Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

MARIPOSA

Protocol 73841937NSC3003;Phase 3
AMENDMENT 4

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

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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 Numbers:

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	14-Nov-2023
Amendment 3	22-Aug-2022
Amendment 2	23-Sep-2021
Amendment 1	22-Apr-2021
Original Protocol	05-Jun-2020

Amendment 4 (14 November 2023)

Overall Rationale for the Amendment:

To continue collecting data of clinical relevance/importance while reducing the burden on participants after the primary progression-free survival (PFS) analysis and unblinding, an open-label extension (OLE) Phase, with reduced protocol-required visits and assessments, is being added to the study. Of note, all efficacy and key safety assessments continue during the OLE phase of the study. After completion of the OLE Phase, a long-term extension (LTE) Phase is also being added, to continue providing access to study treatment..

Additional changes related to the Urgent Safety Measure (venous thromboembolic events [VTE] risk with combination of amivantamab and lazertinib) and changes related to the management of pneumonitis/interstitial lung disease (ILD) have also been added to the protocol to optimize patient safety.

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 73841937NSC3003 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. When changes are provided verbatim, deleted text is shown as strikethrough, and added text is shown as bold font. Changes made in previous protocol amendments are listed in Section 10.16 Appendix 16: Protocol Amendment History.

Section Number and Name	**Description of Change**	**Brief Rationale**
Changes related to adding an OLE Phase and an LTE Phase to the study.		
1.1. Synopsis (Overall Design); 4.1.4. Open-label Extension Phase and Long-term Extension Phase (new subheading)	A description of the new OLE and LTE phases was added, with cross-references to the newly added appendices.	To add the new OLE and LTE phases to the overall study design.
1.2. Schema, Figure 1 (Schematic Overview of the Study)	The schematic was revised to add the new OLE and LTE phases.	To add the 2 new phases (OLE and LTE) to the study design.
1.3. Schedule of Activities (SoA): Table 1	Added text to the title to indicate that the Schedule of Activities for the OLE and LTE phases are provided in Table 16 and Table 17, respectively.	To distinguish the Schedules of Activities in the main study from those in the OLE and LTE phases.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA): Table 2	Added text to the title to indicate that this Schedule of Activities is not applicable to the OLE and LTE phases.	Pharmacokinetic and immunogenicity samples are not collected in OLE and LTE phases.
6.3. Measures to Minimize Bias: Randomization and Blinding	The text below was added under the subheading for Blinding. The study may be unblinded after the primary analysis for PFS.	Clarification following addition of the new OLE and LTE phases to the overall study design.
6.7. Continued Access to Study Treatment After the End of the Study	Text referring to the OLE and LTE phases was added.	For guidance on details related to continued access to study treatment for participants who are still benefiting from study treatment.
10.7. Appendix 7: Clinical Laboratory Tests	Text referring to the Schedule of Activities during the OLE Phase was added.	To distinguish clinical laboratory tests performed during the OLE Phase from those performed in the main study.
10.13. Appendix 13: Anticipated Events	The text shown below was added under the subheading for Safety Assessment Committee (SAC). The review of anticipated events will be stopped after the OLE Phase has started. Following the cessation of SAC reviews of anticipated events, the anticipated events will be evaluated as part of the ongoing medical review.	To transition anticipated events review from SAC to ongoing medical review.
10.14. Appendix 14: Open-label Extension Phase (new appendix)	The study design was modified to include a new study phase (an OLE Phase), to collect data of clinical relevance/importance while reducing the burden on participants after the primary PFS analysis is complete, and other endpoints are still being evaluated. Instructions on study treatment administration, study procedures, and a Schedule of Activities for the OLE Phase are provided in the new appendix. During the OLE Phase, patient-reported outcomes (PROs) will be collected during treatment phase and then additionally for 1 year after end of treatment. During the 1 year after end of treatment, data collection frequency is reduced from every 3 months to every 6 months.	To provide detailed information on study conduct during the OLE Phase.
10.15. Appendix 15: Long-term Extension Phase (new appendix)	The study design was 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 after the final analysis for overall survival is complete.	To provide detailed information on study conduct during the LTE Phase.

Section Number and Name	Description of Change	Brief Rationale
	During the LTE Phase, PROs will not be collected.	
Changes related to the risk of VTE for the combination of amivantamab and lazertinib.		
6.6.1. Withholding Treatment	A new bullet (shown below) has been added under the subheading for combination treatment in Arm A (amivantamab and lazertinib). • **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 study treatment can be resumed at the discretion of the investigator.** Table 7; Footnote "d" has been updated as shown below for VTE in participants being treated with the combination of amivantamab and lazertinib. ~~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.~~ **For VTE events associated with clinical instability (eg, respiratory failure or cardiac dysfunction) in participants being treated with the combination of amivantamab and lazertinib, study treatment should be held until the participant recovers from the event. Thereafter, the study treatment can be resumed at the discretion of the investigator.** Table 8; Footnote "d" (shown below) has been deleted. ~~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.~~	To clarify and align with the latest recommendations for VTE risk mitigation and management.
6.6.3.12. Venous Thromboembolic Events	Section for VTE updated with: Recommendations for further imaging studies in case of persistent symptoms of VTE or worsening VTE. Mitigations in case VTE events are associated with clinical instability. Recommendation if there is a recurrent VTE while on therapeutic anticoagulation therapy.	To clarify and align with the latest recommendations for VTE risk mitigation and management.

Section Number and Name	Description of Change	Brief Rationale
Changes related to the management of pneumonitis/ILD.		
6.6.3.6. Pulmonary Toxicity	The section for Pulmonary Toxicity was updated to add the text shown below. Study treatment should not be restarted until pneumonitis/ILD is ruled out.	To clarify actions for managing pneumonitis/ILD.
Changes related to the EU CTR transition, and other template-specific changes.		
Cover page	The EU Trial number was added.	To comply with the EU CTR transition.
1.1. Synopsis	The IND number, EudraCT number, and EU Trial number were added.	To comply with the EU CTR transition.
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 transition.
5.1 Inclusion Criteria Criterion 10.2	Text has been updated as shown below. A ~~woman~~ **participant** of childbearing potential must have a negative serum pregnancy test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.	To make language more inclusive and gender-neutral.
5.1 Inclusion Criteria Criterion 11.2	Text has been updated as shown below. A ~~woman~~ **participant** must be (as defined in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information) either of the following: • Note: If the childbearing potential changes after start of the study (eg, ~~woman~~ **participant** who is not heterosexually active becomes active, premenarchal woman experiences menarche) the ~~woman~~ **participant** must begin birth control, as described above.	To make language more inclusive and gender-neutral.
5.1 Inclusion Criteria Criterion 12.1	Text has been updated as shown below. A ~~woman~~ **participant** must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 6 months after receiving the last dose of study treatment.	To make language more inclusive and gender-neutral.
5.1 Inclusion Criteria Criterion 13.1	Text has been updated as shown below.	To make language more inclusive and gender-neutral.

Section Number and Name	Description of Change	Brief Rationale
	A ~~man~~ **participant** must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 6 months after receiving the last dose of study treatment. A ~~man~~ **participant** who is sexually active with a ~~woman~~ **person** of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository and ~~his~~ **the** partner must also be practicing a highly effective method of contraception (ie, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]). ~~If the participant is~~**A** vasectomized **participant**~~, he~~ must still use a condom (with or without spermicide) for prevention of passage of exposure through ejaculation, but ~~his female~~ **the** partner is not required to use contraception.	
5.1 Inclusion Criteria Criterion 14.1	Text in strikethrough was deleted. A ~~male~~ participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study treatment.	To make language more inclusive and gender-neutral.
5.4. Screen Failures	Added the text shown below under Participant Identification, Enrollment, and Screening Logs This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS.	To comply with the current protocol template.
6.1. Study Treatments Administered	Added text related to study treatment and a new table categorizing the study treatments as investigational medicinal products (IMPs) or non-investigational medicinal products (NIMPs)/auxiliary medicinal products (AxMPs), and some associated text.	To comply with the current protocol template and with EU CTR guidance.
8.3.4. Regulatory Reporting Requirements for Serious Adverse Events	Text was revised as shown below. For the purposes of this study, anticipated events ~~are discussed~~ **will be periodically analyzed as specified** in Appendix 13: Anticipated Events.	To comply with the current protocol template.
8.3.5. Pregnancy	Text was revised as shown below. All initial reports of pregnancy in ~~female~~ participants or their partners of ~~male~~ participants (**through sperm of participant/from sexual intercourse and** 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	To make language more inclusive and gender-neutral.

Section Number and Name	Description of Change	Brief Rationale
	form.	
10.2.4. Recruitment Strategy (new subheading)	Added text indicating that the study has completed its planned enrollment.	To comply with EU CTR guidance.
10.2.5. Data Protection	Minor changes were made to text.	To comply with the current protocol template.
	Text related to measures by the sponsor to mitigate possible adverse effect in the event of a data security breach was added.	To comply with the EU CTR transition.
10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations; 10.2.5. Data Protection	Replaced "country" with "country/territory".	To comply with the current protocol template.
10.2.8. Publication Policy/Dissemination of Clinical Study Data	Minor changes were made to text.	To comply with the current protocol template.
10.3.4. Special Reporting Situations	Text was revised as shown below. **Participant-specific** special reporting situations should be recorded in the eCRF.	To comply with the current protocol template.
10.4. Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Text was revised to replace "woman / women" with "participant(s)".	To make language more inclusive and gender-neutral.
10.4. Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Text was revised as follows: • permanent~~ly sterile~~ **absence of reproductive potential (for the purpose of this study)** - **Has undergone a procedure that precludes reproductive potential.** - **Has a congenital abnormality that precludes reproductive potential.** ~~Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.~~	To comply with the current protocol template.
10.4. Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Text was revised as follows: (eg, a ~~woman~~ **participant** ~~who is not heterosexually active~~ becomes **sexually** active **where pregnancy can occur**)	To make language more inclusive and gender-neutral.
10.4. Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Text was revised in the section on "Examples of Contraceptives" as follows: • Sexual abstinence **from intercourse where pregnancy could occur** (Sexual abstinence is considered a highly effective method only if defined as refraining from ~~hetero~~sexual intercourse **where the possibility of**	To make language more inclusive and gender-neutral.

Section Number and Name	Description of Change	Brief Rationale
	pregnancy exists during the entire period of risk associated with **exposure to** the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)	
Other miscellaneous changes.		
4.2. Scientific Rationale for Study Design	Text under the subheading **Clinical Pharmacology Assessments** was revised as shown below. Blood samples will be analyzed for amivantamab serum and lazertinib plasma concentrations~~, and estimation of basic PK parameters~~.	Because of sparse PK sample collection for amivantamab and lazertinib, PK parameters will not be estimated.
8.5.3. Pharmacokinetic Parameters and Evaluations	Text in this section was revised as shown below. Pharmacokinetic analysis of serum/plasma concentration data for amivantamab and lazertinib will be performed. Serum (amivantamab) and plasma (lazertinib) concentrations ~~and PK parameters~~ will be listed and summarized by sampling interval.	Because of sparse PK sample collection for amivantamab and lazertinib, PK parameters will not be estimated.
9.4.3. Secondary Endpoints	The definition for time to symptomatic progression and the analysis set for intracranial progression-free survival were revised, for consistency with changes in Addendum 1 of the statistical analysis plan (SAP) for the study.	Death was inadvertently omitted from the definition of TTSP in the protocol. Because of the sparse intracranial disease evaluation schedule (every 24 weeks) for participants without a history of brain metastasis at screening, the intracranial PFS may not be adequately assessed for these participants.
10.1. Appendix 1: Abbreviations	New abbreviations used during Amendment 3 were added. Abbreviations not used in the protocol were deleted.	To provide an updated list of abbreviations.
Throughout the protocol	The words “female” and “male” were removed. The following text was updated as follows ~~“Female~~**Participant** of childbearing potential” and “~~F~~**P**OBCP”	To make the protocol more inclusive and gender-neutral.
Throughout the protocol	Minor editorial and formatting changes were made.	Minor errors, discrepancies, or omissions were noted.

TABLE OF CONTENTS

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 2

TABLE OF CONTENTS 9

LIST OF IN-TEXT TABLES AND FIGURES 13

1. PROTOCOL SUMMARY 14
1.1. Synopsis 14
1.2. Schema 19
1.3. Schedule of Activities (SoA) 20

2. INTRODUCTION 26
2.1. Standard of Care for NSCLC With EGFR Activating Mutations 27
2.2. Amivantamab (JNJ-61186372): A Bispecific Antibody for Both EGFR and MET 28
2.3. Lazertinib: A Third-Generation EGFR TKI 30
2.4. Amivantamab and Lazertinib Combination 31
2.5. Study Rationale 33
2.6. Benefit-Risk Assessment 33
2.6.1. Risks for Study Participation 34
2.6.2. Benefits for Study Participation 34
2.6.3. Benefit-Risk Assessment for Study Participation 34

3. OBJECTIVES AND ENDPOINTS 36

4. STUDY DESIGN 37
4.1. Overall Design 37
4.1.1. Screening Phase 37
4.1.2. Treatment Phase 37
4.1.3. Follow-up Phase 38
4.1.4. Open-label Extension Phase and Long-term Extension Phase 38
4.2. Scientific Rationale for Study Design 39
4.2.1. Study-Specific Ethical Design Considerations 40
4.3. Justification for Dose 41
4.4. End of Study Definition 41

5. STUDY POPULATION 42
5.1. Inclusion Criteria 42
5.2. Exclusion Criteria 45
5.3. Lifestyle Considerations 49
5.3.1. Activity 49
5.4. Screen Failures 50

6. STUDY MEDICATION AND CONCOMITANT THERAPY 50
6.1. Study Treatments Administered 50
6.1.1. Amivantamab 51
6.1.2. Lazertinib 52
6.1.3. Osimertinib 53
6.2. Preparation/Handling/Storage/Accountability 53
6.3. Measures to Minimize Bias: Randomization and Blinding 54
6.4. Study Treatment Compliance 55
6.5. Concomitant Therapy 56
6.5.1. Recording Prestudy and Concomitant Therapies 56
6.5.2. Amivantamab Pre-infusion and Post-infusion Medications 56
6.5.3. Permitted Medications and Therapies 58
6.5.3.1. Supportive Care 58

6.5.3.2. Radiotherapy ... 58
6.5.3.3. Hormonal Contraception ... 58
6.5.3.4. Prophylactic Medications ... 58
6.5.4. Prohibited or Restricted Medications and Therapies ... 58
6.6. Dose Modification Guidance ... 59
6.6.1. Withholding Treatment ... 59
6.6.2. Dose Reduction ... 61
6.6.3. Dose Modifications and Management of Specific Adverse Events ... 62
6.6.3.1. Infusion-Related Reactions (Arm A only) ... 63
6.6.3.2. Rash-Related Adverse Events ... 65
6.6.3.3. Pruritus ... 68
6.6.3.4. Paronychia ... 69
6.6.3.5. Oral Mucositis ... 69
6.6.3.6. Pulmonary Toxicity ... 70
6.6.3.7. Cardiac Adverse Events ... 71
6.6.3.8. Liver Chemistry Abnormalities ... 72
6.6.3.9. Diarrhea ... 72
6.6.3.10. Ocular Toxicity ... 73
6.6.3.11. Paresthesia ... 73
6.6.3.12. Venous Thromboembolic Events ... 74
6.7. Continued Access to Study Treatment ... 75

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL ... 75
7.1. Discontinuation of Study Treatment ... 75
7.2. Participant Discontinuation/Withdrawal From the Study ... 76
7.2.1. Withdrawal From the Use of Research Samples ... 76
7.3. Lost to Follow-up ... 76

8. STUDY ASSESSMENTS AND PROCEDURES ... 77
8.1. Efficacy Assessments ... 78
8.1.1. Disease Assessments ... 78
8.1.2. Symptomatic Progression ... 81
8.1.3. Patient-Reported Outcomes ... 81
8.2. Safety Assessments ... 81
8.2.1. Physical Examinations ... 82
8.2.2. Vital Signs ... 82
8.2.3. Electrocardiograms ... 83
8.2.4. Left Ventricular Ejection Fraction ... 83
8.2.5. Ophthalmologic Assessment ... 83
8.2.6. ECOG Performance Status ... 84
8.2.7. Clinical Safety Laboratory Assessments ... 84
8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting ... 84
8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information ... 84
8.3.2. Method of Detecting Adverse Events and Serious Adverse Events ... 85
8.3.3. Follow-up of Adverse Events and Serious Adverse Events ... 85
8.3.4. Regulatory Reporting Requirements for Serious Adverse Events ... 85
8.3.5. Pregnancy ... 86
8.3.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events ... 86
8.3.7. Adverse Events of Special Interest ... 86
8.4. Treatment of Overdose ... 87
8.5. Pharmacokinetics ... 87
8.5.1. Evaluations ... 87
8.5.2. Analytical Procedures ... 87

8.5.3. Pharmacokinetic Parameters and Evaluations ... 88
8.6. Pharmacogenomics ... 88
8.7. Biomarkers ... 88
8.8. Immunogenicity Assessments ... 89
8.9. Medical Resource Utilization and Health Economics ... 90

