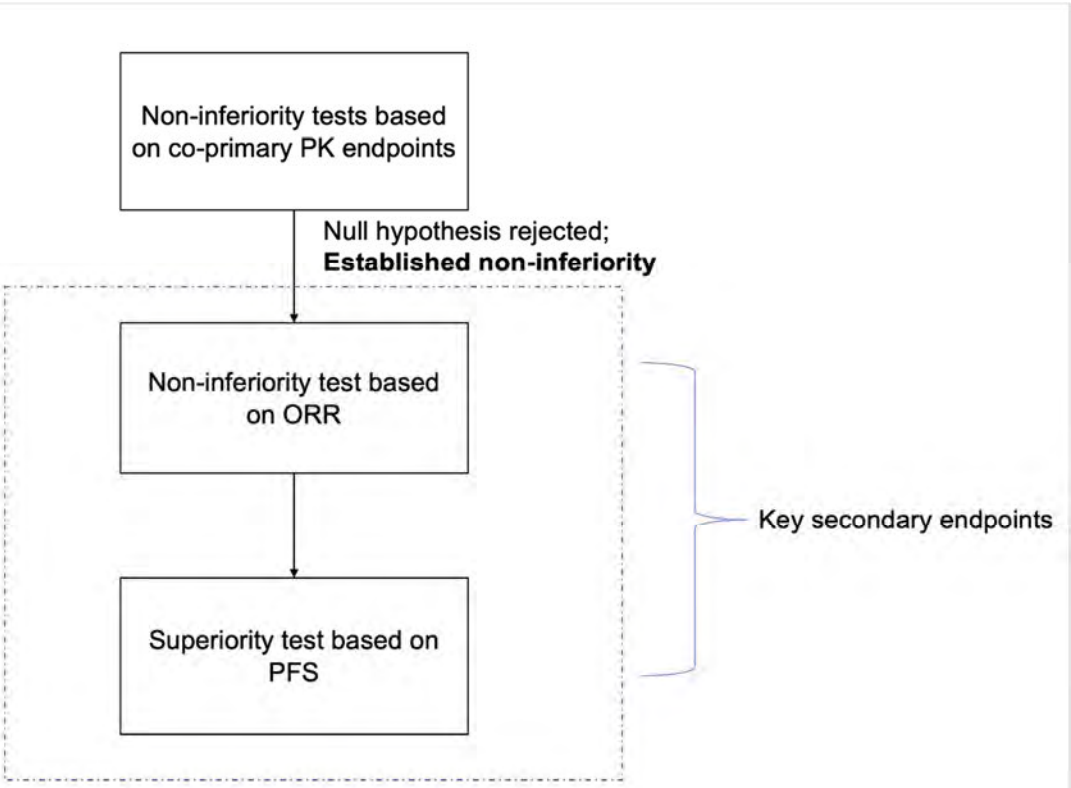
The primary statistical hypothesis of the study is that amivantamab SC-CF, administered via manual injection at the RP2D, is noninferior to amivantamab IV based on the co-primary pharmacokinetics endpoints, C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and $AUC_{D1\text{-}D15}$ in Cycle 2. The hypotheses are the lower bounds of the 90% CI for the ratio of the geometric means of amivantamab SC-CF vs amivantamab IV are at least 80% (non-inferiority margin of 20%) for both C_{trough} (at steady state of amivantamab in Cycle 4 Day 1 for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and $AUC_{D1\text{-}D15}$ in Cycle 2.

A key secondary hypothesis is that amivantamab SC-CF, administered via manual injection at the RP2D, is noninferior to amivantamab IV based on ORR in the aforementioned population. The

hypothesis is that the lower bounds of the 95% CI for the relative risk of amivantamab SC-CF vs amivantamab IV for ORR is ≥60%. Another key secondary hypothesis is that amivantamab SC-CF will reduce the risk of either disease progression or death compared with amivantamab IV.

To control familywise Type I error rate at a two-sided significance level of 0.05, a hierarchical procedure for hypothesis testing between primary PK endpoints and key secondary efficacy endpoints will be implemented. Once the null hypothesis of inferiority is rejected for both the C_{trough} (at steady state for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and $AUC_{D1\text{-}D15}$ in Cycle 2, a testing for ORR and PFS at a two-sided significance level of 0.05 will be tested in a sequential order (Figure 2).

Figure 2: Primary and Key Secondary Endpoints Testing Strategy



9.2. Sample Size Determination

200 participants will be randomized to Arm A and 200 participants will be randomized to Arm B. (Figure 1).

The study is designed to establish noninferiority based on the co-primary pharmacokinetics endpoints, C_{trough} (at steady state of amivantamab in Cycle 4 Day 1 for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and $AUC_{D1\text{-}D15}$ in Cycle 2, between amivantamab SC-CF and amivantamab IV. Amivantamab SC-CF will be considered noninferior to IV if the lower bound of the 90% CI for the ratio of the geometric means of C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than

EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and AUC_{D1D15} in Cycle 2 is at least 80% (noninferiority margin of 20%). The planned 400 participants (200 from Arm A and 200 from Arm B) will provide a power >95% for a one-sided alpha of 0.05 for each of the endpoints. This assumes a true geometric mean ratio of C_{trough} to be 1 and a true geometric mean ratio of the AUC_{D1D15} to be 1 between the 2 treatment groups, and a coefficient of variation (CV) of 56% for both endpoints.

One of the key secondary objectives is to assess efficacy of SC-CF (Arm A) compared to IV (Arm B) in terms of ORR. In a previous clinical study (73841937NSC1001), of 50 participants with locally advanced or metastatic NSCLC with EGFR Exon 19del or Exon 21 L858R mutations whose disease had progressed on or after treatment with osimertinib and platinum-based chemotherapy and who were treated with the combination of amivantamab IV and lazertinib, an ORR of 32.1% (95% CI:23.3%, 41.8%) was observed. Non-inferiority of amivantamab SC-CF to amivantamab IV in the current study is defined using a 60% retention of the lower bound (23.3%) of the 95% CI from Study 73841937NSC1001. With a planned 1:1 randomization, the sample size of 400 participants will provide 80% power to demonstrate the non-inferiority of Arm A compared with Arm B, with a one-sided alpha of 0.025, assuming the true ORR is the same for both treatment arms.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Full analysis set	All participants who were randomized in the study
PK primary endpoint evaluable	For applicable regions per health authority recommendation: • All randomized participants who receive all doses in Cycle 1, without dose modifications and provide Cycle 2 Day 1 C_{trough} • All randomized participants who receive all doses in Cycle 1-3, without dose modifications and provide Cycle 4 Day 1 C_{trough}, OR • All randomized participants who receive all doses up to Cycle 2 Day 1, without dose modifications and provide all necessary PK samples to derive Cycle 2 AUC_{D1-D15} based on which Cycle 4 Day 1 C_{trough} would be predicted using per protocol dosing and population PK modeling and simulation. For all regions: • All randomized participants who receive all doses up to Cycle 2 Day 1, without dose modifications and provide all necessary PK samples to derive primary PK endpoint Cycle 2 AUC_{D1-D15}.
Other PK - evaluable	All randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline concentration measurement. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK.
Safety	All randomized participants who receive at least 1 dose of study drug.
Immunogenicity	All participants who receive at least 1 dose of study drug and provide at least 1 postdose immunogenicity sample.
Biomarker	All participants who receive at least 1 dose of study drug and provide at least 1 postdose biomarker sample.

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

9.4. Statistical Analyses

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

9.4.1. General Considerations

Continuous variables will be summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables will be summarized with frequency counts and percentages. The Kaplan-Meier product limit method and a stratified Cox model will be used to estimate time-to-event variables and to obtain the HR and confidence interval. Unless otherwise specified, stratified log-rank tests will be used to test the treatment effect for time-to-event variables; response rate variables will be evaluated using the chi square statistic or the exact test if the cell counts are small.

9.4.2. Primary Endpoints

The co-primary PK noninferiority endpoints are defined as follows:

All regions other than EU and others accepting Cycle 2 Day 1	EU and any applicable region
C_{trough} on Cycle 4 Day 1	C_{trough} pre-dose on Cycle 2 Day 1

All regions
AUC_{D1-D15} in Cycle 2

The primary estimand for the co-primary PK endpoints, the main clinical quantity of interest to be estimated, is defined by the following components:

- **Study treatment**:
  - **Experimental**: Amivantamab SC-CF administered via manual injection
  - **Control**: Amivantamab IV
- **Population**: participants with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy
- **Variable**: PK endpoint, C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region) and AUC_{D1-D15} in Cycle 2
- **Population-level summary**: Ratio of geometric means (C_{trough} [at steady state Cycle 4 Day 1 for all regions other than EU and others accepting Cycle 2 Day 1 and pre-dose on Cycle 2 Day 1 for EU and any applicable region] and AUC_{D1-D15} in Cycle 2) between SC-CF and IV administrations
- **Intercurrent events and their corresponding strategies:** no additional intercurrent events

The ratio of the geometric means and the corresponding 90% CI between Arm A and Arm B for each primary endpoint will be provided based on the PK Analysis Set. Summary statistics such as the geometric mean, coefficient of variation, median, and range will be provided by treatment group.

9.4.3. Secondary Endpoints

C_{trough}

In regions other than EU and others accepting Cycle 2 Day 1, a C_{trough} of amivantamab pre-dose on Cycle 2 Day 1 will be a secondary endpoint. Similar analysis method used for the primary endpoint will be used.

In EU and any applicable region, a C_{trough} of amivantamab at steady state (Cycle 4 Day 1) will be a secondary endpoint. Similar analysis method used for the primary endpoint will be used.

ORR

The key secondary endpoint of ORR is defined as the proportion of participants who achieve either a complete response or PR as best response, based on RECIST v1.1. Data obtained up until progression or last evaluable disease assessment in the absence of progression will be included in the assessment of ORR. Participants who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate.

The primary estimand for ORR, the main clinical quantity of interest to be estimated, is defined by the following components:

- **Study treatment**:
  - **Experimental**: Amivantamab SC-CF administered via manual injection
  - **Control**: Amivantamab IV
- **Population**: participants with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy
- **Variable**: overall response
- **Population-level summary**: odds ratio of amivantamab SC-CF vs amivantamab IV
- **Intercurrent events and their corresponding strategies**

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment switching to other anticancer therapy	**Hypothetical strategy**: use best overall response until subsequent anti-cancer therapy

ORR will be analyzed using a logistic regression stratified by randomization strata. The results of the analysis will be presented in terms of a risk ratio together with its associated 95% confidence intervals. If the lower bound of the 95% CI is ≥60%, the non-inferiority of amivantamab SC-CF relative to amivantamab IV will be concluded. If non-inferiority in ORR is established and the lower limit of the 95% CI of the relative risk is >100%, the superiority of amivantamab SC-CF relative to amivantamab IV will be concluded.

PFS

The key secondary endpoint of PFS is defined as the time from randomization until the date of objective disease progression or death, whichever comes first, based on RECIST v1.1.

The primary estimand for PFS, the main clinical quantity of interest to be estimated, is defined by the following components:

- **Study treatment**:
  - **Experimental**: Amivantamab SC-CF administered via manual injection
  - **Control**: Amivantamab IV
- **Population**: participants with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy
- **Variable**: time to event, PFS
- **Population-level summary**: odds ratio for amivantamab SC-CF vs amivantamab IV
- **Intercurrent events and their corresponding strategies**

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not study treatment discontinuation had occurred
Study treatment switching to other anticancer therapy	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not started subsequent anticancer therapies
Death	**Composite Variable strategy:** death being a component of the variable

The median PFS and 95% CI in each treatment group will be estimated using the Kaplan-Meier method. The PFS distributions between the 2 treatment groups will be compared using the stratified log-rank test. The treatment effect (hazard ratio) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Duration of Response (DoR)

The DoR is defined as the time from the date of first documented response (PR or CR) until the date of documented progression or death, whichever comes first, for participants who have PR or CR. A Kaplan-Meier plot and median duration of response with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented by treatment group.

Time to Response (TTR)

Time to response (i.e. time to first response) is defined as the time from the date of randomization to the date of first documentation of a response (PR or CR) prior to any disease progression and subsequent anticancer therapy, as defined by RECIST v1.1., for participants who have PR or CR as their best response. A descriptive summary for TTR will be provided.

Modified Therapy Administration Satisfaction Questionnaire

This validated PRO instrument is designed to assess patient satisfaction with cancer therapy. Descriptive statistics will be reported for the individual items and domain scores at baseline and at each visit for absolute value and for change from baseline.

Time and motion analysis

The time and motion analysis is a healthcare burden impact study investigating differences in participant chair time, treatment room time, duration of treatment administration, and active HCP

time for drug preparation, treatment administration, and post-treatment monitoring. Descriptive statistics will be provided for the analysis by country/territory and pooled.

Immunogenicity

The incidence of anti-amivantamab antibodies will be summarized for all participants who receive a dose of amivantamab and have appropriate samples for detection of antibodies to amivantamab. The incidence of anti-rHuPH20 antibodies will be summarized for all participants who receive a dose of amivantamab SC-CF and have appropriate samples for detection of anti-rHuPH20 antibodies.

Model predicted AUC_{ss}

Model-predicted AUC at steady state will estimate exposures for Cycle 4 Day 1- Day 15 using Population PK approach. Population PK analysis of serum concentration-time data of amivantamab will be performed using nonlinear mixed-effects modeling (NONMEM) and may be combined with similar data from other studies, with the aim of providing estimates of AUC_{ss}. Details will be provided in a population PK and exposure-response analysis plan and results of the analysis will be presented in a separate report.

9.4.4. Exploratory Endpoint(s)

Additional details about the exploratory endpoints analyses will be described in the Statistical Analysis Plan or a separate analysis plan.

Biomarkers

Biomarkers analyses will use the Biomarkers Population. Each baseline tumor status may be evaluated by ctDNA NGS analysis, for exploratory purposes, to characterize potential mechanisms of resistance to amivantamab and lazertinib, and to evaluate the presence of mutations across treatment arms, as permitted by local regulations.

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

Efficacy

Overall Survival (OS): The OS is defined as the time from the first dose of study treatment until the date of death due to any cause. The median OS and 95% CI will be estimated using the Kaplan-Meier method for each arm.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. Any AE occurring at or after the initial administration of study treatment through 30 days after the last dose of study treatment but prior to the start of subsequent anticancer therapy, is considered to be treatment emergent. Any SAE that occurs beyond the 30 days after the last dose of study treatment and is considered related to study treatment will be considered as treatment emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an AE, or who experience a ≥Grade 3 AE or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) 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. Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

Ab	antibody
AE	Adverse events
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	Auxiliary Medicinal Product (also known as NIMP)
BCRP	breast cancer resistance protein
BW	body weight
CD4	cluster of differentiation 4
CF	co-formulation
CHF	congestive heart failure
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma/serum concentration
cMET	mesenchymal-epithelial transition factor
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Regulations
ctDNA	circulating tumor deoxyribonucleic acid
C_{trough}	plasma/serum concentration immediately prior the next study treatment administration
CV	coefficient of variation
CYP	cytochrome P450
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
eDC	electronic data capture
EGFR	epidermal growth factor receptor
EU	European Union
FDA	US Food & Drug Administration
FOCBP	female participant(s) of childbearing potential
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HAART	highly active antiretroviral therapy
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCP	health care professional
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFU	instructions for use
Ig	immunoglobulin
ILD	interstitial lung disease
IMP	Investigational Medicinal Product
INR	internationalized normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IV	intravenous(ly)

IWRS	interactive web response system
LARR	local administration related reaction
LLN	lower limit of normal
LTE	long-term extension
LVEF	left ventricular ejection fraction
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRP4	multidrug resistance protein 4
NIMP	Non-Investigational Medicinal Product
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OCT1	Organic Cation Transporter 1
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PO	per os, ie by mouth
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
Q2W	every 2 weeks
QTcF	corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
rHuPH20	recombinant human hyaluronidase
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	Serious adverse events
SC	subcutaneous(ly)
SC-CF	subcutaneous and co-formulated with recombinant human hyaluronidase
SIPPM	Site Investigational Product Procedures Manual
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TASQ	Therapy Administration Satisfaction Questionnaire
TKI	tyrosine kinase inhibitor
TTR	time to response
ULN	upper limit of normal
VTE	venous thromboembolic

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

10.2.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

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

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

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

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree

on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Country/Territory Selection

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

Other Ethical Considerations

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

10.2.2. Financial Disclosure

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

10.2.3. Informed Consent Process

Each participant (or a legally acceptable representative, as permitted by local regulations) must give written consent according to local requirements after the nature of the study has been fully

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

Informed consent may be obtained remotely by telephone or video conferencing where local policies and regulations permit.