9. STATISTICAL CONSIDERATIONS ... 90
9.1. Statistical Hypotheses ... 90
9.2. Sample Size Determination ... 91
9.3. Populations for Analyses Sets ... 91
9.4. Statistical Analyses ... 91
9.4.1. General Considerations ... 91
9.4.2. Primary Endpoint ... 92
9.4.3. Secondary Endpoints ... 92
9.4.4. Exploratory Endpoints ... 94
9.4.5. Safety Analyses ... 94
9.4.6. Other Analyses ... 95
9.5. Interim Analysis ... 96

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS ... 98
10.1. Appendix 1: Abbreviations ... 98
10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations ... 100
10.2.1. Regulatory and Ethical Considerations ... 100
10.2.2. Financial Disclosure ... 103
10.2.3. Informed Consent Process ... 103
10.2.4. Recruitment Strategy ... 104
10.2.5. Data Protection ... 104
10.2.6. Long-Term Retention of Samples for Additional Future Research ... 105
10.2.7. Committees Structure ... 105
10.2.8. Publication Policy/Dissemination of Clinical Study Data ... 106
10.2.9. Data Quality Assurance ... 107
10.2.10. Case Report Form Completion ... 107
10.2.11. Source Documents ... 108
10.2.12. Monitoring ... 109
10.2.13. On-Site Audits ... 109
10.2.14. Record Retention ... 110
10.2.15. Study and Site Start and Closure ... 110
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting ... 112
10.3.1. Adverse Event Definitions and Classifications ... 112
10.3.2. Attribution Definitions ... 113
10.3.3. Severity Criteria ... 113
10.3.4. Special Reporting Situations ... 114
10.3.5. Procedures ... 114
10.3.6. Contacting Sponsor Regarding Safety, Including Product Quality ... 115
10.3.7. Product Quality Complaint Handling ... 115
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information ... 117
10.5. Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status ... 120
10.6. Appendix 6: New York Heart Association Criteria ... 121
10.7. Appendix 7: Clinical Laboratory Tests ... 122
10.8. Appendix 8: Prohibited and Restricted Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5 ... 123
10.9. Appendix 9: Substrates of P-glycoprotein (P-gp), multi-drug resistance protein 4 (MRP4), and Breast Cancer Resistance Protein (BCRP): Exercise Caution ... 125
10.10. Appendix 10: Liver Event Follow-Up and Rechallenge Criteria ... 126
10.11. Appendix 11: Cockcroft-Gault Formula for Estimated Creatinine Clearance ... 127

10.12. Appendix 12: Medications With Potential for QT Interval Prolongation 128
10.13. Appendix 13: Anticipated Events 130
10.14. Appendix 14: Open-Label Extension Phase 132
10.14.1. Eligibility Criteria 132
10.14.2. Study Treatment Administration 132
10.15. Appendix 15: Long-Term Extension Phase 137
10.15.1. Eligibility Criteria 137
10.15.2. Study Treatment Administration 137
10.15.3. Study Procedures 137
10.16. Appendix 16: Protocol Amendment History 140

11. REFERENCES 155

INVESTIGATOR AGREEMENT 158

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Table 1: Schedule of Activities (All Arms, Unless Otherwise Indicated) 20
Table 2: Sample Collection Times for Pharmacokinetics and Immunogenicity Samples (Arm A Only)[d] 25
Table 3: Half-Maximal Inhibitory Concentration of Lazertinib or Osimertinib for Kinase Activity by EGFR Mutation 30
Table 4: Initial Dosages for Study Treatment, by Treatment Arm 51
Table 5: Pre-Infusion Medications 57
Table 6: Post-Infusion Medications 57
Table 7: Guidance for Withholding Doses for Toxicities Based on Grade (Arm A) 60
Table 8: Guidance for Withholding Doses for Toxicities Based on Grade (Arm B or Arm C) 61
Table 9: Recommended Dose Reduction for Amivantamab and Lazertinib Combination Therapy (Arm A) 62
Table 10: Dose Reduction for Double-Blinded Therapy (Arms B and C) 62
Table 11: Management of Infusion-Related Reactions 64
Table 12: Suggested Algorithm for Management of Rash 67
Table 13: Suggested Algorithm for Management of Diarrhea 73
Table 14: Populations for Analyses 91
Table 15: Anticipated Events 130
Table 16: Schedule of Activities in the Open Label Extension Phase (All Arms, Unless Otherwise Indicated) 134
Table 17: Schedule of Activities in the Long-term Extension Phase (All Arms, Unless Otherwise Indicated) 139

FIGURES

Figure 1: Schematic Overview of the Study 19
Figure 2: Activity of Amivantamab in Combination with Lazertinib in Mice 32

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

IND:	146319
EudraCT NUMBER:	2020-000743-31
EU Trial NUMBER:	2023-506576-27

Third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as osimertinib are becoming standard of care as first-line therapy for non-small cell lung cancer (NSCLC) harboring EGFR Exon 19del or L858R mutations. While osimertinib represents a significant advance over earlier EGFR TKIs, almost all patients eventually relapse. There is an unmet need to improve first-line therapy to extend progression-free survival (PFS) beyond the median of 19 months seen with osimertinib. Early data suggest that secondary EGFR mutations such as C797S and mesenchymal-epithelial transition (MET) activation are among the most frequent mechanisms of resistance in this setting.

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against EGFR and MET tyrosine kinase receptors that is being developed for the treatment of solid tumors, including EGFR-mutated NSCLC. It shows clinical activity against tumors with the primary activating EGFR mutations Exon 19del and Exon 21 L858R substitution, EGFR Exon 20ins mutations, the EGFR resistance mutations T790M and C797S, or activation of the MET pathway.

Osimertinib is an oral, highly potent, third-generation, EGFR TKI. It is approved for the treatment of patients with metastatic NSCLC whose tumors have EGFR Exon 19del or Exon 21 L858R mutations as detected by a Food and Drug Administration (FDA)-approved test, and for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

Lazertinib (JNJ-73841937; YH-25448), like osimertinib, is an oral, highly potent, third-generation, EGFR TKI. It selectively inhibits both primary activating EGFR mutations (Exon 19del, Exon 21 L858R substitution) and the EGFR T790M resistance mutation, while having less activity versus wild-type EGFR. Nonclinical data suggest lazertinib has in vitro potency, selectivity, and high blood-brain barrier penetration comparable with osimertinib. Results from participants in early clinical studies of lazertinib are consistent with the clinical activity previously reported with osimertinib.

This randomized, multicenter, Phase 3 study will compare the efficacy and safety of combining amivantamab and lazertinib (Arm A) versus single-agent osimertinib (Arm B) as first-line treatment in participants with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Combining amivantamab and lazertinib may lead to improved treatment outcomes through synergistic anti-EGFR activity, prevention of EGFR- or MET-based resistance to a third-generation EGFR TKI, and potential recruitment of Fc-bearing immune cells in the anti-tumor response. The contribution of amivantamab to the activity of the combination will be assessed by comparing the efficacy observed in the amivantamab and lazertinib combination arm (Arm A) with that in a lazertinib monotherapy arm (Arm C).

BENEFIT-RISK ASSESSMENT

The safety and tolerability of amivantamab and lazertinib, as single agents and in combination, have been shown in Phase 1 studies. The safety and tolerability of amivantamab and lazertinib in combination has also been shown in a Phase 1 Study. The tolerability of osimertinib was shown in clinical trials.

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 review safety and tolerability data periodically. Dose modification guidance is also provided to manage toxicities that occur during the study.

Osimertinib is the standard of care first-line therapy in this patient population. All participants in the study will accordingly be treated with a third-generation EGFR TKI, consistent with the standard of care.

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 in the first-line setting, 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 MET pathways.

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

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the efficacy of the amivantamab and lazertinib combination, compared with osimertinib, in participants with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC	• PFS (using RECIST v1.1 guidelines), as assessed by blinded independent central review
Key Secondary	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Overall survival • Objective response rate • Duration of response • PFS after first subsequent therapy (PFS2) • Time to symptomatic progression • Intracranial PFS
To evaluate the safety and tolerability of the amivantamab and lazertinib combination compared with osimertinib	• Incidence and severity of adverse events and laboratory abnormalities

EGFR epidermal growth factor receptor; NSCLC non small cell lung cancer; PFS progression free survival; RECIST Response Evaluation Criteria in Solid Tumors.

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

Hypothesis

The hypothesis is that the amivantamab and lazertinib combination (Arm A) will demonstrate superior PFS compared with single-agent osimertinib (Arm B).

OVERALL DESIGN

The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. Participants must complete screening procedures within 28 days before randomization. To be randomized, all participants must have been previously diagnosed with NSCLC, characterized by Exon 19del or Exon 21 L858R substitution EGFR mutations.

The Treatment Phase for a participant will begin on Cycle 1 Day 1 and continue as 28day- cycles until the End of Treatment visit, approximately 30 days after discontinuation of study treatment. Participants who discontinue study treatment for any reason will be followed for survival and symptomatic progression in the Follow-up Phase. The Follow-up Phase starts after the End of Treatment Visit and continues until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first.

Following the primary PFS analysis for efficacy, the study will transition to an open-label extension (OLE) Phase (see details provided in Section 10.14 [Appendix 14]). The purpose of the OLE Phase is to continue to collect data of clinical relevance/importance while reducing protocol-required visit procedures and assessments and the burden on participants after the primary PFS analysis and unblinding. Unblinding will occur for blinded Arms B and C. Only active treatment will be provided, without placebo.

Participants will be provided the option to continue their current study treatment in the OLE Phase until the final analysis for overall survival, after which the study will transition to a long-term extension (LTE) Phase.

Participants who continue to benefit from study treatment(s), as determined by their investigator, at the time of completion of the OLE Phase may continue to receive access to study treatment(s) within the study by transferring to the LTE Phase, where only serious adverse event data and study treatment 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 final analysis for overall survival is complete.

The LTE Phase (see details provided in Section 10.15 [Appendix 15]) will begin after the final analysis for overall survival, and will continue until the discontinuation criteria described in Section 7.1 are met, or until 4 years after local marketing authorization is obtained for the studied indication, whichever occurs first.

The OLE phase will begin after approval of Amendment 4 by health authorities of countries/territories in which this study is being conducted at the time of transition, and by study site Independent Ethics Committees/Institutional Review Boards (IECs/IRBs). In addition, for transition to the LTE Phase (after final analysis for overall survival), notification from the sponsor will be provided.

NUMBER OF PARTICIPANTS

Approximately 1000 eligible participants will be randomly assigned to study treatment in a 2:2:1 ratio (Arm A, B, and C respectively). Randomization will be stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent).

STUDY TREATMENT GROUPS AND DURATION

- **Arm A**: Approximately 400 participants will be assigned to open-label treatment with the combination of amivantamab (1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg by intravenous [IV] infusion, once weekly for the first 4 weeks and then once every 2 weeks) and lazertinib (240 mg orally, once daily).
- **Arm B**: Approximately 400 participants will receive double-blind treatment with single-agent osimertinib (80 mg orally, once daily).
- **Arm C**: Approximately 200 participants will receive double-blind treatment with single-agent lazertinib (240 mg orally, once daily).

Study treatments may be withheld and the dosages may be subsequently modified to manage treatment-related toxicity. Refer to the protocol for guidance.

Study treatment should continue until one of the following criteria applies: documented disease progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; withdrawal of consent; the investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study treatment; the participant becomes pregnant; or noncompliance with study treatment or procedure requirements.

EFFICACY EVALUATIONS

Tumor response will be assessed by blinded independent central review (BICR) according to RECIST v1.1. Baseline disease assessments, including brain magnetic resonance imaging (MRI) should be performed no more than 28 days prior to randomization. Repeat imaging will occur at regular intervals, as defined in the Schedule of Activities, until disease progression.

PHARMACOKINETIC EVALUATIONS

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

IMMUNOGENICITY EVALUATIONS

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

BIOMARKER EVALUATIONS

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

SAFETY EVALUATIONS

Safety will be assessed by physical examinations, laboratory tests, vital signs, electrocardiograms, left ventricular ejection fraction (echocardiogram or multigated acquisition), Eastern Cooperative Oncology Group (ECOG) performance status, monitoring of adverse events, and concomitant medication usage.

STATISTICAL METHODS

The statistical hypothesis assumes that, compared with single agent osimertinib (Arm B), the amivantamab and lazertinib combination (Arm A) will prolong median PFS from 19 months to 26 months. Taking account of the accrual period, follow-up, and dropout rate, the sample size needed for the study is approximately 800 participants (400 per Arm A and Arm B). A total of 450 PFS events in Arm A and Arm B combined will provide approximately 90% power to detect a hazard ratio (HR) of 0.73 with the stratified log-rank test (2-sided alpha = 0.05).

The primary efficacy endpoint is PFS, defined as the time from randomization until the date of objective disease progression or death, whichever comes first, based on BICR using RECIST v1.1. The treatment effect of the combination compared to osimertinib on PFS will be analyzed using a log-rank test stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent). The HR for PFS will be calculated, along with its 95% confidence intervals, from a stratified Cox model using the same stratification factors as for the log-rank test.

The key secondary endpoint of OS will be analyzed using the same methodology and model as for the analysis of PFS. A hierarchical testing approach for the primary endpoint and key secondary endpoint will

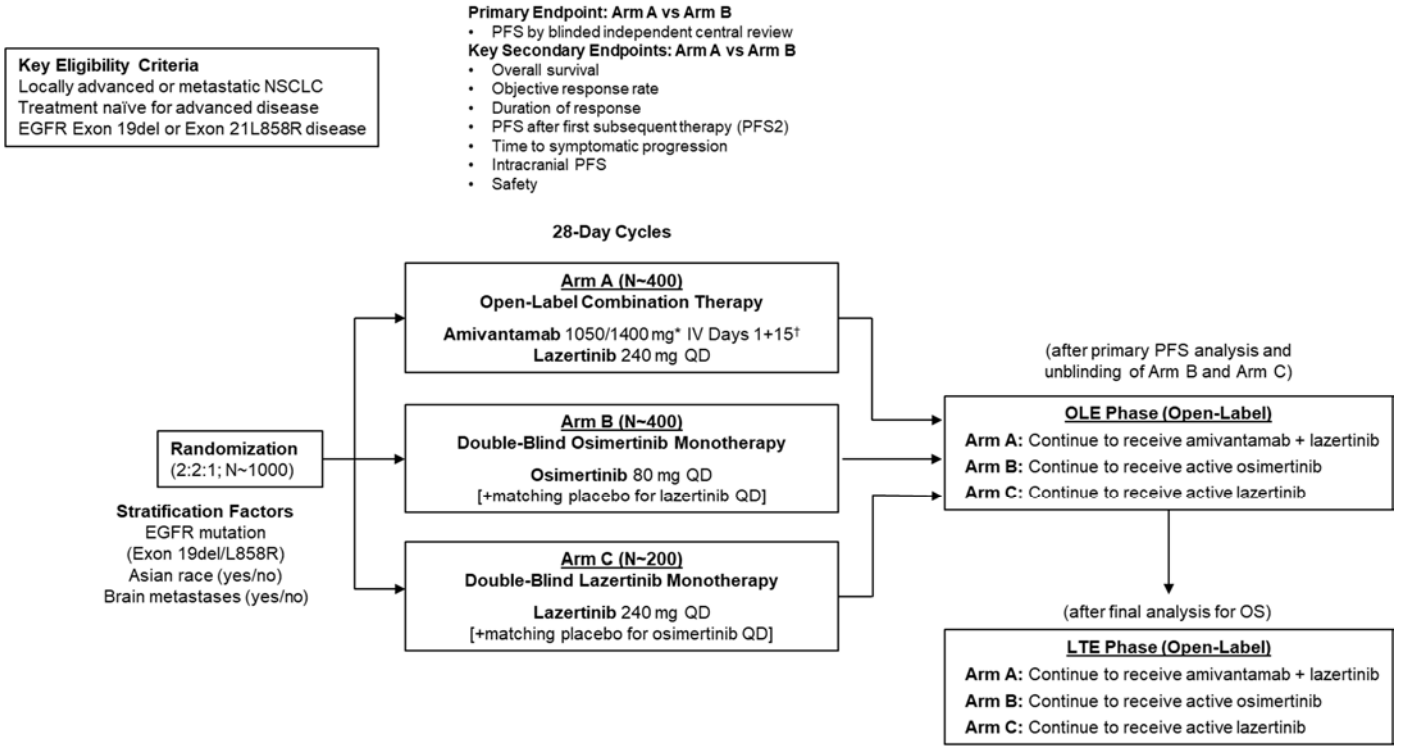
be used: the comparison between the combination and osimertinib for OS will be conducted only if the comparison for PFS shows statistical significance.

The comparison of the combination of amivantamab and lazertinib therapy (Arm A) versus lazertinib monotherapy (Arm C) will also be performed to demonstrate the contribution of amivantamab to the activity of the combination using summary statistics of the primary endpoint and key secondary endpoint (PFS and OS) along with nominal p-values; there will be no hypothesis testing for this comparison.

A futility analysis based on PFS will be conducted when approximately 150 PFS events have occurred overall (all treatment arms combined). An Independent Data Monitoring Committee will be commissioned for this study. Statistical methods for other endpoints will be described in the Statistical Analysis Plan.