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

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

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

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

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

10.2.4. Recruitment Strategy

Recruitment is closed, as of Amendment 4.

10.2.5. Data Protection

Privacy of Personal Data

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

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

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

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

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

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

10.2.6. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand amivantamab or lazertinib, to

understand differential treatment responders, and to develop tests/assays related to amivantamab, lazertinib, or NSCLC. The research may begin at any time during the study or the post-study storage period.

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

10.2.7. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. A first IDMC meeting will be held after the first 20 participants complete 2 cycles of treatment. After the review, the IDMC will make recommendations regarding the continuation of the study.

10.2.8. Publication Policy/Dissemination of Clinical Study Data

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

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

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

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright

protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

10.2.9. Data Quality Assurance

Data Quality Assurance/Quality Control

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

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor may review the eCRF for accuracy and completeness during

on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.2.10. Case Report Form Completion

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

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

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

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

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

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

10.2.11. Source Documents

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

The author of an entry in the source documents must be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

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

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

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

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

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

10.2.12. Monitoring

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

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

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

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

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

10.2.13. On-Site Audits

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

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.2.14. Record Retention

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. For trials performed under Regulation [EU] No 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

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

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

10.2.15. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

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.

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

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

10.3. Appendix 3: Adverse Events, 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 adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference 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 adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

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

Serious Adverse Event

A serious adverse event 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*

Note: Events that do not qualify as an AE cannot be reported as a SAE, even if the conditions for seriousness are met. In particular, this is the case for events due to disease progression leading to death, hospitalization, etc.

* 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 may not 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.

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

For combination products with a device constituent, SAEs include adverse device effects that resulted in any of the consequences characteristic of an SAE. An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3. Benefit-Risk Assessment).

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 the combination of lazertinib with either amivantamab and lazertinib, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.3.2. Attribution Definitions

Assessment of Causality

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

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

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

Special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF.

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 CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the 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 24hour 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 the study, 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 CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the

underlying condition for which the hospitalization was planned has not worsened, will not be considered 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.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment, protocol design, or protocol procedures 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.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

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.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study treatment. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

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.

Any device identified as having a product-defect related PQC will be returned to the sponsor or sponsor delegate for analysis in the original packaging.

Product quality complaints (PQC) will be reported for use error or product defects. Investigational product with product defect complaints will be sent back to sponsor for root cause analysis per the PQC process. Note that while all devices will be returned to the sponsor, devices with a PQC should be returned via the PQC process and returned in a special container provided by the sponsor.

10.3.7. 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.

10.4. Appendix 4: Anticipated Events

An anticipated event is an AE (serious or nonserious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. For the purposes of this study, the events in Table 12 will be considered anticipated events:

Table 12: 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
	Anemia
Malignant pleural effusion	
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

Reporting of Anticipated Events

All AEs will be recorded in the eCRF, regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 8.3. Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 8.3. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) per applicable clinical trial legislation to Health Authorities and IRB/IECs (Note: Japan will not identify anticipated events for the Health Authorities). If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

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

Safety Assessment Committee (SAC)

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

Statistical Analysis

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

10.5. Appendix 5: Contraceptive and Barrier Guidance

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

Definitions

Females of Childbearing Potential (FOCBP)

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

Females Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in a female participant on HRT, the female participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.

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

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

Contraceptive (birth control) use by male or female participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

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

Examples of Contraceptives

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

a) Typical use failure rates may differ from those when used consistently and correctly. Use must 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.
c) Male condom and female condom must not be used together (due to risk of failure with friction).

10.6. Appendix 6: Clinical Laboratory Tests

The following tests will be performed by the local laboratory according to the Schedule of Activities:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hemoglobin Platelet count Mean corpuscular volume (MCV)	Absolute neutrophil count White blood cell (WBC) count with differential
Clinical Chemistry	**At Each Assessment (Including Screening)** Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase Total bilirubin Lactic acid dehydrogenase (LDH) Magnesium Potassium Calcium Sodium Creatinine[a] Albumin	**Additional Tests at Screening only** Total protein Blood urea nitrogen (BUN) or Urea[b] Blood glucose
Urinalysis (Dipstick)	Specific gravity pH Glucose Protein Blood	Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase
Coagulation	Prothrombin time (PT)	Activated partial thromboplastin time (APTT) International normalized ratio (INR)
Serology	• Anti-HIV antibody. For known HIV positive participants, HIV viral load and CD4 count. • Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb). For participants with resolved infection, screen using RT-PCR measurement of HBV DNA levels. • Anti-hepatitis C virus (HCV) antibody (participants with a history of HCV are also required to have HCV RNA quantification.)	

a. Creatinine clearance, calculated using the MDRD formula, will be recorded in the eCRF.
NOTE: 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.
b. For sites that cannot calculate BUN.

10.7. Appendix 7: Liver Safety: Follow-up Assessments and Study Treatment Rechallenge Guidelines

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, ALP, bilirubin [including bilirubin fractions], and INR), creatinine phosphokinase, and lactate dehydrogenase, 1 to 2 times per week until resolution, stabilization, or return to participant's baseline values
- Monitor clinical condition closely
- Draw blood samples for unscheduled PK analysis at timepoints when liver chemistry is assessed
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or known hepatotoxins
- Record alcohol use in the CRF
- Check the viral hepatitis serology as appropriate and include:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B core antibody (IgM)
  - Hepatitis C RNA
  - Hepatitis E IgM antibody
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or equivalent test)
- Assess anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies
- Conduct liver imaging (ultrasound, magnetic resonance imaging [MRI], or computerized tomography [CT]) to evaluate liver disease
- Refer to a specialist as appropriate

Rechallenge Criteria

Resumption of study drug administration may be considered if the following criteria are met:

- Hy's Law has been excluded
- A reversible underlying cause not associated with study treatments (eg, alcohol use or concomitant medication) is clearly identified and agreed upon in consultation with sponsor's medical monitor
- Liver chemistry abnormalities have resolved or values have returned to baseline

10.8. Appendix 8: 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 pre-existing 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 participants 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.

Reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

10.9. Appendix 9: New York Heart Association Criteria

The following table presents the NYHA classification of cardiac disease:

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class 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.	**B.** Objective evidence of minimal cardiovascular disease.
Class 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.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class 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.	**D.** Objective evidence of severe cardiovascular disease.

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

10.10. Appendix 10: Eastern Cooperative Oncology Group (ECOG) Performance Status Score

Grade	Eastern Cooperative Oncology Group (ECOG) Performance Status
0	Fully active, able to carry on all pre-disease 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

Source: Oken 1982

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655

10.11. Appendix 11: Health Care Provider (HCP) - Ease of Use and Satisfaction Questionnaires

To be completed by HCPs that cared for all participants:

1) How was this participant administered amivantamab?				
IV infusion		SC manual injection		
2) How satisfied or dissatisfied were you with the therapy administration?				
Very satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
3) How convenient is it for you to administer the therapy?				
Very Convenient	Convenient	Neutral	Inconvenient	Very Inconvenient
4) How bothered were you by the amount of time it takes to administer the therapy?				
Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

10.12. Appendix 12: 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) is:

$$eGFR\ (mL/min) = 175 \times [\text{standardized } S_{Cr}\ (mg/dL)]^{-1.154} \times age^{-0.203} \times 1.212_{\text{if black}} \times 0.742_{\text{if female}} \times BSA^{*} / 1.73$$

Creatinine levels conversion from µmol/L to mg/dL:

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

* BSA to be calculated using the Mosteller formula (weight in kg and length in cm):
BSA (m^2) = square root of (length * weight/3600)

Standardized SCr: Creatinine assay calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure (this is the case for most assays).