1.2. Schema

Figure 1: Schematic Overview of the Study



EGFR epidermal growth factor receptor; IV intravenous; LTE long term extension; NSCLC non small cell lung cancer; PFS progression free survival; OLE open label extension; OS overall survival; QD once daily.
*Weight based dosing: <80 kg/≥80 kg
†Cycle 1: Days 1/2 (split dose), 8, 15, 22; Cycles 2+: Days 1, 15

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities (All Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 16 and Table 17, respectively.

Phase		Treatment (28 Days/Cycle)									End of Treatment Visit[b]	Follow-Up (Visit or Call)
Study Period		Cycle 1					Cycle 2		Cycles 3+		30 Days After Last Dose of Study Treatment	Q12 Weeks From the Last Dose of Study Treatment
Cycle Day	Screening	1	2	8	15	22	1	15	1	15		
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±1	±1	±2	±2	+7	±14
STUDY PROCEDURES (Perform assessments on dosing days before study drug administration, unless otherwise stated.)												
Screening Assessments If an assessment was performed as part of the participant's routine clinical evaluation and not specifically for this study, it need not be repeated after signed informed consent has been obtained, provided the assessments fulfill the study requirements. Results of the screening assessments must be reviewed by the investigator prior to enrollment. Participants who fail screening may be rescreened if their condition changes but must sign a new ICF.												
Informed consent (ICF) The ICF must be signed before the first study related activity is conducted. If a fresh tumor biopsy is required to meet eligibility (see Section 8.7), the biopsy can be obtained at any time before randomization, provided informed consent has been given. All other screening procedures must be completed within 28 days before randomization.	X											
Inclusion/exclusion criteria Confirm all criteria are met before randomization	X											
Demography Age (year of birth), gender, ethnicity, race	X											
Disease characteristics Tumor type, tumor stage (initial and current), diagnosis date (initial and current), prior anticancer therapies, date of disease progression	X											
Medical history Diagnoses, relevant surgeries/procedures, conditions, symptoms (with grade)	X											
ECOG performance status	X	X[a]									X	
Hematology/Chemistry (Appendix 7) May be collected up to 72 hours before the study visit; additional testing as clinically indicated as per local guidelines and practice; clinically significant abnormalities should be reported as adverse events	X	X[a]		Arm A only	Arm A only	Arm A only	X	Arm A only	X		X	
Serology (HIV, HBV, HCV; Appendix 7)	X											
Coagulation (Appendix 7)	X	As clinically indicated										
Urinalysis (Appendix 7)	X	As clinically indicated										
Ophthalmologic examination	X	As clinically indicated										

Table 1: Schedule of Activities (All Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 16 and Table 17, respectively.

Phase		Treatment (28 Days/Cycle)									End of Treatment Visit[b]	Follow-Up (Visit or Call)
Study Period		Cycle 1					Cycle 2		Cycles 3+		30 Days After Last Dose of Study Treatment	Q12 Weeks From the Last Dose of Study Treatment
Cycle Day	Screening	1	2	8	15	22	1	15	1	15		
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±1	±1	±2	±2	+7	±14
Pregnancy test	X	X[a]	For participants of childbearing potential, a serum pregnancy test is required at Screening and within 72 hours before the first dose of Cycle 1. A serum or urine pregnancy test is required within 72 hours before the first dose of each subsequent treatment cycle. 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 center. A final pregnancy test, serum or urine, is required at the End of Treatment visit at least 30 days after the last dose of study treatment.									
Efficacy Assessments												
CT or MRI tumor imaging CT with contrast is preferred; use same method throughout study. Continue to submit disease evaluations until disease progression is confirmed by BICR.	X	Disease assessment of the chest, abdomen, pelvis, and any other disease location every 8 weeks (±1 week) for the first 30 months and then every 12 weeks (±1 week). Timing of imaging is relative to randomization. Notes: Continue imaging until disease progression is confirmed by BICR. Submit images to central vendor per Imaging Manual until BICR confirmed disease progression. For participants who discontinue treatment prior to disease progression, tumor imaging should continue until BICR confirmed disease progression. If participant begins a new cancer therapy before BICR confirmed disease progression, obtain tumor imaging before the new therapy. If a participant receives study treatment beyond disease progression, continue disease assessments as per the schedule of assessments. See Section 8.1.1 for further details.									
Brain MRI Or brain CT scan, if MRI contraindicated Continue brain imaging until disease progression is confirmed by BICR	X	Participants with a history of brain metastasis at Screening will undergo postbaseline brain MRI every 8 weeks (±1 week) for the first 30 months and then every 12 weeks (±1 week); participants with no history of brain metastasis at Screening will undergo postbaseline surveillance brain MRI every 24 weeks (±1 week). Timing is relative to randomization. Notes: Continue imaging until disease progression is confirmed by BICR. Submit images to central vendor per Imaging Manual until BICR confirmed disease progression. For participants who discontinue treatment prior to disease progression, tumor imaging should continue until BICR confirmed disease progression. If participant begins a new cancer therapy before BICR confirmed disease progression, obtain tumor imaging before the new therapy. If a participant receives study treatment beyond disease progression, continue disease assessments as per the schedule of assessments. Repeat imaging can be obtained at any time as clinically indicated See Section 8.1.1 for further details.									
Symptomatic progression events Collect continuously from randomization (including during the Follow up Phase).		X										
Survival/disease status												X
Subsequent anticancer therapy												X

Table 1: Schedule of Activities (All Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 16 and Table 17, respectively.

Phase			Treatment (28 Days/Cycle)										End of Treatment Visit[b]	Follow-Up (Visit or Call)
Study Period			Cycle 1					Cycle 2		Cycles 3+			30 Days After Last Dose of Study Treatment	Q12 Weeks From the Last Dose of Study Treatment
Cycle Day		Screening	1	2	8	15	22	1	15	1	15			
Visit Window (Days)		-28 to -1	-	-	±1	±1	±1	±1	±1	±2	±2		+7	±14
Safety Assessments														
12 lead ECG Triplicate at Screening, C1D1 (preinfusion), C2D1 (Arm A: ≤30 min after amivantamab infusion; Arms B/C: 2 4h after oral drug administration), then to confirm a clinically significant finding; approximately 2 min between each ECG; digital copy of triplicate ECG will be collected. Collect around the same time of day (±4h) at C1D1 and C2D1. Send copy of ECGs to central vendor		X	X[a]					X		As clinically indicated				
ECHO or MUGA (May be collected up to72 hours prior to study visit). Send copy of ECHO or MUGA to central vendor		X								Every 3 cycles starting with C4D1			X	
Vital signs Heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation	Arm A (≤30 min before infusion of amivantamab, ~30 min intervals (±5 min) during each infusion, and at end of infusion (+5 min)	X	X	X	X	X	X	X	X	X	X		X	
	Arms B/C	X	X					X		X			X	
Physical examination Full exam and height at screening; then symptom directed exams[c]; weight at Screening and Day 1 of each cycle	Arm A	X	X[a]		X	X	X	X	X	X			X	
	Arms B/C	X	X[a]					X		X			X	
Adverse events (serious or non serious)		Collect continuously from ICF through 30 days after the last dose of study treatment (>30 days for a serious adverse event if considered related to study treatment)												
Prestudy and concomitant medications		Collect continuously from ICF through 30 days after the last dose of study treatment (or start of subsequent anticancer therapy). Concomitant medications administered >30 days after the last dose of study treatment in conjunction with serious adverse events considered related to study treatment must continue to be collected until resolution of event or start of subsequent therapy.												
Prophylactic dose anticoagulation[d]			Recommended during the first 4 months of treatment for participants receiving the combination of amivantamab and lazertinib											

Table 1: Schedule of Activities (All Arms, Unless Otherwise Indicated)

For OLE and LTE phases, refer to Table 16 and Table 17, respectively.

Phase		Treatment (28 Days/Cycle)									End of Treatment Visit[b]	Follow-Up (Visit or Call)
Study Period		Cycle 1					Cycle 2		Cycles 3+		30 Days After Last Dose of Study Treatment	Q12 Weeks From the Last Dose of Study Treatment
Cycle Day	Screening	1	2	8	15	22	1	15	1	15		
Visit Window (Days)	-28 to -1	-	-	±1	±1	±1	±1	±1	±2	±2	+7	±14
Study Treatment												
Randomization: start study treatment within 3 days or 72 hours of randomization		X										
Arm A: IV amivantamab (open label) Split first dose on C1D1 and C1D2 Starting with C2, infusions delayed >7 days cannot be made up. The delayed dose should be skipped, and the participant dosed at the next scheduled visit.		X	X	X	X	X	X	X	X	X		
Arm A: oral lazertinib (open label)[e]		C1D1 (<15 min pre infusion), then approximately the same time each day, with or without food										
Arms B/C: oral osimertinib or lazertinib (blinded)		C1D1, then approximately the same time each day, with or without food										
All arms: record oral study treatment compliance							X		X			
Patient-Reported Outcomes (Should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses)												
EQ 5D 5L, EORTC QLQ C30, NSCLC SAQ		X					X		Every 2 cycles starting with C3D1		X	X (up to 1 year after EOT)
PGIS		X					X		Every 2 cycles starting with C3D1		X	
PGIC							X		Every 2 cycles starting with C3D1		X	
Pharmacokinetics and Immunogenicity (see Table 2)												
Biomarkers												
Tumor biopsy Submission of an archival or fresh tumor biopsy sample for central mutation analysis is mandatory. The sample must be obtained at or after the diagnosis of locally advanced or metastatic NSCLC. See Section 8.7	X (up to 2 weeks after C1D1)										Post progression biopsy, if medically feasible, within 30 days of PD; obtain before next anticancer therapy	
ctDNA (predose) Blood sample	X										Blood sample within 30 days of PD; obtain before next anticancer therapy	
ddPCR (predose) Blood sample (After C7, sample can be collected on day of disease assessment or with the next safety laboratory assessment.)	X						X		Day 1 of Cycles 3 through 7, then at each disease assessment		Blood sample within 30 days of PD; obtain before next anticancer therapy	
Exploratory biomarkers Serum sample (predose at C1D1)		X									X	
Pharmacogenomic testing for GSTM 1 (Arm A only)		X										

BICR blinded independent central review; C#D# Cycle # Day #; CT computerized tomography; ctDNA circulating tumor deoxyribonucleic acid; ddPCR digital droplet polymerase chain reaction; ECG electrocardiogram; ECHO echocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC QLQ C30 European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ 5D 5L EuroQol five dimensional descriptive system (5 level version); GSTM 1 glutathione S transferase Mu 1; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; ICF informed consent form; IV intravenous; MUGA multigated acquisition; MRI magnetic resonance imaging; NSCLC SAQ Non Small Cell Lung Cancer Symptom Assessment Questionnaire; PD progressive disease; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; VTE venous thromboembolic; Q12 weeks every 12 weeks.

a. If performed within 72 hours before the first dose of study treatment, then the assessment does not need to be repeated at Cycle 1 Day 1.
b. 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 anti cancer therapy is to be initiated.
c. Evaluate for early signs and symptoms of VTE. A focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed.
d. See Section 6.6.3.12 for additional information. Please refer to NCCN Guidelines [22] Version 1.2022 cancer associated venous thromboembolic disease section VTE B for examples of prophylactic dose anticoagulants in ambulatory cancer patients.
e. Study participants who permanently discontinue amivantamab and continue open label lazertinib can follow the visit schedule for Arms B/C if the discontinuation occurs after C1.

Table 2: Sample Collection Times for Pharmacokinetics and Immunogenicity Samples (Arm A Only)[d]

Not applicable for OLE and LTE phases.

Phase	Treatment (28 Days/Cycle)				End of Treatment [e]
Study Period	Cycle 1		Cycles 2	Cycles 3, 5, 7, 9, 11, 13	30 Days After Last Dose
Cycle Day	D1	D2	D1	D1	-
Visit Window (days)	-	-	±1	±2	+7
Lazertinib Plasma Pharmacokinetics Samples					
Lazertinib predose (up to 2h before planned dose)	X		X	X	
Lazertinib 2h postdose (1 3h postdose)	X		X		
Lazertinib 4h postdose (3 5h postdose)[a]	X		X		
Lazertinib end of treatment					X
Amivantamab Serum Pharmacokinetics Samples[b]					
Amivantamab predose (up to 2h before planned dose)	X	X	X	X	
Amivantamab end of infusion (0 15 min)[c]	X	X	X	X	
Amivantamab end of treatment					X
Amivantamab Serum Immunogenicity Samples[b]					
Amivantamab predose (up to 2h before planned dose)	X		X	X	
Amivantamab end of treatment					X

a. Lazertinib 4h postdose plasma pharmacokinetics sample will be obtained after amivantamab end of infusion. If amivantamab infusion goes beyond 5 hours, then the lazertinib 4h postdose sample should still be collected within the 3 5h window stated above.
b. Separate blood draws are not required for amivantamab pharmacokinetics and immunogenicity when collected at the same time point.
c. Blood sample should not be collected from the same extremity where the amivantamab infusion is being administered.
d. If an amivantamab dose is skipped on a visit where PK collection was required, the pre dose sample should be collected. When amivantamab is restarted, the pre and postdose/postinfusion sampling should occur at the next dose administration. Subsequent PK sampling should occur per SoA.
e. 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 anti cancer therapy is to be initiated.

2. INTRODUCTION

Third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as osimertinib are becoming standard of care as first-line therapy for non-small cell lung cancer (NSCLC) harboring EGFR Exon 19del or L858R mutations. While osimertinib represents a significant advance over earlier EGFR TKIs, almost all patients eventually relapse. There is an unmet need to improve first-line therapy to extend progression-free survival (PFS) beyond the median of 19 months seen with osimertinib. Early data suggest that secondary EGFR mutations such as C797S and mesenchymal-epithelial transition (MET) activation are among the most frequent mechanisms of resistance in this setting.

Amivantamab (JNJ-61186372) is a low fucose, fully human IgG1-based bispecific antibody directed against EGFR and MET tyrosine kinase receptors that is being developed for the treatment of solid tumors, including EGFR-mutated NSCLC. It shows clinical activity against tumors with the primary activating EGFR mutations Exon 19del or Exon 21 L858R substitution, EGFR Exon 20ins mutations, the EGFR resistance mutations T790M or C797S, and activation of the MET pathway.[12]

Osimertinib is an oral, highly potent, third-generation, EGFR TKI. It is approved for the treatment of patients with metastatic NSCLC whose tumors have EGFR Exon 19del or Exon 21 L858R mutations as detected by a Food and Drug Administration (FDA)-approved test, and for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.[37]

Lazertinib (JNJ-73841937; YH-25448), like osimertinib, is an oral, highly potent, third-generation, EGFR TKI. It selectively inhibits both primary activating EGFR mutations (Exon 19del, Exon 21 L858R substitution) and the EGFR T790M resistance mutation, while having less activity versus wild-type EGFR. Nonclinical data suggest lazertinib has in vitro potency, selectivity, and high blood-brain barrier penetration comparable with osimertinib.[13,39] Results from participants in early clinical studies of lazertinib are consistent with the clinical activity previously reported with osimertinib.[3]

This randomized, multicenter, Phase 3 study will compare the efficacy and safety of combining amivantamab and lazertinib (Arm A) versus single-agent osimertinib (Arm B) as first-line treatment in participants with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Both amivantamab and lazertinib are new investigational products. The contribution of amivantamab to the activity of the combination will be assessed by comparing the efficacy observed in the amivantamab and lazertinib combination arm (Arm A) with that in the lazertinib monotherapy arm (Arm C).

The term “study treatment” throughout the protocol, refers to study drug (amivantamab, lazertinib, or osimertinib), as defined in Section 6.1. The term "sponsor" used throughout this document refers

to the entities listed in the Contact Information page(s), which will be provided as a separate document. The term "participant" throughout the protocol refers to the common term "subject".

For the most comprehensive nonclinical and clinical information regarding amivantamab or lazertinib, refer to the latest version of the Investigator's Brochure (IB).[12,13] For additional information regarding osimertinib, refer to local prescribing information.[37]

2.1. Standard of Care for NSCLC With EGFR Activating Mutations

Worldwide, lung cancer is the most commonly diagnosed cancer (11.6% of total cases) and the leading cause of cancer death (18.4% of total cancer deaths).[8] NSCLC accounts for 80% to 85% of lung cancers.[1] Five-year survival rates for NSCLC depend on the stage at diagnosis, ranging from 57% for localized cancer to 5% for cancer that has spread to distant locations.[36] In patients with metastatic NSCLC, clinical guidelines recommend testing for activating mutations.[21,27] Among patients with NSCLC, the most prevalent actionable driver mutations are those that result in the activation of EGFR. These are identified in more than 15% of patients with adenocarcinoma[24] and up to 50% of the corresponding Asian population.[14] Approximately 85% to 90% of primary activating EGFR mutations are Exon 19 deletions (Exon 19del) or Exon 21 L858R substitutions (L858R).[34]

Initially, first-generation anti-EGFR TKIs such as erlotinib or gefitinib were the standard of care as first-line therapy for adenocarcinoma in patients with tumors harboring Exon 19del or L858R mutations.[7,32] First-generation EGFR TKIs demonstrated both improved initial response rates and prolonged PFS in direct comparisons with combination chemotherapy. Although tumors bearing Exon 19del or L858R primary activating mutations are initially responsive to first-generation EGFR TKIs, virtually all of these tumors acquire resistance, with the majority (approximately 60%) acquiring a second-site point mutation, T790M.[16,25] Patients with T790M+ NSCLC are typically treated in second-line with third-generation TKIs (eg, osimertinib), which are active against T790M+, while patients without this mutation (ie, T790M-negative NSCLC) are treated with chemotherapy.[21,27] Compared with older EGFR TKIs, osimertinib penetrates the blood-brain barrier better and treats brain metastasis more effectively, which occurs in approximately 10% to 20% of patients with treatment-naïve EGFR-mutated NSCLC.[31]

More recently, the FLAURA study compared the third-generation EGFR TKI osimertinib versus a standard EGFR TKI (gefitinib or erlotinib) as first-line therapy for patients with metastatic NSCLC and Exon 19del or L858R mutations.[35] With its demonstrated activity against the EGFR T790M+ resistance mutation, it was hypothesized that osimertinib as a first-line treatment would delay the emergence of T790M+ mediated resistance, resulting in improved disease control. Correspondingly, FLAURA demonstrated a statistically significant improvement in PFS and overall survival (OS) for participants randomized to osimertinib versus a first-generation EGFR TKI: median PFS was 18.9 vs 10.2 months, respectively, with a hazard ratio (HR) of 0.46; and median OS was 38.6 vs 31.8 months, respectively, with a HR of 0.80.[30,35] This significant improvement in median PFS with osimertinib treatment was not associated with an improved response rate, suggesting that the majority of benefit may have been derived from its activity

against the T790M resistance mutation and improved activity within the central nervous system (CNS).

Despite the improved initial disease control, however, almost all patients treated with first-line osimertinib will relapse, and there are no approved targeted therapies for treatment of these patients once resistance has developed. The mechanisms underlying osimertinib relapse are less well understood, but early data suggest that secondary EGFR mutations, such as C797S and MET activation, are among the most frequent mechanisms of resistance in this setting.[9,29] While osimertinib represents a significant advance over earlier EGFR TKIs, there is a need to improve on first-line treatment prior to the development of resistance in order to extend PFS beyond the median of 19 months seen with osimertinib monotherapy.

2.2. Amivantamab (JNJ-61186372): A Bispecific Antibody for Both EGFR and MET

Unlike EGFR TKIs, which bind to the intracellular portion of the EGFR, amivantamab is a novel bispecific antibody that targets the extracellular domain of both EGFR and MET. Nonclinical data have demonstrated at least 3 potential mechanisms of action, including 1) inhibition of ligand-dependent signaling, 2) receptor degradation, and 3) initiation of antibody-dependent cellular cytotoxicity (ADCC).[12] It is hypothesized that by targeting the extracellular domain of EGFR and MET, amivantamab can inhibit tumor growth driven by EGFR and MET receptors, including tumors that display primary resistance to EGFR TKIs (Exon 20ins) or have acquired resistance through either EGFR resistance mutations (T790M or C797S) or secondary activation of the MET pathway (MET amplification).

An ongoing Phase 1 study of amivantamab (Study 61186372EDI1001) enrolled more than 250 participants as of the 30 October 2019 data cutoff date. The recommended Phase 2 dose (RP2D) was determined to be 1050 mg in participants <80 kg (1400 mg in participants ≥80 kg) by intravenous (IV) infusion, administered weekly for the first 4 weeks, and then biweekly thereafter. Amivantamab has a manageable safety profile up to the dose of 1750 mg, with no dose-limiting toxicities (DLTs) reported during dose escalation and no maximum tolerated dose (MTD) identified (see IB).[12] The most common treatment-emergent adverse events (TEAEs) in 153 participants treated at the RP2D were infusion-related reactions (IRRs; 61%), rash (31%) and dermatitis acneiform (29%), paronychia (28%), constipation (22%), dyspnea (21%), fatigue (20%), and hypoalbuminemia (20%). The majority of TEAEs were of Grade 1-2 severity. TEAEs of Grade 3 or Grade 4 severity considered by the investigator to be related to amivantamab were reported in 14 subjects (9%) treated at the RP2D, the most common being rash in 2 (1%) subjects.

Consistent with the overall safety profile at the RP2D, dose reduction and discontinuation of treatment due to TEAE were infrequent. Eight subjects (5%) treated at the RP2D experienced at least 1 TEAE considered related to amivantamab that led to dose reduction. These TEAEs included dermatitis acneiform (2 subjects) and rash, fatigue, edema peripheral, cellulitis, paronychia, and lactic acid dehydrogenase elevation (1 subject each). Six subjects (4%) treated at the RP2D experienced at least 1 TEAE leading to discontinuation of amivantamab treatment, with 3 (2%)

reported as related to amivantamab: these 3 TEAEs leading to discontinuation were IRR (2 subjects) and paronychia.

Infusion-related reactions have been commonly observed, typically within the first 90 minutes of beginning the first infusion of amivantamab. Subsequent infusions, including Cycle 1 Day 2, are associated with dramatically reduced IRR risk, such that predose steroids are not required starting with Cycle 1 Day 8. As of the 30 October 2019 data cutoff date, 158 of 252 (63%) total treated subjects experienced at least 1 IRR. Adverse events associated with IRRs that occurred in more than 10% of all treated subjects included the following: nausea (21%), chills and dyspnea (19% each), flushing (16%), and chest discomfort (12%). Transient increases in mean blood pressure, mean pulse rate, and mean respiratory rate, and decreases in mean oxygen saturation were noted during the first infusion of amivantamab in all dose cohorts. The majority of IRRs were of Grade 2 severity, reflecting the guidance to temporarily interrupt infusion at the first sign of IRR symptoms. In rare cases, IRRs of Grade 3 severity were reported. Re-occurrence of IRRs on subsequent doses was infrequent; the occurrence of an IRR on first infusion should not be considered a contraindication to further treatment with amivantamab.

Evidence of clinical activity has been observed across patients with diverse EGFR-mutated disease, including those characterized by primary EGFR L858R, Exon 19del, G719A, and Exon 20ins disease, as well as EGFR T790M or C797S resistance mutations, and MET-based EGFR TKI resistance (both MET amplification and MET Exon 14skip mutation).[10,12] Based on interim data for evaluable subjects in the Phase 1 study, 32 of 108 subjects (30%) experienced tumor best response of partial response (PR), including subjects who were primarily resistant to third-generation EGFR TKI therapy (including primary EGFR Exon 20ins disease), as well as EGFR C797S mutation or MET amplification after third-generation EGFR TKI relapse.[12] Based on the preliminary activity observed in the Exon 20ins population, amivantamab was granted Breakthrough Therapy Designation by the United States (US) FDA for the treatment of patients with EGFR Exon 20ins disease who have progressed after prior treatment with platinum-based chemotherapy. Given the monotherapy activity observed with amivantamab in third-generation EGFR TKI relapsed disease characterized by EGFR C797S resistance mutation or MET-based EGFR TKI resistance pathways, it is anticipated that administration of amivantamab in the first-line setting, in combination with lazertinib, will prolong disease control by suppressing the emergence of EGFR and MET resistance pathways to third-generation EGFR TKIs.

Amivantamab has also been demonstrated to induce ADCC in nonclinical models, via its Fc domain that has been optimized for interaction with Fc-bearing immune cells.[12] In these models, treatment with an analogous molecule with a silent Fc domain reduced anti-tumor activity by up to approximately 50%. These data suggest that inclusion of amivantamab in the first-line setting provides an opportunity to recruit immune cells in an anti-tumor response, in a disease that is considered to be relatively resistant to currently approved anti-PD(L)1 agents, due to their inherent low mutational burden.

2.3. Lazertinib: A Third-Generation EGFR TKI

Lazertinib, like osimertinib, is a third-generation, irreversible EGFR TKI that has high affinity for and inhibits both primary activating Exon 19del or Exon 21 L858R substitution EGFR mutations and the EGFR T790M+ resistance mutation, while having lower affinity for EGFR wild-type to minimize EGFR-related toxicities. In cell-free kinase activity studies, lazertinib selectively inhibited EGFR single- or double-mutant kinase compared with wild-type EGFR (Table 3). In non-clinical studies, lazertinib exhibited high blood-brain barrier penetration and excellent therapeutic efficacy against both primary lung tumors and brain metastases in a T790M mutant NSCLC xenograft model, and achieved cerebrospinal fluid (CSF) concentrations exceeding the IC_{50} value for p-EGFR inhibition in vitro.[39]

Table 3: Half-Maximal Inhibitory Concentration of Lazertinib or Osimertinib for Kinase Activity by EGFR Mutation

EGFR Kinase Genotype	IC_{50}, nM	
	Lazertinib	Osimertinib
Wild-type	76.0	54.0
Del19	5.3	8.6
L858R	20.6	12.2
Del19/T790M	1.7	2.2
L858R/T790M	2.0	8.0
ErbB2	364.0	44.0
ErbB4	1017.0	54.0

EGFR=epidermal growth factor receptor; IC_{50}=half-maximal inhibitory concentration.
Adapted from Yun 2019.[39]

The safety and activity of lazertinib were evaluated in a Phase 1/2 study (73841937NSC2001; YH25448-201).[13] As of the date of data cutoff on 30 September 2019, there were 181 subjects who were evaluable for efficacy with EGFR-mutated advanced NSCLC that had progressed after therapy with a first- or second-generation EGFR TKI.[13] Among 162 subjects with T790M+ disease (n 162), the objective response rate (ORR) was 59% and the median PFS was 10.9 months across all dose levels, as assessed by independent central review.[3,13] These results were comparable to those of osimertinib in the Phase 1 AURA study, in which participants with T790M+ disease showed an ORR of 61% and a median PFS of 9.6 months across all dose levels.[15] In the lazertinib Phase 1/2 study, among 22 subjects with measurable brain lesions the intracranial ORR by independent central review and investigator assessment were 55% and 64%, respectively, and intracranial PFS was not reached at a follow-up of 20.5 months, indicating lazertinib achieves effective blood-brain barrier penetration.[13,26] In 62 subjects with T790M+ disease who received lazertinib 120 mg, 160 mg, or 240 mg, the median PFS was 12.3 months.[3]

Lazertinib was well tolerated across all doses (from 20 mg up to 320 mg) in 252 subjects who were evaluable for safety.[3,13] No DLTs occurred in dose escalation. The most commonly reported TEAEs occurring in >20% of subjects (any grade) were rash, pruritus, diarrhea, paresthesia, constipation, upper respiratory infection, and decreased appetite. Grade 3 or 4 events were observed in 35.3% of subjects. The most commonly reported (>1%) serious TEAEs were pneumonia, asthenia, dyspnea, and pulmonary embolism. Drug-related serious TEAEs were

reported in 8 (3.2%) subjects. TEAEs leading to death occurred in 5 subjects (pulmonary embolism in 2 subjects, death, dyspnea, and atypical pneumonia in 1 subject each) but none were considered to be possibly related to lazertinib. TEAEs leading to dose reduction or drug discontinuation were observed in 11.1% and 7.9% of subjects, 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.[15] However, cardiac safety assessment in these subjects has shown that lazertinib has no clinically relevant effect on QT interval and left ventricular ejection fraction (LVEF).[3]

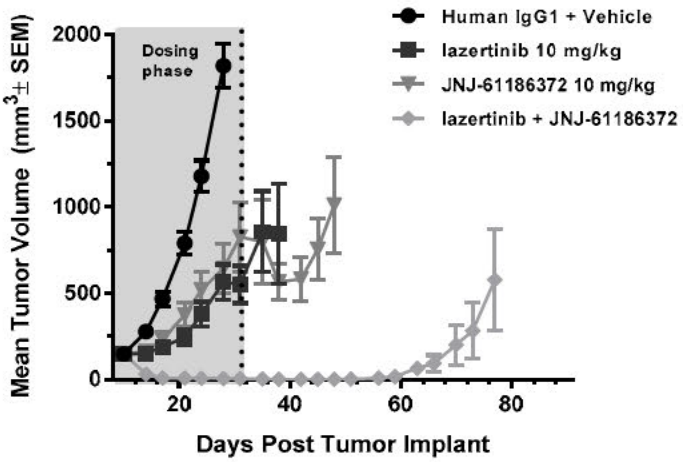
Based on pharmacokinetics (PK), efficacy, and safety, the RP2D for T790M-positive subjects was selected as 240 mg once daily. Another Phase 3, randomized, double-blind study (YH25448-301; LASER301) will assess the efficacy and safety of lazertinib versus gefitinib as first-line treatment in subjects with locally advanced or metastatic NSCLC with EGFR Exon 19del or L858R mutations.[28]

2.4. Amivantamab and Lazertinib Combination

The current clinical experience with lazertinib suggests activity at least equivalent to current standard of care osimertinib, and clinical experience with amivantamab demonstrates activity in third-generation EGFR TKI-relapsed disease. Thus, combining these agents in the first-line treatment of patients with EGFR-mutated NSCLC may lead to improved treatment outcomes through synergistic anti-EGFR activity, prevention of EGFR- or MET-based resistance to a third-generation EGFR TKI, and potential recruitment of Fc-bearing immune cells in the anti-tumor response.

Nonclinical studies have evaluated the efficacy of amivantamab in combination with lazertinib using a H1975-HGF NSCLC xenograft model in mice.[12,19] These xenografts model NSCLC tumors with an activating EGFR mutation (L858R), a second-site resistance EGFR mutation (T790M+), and activation of the MET pathway by autocrine expression of the MET ligand, hepatocyte growth factor (HGF). Single-agent treatment with amivantamab or lazertinib resulted in significant tumor growth inhibition (70% and 75%, respectively) as compared to isotype and vehicle-treated controls at Day 28 (p 0.0059 and p 0.0030; Figure 2). The combination of amivantamab with lazertinib resulted in significant tumor growth inhibition (109%) as compared to isotype- and vehicle-treated controls at Day 28 ($p<0.0001$). The combination of amivantamab with lazertinib also demonstrated statistically significant tumor growth inhibition as compared to single-agent treatment ($p<0.0001$). These nonclinical data are consistent with the hypothesis that through their complementary mechanisms of action, the amivantamab and lazertinib combination can result in significantly better anti-tumor activity than either agent alone in H1975-HGF xenografts.

Figure 2: Activity of Amivantamab in Combination with Lazertinib in Mice



JNJ-61186372=amivantamab. Female nude mice were inoculated with 5×10^6 H1975-HGF tumor cells. Tumors were measured twice weekly and data graphically represented as mean tumor volume (mm^3) ± standard error of the mean (SEM), n=10/group. Group means were plotted up to the point that at least 8/10 mice remained in each group. Animals were treated for 21 days.

The combination of amivantamab and lazertinib has been explored in the Phase 1 Study 61186372EDI1001.[13] As of 22 December 2020, a total of 91 subjects have been treated with amivantamab in combination with lazertinib. Enrolled subjects have NSCLC with either EGFR Exon 19del or L858R activating mutation.[13] Dose escalation included an initial dose cohort combining amivantamab 700/1050 mg (ie, 700 mg in subjects weighing <80 kg and 1050 mg in subjects weighing ≥80 kg) and lazertinib 240 mg. A subsequent dose cohort combined each agent at its RP2D from monotherapy studies, namely amivantamab 1050/1400 mg and lazertinib 240 mg. No DLT was observed at either dose of the combination. Pharmacokinetic data demonstrated a lack of drug-drug interaction, as the PK profile of each drug when administered in combination was consistent with the PK profile of each drug when administered as a monotherapy. Based on these data, the recommended Phase 2 combination dose (RP2CD) is amivantamab 1050 mg (1400 mg for body weight ≥80 kg) and lazertinib 240 mg (the RP2D of each agent combined).

The safety and preliminary activity of the lazertinib plus amivantamab combination from Study 61186372EDI1001 was recently reported for all 91 subjects with a median follow-up of 6 months and a median treatment duration of 5 months.[4,13] Treatment related adverse events overall were predominantly Grade 1-2 and were events seen with the study drugs as single agents. There was a total of 6% treatment related serious adverse events, 11% treatment related adverse events Grade 3 or higher, and 19% treatment related adverse events leading to dose interruption or reduction of either or both drugs. Treatment related adverse events leading to discontinuation of either or both drugs occurred in only 6% of subjects. The most common TEAEs (occurring in >20% of subjects) were rash (85%), IRR (65%), paronychia (53%), hypoalbuminemia (37%), stomatitis (33%), pruritis (28%), nausea (28%), and increased ALT (21%). Median time to onset for rash was 16 days, with a median duration of 29 days; Grade 3 rash occurred in 4% of subjects. The majority of IRRs occurred during the first infusion, with no discontinuations due to IRRs and

no impact on subsequent dosing. Incidence of diarrhea remains low at 18% and again mostly Grade 1-2. The safety profile indicates amivantamab and lazertinib are combinable.

Of the 91 subjects with EGFR Exon19del or L858R disease treated with the combination, 26 subjects were in the dose escalation cohort, 45 were osimertinib- resistant but chemotherapy-naïve, and 20 subjects were treatment naïve. In the osimertinib-relapsed but chemotherapy-naïve cohort (N 45) the combination of lazertinib and amivantamab demonstrated a confirmed ORR of 36% (95% CI, 22%-51%), including 1 complete response and 15 partial responses, and a clinical benefit rate of 60%. In the 20 patient cohort with treatment-naïve EGFR Exon 19del or L858R disease, the combination of lazertinib and amivantamab demonstrated an investigator-assessed confirmed partial response in all 20 subjects, for an ORR of 100% (95% CI, 83%-100%), with a median time to first response of 1.5 months. After 18 months of follow-up, the median duration of response was not estimable with 16 of 20 subjects remaining on therapy without progression.