Sources: Levey (2006, 2007) and Mosteller (1987)

10.13. Appendix 13: Allowed Recent Second or Prior Malignancies

i. Any malignancy that was not progressing nor requiring treatment change in the last 12 months.

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 ≤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.

10.14. Appendix 14: Modified Therapy Administration Satisfaction Questionnaires for IV infusion (TASQ-IV) or SC injections (TASQ-SC)

The wording of question 11 in these questionnaires differs from the original. The original wording specified that the SC injection would take place in the "thigh," but these modified questionnaires specify that the injection will take place in the "skin".

Therapy Administration Satisfaction Questionnaire (TASQ-IV)©

Instructions: Cancer treatment can be given through a port or a thin plastic tube and a needle that put directly into a vein in your arm, called an intravenous or IV infusion.

Please answer the questions based on your most recent IV infusion.

1. How satisfied or dissatisfied were you with the IV infusion?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. How much pain did you experience at the IV site?

None	Mild	Moderate	Severe	Very Severe

3. How much swelling was there at the IV site?

None	Mild	Moderate	Severe	Very Severe

4. How much redness did you experience at the IV site?

None	Mild	Moderate	Severe	Very Severe

5. When receiving the IV infusion, do you feel restricted?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. How convenient is it for you to have your IV infusion?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

7. How bothered are you by the amount of time it takes to have the infusion?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

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8. Does setting up the IV infusion mean you lose or gain time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

9. When you receive the IV infusion treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- ☐ Yes, I had more than enough time to talk to my nurse and/or doctor.
- ☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.
- ☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- ☐ No, I did not have enough time to talk to my nurse and/or doctor.
- ☐ No, I did not talk to my nurse and/or doctor at all.

10. Does the IV infusion impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes No

11. There are two ways to get cancer treatment:

a) IV infusion given through a port or small tube

b) SC (subcutaneous) injection in your skin

Which would you prefer?

a) IV

b) SC

c) no preference

12. Thinking about the IV treatment, would you recommend the way you received the treatment (IV infusion) to another patient?

Definitely yes	Probably yes	I don't know	Probably not	Definitely not

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Therapy Administration Satisfaction Questionnaire (TASQ-SC)©

Instructions: Cancer treatment can be given through an injection in your skin.

Please answer the questions based on your most recent SC injection.

1. How satisfied or dissatisfied were you with the SC injection?

Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

2. How much pain did you experience at the site of the SC injection?

None	Mild	Moderate	Severe	Very Severe

3. How much swelling did you experience at the site of the SC injection?

None	Mild	Moderate	Severe	Very Severe

4. How much redness did you experience at the site of the SC injection?

None	Mild	Moderate	Severe	Very Severe

5. When receiving the SC injection, how restricted did you feel?

Not at all	A little bit	Somewhat	Quite a bit	Very much

6. How convenient is it for you to get your SC injection?

Very convenient	Convenient	Neither convenient nor inconvenient	Inconvenient	Very inconvenient

7. How bothered are you by the amount of time it takes to have the SC injection?

Not at all bothered	A little bothered	Moderately bothered	Quite bothered	Very bothered

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8. Does setting up the SC injection mean you lose or gain time for other things?

Lost a lot of time	Lost some time	Neither lost nor gained time	Gained some time	Gained a lot of time

9. When you receive the SC injection treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness? (please only check ONE answer)

- ☐ Yes, I had more than enough time to talk to my nurse and/or doctor.
- ☐ Yes, but I would have liked more time to talk to my nurse and/or doctor.
- ☐ It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment.
- ☐ No, I did not have enough time to talk to my nurse and/or doctor.
- ☐ No, I did not talk to my nurse and/or doctor at all.

10. Does the SC injection impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?

Yes	No

11. There are two ways to get cancer treatment:

a) IV infusion given through a port or small tube

b) SC (subcutaneous) injection in your skin

Which would you prefer?

a) IV

b) SC

c) no preference

12. Would you recommend the way you received the treatment (SC injection) to another patient?

Definitely yes	Probably yes	I don't know	Probably not	Definitely not

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10.15. Appendix 15: Long-term Extension Phase

The purpose of the LTE Phase is to continue providing participants access to study treatment(s) within the study while further reducing protocol-required visit procedures and assessments, and burden on participants, after the primary analysis is complete. The LTE Phase will begin after the primary analysis and will continue until the discontinuation criteria described in Section 7.1 are met, or until 3 years after local marketing authorization is obtained, whichever occurs first. After notification from the sponsor, participants that are on treatment and who remain in the study after completion of the primary analysis will be provided with the option to enter the LTE Phase.

Data collection will be limited during this phase. Study treatment compliance will be recorded. Serious adverse events will be reported on the appropriate SAE form and recorded by the sponsor in the Global Medical Safety database. Pregnancy reporting should continue as described in Section 8.3.5. Other safety and efficacy data will not be collected during the LTE Phase. No analyses other than routine periodic safety reviews consisting of reported SAEs are planned for the LTE Phase.

Participants who had discontinued study treatment, or participants who elect not to enter the LTE Phase will be discontinued from the study upon the start of the LTE Phase.

Participants entering the LTE Phase will continue to receive the study treatment(s) they were receiving at the completion of the primary analysis. The sponsor will continue to provide study drugs until the discontinuation criteria described in Section 7.1 are met, or until 3 years after local marketing authorization is obtained, whichever occurs first. Study treatment dispensation and accountability will be performed via IWRS.

10.15.1. Eligibility Criteria

All participants on study treatment(s) still in the study, and who are willing and able to provide informed consent to participate, are eligible to enter the LTE Phase.

10.15.2. Study Treatment Administration

Study treatment(s) should continue as specified in Section 6.

10.15.3. Study Procedures

All participants in the LTE Phase should follow the Schedule of Activities for the LTE Phase (Table 13).

Participants in the LTE Phase should be followed up for safety per local practice and local label requirements. No efficacy data will be collected. Only SAEs will be collected via the SAE form per the SAE reporting process. Pregnancy reporting should continue as described in Section 8.3.5. A positive pregnancy test should be documented in the subject file/source notes.

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

Table 13: Schedule of Activities in the Long-term Extension Phase (All Arms, Unless Otherwise Indicated)

Phase	Treatment Phase	End of Treatment Visit[a]	Follow-up (Visit or Call[e]	
Study Procedure	**Subject Continuing on Previously Received Study Treatment on a 28-day cycle (±2 days)**	**30 (+7) Days After Last Dose of Study Treatment**	**Q12 (±2) Weeks From the Last Dose of LTE Phase Study Treatment**	**Comment**
Screening Assessments				
Informed consent	X (all participants)			Must be signed before the first study-related procedures in the LTE Phase.
Pregnancy test[b]	As clinically indicated, according to local regulatory requirements, or following the local practice of the center.	X		Pregnancy reporting should continue as described in Section 8.3.5. A positive pregnancy test should be reported via the AE/SAE process (see Section 8.3.5 and Appendix 3).
Safety Assessments				
Adverse events (SAEs only)	Collect continuously from ICF through 30 days after the last dose of study treatment (or >30 days for a serious adverse event if considered related to study treatment)			
Safety Assessments	All participants continuing in the LTE Phase should be followed up for safety per the local practice and following the local label(s).			
Clinical Laboratory Tests				
Hematology and chemistry	Clinical laboratory tests should be performed per the local practice.			
Study Treatment				
Arm A: amivantamab SC-CF IV (open-label)	X (on Days 1 and 15)			
Arm B: amivantamab IV (open-label)	X (on Days 1 and 15)			
Arms A and B: oral lazertinib (open-label)	X (Days 1 to 28)[f]			
All arms: record oral study treatment compliance	X (Day 1)			
Pre- and Postdose Medications				
Predose medications[c]	X			
Postdose medications[d]	X			