In conclusion, the clinical data from Study 61186372EDI1001 indicate that amivantamab can be safely combined with lazertinib and suggest that the combination is efficacious in advanced EGFRm NSCLC including subjects who are treatment naïve.

The combination of amivantamab and lazertinib is being explored further in Study 73841937NSC1001 in a cohort of patients with either EGFR Exon19del or L858R NSCLC who have progressed after osimertinib and subsequent platinum-based doublet chemotherapy, or in patients with other EGFR mutations.

2.5. Study Rationale

The FLAURA study has demonstrated that an effective approach to improving treatment outcomes in EGFR mutation driven NSCLC is to employ first-line therapies with activity against potential mechanisms of resistance, either through resistance mutations, or via escape through sanctuary sites such as the CNS. Given the observed broad activity of amivantamab in EGFR- or MET-driven disease, its use in the first-line setting may provide improved clinical benefit by suppressing the development of C797S mutations and MET amplification when given together with lazertinib, a third-generation EGFR TKI with demonstrated CNS activity. In addition, combination of amivantamab with lazertinib is anticipated to provide synergistic activity against the primary EGFR activating mutations as demonstrated in nonclinical models (Figure 2). Finally, the inclusion of amivantamab in the first-line setting may also uniquely recruit immune cells as part of its anti-tumor response, via its Fc domain designed to maximize affinity with immune cell Fc receptors. In this manner, the combination of amivantamab and lazertinib has the potential to build upon the improvements of osimertinib, as demonstrated by the FLAURA study, but also introduce new anti-tumor mechanisms of anti-tumor activity in the first-line setting.

2.6. 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.[12,13] Information about the benefits and risks of osimertinib may be found in the local prescribing information.[37]

2.6.1. Risks for Study Participation

The safety and tolerability of amivantamab monotherapy was shown in the Phase 1 Study 61186372EDI1001 (Section 2.2). The safety and tolerability of single-agent lazertinib was shown in the Phase 1/2 Study 73841937NSC2001 (refer to Section 2.3). The safety and tolerability of amivantamab and lazertinib in combination was also shown in the Phase 1 Study 61186372EDI1001 (Section 2.4). The tolerability of osimertinib was shown in clinical trials (refer to local prescribing information[37]).

Unforeseen safety risks associated with the study treatments are possible. This study protocol includes the following elements to mitigate risks for study participants:

- An Independent Data Monitoring Committee (IDMC) will review safety and tolerability data periodically and review pre-planned efficacy analyses as per protocol.
- Participants will be monitored closely for safety throughout the study (refer to Section 8.2).
- Dose modification guidance is provided to manage toxicities that occur during the study (refer to Section 6.6), including specific guidance for IRRs, rash, pruritus, interstitial lung disease (ILD), pulmonary toxicity, paresthesia, cardiac adverse events, liver chemistry abnormalities, oral mucositis, paronychia, diarrhea, ocular toxicity, and venous thromboembolic (VTE) events.

2.6.2. Benefits for Study Participation

Osimertinib is the standard of care first-line therapy in this patient population. All participants in the study will accordingly be treated with a third-generation EGFR TKI, consistent with the standard of care.

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 in the first-line setting, 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 MET pathways.

2.6.3. Benefit-Risk Assessment for Study Participation

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

For the duration of this ongoing study, the assessment of risk has been monitored by the IDMC, who have reviewed unblinded safety data through the protocol-specified futility analysis on 20 July 2022, when the IDMC first reviewed the unblinded safety and efficacy data of

1,038 randomized participants in the study. After reviewing the unblinded safety and efficacy data, 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 VTE events in Arm A 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 VTE events were identified, and only 1 participant discontinued study treatment due to VTE events.

VTE-related changes implemented during protocol Amendment 3 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 treatment-emergent 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 adopted, after IDMC review, to further optimize the benefit-risk balance for participants in the study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the efficacy of the amivantamab and lazertinib combination, compared with osimertinib, in participants with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC	• PFS according to RECIST v1.1 by blinded independent central review
Secondary	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Overall survival • Objective response rate • Duration of response • PFS after first subsequent therapy • Time to symptomatic progression • Intracranial PFS
To evaluate the safety and tolerability of the amivantamab and lazertinib combination compared with osimertinib	• Incidence of severity of adverse events and clinical laboratory abnormalities, assessment of vital signs, and physical examination abnormalities
To evaluate pharmacokinetics or immunogenicity for amivantamab and pharmacokinetics for lazertinib and assess their relationship to 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
To assess health related quality of life and disease related symptoms in participants treated with the amivantamab and lazertinib combination compared with osimertinib	• NSCLC SAQ • EORTC QLQ C30
To assess the efficacy of the amivantamab and lazertinib combination, compared with lazertinib monotherapy, in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• PFS • Overall survival
Exploratory	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Disease control rate • Time to treatment discontinuation • Time to subsequent therapy
To assess the intracranial activity of the amivantamab and lazertinib combination compared with osimertinib.	• Intracranial objective response rate • Intracranial duration of response • Time to intracranial disease progression
To further assess health related quality of life in participants treated with the amivantamab and lazertinib combination compared with osimertinib	• EQ 5D 5L
To explore genetic biomarkers predictive of improved outcome in participants treated with amivantamab in combination with lazertinib, compared with lazertinib and osimertinib monotherapies.	• Characterization of tumor genetics by NGS of ctDNA and genetic analysis of tumor biopsy material at baseline, and at progression • Characterization of circulating EGFR mutation levels by ddPCR of ctDNA at baseline, on therapy, and at progression
To explore mechanisms of resistance to amivantamab and lazertinib and amivantamab/lazertinib combination therapy	• Characterization of tumor protein markers by immunohistochemistry (eg, EGFR, MET) at baseline and at progression • Characterization of changes in tumor genetics, relative to baseline, by NGS of ctDNA and genetic analysis of tumor biopsy material at progression

ctDNA circulating tumor deoxyribonucleic acid; ddPCR digital droplet polymerase chain reaction; EGFR epidermal growth factor receptor; EORTC QLQ C30 European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ 5D 5L EuroQol five dimensional descriptive system (5 level version); MET mesenchymal epithelial transition; NGS next generation sequencing; NSCLC non small cell lung cancer; NSCLC SAQ Non Small Cell Lung Cancer Symptom Assessment Questionnaire; PFS progression free survival; RECIST Response Evaluation Criteria in Solid Tumors.

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

HYPOTHESIS

The hypothesis is that the amivantamab and lazertinib combination (Arm A) will demonstrate superior PFS compared with single-agent osimertinib (Arm B).

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, multicenter, Phase 3 study to compare the efficacy and safety of combined amivantamab and lazertinib therapy (Arm A) versus single-agent, standard of care, osimertinib (Arm B) as first-line treatment in participants with EGFR-mutated locally advanced or metastatic NSCLC. The contribution of amivantamab to the activity of the combination will be assessed by comparing the efficacy observed in the amivantamab and lazertinib combination arm (Arm A) with that in the lazertinib monotherapy arm (Arm C). The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase.

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.

4.1.1. Screening Phase

The informed consent form (ICF) must be signed before the first study-related activity is conducted. If a fresh tumor biopsy is required to meet eligibility, the biopsy can be obtained at any time before randomization, provided informed consent has been given. All other screening procedures must be completed within 28 days before randomization.

To be eligible for participation, all participants must have been previously diagnosed with Exon 19del or Exon 21 L858R substitution EGFR mutations, as determined by local testing with an FDA-approved or other validated test in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (sites in the US) or accredited local laboratory (sites outside of the US). Tumor tissue must be collected at or after the diagnosis of locally advanced or metastatic NSCLC and must be submitted to the sponsor (Section 8.7). A copy of the test report documenting the EGFR mutation must be included in the participant records and a de-identified copy must also be submitted to the sponsor.

4.1.2. Treatment Phase

The Treatment Phase for a participant will begin on Cycle 1 Day 1 and continue as 28-day cycles until the End of Treatment visit, approximately 30 days after discontinuation of study treatment. Approximately 1000 eligible participants will be randomly assigned to study treatment in a 2:2:1 ratio (Arm A, B, and C respectively). Randomization will be stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent).

- **Arm A**: Approximately 400 participants will be assigned to open-label treatment with the combination of amivantamab (1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg IV, once weekly for the first 4 weeks and then once every 2 weeks) and lazertinib (240 mg orally, once daily).
- **Arm B**: Approximately 400 participants will receive double-blind treatment with single-agent osimertinib (80 mg orally, once daily).
- **Arm C**: Approximately 200 participants will receive double-blind treatment with single-agent lazertinib (240 mg orally, once daily).

Study treatment should continue until documented disease progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 confirmed by BICR or another reason for discontinuation of study treatment (Section 7.1). Continuation of study treatment after disease progression is allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believes the participant is deriving clinical benefit. Participants continuing treatment after progression will continue within the Treatment phase of the study and comply with associated visits and procedures, including scheduled disease assessments, until the termination of study treatment.

4.1.3. Follow-up Phase

Participants who discontinue study treatment for any reason will be followed for survival and symptomatic progression in the Follow-up Phase.

Survival, subsequent anticancer treatment, and disease status will be assessed every 12 weeks (±14 days) after the last dose of study treatment or disease progression (whichever occurs first), until the end of study, death, lost to follow-up, or withdrawal of consent, 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).

Note: For participants who discontinue study treatment prior to disease progression confirmed by BICR, tumor imaging should continue per schedule of activities, until PD is confirmed by BICR review.

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

Following the primary PFS analysis for efficacy, the study will transition to an open-label extension (OLE) Phase (see details provided in Section 10.14 [Appendix 14]). The purpose of the OLE Phase is to collect data of clinical relevance/importance while reducing protocol-required visit procedures and assessments and the burden on participants after the primary PFS analysis and unblinding. Unblinding will occur for blinded Arms B and C. Only active treatment will be provided, without placebo.

Participants will be provided the option to continue their current study treatment in the OLE Phase until the final analysis for overall survival, after which the study will transition to a long-term extension (LTE) Phase. Unblinding will occur for blinded Arms B and C. Only active treatment will be provided, without placebo.

Participants who continue to benefit from study treatment(s), as determined by their investigator, at the time of completion of the OLE Phase may continue to receive access to study treatment(s) within the study by transferring to the LTE Phase, where only serious adverse event data and study treatment 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 final analysis for overall survival is complete.

The LTE Phase (see details provided in Section 10.15 [Appendix 15]) will begin after the final analysis for overall survival, and will continue until the discontinuation criteria described in Section 7.1 are met, or until 4 years after local marketing authorization is obtained for the studied indication, whichever occurs first.

The OLE phase will begin after approval of Amendment 4 by health authorities of countries/territories in which this study is being conducted at the time of transition, and by study site Independent Ethics Committees/Institutional Review Boards (IECs/IRBs). In addition, for transition to the LTE Phase (after final analysis for overall survival), notification from the sponsor will be provided.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Treatment Groups

Active controls will be used to establish the frequency and magnitude of changes in clinical endpoints that occur with the combination of amivantamab and lazertinib (Arm A), as compared to single-agent osimertinib (Arm B) or single-agent lazertinib (Arm C). 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. Blinded treatment will be used in the control arms (Arms B and C) to reduce potential bias during data collection and evaluation of clinical endpoints. Open-label treatment will be used in Arm A; only the participants in this treatment arm will receive infusions.

Clinical Pharmacology Assessments

Blood samples will be analyzed for amivantamab serum and lazertinib plasma concentrations. Immunogenicity (antibodies to amivantamab) will be evaluated for impact on PK, safety, and efficacy. A population PK model will be developed for exposure response analysis to support regulatory submission.

DNA and Biomarker Collection

Tumor tissue and ctDNA will be collected to centrally confirm the pretreatment mutational status of EGFR (Exon 19del or L858R). In addition, these samples may be evaluated to identify co-occurring EGFR mutations, MET 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. Circulating tumor deoxyribonucleic acid (ctDNA) and biomarker samples may be used to explore their potential to predict clinical benefit, relapse, and/or identify mechanisms of resistance to assigned therapy.

The pharmacogenomic samples will be collected to test for null or non-null glutathione S- -transferase Mu-1 (GSTM-1) genotype for participants in Arm A on Cycle 1 Day 1. The goal of the pharmacogenomic sample is to collect deoxyribonucleic acid (DNA) to allow the identification of GSTM-1 polymorphism that may influence the PK, safety/tolerability or efficacy of lazertinib.

4.2.1. Study-Specific Ethical Design Considerations

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

Thorough scientific evaluation of any treatment before market authorization is an ethical requirement. As the benefits and risks of the combination of amivantamab and lazertinib in this study population are not fully known, this study will evaluate the safety and clinical activity of these agents in combination, and of lazertinib as a monotherapy. Participants will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit. The IDMC will review evolving safety data from this study, as well as efficacy data as appropriate. Based on the mechanism of action of both amivantamab and lazertinib 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 the underlying disease. Participants will also have pre- and post-treatment tumor biopsies. In general, these procedures are routinely performed during a participant's diagnostic workup and follow-up care. Archival tumor material collected at or after the time of locally advanced or metastatic diagnosis may be submitted in lieu of pre-treatment biopsies. 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 to minimize delay to treatment initiation. Archival or fresh tissue from the corresponding biopsy is required for central confirmation of mutation status. If insufficient, a new biopsy will be required. Although biopsy

collection is associated with risk, the complication rate for these procedures is low. The data obtained from this procedure is required to confirm eligibility and will generate valuable scientific data on the pharmacodynamic effect of the combination of these study treatments in this study population. 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 to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.[2]

4.3. Justification for Dose

The doses selected for this study are supported by the following safety and activity results from clinical studies of participants with advanced NSCLC and EGFR mutations:

- Lazertinib: Lazertinib was generally well tolerated in a Phase 1/2 study, with no DLTs reported during dose escalation and no MTD identified.[3,13] Partial responses were observed across all assessed doses from 20 to 320 mg. The RP2D was determined to be 240 mg orally once daily, based on the totality of exposure, safety, and efficacy data.
- Amivantamab: 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.[10,12] Based on the totality of exposure, safety, and efficacy data, the RP2D was determined to be 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, administered by IV infusion in 28day- cycles: once weekly in Cycle 1 (with a split dose on Days 1-2), and then every 2 weeks in subsequent cycles.
- Amivantamab and lazertinib in combination: Based on the totality of exposure, safety, and efficacy data, the RP2D for the combination in a Phase 1 study was determined to be amivantamab 1050/1400 mg and lazertinib 240 mg (ie, each component of the combination at its respective RP2D).[12] No DLTs were observed with the proposed doses and regimens for both amivantamab and lazertinib and PK data analysis was consistent with no drug-drug interaction between amivantamab and lazertinib.
- Osimertinib: The dose of osimertinib selected for a control arm in this study (80 mg, administered orally once daily) was shown to be safe and effective in Phase 3 studies of participants with advanced NSCLC and EGFR mutations and is the recommended dose. Refer to the local prescribing information for additional details.[37]

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has died before the end of the study or has not prematurely discontinued the study for another reason (Section 7.1) by the end of 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.

5.1. Inclusion Criteria

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

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

2. Criterion modified per Amendment 1.

   2.1 Participant must have newly diagnosed, histologically or cytologically confirmed, locally advanced or metastatic NSCLC that is treatment naïve and not amenable to curative therapy including surgical resection or chemoradiation.

3. Criterion modified per Amendment 1.

   3.1 The tumor (meeting criteria described in Inclusion Criterion no. 2) harbors Exon 19del or Exon 21 L858R substitution, as detected by an FDA-approved or other validated test in a CLIA certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US) in accordance with site standard of care. (Note: A copy of the test report documenting the EGFR mutation must be included in the participant records and must also be submitted to the sponsor.)

4. Criterion modified per Amendment 1.

   4.1 Mandatory submission of unstained tissue from tumor meeting criteria described in Inclusion Criterion no. 2 (in a quantity sufficient to allow for central analysis of EGFR mutation status) and blood (for ctDNA, digital droplet polymerase chain reaction [ddPCR], and pharmacogenomic analysis). See Section 8.7.

5. Any toxicities from prior anticancer therapy must have resolved to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or baseline level.

6. Participant must have at least 1 measurable lesion, according to RECIST v1.1 that has not been previously irradiated. Measurable lesions should not have been biopsied during screening, but if only 1 non-irradiated measurable lesion exists, it may undergo a diagnostic biopsy and be acceptable as a target lesion, provided the baseline tumor assessment scans are performed at least 14 days after the biopsy.

7. Criterion modified per Amendment 1.

7.1 Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion, platelet transfusion, or granulocyte colony-stimulating factor (G-CSF) within 7 days prior to the date of the test.

- Hemoglobin ≥10 g/dL
- Absolute neutrophil count ≥1.5 × 10^9/L, without any prior use of G-CSF
- Platelets ≥75 × 10^9/L
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × upper limit of normal (ULN)
- Total bilirubin ≤1.5 × ULN (participants with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits)
- Serum creatinine <1.5 × ULN and creatinine clearance >45 mL/min as measured or calculated; refer to Appendix 11: Cockcroft-Gault Formula for Estimated Creatinine Clearance
- If urinalysis reveals bacteria and leukocytes, a urine culture must be done to rule out a urinary tract infection prior to randomization.