AE=adverse event; ICF=Informed consent form; IV=intravenous; LTE=Long-term extension; Q12W=every 12 weeks; SAE=serious adverse event; SC-CF=subcutaneous and co-formulated with recombinant human hyaluronidase

a. With the exception of the end-of-treatment pregnancy test for participants of childbearing potential, which must occur at least 30 days after the last dose of study treatment, end-of-treatment procedures may be conducted before 30 days after last dose of study treatment if new anticancer therapy is to be initiated.
b. For participants of childbearing potential.
c. Required predose medications are an antihistamine and antipyretic on amivantamab dosing days. Required predose medications and optional predose medications for amivantamab are summarized in Table 7.
d. Optional postdose medications may be prescribed and continued for up to 48 hours after any amivantamab dose if clinically indicated, at the discretion of the investigator. Optional postdose medications for amivantamab are summarized in Table 8.
e. Participants for whom there is no safety concern may have telehealth (conducted via phone or video conference) visits.
f. On infusion or injection days, lazertinib should be taken more than 15 minutes prior to premedication for amivantamab initiation and then at approximately the same time each day, with or without food.

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 (TOC).

Amendment 4 (21 November 2023)

Overall Rationale for the Amendment:

The overall purpose of this amendment is to clarify the PK evaluable analysis set for each of the primary PK endpoints following Health Authority interactions and to implement minor updates from various study documents.

The changes made to the clinical protocol 61186372NSC3004 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.16.

Section Number and Name	Description of Change	Brief Rationale
9.3 Populations for Analysis Sets	A description of the hybrid approach to evaluate the study PK co-primary endpoint (Cycle 4 Day 1 C_{trough}) was added.	To clarify the PK evaluable analysis set for the study PK co-primary endpoint (Cycle 4 Day 1 C_{trough}) following FDA feedback.
1.1 Synopsis, Statistical Methods; 3. Objectives and Endpoints; 4.2 Scientific Rationale for Study Design; 8.4.3 Pharmacokinetic Parameters and Evaluations; 9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.3 Populations for Analysis Sets; 9.4.2 Primary Endpoints; 9.4.3 Secondary Endpoints	• Throughout the protocol, the following text in bold has been added: 'C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than EU **and others accepting Cycle 2 Day 1** and pre-dose on Cycle 2 Day 1 for EU **and any applicable region**)'. • Section 9.3 – updates were made to clarify the PK evaluable analysis set for each of the primary PK endpoints.	Updates made following Health Authority interactions.
1.3.1 Schedule of Activities	• Study Procedure note was revised as shown below: During Cycle 2, if a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule (except disease assessments) should be delayed accordingly to ensure sampling relative to amivantamab dose administration**, which would trigger the start of the next cycle.** • The following text was added to footnote 'n': **If unable to collect during the disease evaluation visit, the sample may be collected at the next visit prior to subsequent study treatment administration.** • Added the following footnote ('v') to Day 1 Cycle 4+:	Minor clarification from existing information in various study documents.

	PK samples are collected on Day 1 of Cycles 5, 7, 9, and 11 (see Table 2).	
1.3.1 Schedule of Activities 6.1 Study Treatments Administered (Description of Treatments Table)	Text was updated to provide clarification that lazertimib dose is to be administered prior to premedication for amivantamab.	Minor clarification from existing information in the training manual and site dosing instructions.
1.3.1 Schedule of Activities 8.1 Efficacy Assessments	Brain imaging frequency was clarified: every 6 weeks if brain mets are present at baseline and being followed as non-target lesions and if no brain mets at baseline, only as clinically indicated.	Clarification as outlined in the existing imaging manual.
1.3.2 Collection Times for PK and Immunogenicity Samples	• Updated the window for the EOI ±168 hrs visit from ±4 hrs to ±1 day. • Deleted foontotes 'c' and 'd' and updated the order of subsequent footnotes.	• Pharmacokinetic window is updated to match study visit window. • Inadvertently not removed during Amendment 2.
1.3.2 Collection Times for PK and Immunogenicity Samples 8 Study Assessments and Procedures Sample Collection and Handling	The following text was added to Section 8 and Cycle 4 Day 1 for amivantamab serum PK sample (as footnote 'e'): **If Cycle 4 Day 1 dose is delayed or withheld, the amivantamab serum PK sample should be collected on the planned day per protocol. This collection will be considered an unscheduled serum PK sample.**	To provide flexibility on sample collection for the co-primary endpoint.
5.3 Lifestyle Considerations	Updated Criterion 2 that osimertinib must be discontinued at least 8 days prior to first dose of study drug rather than randomization.	To clarify the washout period is required prior to the first dose (C1D1).
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. 9.4.5 Safety Analysis Adverse Events	Clarified that AEs are reported through 30 days after the last study treatment dose.	To align the protocol language with the schedule of activities.
8.3.7 Adverse Events of Special Interest	Added '**(ie, via email)**' to provide example of reporting method.	To clarify the reporting method for severe IRR.
9.4.3 Secondary Endpoints Time to Response (TTR) Modified Therapy Administration Satisfaction Questionnaire	• Deleted 'BICR using' • Text was reviewed as shown below: This validated PRO instrument is designed to assess patient satisfaction with cancer therapy. Descriptive statistics will be reported for the individual ~~scores~~ **items** and ~~total~~ **domain** score**s** at baseline and at each visit for absolute value and for change from baseline.	• Typographical error. • Clarification that the TASQ has no total score. The measure has scores for individual items and for each of five domains.
10.6. Appendix 6: Clinical Laboratory Tests	Added **Urea** and added footnote 'b' to the table: For sites that cannot calculate BUN.	To allow for urea collection for sites that cannot test for BUN.
1.1 Synopsis	Text was added to clearly describe the study.	Updated for clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (11 August 2023)

Overall reason for the Amendment:

The overall purpose of this protocol amendment is to clarify risk mitigation strategies for VTE among patients treated with combination of amivantamab and lazertinib.

The changes made to the clinical protocol 61186372NSC3004 as part of Protocol Amendment 3 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
5.2 Exclusion Criteria	Criterion 10 has been updated to add participants who have a significant genetic predisposition to venous thromboembolic events such as Factor V Leiden or have a prior history of VTE and is not on appropriate therapeutic anticoagulation as per NCCN or local guidelines.	To clarify and align with the VTE risk mitigation and management.
6.5.1 Dose Delay Guidance	Resolutions in case of VTE events associated with clinical instability text was added.	
6.5.2 Dose Modification of Amivantamab and Lazertinib	Table 4; Footnote 'd' updated for VTE in participants being treated with the combination of amivantamab and lazertinib.	
6.5.3.10 Venous Thromboembolic Events	Recommendations in case of recurrent VTEs have been included.	
10.15 Country-specific Requirements	Appendix 15 (Country-specific Requirements) was deleted.	No longer applicable.

Amendment 2 (27 October 2022)

Overall reason for the Amendment: Due to the impact of the On Body Delivery System (OBDS) availability globally, the sponsor decided to only conduct Part 1 of the study. Part 2 of this study, which used the OBDS, has been removed.

The rationale for and description of the changes made during this protocol amendment and the affected section numbers are provided below. The revisions noted below are representative of the changes. When changes are provided verbatim, deleted text is shown as strikethrough, and added text is shown as bold font.

The changes made to the clinical protocol 61186372NSC3004 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.16 Appendix 16: Protocol Amendment History.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis	Removal of text relating to Part 2 of the study. Also, deletion of any text that refers to Part 1 as an identifier.	Part 2 of the study has been deleted. The study now only has one part, therefore headings and text identifying parts is not required.
1.2 Schema	Adapting diagram after removal of Part 2 of the study.	Part 2 of the study has been deleted.
1.3 Schedule of Activities	Table 1, Table 2 (previous Table 3) titles have 'for Part 1' removed. Table 2 and Table 4 for Part 2 are now deleted.	Part 2 of the study has been deleted. The study now only has one part, therefore headings and text identifying parts is not required.
1.3 Schedule of Activities	Table 1 has predose timings added for cDNA and exploratory biomarker bloodsamples. And a footer (u) for exploratory biomarker samples was also added to clarify that the samples are not required to be collected beyond Cycle 4. The CT/MRI imaging row has the following text added: **Imaging obtained as part of standard care before signing the ICF, but within 28 days of randomization, may be used for the screening assessment if parameters meet the imaging manual requirements.** Table 2 (previous Table 3) has had cDNA and exploratory biomarker bloodsamples rows removed.	Timings were added to instruct the site when to collect the samples. Alignment with previous amivantamab studies to provide more flexibility. This information is now provided in Table 1.
2 Introduction	Removal of text related to Part 2 of the study. Also, deletion of any text that refers to Part 1 as an identifier.	Part 2 of the study has been deleted.
2.1 Study Rationale	Removed text related to OBDS.	Part 2 of the study has been deleted.
2.2.2.1 Amivantamab IV	Adding the lazertinib IB as a reference, in addition to the amivantamab IB.	For clarity.
2.2.2.2 Amivantamab SC-CF	Removed text related to OBDS.	Part 2 of the study has been deleted.
2.2.5 On Body Delivery System Combination Product	This section was removed.	Part 2 of the study has been deleted.
2.3.1 Risks for Study Participation	Removed text relating to the risks for OBDS.	Part 2 of the study has been deleted.
2.3.3. Benefit-Risk Assessment for Study Participation	Removed text relating to OBDS.	Part 2 of the study has been deleted.

Section number and Name	Description of Change	Brief Rationale
3. OBJECTIVES AND ENDPOINTS	Deletion of any text that refers to Part 1 as an identifier. Removed objectives and endpoints related to Part 2 and OBDS. Removed hypothesis for Part 2.	Part 2 of the study has been deleted. The study now only has one part, therefore text identifying parts is not required.
4.1 Overall Design	Removal of text relating to Part 2 of the study. Also, deletion of any text that refers to Part 1 as an identifier.	Part 2 of the study has been deleted. The study now only has one part, therefore text identifying parts is not required.
4.1.1 Screening	Deletion of text that refers to Part 1 as an identifier; deletion of reference to Table 2 for Part 2.	Part 2 of the study has been deleted. The study now only has one part, therefore text identifying parts is not required.
4.1.2 Treatment Phase	Removal of text relating to Part 2 of the study. Also, deletion of any text that refers to Part 1 as an identifier.	Part 2 of the study has been deleted. The study now only has one part, therefore text identifying parts is not required.
4.2. Scientific Rationale for Study Design	Removal of text relating to Part 2 of the study. Also, deletion of any text that refers to Part 1 as an identifier.	Part 2 of the study has been deleted. The study now only has one part, therefore text identifying parts is not required.
4.2.1. Study-Specific Ethical Design Considerations	Removal of text referring to OBDS.	Part 2 of the study has been deleted.
4.4 End of Study Definition	The participant study completion definition has been updated.	Updating study completion definition.
5.1 Inclusion Criteria 5.2 Exclusion Criteria	Criterion 16 has been moved from the Exclusion Criteria to the Inclusion Criteria.	To align with the Sponsor protocol template and to address Health Authority request.
6.1 Study Treatments Administered	Removal of header text relating to Part 2 of the study.	Part 2 of the study has been deleted.
6.1.2. Amivantamab SC-CF by Manual Injection (Arm A)	Removal of header text relating to Part 2 of the study.	Part 2 of the study has been deleted.
6.1.3. Amivantamab IV (Arm B)	Header updated from B1 to B.	Part 2 of the study has been deleted.
6.1.4 Amivantamab SC-CF OBDS (Arm B2)	This section has been deleted as it contained text related to OBDS. The following lazertinib section has now become Section 6.1.4.	Part 2 of the study has been deleted.
6.2. Preparation/Handling/ Storage/Accountability	Text relating to amivantamab SC-CF IFU has been deleted	Part 2 of the study has been deleted
6.4 Study treatment compliance	Text relating to OBDS has been deleted.	Part 2 of the study has been deleted.

Section number and Name	Description of Change	Brief Rationale
6.5.2. Dose Modification of Amivantamab and Lazertinib	Text relating to OBDS has been deleted.	Part 2 of the study has been deleted.
6.5.3.1. Infusion-Related Reactions and Local Administration-Related Reactions	Deletion of any text that refers to Part 1 or Part 2 as an identifier. Removal of text relating to Part 2 of the study.	Part 2 of the study has been deleted.
8. STUDY ASSESSMENTS AND PROCEDURES	Text relating to OBDS has been deleted.	Part 2 of the study has been deleted.
8.1.2 Amivantamab SC-CF OBDS Performance 8.1.2.1 Amivantamab SC-CF OBDS Successful Completion 8.1.2.2 HCP Questionnaire	Sections relating to OBDS have been deleted.	Part 2 of the study has been deleted.
8.4.1. Evaluations	Deletion of any text that refers to Part 1 or Part 2 as an identifier.	Part 2 of the study has been deleted.
8.4.3. Pharmacokinetic Parameters and Evaluations	Deletion of any text that refers to Part 1 or Part 2 as an identifier. Removal of text relating to Part 2 of the study.	Part 2 of the study has been deleted.
9.1.Statistical Hypotheses	The primary hypothesis text for Part 2 has been deleted.	Part 2 of the study has been deleted.
9.2. Sample Size Determination	Deletion of any text that refers to Part 1 or Part 2 as an identifier. Removal of text relating to Part 2 of the study.	Part 2 of the study has been deleted.
9.3. Populations for Analysis Sets	Deletion of any text that refers to Part 1 or Part 2 as an identifier. Removal of text relating to Part 2 of the study.	Part 2 of the study has been deleted.
9.4.2 Primary Endpoints	Deletion of any text that refers to Part 1 or Part 2 as an identifier. Removal of text relating to Part 2 of the study.	Part 2 of the study has been deleted.
9.4.3. Secondary Endpoints	Deletion of any text that refers to Part 1 or Part 2 as an identifier. Removal of text relating to Part 2 of the study. Text relating to OBDS has been deleted.	Part 2 of the study has been deleted.
9.5 Interim Analysis	Deleted as is no longer being carried out now that Part 2 is removed.	Part 2 of the study has been deleted.
10.1. Appendix 1: Abbreviations	OBDS and SC-CF OBDS have been deleted.	Part 2 of the study has been deleted.

Amendment 1 (25 August 2022)

Overall Rationale for the Amendment: This amendment is being implemented to describe an EU-specific approach for the co-primary endpoint of C_{trough} based on European Medicines Agency (EMA) recommendation and

to address other health authority recommendations; to incorporate guidance related to the Urgent Safety Measure for venous thromboembolic events (VTEs); and to apply additional modifications and clarifications.

The rationale for and description of the changes made during this protocol amendment and the affected section numbers are provided below. The revisions noted below are representative of the changes. When changes are provided verbatim, deleted text is shown as strikethrough, and added text is shown as bold font.