8. Participant must have Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 (refer to Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status).

9. Participant must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

10. Criterion modified per Amendment 1.

10.1. Criterion modified per Amendment 4.

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

11. Criterion modified per Amendment 1.

11.1 Criterion modified per Amendment 2.

11.2 Criterion modified per Amendment 4.

11.3 A participant must be (as defined in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information) either of the following:

a. Not of childbearing potential

b. Of child-bearing potential and practicing true abstinence during the entire period of the study, including up to 6 months after the last dose of study treatment is given

c. Of childbearing potential and practicing 2 methods of contraception, including 1 highly effective user independent method and a second method (examples of highly effective methods of contraception are located in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information).

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

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

12. Criterion modified per Amendment 4

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

13. Criterion modified per Amendment 4

13.1 A participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 6 months after receiving the last dose of study treatment. A participant who is sexually active with a person of childbearing potential must agree to use a condom with spermicidal foam/gel/film/cream/suppository and the partner must also be practicing a highly effective method of contraception (ie, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]).

A vasectomized participant must still use a condom (with or without spermicide) for prevention of passage of exposure through ejaculation, but the participant's partner is not required to use contraception.

14. Criterion modified per Amendment 4

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

15. Participant must be willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

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

1. Criterion modified per Amendment 1

1.1 Criterion modified per Amendment 2.

1.2 Participant has received any prior systemic treatment at any time for locally advanced Stage III or metastatic Stage IV disease (adjuvant or neoadjuvant therapy for Stage I or II disease is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease).

2. Criterion modified per Amendment 1.

2.1 Participant has symptomatic brain metastases. A participant with asymptomatic or previously treated and stable brain metastases may participate in this study. Participants who have received definitive radiation or surgical treatment for symptomatic or unstable brain metastases and have been clinically stable and asymptomatic for at least 2 weeks before randomization are eligible, provided they have been either off corticosteroid treatment or are receiving low-dose corticosteroid treatment (≤10 mg/day prednisone or equivalent) for at least 2 weeks prior to randomization.

3. Participant has an active or past medical history of leptomeningeal disease.

4. Criterion modified per Amendment 1.

4.1 Participant with untreated spinal cord compression. A participant that has been definitively treated with surgery or radiation and has a stable neurological status for at least 2 weeks prior to randomization is eligible provided they are off corticosteroid treatment or receiving low-dose corticosteroid treatment ≤10 mg/day prednisone or equivalent.

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

6. Participant has an active or past medical history of ILD/pneumonitis, including drug-induced or radiation ILD/pneumonitis.

7. Criterion modified per Amendment 1.

7.1 Participant has an uncontrolled illness, including but not limited to:

- 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
- Impaired oxygenation requiring continuous oxygen supplementation
- 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, social situation, or any other circumstances that would limit compliance with study requirements
- Any ophthalmologic condition that is clinically unstable

8. Criterion modified by Amendment 1.

8.1 Participant has concurrent or prior malignancy other than the disease under study. The following exceptions require consultation with the Medical Monitor:

d. Non-muscle invasive bladder cancer (NMIBC) treated within the last 24 months that is considered completely cured.

e. Skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.

f. Non-invasive cervical cancer treated within the last 24 months that is considered completely cured.

g. Localized prostate cancer (N0M0):

- with a Gleason score of 6, treated within the last 24 months or untreated and under surveillance,
- with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence,

- or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.

h. Breast cancer:

- lobular carcinoma in situ or ductal carcinoma in situ that is considered completely cured.

f. Participant has undergone curative therapy and is considered cured after 5 years with no evidence of disease recurrence since initiation of that therapy.

9. Criterion modified per Amendment 1.

9.1 Participant has active cardiovascular disease including, but not limited to:

- A medical history of deep vein thrombosis or pulmonary embolism within 1 month prior to randomization or any of the following within 6 months prior to randomization: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated thrombus, incidental or asymptomatic pulmonary embolism, are not exclusionary.
- Prolonged corrected QT interval by Fridericia's (QTcF >470 msec), clinically significant cardiac arrhythmia (eg, atrial fibrillation with uncontrolled rate) or abnormalities in conduction or morphology of electrocardiogram (ECG) (eg, complete left bundle branch block, third- or second-degree heart block, PR interval >250 msec), or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator).
- Any factors that increase the risk of corrected QT interval (QTc) prolongation or risk of arrhythmic events such as, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first degree relatives or any concomitant medications known to prolong QT interval or induce Torsades de Pointes.
- Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg.
- Congestive heart failure (CHF), defined as New York Heart Association (NYHA) class III-IV or hospitalization for CHF (any NYHA class; refer to Appendix 6: New York Heart Association Criteria) within 6 months of randomization.
- An active or past medical history of pericarditis, pericardial effusion that is clinically unstable, or myocarditis. Pericardial effusion considered due to the disease under study is permitted if clinically stable at Screening.
- Baseline LVEF either <50% or below the lower limit of normal (LLN) per institutional guidelines, as assessed by screening echocardiogram (ECHO) or multigated acquisition (MUGA) scan.

10. Participant has known allergy, hypersensitivity, or intolerance to the excipients used in formulation of amivantamab, lazertinib, or osimertinib, or any contraindication to the

use of osimertinib (refer to amivantamab and lazertinib IBs and local prescribing information for osimertinib).[12,13,37]

11. Criterion modified per Amendment 1.

11.1 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 (see Appendix 8: Prohibited and Restricted Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5).

12. Participant has received any prior treatment with an EGFR TKI.

13. Participant has received an investigational medication within 12 months before randomization or is currently enrolled in an investigational study.

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

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

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

17. Participant has at Screening:

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

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

- Positive hepatitis C (hepatitis C virus [HCV]) antibody (anti-HCV)

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

- Other clinically active infectious liver disease

18. Participant is positive for human immunodeficiency virus (HIV), with 1 or more of the following:

- Not receiving highly active antiretroviral therapy (ART)
- Had a change in ART within 6 months of the start of screening

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

19. Criterion modified per Amendment 1.

19.1 Participant had major surgery excluding placement of vascular access or tumor biopsy, or had significant traumatic injury within 4 weeks before randomization, 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.

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 re-confirmed prior to randomization. The required source documentation to support meeting the enrollment criteria are noted in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.5.4 for details regarding prohibited and restricted therapy during the study.

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

5.3.1. Activity

1. Agree to use sun protective measures (such as a hat, sunglasses, and protective clothing), limit prolonged exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) from baseline until the last dose of study treatment. Avoid unnecessary exposure to sunlight. Use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥30 (refer to Section 6.6.3.2).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness. This study will use interactive web response system (IWRS). The investigator will generate screening and enrollment logs directly from IWRS.

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

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

6. STUDY MEDICATION AND CONCOMITANT THERAPY

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 use as indicated for this protocol.

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

6.1. Study Treatments Administered

For this study, "study treatment" refers to amivantamab, lazertinib, and osimertinib. Amivantamab, lazertinib, and osimertinib are considered investigational medicinal products (IMPs).

All other study-specified medications (see Section 6.5) are considered concomitant medications.

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

Authorization Status in the EU:
<table><tr><td>Authorized</td><td>amivantamab, osimertinib</td></tr><tr><td>Unauthorized</td><td>lazertinib</td></tr></table>
Used in accordance with Marketing Authorization: osimertinib
Used not in accordance with Marketing Authorization: amivantamab</td></tr>
</table>

Designation	Product
Non-investigational Medicinal Products (NIMPs)/Auxiliary Medicinal Products (AxMPs)	Not applicable

Eligible participants will be randomly assigned to 1 of 3 treatment arms: open-label treatment with amivantamab and lazertinib (Arm A), double-blind treatment with single-agent osimertinib (Arm B), or single-agent treatment with lazertinib (Arm C). Initial dosages for study treatment, by treatment arm, are shown in Table 4. To maintain the blind between active osimertinib and placebo osimertinib, both active and placebo osimertinib tablets will be over-encapsulated to look identical. Active and placebo lazertinib tablets look identical without over-encapsulation. Participants in Arm B and Arm C will take an initial dosage of 4 pills, once daily: 1 osimertinib capsule (or 1 matching placebo) and 3 lazertinib tablets (or 3 matching placebos). All cycles are 28 days and each study visit must be scheduled based on date of Cycle 1 Day 1. The site should not re-adjust visit schedule based on treatment interruptions or delays.

Table 4: Initial Dosages for Study Treatment, by Treatment Arm

	Arm A (Open-Label)	Arm B (Double-Blind)	Arm C (Double-Blind)
Amivantamab (350 mg/vial)	1050 mg (1400 mg if ≥80 kg) IV infusion in 28-day cycles Cycle 1: Days 1/2[a], 8, 15, and 22 Cycles 2+: Day 1 and Day 15	-	-
Osimertinib (80 mg capsule)	-	1 osimertinib capsule[b] once daily	1 placebo capsule once daily
Lazertinib (80 mg tablet[c])	3 lazertinib tablets once daily	3 placebo tablets once daily	3 lazertinib tablets once daily

IV=intravenous.

a. The first dose of amivantamab will be split over 2 days as follows: Cycle 1 Day 1, 350 mg (regardless of body weight); Cycle 1 Day 2, 700 mg (1050 mg if ≥80 kg).
b. Osimertinib will be provided as 80-mg tablet (initial dose) and 40-mg tablet (as needed for dose reduction) and over-encapsulated to maintain the blind.
c. Lazertinib will be provided as 80 mg tablets (initial dose is three tablets [240 mg]).

6.1.1. Amivantamab

Amivantamab is supplied for this study in a glass vial containing 350 mg/vial with concentration 50 mg/mL in a 7 mL vial. Amivantamab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients. The IV infusion will be prepared at the site in 250 mL of diluent (Refer to IPPI).

The dosage of amivantamab will be based on the participant's body weight at Screening: 1050 mg (if body weight is <80 kg) or 1400 mg (if body weight is ≥80 kg). The dose remains based on body weight at Screening regardless of subsequent changes in body weight during the course of treatment. Qualified site personnel will administer amivantamab as an IV infusion in 28-day cycles as follows:

- Cycle 1: once weekly (with the first dose split over Day 1 [350 mg] and Day 2 [700 mg if body weight is <80 kg or 1050 mg if body weight is ≥80 kg])
- Cycles 2+: Days 1 and 15 of each cycle

Amivantamab will be administered intravenously using the escalating infusion rate regimen as specified in the IPPI. At the discretion of the investigator, the infusion rate can be slower, but not faster than 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.

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

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

- On Day 1 of each cycle, review results of hematology and chemistry laboratory assessments before administering study treatment.
- Amivantamab must be diluted and administered as described in the IPPI
- Do not mix or dilute amivantamab with other drugs.
- Amivantamab must not be administered as an IV push or bolus.
- The administration set IV line will be primed with diluent prior to the initiation of each IV bag of diluted amivantamab as described in the IPPI.

After 12 cycles of amivantamab (1 year), participants receiving the full dosage of amivantamab can skip up to 3 doses in a year and participants on a reduced dose of amivantamab (refer to Section 6.6.2) can skip up to 2 doses in a year, as needed for life events. The skipped doses should be at least 3 months apart and should be avoided when feasible.

6.1.2. Lazertinib

Lazertinib 80 mg for oral administration is an oblong, yellow, and film-coated tablet. Refer to the IB for a list of excipients. The matching placebo tablet (for Arm B) is an oblong, yellow, and film-coated tablet, matched in appearance to the lazertinib 80 mg tablet.

Participants will self-administer lazertinib (or matching placebo tablets in Arm B) as an oral therapy, with an initial dosage of 240 mg (3 tablets) once daily. Lazertinib tablets can be administered with or without food. In Arm A, lazertinib should be dosed no more than 15 minutes before the start of each amivantamab infusion. Lazertinib should be taken at approximately the same time each day, approximately 24 hours apart, if possible. If a participant misses taking 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 his/her study treatment, he/she 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.

6.1.3. Osimertinib

Osimertinib 80 mg for oral administration is provided as over-encapsulated tablets in red capsules to maintain the blind for this study. Osimertinib 40 mg (also over-encapsulated tablets in red capsules) is provided for dose reduction, as needed. Refer to the local prescribing information for a list of excipients.[37] Inactive placebo capsules (for Arm C) are matched in appearance to the over-encapsulated osimertinib tablets.

Participants will self-administer osimertinib capsule (or an inactive capsule in Arm C) as an oral therapy, with an initial dosage of 80 mg (1 capsule) once daily. Osimertinib can be administered with or without food. Osimertinib should be taken at approximately the same time each day, approximately 24 hours apart, if possible. If a participant misses taking 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 his/her study treatment, he/she 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. Refer to the pharmacy manual/study SIPPM for additional guidance on study treatment preparation, handling, and storage.

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 (or inactive) and osimertinib (or inactive), 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.

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

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

Study treatment should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study treatment will be supplied only to participants participating in the study. Returned study treatment must not be dispensed again, even to the same participant. Whenever a participant brings his or her study treatment to the study site for pill count, this is not seen as a return of supplies. Study treatment may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study treatments are provided in the SIPPM.

6.3. Measures to Minimize Bias: Randomization and Blinding

Treatment Allocation

Procedures for Randomization and Stratification

Participants will be randomly assigned to 1 of 3 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 mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent). Participants who have undergone treatment for metastatic brain lesions, including a complete resection must be stratified as brain metastasis present. For randomization and statistical analyses, a participant will be stratified as Asian if they report their race is either Asian or mixed, with any Asian component.

The ~~interactive web response system (~~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

To maintain the study blind in Arm B and Arm C, the study treatment container will have a label containing the study name, study treatment number, and reference number. The label will not identify the study treatment in the container. However, if it is necessary for a participant's safety, the study blind may be broken and the identity of the study treatment ascertained. The study treatment number will be entered in the eCRF when the study treatment is dispensed. The study treatments will be identical in appearance and will be packaged in identical containers.

Data that may potentially unblind the treatment assignment (ie, study treatment preparation/accountability data, treatment allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until the database is finalized, and given the similarity of the blinded treatments (each is a third-generation EGFR TKI), it is anticipated that need for unblinding will be infrequent. The investigator may in an emergency determine the identity of the treatment by contacting the IWRS. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the source document.

Participants who have had their treatment assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those participants included in the interim analysis. The study may be unblinded after the primary analysis for PFS; see details for the OLE Phase (Section 10.14 [Appendix 14]) and the LTE Phase (Section 10.15 [Appendix 15]).

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. Study treatments may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing. The study personnel at the study site will account for all treatments dispensed and for appropriate return. The certificates of delivery and return should be signed.

6.5. Concomitant Therapy

6.5.1. 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 serious adverse events considered related to study treatment, until resolution of event or start of subsequent therapy.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study treatment must be recorded in the eCRF. 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.

6.5.2. Amivantamab Pre-infusion and Post-infusion Medications

Amivantamab Pre-Infusion Medications

Required and optional amivantamab pre-infusion medications for IRRs are summarized in Table 5.

Table 5: Pre-Infusion Medications

Medication	Dose	Route of Administration	Recommended Dosing Window Before Infusion	Cycle/Day
Required Pre-Infusion Medications[a, b, d, e]				
Glucocorticoid	Dexamethasone (10 mg) or Methylprednisolone (40 mg)	IV or Oral	45 to 60 minutes	Cycle 1 Day 1 Cycle 1 Day 2
Antihistamine	Diphenhydramine (25 to 50 mg) or equivalent	IV or	15 to 30 minutes	All
		Oral	30 to 60 minutes	
Antipyretic	Paracetamol (acetaminophen 650 to 1,000 mg) or equivalent	IV or	15 to 30 minutes	All
		Oral	30 to 60 minutes	
Optional Additional Pre-Infusion Medications[a, f]				
Glucocorticoid[c]	Dexamethasone (10 mg) Methylprednisolone (40 mg)	IV or	45 to 60 minutes	Cycle 1 Day 8 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	

IV intravenous.
a. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.
b. Participants for whom required medications are contraindicated should explore alternative medications with their study physician. 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 if clinically indicated for participants who experienced an infusion related reaction on Cycle 1 Day 1 or Cycle 1 Day 2.
d. The recommended dose of dexamethasone to be administered is 10 mg and should not be lower than 9. 8 mg.
e. Required Pre Infusion glucocorticoid, antihistamine, and antipyretic may be administered IV or oral route.
f. Optional Pre Infusion glucocorticoid may be administered by IV push or oral route.

Amivantamab Post-Infusion Medications

Optional amivantamab post-infusion medications may be prescribed and continued for up to 48 hours after the infusion if clinically indicated, at the discretion of the investigator (Table 6).

Table 6: Post-Infusion Medications

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

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

6.5.3. Permitted Medications and Therapies

6.5.3.1. Supportive Care

Supportive care (eg, antibiotics, analgesics, transfusions, diet, osteoclast inhibitors) and concomitant medications may be administered according to the standard of care at the site, and at the treating physician's discretion, as clinically indicated.

6.5.3.2. Radiotherapy

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

6.5.3.3. Hormonal Contraception

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

6.5.3.4. Prophylactic Medications

Prophylactic medications are described in Section 6.6.3.

6.5.4. Prohibited or Restricted Medications and Therapies

Prohibited Medications and Therapies

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

- Any chemotherapy, systemic anticancer therapy, or experimental therapy (other than study treatments).
- Radiotherapy to tumor lesions being assessed for tumor response prior to radiographic progression.
- Medications, herbal supplements and/or ingestions of foods with known potent (strong) inducer effects on CYP3A4/A5 activity. Use of medications known to be strong inhibitors of CYP3A4 is restricted and should be avoided, when possible, or used with caution. Guidance on drugs that require close monitoring and washout periods is given in Appendix 8: Prohibited and Restricted Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5.

Restricted Medications and Therapies

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

- Avoid co-administration of medicines that prolong QT interval (Appendix 12: Medications With Potential for QT Interval Prolongation). If there are no other alternative medications that can be used, limit treatment duration when possible.
- Medications that are substrates of P-glycoprotein (P-gp), multi-drug resistance protein 4 (MRP4) Breast Cancer Resistance Protein (BCRP), and Organic Cation Transporter 1 (OCT1) should be used with caution. A list of substrates is provided in Appendix 9: Substrates of P-glycoprotein (P-gp), multi-drug resistance protein 4 (MRP4), and Breast Cancer Resistance Protein (BCRP): Exercise Caution.
- Avoid concomitant use of CYP1A2 or CYP3A4/5 substrate drugs. If no other alternatives exist monitor participants more closely for adverse reactions. Guidance on CYP1A2 or CYP3A4/5 substrates that require close monitoring (Appendix 8: Prohibited and Restricted Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5).
- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.

6.6. Dose Modification Guidance

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

6.6.1. Withholding Treatment

If a participant experiences a clinically significant CTCAE grade 3 or higher and/or unacceptable toxicity (any grade) not attributable to the disease or disease-related processes under investigation, and the investigator considers the adverse event of concern to be specifically associated with the study treatment, then dosing should be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. For the majority of clinically significant toxicities withholding doses and dose modifications should occur as per the guidelines described in Table 7 (for Arm A) and in Table 8 (for Arm B or Arm C), with the following additional considerations for all treatment arms:

- 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 study treatment is withheld for more than 28 days, consider a dose reduction per Table 9 or Table 10 when restarting study treatment.

The following additional considerations apply to combination treatment in Arm A (amivantamab and lazertinib combination):

- If withholding one treatment is felt to be clinically indicated (eg, moderate toxicity), dosing with amivantamab should be preferentially withheld, unless the experienced toxicity is strongly suspected to be related to lazertinib alone (refer to respective IBs).

- If both agents are withheld, one or both agents can be restarted upon resolution of toxicity. In general, if both are to be continued, lazertinib should be restarted at least 7-14 days prior to the next infusion of amivantamab to ensure stability on monotherapy.
- Starting with Cycle 2, amivantamab infusions delayed >7 days cannot be made up. The delayed dose should be skipped and the participant dosed at the next scheduled visit.
- If amivantamab is withheld for 2 or more consecutive doses for any reason, consult with the Medical Monitor before restarting amivantamab to discuss plans for infusion.
- 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 study treatment can be resumed at the discretion of the investigator.

While recommendations in Table 7 and Table 8 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 agents' potential contribution to the toxicity, as well as each agent's potential contribution to any observed clinical benefit. For specific guidance regarding the management of IRRs in Arm A and rash, refer to Section 6.6.3.1 and Section 6.6.3.2, respectively.

Table 7: Guidance for Withholding Doses for Toxicities Based on Grade (Arm A)

Grade[a]	Action[b]	Dose Modification After Resolution of Toxicity[c, d]
1	None	Continue both agents at current dose level; consider supportive care according to local standards as appropriate
2	None, or consider either withholding dose or dose reduce amivantamab (or lazertinib if the experienced toxicity is strongly suspected to be related to lazertinib alone)	If withheld <28 days, restart study treatment at current dose level or consider dose reduction.
3 or 4	Withhold amivantamab and lazertinib	After consultation with the Medical Monitor, may restart study treatment at current dose level or consider dose reduction of study treatment

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

Table 8: Guidance for Withholding Doses for Toxicities Based on Grade (Arm B or Arm C)

Grade[a]	Action[b]	Dose Modification After Resolution of Toxicity[c, ~~d~~]
1	None	Continue at current dose level: consider supportive care according to local standards as appropriate
2	None, or consider either withholding or dose reduce study treatment	If withheld up to 28 days, restart at current dose level or consider dose reduction. If withheld ≥28 days, consult the Medical Monitor before restarting
3 or 4	Withhold study treatment	After consultation with the Medical Monitor, restart study treatment at current dose level or consider dose reduction

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. 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.
~~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.~~

A participant for whom treatment was withheld should be assessed at least weekly to ensure adequate supportive care is being administered and to assess for improvement of toxicity. In instances of prolonged treatment interruptions, subsequent dose reductions may be indicated and should occur in accordance with Section 6.6.2. Dose adjustment should be overseen by medically qualified study-site personnel (preferably the principal or sub-investigator) unless an immediate safety risk appears to be present. Guidelines for management of specific toxicities are provided in the following sections.

Dose modifications should be recorded in the eCRF as close to the scheduled dosing day as possible, in accordance with the eCRF guidelines. A change to study treatment dosing (ie, withholding doses, change in dose, change in infusion rate), and the reason for the change, must be recorded in the eCRF. For withheld doses, the duration of withholding study treatment is to be recorded. Infusion rate must also be noted for each dose of amivantamab.

6.6.2. Dose Reduction

If a participant in Arm A experiences a toxicity requiring dose reduction after withholding study treatment and resolution, then the dose of amivantamab should be preferentially reduced, as outlined in Table 9, unless the experienced toxicity is strongly suspected to be related to lazertinib alone (refer to respective IBs), in which case lazertinib can be reduced.

Given the potential for increased anti-EGFR activity in the combination Arm A, accelerated (ie, proactive) dose reductions are allowed if toxicity is encountered. Upon resolution of the toxicity, or with improved control with supportive measures, reescalation of the reduced therapy dose may be subsequently increased to the previous dose.

In Arm A, if the decision is made to withhold amivantamab, lazertinib may be escalated to its 240 mg dose (ie, Dosage Level 5) with subsequent dose reduction to 160 mg if needed, consistent with dosing in Arm C. Amivantamab may be restarted, if the symptoms have improved and treatment with the combination is thought to be in the participant's best interest. If 2 consecutive doses of amivantamab are withheld, please consult the medical monitor.

Table 9: Recommended Dose Reduction for Amivantamab and Lazertinib Combination Therapy (Arm A)

Combination Dosage Level	Amivantamab		Lazertinib[a]
	Participant <80 kg	Participant ≥80 kg	
1 (initial dosage)	1050 mg Q2W	1400 mg Q2W	240 mg (3 tablets)
2	700 mg Q2W	1050 mg Q2W	240 mg (3 tablets)
3	700 mg Q2W	1050 mg Q2W	160 mg (2 tablets)
4	350 mg Q2W	700 mg Q2W	160 mg (2 tablets)
5	Withhold	Withhold	240 mg (3 tablets)

Q2W=every 2 weeks (eg, Day 1 and Day 15 of each 28-day cycle).

a. Table is a guide, alternatively, lazertinib can be preferentially reduced if toxicity is considered related to this drug.

If a participant in Arm B or Arm C experiences a toxicity requiring dose reduction after withholding study treatment and resolution, then the dose of study treatment should be reduced to osimertinib (or placebo) 40 mg (ie, switch to lower strength over-encapsulated tablet) and lazertinib (or placebo) 160 mg (ie, lower number of tablets from 3 to 2). To maintain the double-blind, dose reduction in these arms will be achieved by reducing the total study treatment from 4 pills (1 capsule and 3 tablets) to 3 pills (1 capsule and 2 tablets), as summarized in Table 10.

Table 10: Dose Reduction for Double-Blinded Therapy (Arms B and C)

Dosage Level	Arm B	Arm C
1 (initial dosage)	Osimertinib 80 mg (1 capsule) Lazertinib placebo (3 tablets)	Osimertinib 80 mg placebo (1 capsule) Lazertinib 240 mg (3 tablets)
2	Osimertinib 40 mg (1 capsule) Lazertinib placebo (2 tablets)	Osimertinib 40 mg placebo (1 capsule) Lazertinib 160 mg (2 tablets)

For all arms, if treatment is withheld for an adverse event that resolves within 28 days and the participant restarts at the same dose, and then a subsequent adverse event requires withholding study treatment again, dose modification should occur as follows:

- If the same adverse event recurs in the same cycle and requires withholding study treatment again, study treatment should be restarted at one dose level lower or withdrawn if already at the lowest dose level.
- If a different adverse event subsequently requires withholding study treatment, study treatment may be restarted at the same dose or a lower dose.

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

6.6.3. Dose Modifications and Management of Specific Adverse Events

Refer to Table 7, Table 8, Table 9, and Table 10 for dose modifications in case of toxicities defined under this section, unless specific instructions are provided for certain toxicities in the individual sections.

6.6.3.1. Infusion-Related Reactions (Arm A only)

General Guidelines for Infusion-Related Reactions

Infusion-related reactions have been commonly observed during treatment with amivantamab, predominantly with the first exposure on Cycle 1 Day 1, and typically within the first 90 minutes of the infusion. The majority of IRRs are Grade 1 or 2 (Section 2.2). 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 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, respiratory rate, and oxygen saturation measurements.

Particularly with the initial dose (Cycle 1, Days 1 and 2), participants should be educated on 1) the likelihood of experiencing an IRR with the initial dose, 2) the symptoms to anticipate (which include chills, dyspnea, chest discomfort, fever, flushing, among others), 3) that they should alert nursing staff if they experience these symptoms, and 4) that the experience of an IRR will not preclude further therapy with amivantamab. Participants must be monitored closely for early signs and symptoms indicative of an acute IRR. Even with mild symptoms, the study treatment infusion should be interrupted immediately, as described in the tables below, to prevent more serious grade IRRs from occurring. Trained clinical personnel should be prepared to intervene in the event of IRRs. Resources necessary for resuscitation (ie, agents such as epinephrine, aerosolized bronchodilator, IV antihistamines, IV corticosteroids; medical equipment such as oxygen, airway management equipment including suction, and a defibrillator) must be readily available.

Prevention of Infusion-Related Reactions

Required prophylaxis for IRRs is described in Section 6.5.2.

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 11. With the initial dose of amivantamab (Cycle 1, Days 1 and 2), interrupting the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR. All Grade 3 or 4 IRRs should be reported within 24 hours to the Medical Monitor.

Table 11: Management of Infusion-Related Reactions

Toxicity Grade*	Treatment	Premedication at Subsequent Dosing or Other Action to be Taken
Grade 1 Mild reaction	Monitor participant as medically indicated until recovery from symptoms. If occurring with initial dose (ie, Cycle 1 Day 1 or Day 2), consider early infusion interruption to prevent more severe symptoms. If infusion is interrupted, please follow the guidance for Grade 2 interruptions.	Antihistamine, antipyretic, and glucocorticoid, as per Table 5.
Grade 2 Mild to moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment	**Interrupt infusion** If clinically indicated, start IV fluids; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol (acetaminophen) 650 to 1000 mg; consider corticosteroids and bronchodilator therapy; H1 and H2 antagonist, antiemetic and; supplemental oxygen; monitor participant closely until recovery from symptoms **First interruption for IRR: Restart infusion at 50% of the rate at the time of interruption**: if no further evidence of IRR after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely. Infusion rate escalation may resume per the 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, as per Table 5. Consider meperidine if participant experiences chills and rigors.
Grade 3 or 4 Severe reaction Grade 3: prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: life threatening; pressor or ventilator support indicated	Stop infusion Start IV saline infusion; recommend bronchodilators, supplemental oxygen; epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed (other drugs as appropriate). 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. Grade 4: Do not re challenge

eCRF electronic case report form; IPPI Investigational Product Preparation Instructions; IRR infusion related reaction; IV intravenous.
*Per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0

6.6.3.2. 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. For participants receiving combination amivantamab and lazertinib, more proactive management of rash is warranted, given the anticipated synergistic anti-EGFR activity.

Prophylaxis Recommendations

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

- Avoid exposure to sunlight.
- Wear protective clothing (including hat, sunglasses, etc.).
- Use broad-spectrum sunscreen with an SPF of ≥30 and reapply as necessary. UVA light can penetrate glass; therefore, sunscreen should also be worn indoors and in vehicles if exposed to direct sunlight. Recommended active sunscreen ingredients are zinc oxide and/or titanium dioxide.
- Apply alcohol-free emollient cream or ointments (eg, glycerin, cetomacrogol, or ceramide-based cream) or skin moisturizer on dry areas of the body. 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.
- **In addition, for participants randomized to Arm A,** a more 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: both a topical antibiotic (clindamycin, mupirocin, or fusidic acid) on sun-exposed skin, and 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 adverse event.

- Strongly consider consultation with a dermatologist, especially if the rash is Grade 3, atypical in appearance or distribution, or does not improve within 2 weeks (for Grade 2 rash).

- Initiate a topical corticosteroid (cream or ointment) twice daily
  - Examples to use for face: betamethasone valerate 0.05%, hydrocortisone valerate 0.2% or desonide 0.05%
  - Examples to use for body: betamethasone valerate 0.1%, triamcinolone acetonide 0.1%
- If not already initiated for prophylaxis, initiate systemic antibiotic (such as doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily), or increase the dosing if already administered.
- If an associated skin infection is suspected, obtain bacterial and fungal cultures followed by adjustment of antibiotic or antifungal therapy, based upon culture and susceptibility determination.
- For reactive management of pruritic lesions, see Section 6.6.3.3.
- For skin fissures, use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is recommended.
- For xerosis, fragrance-free moisturizing creams or sprays are recommended.
- For desquamation, emollients and mild soap are recommended.
- After the rash is controlled, consider de-escalating broad spectrum antibiotic and continuing or resuming prophylactic antibiotics.

A suggested algorithm for stepwise management of rash is provided in Table 12. Refer to Table 7 and Table 9 for recommended dose adjustment.

Table 12: Suggested Algorithm for Management of Rash

Grade[a]	Management	Dose Adjustment[b,c]
1	• Initiate reactive management as above • Reassess after 2 weeks	• Continue current dose(s) of study treatment
2	• Initiate reactive management as above • Reassess after 2 weeks	• Continue current dose(s) of study treatment or consider dose reduction
3	• Initiate reactive management as above • Start moderate strength topical corticosteroids[d] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (2030 mg/day) • Reassess weekly • Consider dermatology consultation and manage rash per recommendation	• Temporarily withhold study treatment until rash improves to ≤Grade 2 • For guidance on withholding study treatment and dose reduction, refer to Table 7 and Table 9 for Arm A, and Table 8 and Table 10 for Arms B and C
4	• Initiate reactive management • Start moderate strength topical corticosteroidsc 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 • Please refer to the dose modification guidance Section 6.6.3 for further instructions • Permanently discontinue amivantamab
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 2 consecutive doses, consult the Medical Monitor. Participants considered by the investigator and sponsor to be benefiting from treatment may be continued, potentially at a lower dose upon satisfactory resolution of the toxicity.
c. Resolution defined as: ≤Grade 1 non-hematologic toxicity or back to baseline.
d. For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream.

Scalp Rash

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

- A topical steroid shampoo (eg, clobetasol 0.05%), or an antidandruff shampoo with anti-inflammatory, antibacterial, and antifungal properties (eg, ketoconazole, selenium sulfide [Selsun®], zinc pyrithione [Head and Shoulders®], or Ciclopirox). These shampoos should be used twice/week, massaging into scalp, leaving on for 2-5 minutes, and then rinsing.
- Topical Acetic acid 0.25% solution irrigation
- Application of a steroid lotion may also be effective (eg, betamethasone valerate 0.1% lotion, mometasone furoate 0.1% lotion, fluocinonide 0.05% lotion, or betamethasone dipropionate 0.05% lotion).
- Initiation of a systemic antibiotic (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily) may also be used to treat acute scalp infection.

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

6.6.3.3. Pruritus

Reactive Management Recommendations[6]

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).

6.6.3.4. Paronychia

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

Prophylaxis Recommendations

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

Reactive Management Recommendations

Grade 1 paronychia:

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

Grade 2 or 3 paronychia:

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

6.6.3.5. Oral Mucositis

Mucositis is a well-recognized toxicity associated with anti-EGFR therapeutics, and may be mild/moderate and localized (Grades 1-2) or severe and widespread (≥Grade 3). As a result, there are recommendations that should be followed to prevent or minimize patient 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.