Section Number and Name	**Description of Change**	**Brief Rationale**
Synopsis, Statistical Methods; 3. Objectives and Endpoints; 4.2 Scientific Rationale for Study Design; 8.4.3 Pharmacokinetic Parameters and Evaluations; 9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.3 Populations for Analysis Sets; 9.4.2 Primary Endpoints; 9.5 Interim Analysis	Throughout the protocol, where the co-primary endpoint 'C_{trough} at steady state (Cycle 4 Day 1)' is described, the modified text has been added: 'C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than EU and pre-dose on Cycle 2 Day 1 for EU only)'.	Changes to the primary endpoint (and corresponding changes to secondary endpoint) following EMA advice.
3. Objectives and Endpoints; 9.4.3 Secondary Endpoints	Secondary endpoint for C_{trough} has been revised from: 'For Part 1, a C_{trough} for amivantamab will be drawn on Cycle 2 Day 1. Similar analysis method used for the primary endpoint will be used.' To read as follows: 'In regions other than EU, a C_{trough} of amivantamab pre-dose on Cycle 2 Day 1 will be a secondary endpoint. Similar analysis method used for the primary endpoint will be used in Part 1. In EU, a C_{trough} of amivantamab at steady state (Cycle 4 Day 1) will be a secondary endpoint. Similar analysis method used for the primary endpoint will be used in Part 1.'	
1.2 Schema	The following text (in **bold**) has been added to the note immediately below Figure 1: NOTE: As OBDS is a combination product, the sponsor will ensure provision of regulatory guidance throughout the device development process **and provide further background information through a substantial protocol amendment** prior to initiation of Part 2.	To provide additional clarity on this aspect of study conduct based on health authority input.
1.3.1 Schedule of Activities for Part 1 (Table 1); 1.3.2 Schedule of Activities for Part 2 (Table 2)	For both tables, row added for prophylactic-dose anticoagulation during the first 4 months of treatment, and VTE-related footnotes added for physical examination and anticoagulation. For Table 1 only, row added for blood samples for exploratory biomarkers.	To implement the adverse event of special interest of venous thromboembolic (VTE) events, as well as associated measures for

Section Number and Name	Description of Change	Brief Rationale
2.3.1 Risks for Study Participation	VTE has been added to the list of possible risks for the amivantamab and lazertinib combination.	monitoring and prophylaxis of these events.
2.3.3 Benefit-Risk Assessment for Study Participation	The rationale for and aims of the VTE-related measures have been added.	
6.5.2 Dose Modification of Amivantamab and Lazertinib (Table 6)	The following text has been added to note 'd': **No dose reduction required for VTE events. Study treatment initially held for stable, treated pulmonary embolism and deep vein thrombosis ≤Grade 3 can be resumed at the discretion of the investigator.**	
6.5.3.10 Venous Thromboembolic Events	A new section has been added to provide guidance on management of venous thromboembolic events.	
8.2.1 Physical Examinations	Additional guidance has been added for detection of VTE through physical examination.	
8.3.7 Adverse Events of Special Interest	VTE has been added to the list of AEs of special interest. It is noted that events of VTE should follow standard reporting guidelines.	
8.6 Biomarkers	The following text has been added: **Blood samples will also be collected at the time points specified in the Schedule of Activities and may be analyzed to investigate circulating factors, eg cytokines, associated with response to treatment.**	
11 References	Three new references (Carrier 2019, NCCN 2022, and Rutjes 2020) have been added to the list of references to support VTE-related information.	
1.3.1 Schedule of Activities for Part 1 (Table 1)	Vital signs to be collected at Cycle 1 Days 2, 8, 15, and 22.	These assessments were inadvertently omitted in the original protocol.
1.3.1 Schedule of Activities for Part 1 (Table 1)	Lazertinib administration row, text changed: '…lazertinib should be taken ~~about 30 minutes~~ **more than 15 minutes** prior to premedication or amivantamab initiation…'	This text has been changed to align with other sections of the protocol.
1.3.2 Schedule of Activities for Part 1 (Table 2)	Lazertinib administration row, text changed: '…lazertinib should be taken ~~about 30 minutes~~ **more than 15 minutes** prior to premedication or amivantamab initiation…'	This text has been changed to align with other sections of the protocol.

Section Number and Name	Description of Change	Brief Rationale
1.3.3 Collection Times for PK and Immunogenicity Samples for Part 1 (Table 3)	The footnote below has been added to Table 3 and applied to Cycle 2 Days 1 (EOI + 6 hours assessment only), 2, 3, 4, 5, and 8. **If on-site visit is not possible, the PK draw could be performed outside of the clinic, through a Sponsor-designated home health care vendor, if approved and allowed by local regulations and after requisite consultation with the medical monitor.**	To allow pharmacokinetic (PK) blood draws for certain visits to be performed at home by a vendor.
1.3.3 Collection Times for PK and Immunogenicity Samples for Part 1 (Table 2)	Text in bold has been added to footnote 'b': Separate blood draws are not required for amivantamab PK and immunogenicity when collected at the same time point. A separate blood draw is required for rHuPH20 plasma immunogenicity **for Arm A participants only**.	Correction.
1.3.4 Collection Times for PK and Immunogenicity Samples for Part 2 (Table 4)	Text in bold has been added to footnote 'b': Separate blood draws are not required for amivantamab PK and immunogenicity when collected at the same time point. **A separate blood draw is required for rHuPH20 plasma immunogenicity.**	This text was inadvertently omitted in original protocol, now aligned with guidance for collections in Part 1 of the study.
2.2.2.2 Amivantamab SC-CF; 2.3.1 Risks for Study Participation; 4.3.2 Amivantamab SC-CF Dose	Wording has been updated to reflect that the SC Q2W RP2D for this study has been confirmed via Study 61186372NSC1003.	SC Q2W RP2D for this study has been confirmed in Study 61186372NSC1003.
3. Objectives and Endpoints; 9.4.4 Exploratory Endpoints	Overall survival has been added as an exploratory endpoint.	To explore the direct measure of clinical benefit in the study population.
4.1 Overall Design	The following text has been incorporated: **Country-specific requirements are described in Appendix 15.**	To outline countries that will require formal approval before initiation of Part 2 of the study.
Appendix 15, Country-specific Requirements	A new appendix has been added.	
4.1 Overall Design	The following text (in bold) has been added: The study will aim to enroll a participant population that is geographically reflective of the overall incidence/prevalence of this disease. **Enrollment of study participants in a given country may continue beyond the global enrollment period defined to reach the overall planned sample size, to ensure adequate representation in the study.**	To include patients from underrepresented and/or underserved racial and ethnic backgrounds within each country.
5.1 Inclusion Criteria	In Inclusion Criterion 3, the following modifications have been made: Have progressed on or after osimertinib **(or another approved 3rd generation EGFR TKI)** and platinum-based chemotherapy (irrespective of order).	To allow for global enrollment to the trial, recognizing heterogeneous access to osimertinib.

Section Number and Name	Description of Change	Brief Rationale
	• ~~Osimertinib~~ **The 3rd generation EGFR TKI** must have been administered as the first EGFR TKI for metastatic disease or as the second TKI after prior treatment with first- or second-generation EGFR TKI in participants with metastatic EGFR T790M mutation positive NSCLC. • Participants who decline or are otherwise ineligible for chemotherapy may be enrolled after discussion with the medical monitor. • Any adjuvant or neoadjuvant treatment, whether with ~~osimertinib~~ **a 3rd generation EGFR TKI** or platinum-based chemotherapy, would count towards the prior treatment requirement if the participant experienced disease progression within 6 months of the last dose.	
Throughout protocol	Where 'osimertinib' appears in reference to the design of this study, the following text has been added: '(or another approved 3rd generation EGFR TKI)'.	
5.2 Exclusion Criteria	Exclusion Criterion 14 has been modified to remove the reference to Appendix 11.	Interactions text has been updated to reflect the latest guidance.
6.8.3 Prohibited or Restricted Medications and Therapies	The wording related to CYP3A4/5 inducers has been revised. Reference to Appendix 11 has been removed and replaced with US FDA guidance. The wording related to CYP3A4/5 inhibitors and to substrates of P-gp, MRP4, BCRP, and OCT1 has been revised. References to Appendix 11 and Appendix 12 have been removed and replaced with US FDA guidance.	
Appendix 11, Prohibited and Restricted Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5	This appendix has been removed.	
Appendix 12, Substrates of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and multi-drug resistance protein 4 (MRP4): Exercise Caution	This appendix has been removed.	
References	The following citation has been added: US FDA. Drug development and drug interactions: Table of Substrates, Inhibitors and Inducers. https://www fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 2 May 2022.	
5.2. Exclusion Criteria	An exclusion criterion (Criterion 16) was added: **A female participant must agree not to be pregnant, breast-feeding, or planning to become**	To clarify exclusion of pregnant and breast-feeding women based on health authority feedback.

Section Number and Name	Description of Change	Brief Rationale
	pregnant while enrolled in this study or within 7 months after the last dose of study treatment.	
5.3 Lifestyle Considerations	The following modifications have been made to item 2: For agents **such as immunotherapy** with **a** long half-li**f**~~eves~~, the maximum required time since last dose is 6 weeks.	This text has been revised to ensure an appropriate washout period for immunotherapy.
6.1 Study Treatments Administered	The following text (in bold) has been added: Study treatment administration must be captured in the source documents and the eCRF. Study site personnel will instruct participants on how to store study treatment for at-home **(lazertinib only)** use as indicated for this protocol.	To clarify that at-home storage of study medication is only applicable to lazertinib.
6.2 Preparation/Handling/ Storage/Accountability	The following text modifications have been made: ~~Study~~ **Amivantamab** treatment must be handled in strict accordance with the protocol and as indicated on 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.	
6.5.2 Dose Modification of Amivantamab and Lazertinib (Table 6, Guidance for Withholding Doses for Toxicities Based on Grade)	The following text (in strikethrough) has been removed from Table 6: If amivantamab is withheld <21 days, restart study treatment at current dose level. If lazertinib is withheld, restart on Day 1 of next cycle at a reduced dose. ~~If 2 consecutive doses of amivantamab are withheld, consult the Medical Monitor before restarting~~	Based on increased experience with the incidence of recurrent IRR with amivantamab IV and amivantamab SC-CF.
6.5.3.1 Infusion-Related Reactions and Local Administration-Related Reactions	The following text (in strikethrough) has been removed: The monitoring should include heart rate, blood pressure, temperature, ~~respiratory rate,~~ and oxygen saturation measurements.	This text has been removed to align with other sections of the protocol.
6.5.3.1 Infusion-Related Reactions and Local Administration-Related Reactions	The following text has been added: **For Cycle 1 Day 1 only, participants in Arms A1, A2, and B2 will remain at the site for at least 4 hours after the amivantamab injection for observation. For participants in Arm B1, the 4-hour infusion time is considered adequate for observation; no additional observation time is needed.**	This text has been added in order to specify observation period required after study drug administration.
6.5.3.2 Rash-related Adverse Events (Table 12, Suggested Algorithm for Management of Rash)	The Grade 4 rash row has been separated from the Grade 3 rash row, to show different guidance in management for these 2 toxicity grades. A row has been added to provide guidance for '**Severe bullous, blistering, or exfoliating skin**	This table has been updated based on health authority feedback.

Section Number and Name	Description of Change	Brief Rationale
	conditions including toxic epidermal necrolysis (TEN)'.	
6.5.3.4 Cardiac Adverse Events; 6.8.3 Prohibited or Restricted Medications and Therapies; Appendix 10, Medications With Potential for QT Interval Prolongation	Appendix 10 has been removed from the protocol, along with any references to this appendix in the protocol body. The wording related to co-administration of medicines that prolong QT interval has been removed.	Emerging data indicate study treatments have no impact on QT interval.
6.8.3 Prohibited or Restricted Medications and Therapies	The following text has been removed: • Nephrotoxic or ototoxic agents should be used cautiously.	This text is not applicable to PALOMA-3, as none of the study treatments are nephrotoxic or ototoxic.
8. Study Assessments and Procedures	The following revisions have been applied: The modified TASQ should be completed after study drug administration. ~~Other PRO assessments~~ **PGIS** should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses, when possible.	To align this text with guidance in footnote 'm' for Table 1 andTable 2.
8.1.1 Patient-Reported Outcomes	The text in strikethrough has been deleted: The PGIS ~~and PGIC~~ should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses, when possible.	
8.2.2 ECOG Performance Status	The text in bold has been added: **Assessment of ECOG status should be part of regular ongoing clinical monitoring of patients.** Decline in ECOG performance status score (refer to Appendix 10: Eastern Cooperative Oncology Group (ECOG) Performance Status) should be reported as an AE.	To recommend regular monitoring that would permit detection of a decline in ECOG performance status score.
10.3.3. Severity Criteria	The following text has been removed: ~~Any AE will be graded as per the above. Should an AE become fatal or have a fatal outcome, the original grade is not changed but "fatal" shall be reported as an outcome.~~ ~~A Grade 5 event is to be reported only in the following cases:~~ ~~• Death NOS: only for deaths due to unknown reason (pending follow-up information; if further information becomes available this should be adapted as adequate)~~ ~~• Sudden death: a sudden (defined as instantaneous or within 1 hour of the onset of symptoms) cessation of life that cannot be attributed to a CTCAE term~~	To ensure all Grade 5 events are captured.

Section Number and Name	Description of Change	Brief Rationale
COVID-19 Appendix (standalone)	This appendix has been modified to incorporate additional detail for the following topics: consent/screening, study treatment, treatment and follow-up visits, telemedicine/teleconferencing/videoconferencing, home health care, and monitoring visits.	This appendix has been updated for consistency across amivantamab/lazertinib protocols.
Globally	'Study agent' has been updated throughout to 'study treatment'.	For consistency across amivantamab/lazertinib protocols.
Throughout the protocol	Minor formatting changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

JNJ-61186372 (amivantamab) and JNJ-73841937 (lazertinib) Clinical Protocol 61186372NSC3004 Amendment 5

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: _____

(Day Month Year)

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

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Status: Approved, Date: 31 May 2024

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

A Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy

PALOMA-3

Protocol 61186372NSC3004; Phase 3

JNJ-61186372 (amivantamab) and JNJ-73841937 (lazertinib)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries/territories. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

Regulatory Agency Identifier Number(s):
IND: 146319
EudraCT NUMBER: 2022-000525-25

Status: Approved
Date: 01 November 2022
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-704162, 3.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

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

Confidentiality Statement

The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the COVID-19 pandemic 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 COVID-19 pandemic, 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 "COVID-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If the participant has tested positive for COVID-19, 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 COVID-19 pandemic 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 potential COVID-19 exposure and local travel restrictions. If the situation suggests that this is not possible, the participant may be screen failed and re-screened when conditions improve.
- COVID-19 screening procedures that may be mandated by local healthcare systems do not need to be reported as an amendment to the protocol even if done during clinical study visits.
- As SARS-CoV-2 represents a new infectious agent, and COVID-19 a new clinical syndrome, it is unclear how infection with this virus will impact the benefit/risk assessment with regards to study treatment, particularly given its association with the risk of severe viral pneumonia. As per the study exclusion criteria, participants with active infection, including viral illnesses such as COVID-19, should be excluded from study participation.

Study Treatment

Study treatment should continue to be administered at the investigative site in accordance with the protocol. Potential interruptions to therapy should be assessed on a case by case basis and include consideration of potential impact on participant's safety. If doses are missed or delayed due to COVID-19 related circumstances, these deviations should be noted in the appropriate CRF page, as "missed or delayed due to COVID-19". The sponsor's medical monitor should be alerted to any anticipated interruption in 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. Please 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 to the protocol, unless COVID-19 related staffing shortages, site policies, or travel restrictions render these infeasible. In such cases, the following modifications may be implemented:

- If study imaging procedures cannot be performed at the active clinical study site, participants will be permitted to use other local imaging facilities (eg, at hospitals that are not the active study site). In these cases, digital copies should be made available to the investigator for submission to the central imaging vendor.

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

Telemedicine/Teleconferencing/Videoconferencing:

If the 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 which access is determined to be appropriate by the Investigator and Sponsor. At each telephone or telemedicine contact:

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

Home Health Care

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

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

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

Monitoring Visits

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

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

INVESTIGATOR AGREEMENT

Guidance on Study Conduct During the COVID-19 Pandemic
JNJ-61186372 (amivantamab) and JNJ-73841937 (lazertinib) Clinical Protocol 61186372NSC3004

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: Janssen Research & Development

Signature: PPD _____ Date: _____
(Day Month Year)

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

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Status: Approved, Date: 01 November 2022