6.6.3.6. Pulmonary Toxicity

Patients with NSCLC are at risk of multiple adverse events affecting pulmonary function, including disease progression, pulmonary embolus, infectious pneumonias, and more rarely, drug-related ILD/pneumonitis. Patient respiratory status should be assessed at every visit; any clinically significant change in respiratory status should prompt immediate investigation into the etiology in accordance with local practice/guidelines to institute appropriate treatments and to rule out early ILD/pneumonitis. If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pulmonary 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 computerized tomography (CT) scan (high-resolution CT is preferred).
- Infectious evaluation, including blood and sputum cultures, atypical pneumonia panels, and SARS-CoV-2 testing, if indicated
- Hematology and other laboratory tests, including serum albumin levels
- Referral to pulmonologist for evaluation, including bronchoscopy with biopsy, cell counts, and cultures as feasible

- Evaluation of cardiac function, if indicated

Where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered, and study treatment permanently discontinued. Study treatment should not be restarted until pneumonitis/ILD is ruled out. For symptomatic patients with pneumonitis (Grade 2 and above), treatment with steroids should be initiated per local guidelines, in addition to withholding of study treatment. Confirmation of ILD/pneumonitis of any grade should prompt discontinuation of all study treatment and should be reported as a serious adverse event (see Section 8.3.1). In the absence of a diagnosis of ILD/pneumonitis, study treatment may be restarted.

6.6.3.7. Cardiac Adverse Events

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

QTcF Prolongation

- Check the quality of ECG recording and check for electrolyte abnormalities (eg, potassium, calcium, magnesium); correct as needed.
- QTc prolongation of >60 msec from baseline, or absolute value of >500 msec
  - For QTcF prolongation >60 msec from baseline, or absolute value >500 msec (from a manual ECG read), medications should be reviewed to rule out new or existing concomitant medications with potential for QT prolongation (Appendix 12: Medications With Potential for QT Interval Prolongation), and these should be discontinued, if possible, with action reported in eCRF.
  - Check for electrolyte abnormalities and correct as needed (eg, potassium, calcium, magnesium).
  - If QTcF prolongation is confirmed and potentially attributable to study treatments, then study treatment should be withheld.
  - Retreatment, at a reduced dose, should only occur once QTc interval is less than 481 msec, as measured by repeat triplicate ECG, or recovery to baseline is documented. If retreatment is indicated, Arms B and C should be dose reduced to Dose Level 2 (see Table 10) and lazertinib in Arm A should be dose reduced to Dose Level 3 (see Table 9).
  - Treat as per local standard of care in consultation with a cardiologist.
- QTc interval prolongation with signs/symptoms of life-threatening arrhythmia, including but not limited to the following: documented episode of ventricular tachycardia, ventricular fibrillation, complete heart block (Grade III atrioventricular block) or second-degree atrioventricular block Mobitz type II, QTc >500 msec at repeated ECG measurements, after dose adjustment was performed
  - Permanently discontinue study treatment.

Change in LVEF

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

6.6.3.8. Liver Chemistry Abnormalities

Liver chemistry threshold stopping criteria have been established to provide safety to the participants and to better assess the etiology of a liver event. Liver chemistry should be monitored according to the Schedule of Activities and study treatment should be withheld for any liver chemistry abnormality of ≥Grade 3 severity (refer to Section 6.6.1). In addition, if the following criteria are observed, the event should be reported as a serious adverse event to the sponsor within 24 hours:

a) ALT or AST ≥3x ULN and bilirubin ≥2x ULN (>35% direct bilirubin) (or ALT ≥3x ULN and INR >1.5, if INR measured).

   - Exception to the bilirubin elevation is made if the participant has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.

b) ALT or AST ≥3x ULN (if baseline was normal) with the concomitant appearance of worsening symptoms suggestive of drug induced liver injury, such as the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or new onset eosinophilia (>5%).

In the event abnormalities of liver function tests require withholding study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. Etiology of the liver chemistry abnormality should be investigated, as described in Appendix 10: Liver Event Follow-Up and Rechallenge Criteria. If no alternative etiology of liver toxicity is identified, study treatment should be permanently discontinued.

6.6.3.9. Diarrhea

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 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 13.

Table 13: 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
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.
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.

6.6.3.10. Ocular Toxicity

Ophthalmologic complications are infrequently observed with anti-EGFR therapeutics. In the case of signs or symptoms associated with ophthalmologic toxicity, including change in vision (including change in acuity or visual distortion), eye inflammation, lacrimation, light sensitivity, or eye pain, among others, the participant should be referred for ophthalmologic assessment (Section 8.2.5). Participants should be advised of the increased risk for eye toxicity associated with anti-EGFR therapeutics with the use of contact lenses.

6.6.3.11. Paresthesia

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

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

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

- Grade 1: Nutraceutical/non-pharmacologic interventions may be considered (ie, vitamin supplementation including vitamins B1, B6, B9, B12, E, glutamine, alpha-lipoic acid, glutathione, calcium/magnesium, copper). Topical therapy (eg, capsaicin) may be considered.
- Grade 2: Duloxetine, pregabalin, or gabapentin are recommended. Titrate dose for efficacy and tolerability. Adding tricyclic or selective serotonin reuptake inhibitor antidepressant may be considered. Opioids (tramadol or strong opioids) may be considered. Neurologic consultation if symptoms persist on medication.
- Grade 3: Neurologic consultation. Duloxetine, pregabalin, or gabapentin are recommended. Titrate dose for efficacy and tolerability. Adding tricyclic or selective serotonin reuptake inhibitor antidepressant may be considered. Opioids (tramadol or strong opioids) may be considered.

If treatment modification is indicated, consider preferential interruption or dose reduction of lazertinib for participants in Arm A or lazertinib/osimertinib in Arms B/C.

6.6.3.12. Venous Thromboembolic Events

Patients with NSCLC are at risk of developing complications, including VTE events. Investigators should closely monitor all participants for signs and symptoms of VTE events, specifically pulmonary embolism and deep vein thrombosis, throughout the duration of the study. Physical examinations (see Section 8.2.1) should include focus on signs and symptoms of VTE events, including upper- or lower-extremity swelling and discoloration. There should be a low threshold to perform additional diagnostic testing (eg, CT angiogram or lower-extremity ultrasound) for VTE events beyond the scheduled disease evaluations. For participants who 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 receiving the combination of amivantamab and lazertinib (Arm A) 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. [4, 33]

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 participant recovers from the event. Thereafter, the study 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 study treatment with either amivantamab or lazertinib (but not both) at the discretion of the treating physician.

Refer to Table 7, Table 8, Table 9, and Table 10 for recommended dose adjustment for any adverse events.

6.7. Continued Access to Study Treatment

Participants who are still benefiting from study treatment, as determined by the investigator, will be able to receive continued access to investigational drug; see details for the OLE Phase (Section 10.14 [Appendix 14]) and the LTE Phase (Section 10.15 [Appendix 15]).

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, adverse event) it is in the best interest of the participant to discontinue study treatment
- The participant becomes pregnant. Refer to Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information.
- Noncompliance with study treatment or procedure requirements as judged by investigator
- Radiographic disease progression (RECIST, Version 1.1) (**Exception**: Continuation of study treatment after disease progression is allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believes the participant is deriving clinical benefit)
- Disease progression that, at the discretion of the treating investigator, requires the initiation of a new systemic anti-cancer treatment.

Participants who discontinue study treatment for any reason should have the End of Treatment assessments, document any subsequent therapy in the eDC and continue to be followed up in accordance with the -Follow up phase (Section 4.1.3).

Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant. Further guidance on study drug discontinuation can be found in Section 8.1.1.

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 eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

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

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

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

7.3. Lost to Follow-up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of measurements applicable to this study.

When possible, all PRO assessments should be conducted/completed before tests, procedures, or other consultations to prevent influencing participant perceptions.

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

The total blood volume to be collected from each participant depends upon the duration of participation, but the approximate volume for participants in Arm A is 540 mL, including screening, 26 dosing cycles, and the End of Treatment Visit.

Sample Collection and Handling

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

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

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

Study-Specific Materials

The investigator will be provided with the following supplies:

- Clinical Protocol
- IB for amivantamab
- IB for lazertinib

- Local prescribing information for osimertinib
- IPPI and SIPPM
- Laboratory Manual and kits
- Electronic data capture (eDC) Manual
- IWRS Manual
- Imaging Manual
- ECG Manual
- ECHO/MUGA Manual
- NCI CTCAE Version 5.0
- RECIST guidelines, Version 1.1
- Sample ICF
- Wallet cards
- Study treatment
- Ancillary supplies (as needed)
- Tablet (for PRO collection)

8.1. Efficacy Assessments

8.1.1. Disease Assessments

RECIST v1.1 criteria will be used to assess participant response to treatment: complete response, PR, stable disease, progressive disease, or unevaluable. Disease assessments will include imaging of the chest, abdomen, and pelvis, and any other disease location(s). Baseline disease assessments should be performed no more than 28 days prior to randomization. Post-randomization disease assessments will occur every 8 weeks (±1 week) for the first 30 months, and then every 12 weeks (±1 week) relative to randomization until disease progression is confirmed by BICR, even if a participant discontinues treatment prior to progression or receives another systemic anti-cancer therapy. If an imaging assessment is performed outside of the scheduled visit and the participant has not progressed, every attempt should be made to perform the subsequent assessment at their scheduled visit timepoint. Refer to the latest Imaging Site manual.

CT scan of the chest, abdomen, pelvis, and any other disease location(s) should be performed with an IV contrast agent and oral contrast. Participants not able to undergo CT scans with IV contrast (eg, due to allergy or renal insufficiency) may have non-contrast CT of the thorax and contrast enhanced magnetic resonance imaging (MRI) of the abdomen and pelvis. Participants with contraindications to IV CT and MRI contrast may be able to undergo non-IV contrast CT exams of the chest abdomen and pelvis with proper documentation of medical contraindication. Oral contrast should be used for CT exams of the abdomen and pelvis. Contraindications to the CT scan with IV contrast that develop postbaseline require investigator discretion. MRI can also be used to

evaluate sites of disease that cannot be adequately imaged using CT. If possible, the same imaging modality should be used for disease assessment at baseline and throughout the course of the study to characterize each identified and reported lesion to document disease status. Any site at which new disease is suspected should also be imaged. Techniques other than CT or MRI may be used based upon investigator's judgment, local standard of care, and RECIST v1.1 guidelines for the use of these alternative techniques. For example, bone scintigraphy may be used to identify bone lesions at screening or new bone lesions during treatment, but bone lesions will not be considered target lesions. Further details are provided in the Imaging Manual.

Brain MRI (or brain CT scan if MRI is contraindicated) will also be performed at Screening. Participants with a history of brain metastasis at Screening will undergo postbaseline brain MRI every 8 weeks (±1 week) for the first 30 months and then every 12 weeks (±1 week) until disease progression. Participants with no history of brain metastasis at Screening will undergo postbaseline surveillance brain MRI every 24 weeks (±1 week). Postbaseline brain MRI will be scheduled relative to randomization and will continue until disease progression is confirmed by BICR. Unscheduled brain MRI may also occur if new disease or progressive disease in the brain is suspected at any time. Further details are provided in the Imaging Manual.

The primary endpoint for this study is PFS as assessed by BICR. Sites will be required to obtain digital copies of radiologic images (eg, CT, MRI) used for all scheduled and unscheduled disease assessments and submit them to a Janssen-appointed Clinical Research Organization (CRO) for BICR.

During the independent radiology review, radiographic exams will be evaluated using RECIST 1.1. A clinical oncology review will be performed for participants with relevant clinical data in addition to the radiographic review. The BICR will determine an overall (integrated radiographic and clinical) assessment at the primary analysis of PFS. The BICR will also conduct a separate review of intracranial disease assessed using modified RECIST 1.1 criteria. Investigator assessed PFS will be based on data collected in the imaging assessment eDC forms.

In the event the Investigator suspects radiographic disease progression in a participant, a set of imaging scans will be submitted to the BICR CRO together with the appropriate documentation. These scans may be from a regularly scheduled time point or an unscheduled time point. The BICR CRO will initially perform an expedited review to confirm radiographic progression. Investigators should use BICR of imaging data to guide decisions regarding treatment discontinuation for radiographic progression.

The Investigator should not discontinue study treatment until confirmation of progression has been received from the BICR CRO. If radiographic progression is not confirmed by BICR the participant should continue to receive study treatment and undergo imaging in accordance with the protocol, although a set of imaging scans to re-assess suspected progression can be repeated prior to the scheduled disease assessment (eg, at 4 weeks).

If the Investigator suspects clinical progression, full details (procedures, biopsy data, cytology data, AEs) must be documented in eDC forms. In addition, a set of imaging scans should be performed at the time of suspected progression and submitted to the BICR CRO together with the appropriate documentation. All participants suspected of clinical progression but without disease progression confirmed by BICR should continue study treatment, and undergo imaging assessments according to the protocol until progression is confirmed.

After progression has been confirmed by BICR, participants who remain on study treatment should undergo disease assessments according to the protocol. Participants who switch to a new systemic anti-cancer therapy after BICR confirmed progression should have disease assessments as per local standard of care and provide documentation of best response, progression information (PFS2) and other data in the eDC Subsequent Systemic Therapy forms.

If the participant is suspected of having disease progression and the Investigator considers that it is in the best interest of the participant not to wait for confirmation of progression by BICR, the Sponsor should be consulted before discontinuing study drug or beginning a new systemic anti-cancer therapy. A set of imaging scans should be performed before starting a new systemic anti-cancer treatment. Every effort should be made to continue tumor imaging in accordance with the protocol until progressive disease has been confirmed by BICR, even if a participant receives another systemic anti-cancer therapy.

For all participants who discontinue study treatment prior to BICR confirmed progressive disease, every effort should be made to continue tumor imaging in accordance with the protocol until progressive disease has been confirmed by BICR. This includes participants who discontinue study treatment due to toxicity, withdraw consent for study treatment, or switch to another anti-cancer therapy.

All participants who discontinue study treatment for any reason should have the End of Treatment assessments, document any subsequent therapy in the eDC, and continue to be followed up in accordance with the Follow-up phase (Section 4.1.3). Additional follow-up calls may be made in the 2 weeks before a data cutoff date to assess participant survival before the next scheduled assessment.

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

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

8.1.2. Symptomatic Progression

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

8.1.3. Patient-Reported Outcomes

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

The Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NSCLC-SAQ) was developed in accordance with US FDA PRO Guidance and scientific best practices for use in clinical trials of NSCLC.[17] It contains 7 items that assess cough, pain, dyspnea, fatigue, and poor appetite over a 7-day recall period.

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 NSCLC-SAQ. The PGIS and PGIC should be administered prior to other PRO assessments. The PGIC will not be administered at the first visit because it captures change.

The EQ-5D-5L is a validated tool to measure health status and health utility, including mobility, self-care, usual activities, pain, discomfort, and anxiety/depression.[11]

The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) assesses functioning domains and common cancer symptoms with recall in the past week.[18]

8.2. Safety Assessments

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

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

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the 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.

To align frequency of safety assessments across treatment arms, participants in Arm A are not required to be evaluated by a physician on Day 15 of Cycles 3 and beyond, unless clinically indicated.

8.2.1. Physical Examinations

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

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 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 body weight will be obtained using a calibrated scale.

8.2.2. Vital Signs

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

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

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

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

8.2.3. Electrocardiograms

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Triplicate ECGs are required at Screening, Cycle 1 Day 1 (within 72 hours before study treatment), Cycle 2 Day 1 (Arm A: within 30 minutes postinfusion; Arms B/C: 2-4 hours after oral administration), and then to confirm any clinically significant finding during the study. 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. Refer to the ECG Manual for additional details.

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. Triplicate ECGs will be submitted to a Janssen-appointed CRO on an ongoing basis.

8.2.4. Left Ventricular Ejection Fraction

During the Screening Phase each participant will undergo a baseline LVEF assessment performed locally by cardiac ECHO or MUGA scan in order to demonstrate eligibility (ie, a LVEF within the normal range [refer to Appendix 6: New York Heart Association Criteria]). Participants will undergo postbaseline LVEF assessments according to the Schedule of Activities. ECHO or MUGA scans will be submitted to a Janssen-appointed CRO on an ongoing basis.

8.2.5. 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. Any clinically significant findings, including those confirmed by the ophthalmologist must be reported as an adverse event. 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 on the procedures page in the database.

8.2.6. ECOG Performance Status

ECOG performance status score (refer to Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status) will be determined during the Screening Phase and at time points listed in the Schedule of Activities. Any decline in ECOG performance status score should be reported as an adverse event.

8.2.7. 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 7: Clinical Laboratory Tests will be collected at the times listed in the Schedule 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 from clinical studies including adverse events, serious adverse events, and product quality complaints (PQC) are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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

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

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

All Adverse Events

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

Serious Adverse Events

All serious adverse events as well as PQC occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using a serious adverse event form. A serious adverse event spontaneously reported to the investigator more than 30 days after the last dose of study treatment must also be reported using a serious adverse event form, if the investigator considers the event to be related to study treatment. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the 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 a serious adverse event should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

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

Unsolicited Adverse Events

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

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

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

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

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational

institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study, anticipated events will be periodically analyzed as specified in Appendix 13: Anticipated Events.

8.3.5. Pregnancy

All initial reports of pregnancy in participants or their partners of participants (through sperm of participant/from sexual intercourse and 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 serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study treatment.

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

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

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

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

8.3.7. Adverse Events of Special Interest

Adverse events of special interest are pneumonitis/ILD, rash, IRR, and VTE. Additional information will be collected for these events. Refer to the monitoring and management guidelines for these events in Section 6.6.3. Confirmed cases of pneumonitis/ILD (regardless of grade) should be reported as serious adverse events (see Section 8.3.1). All Grade 3 or 4 IRRs should be reported within 24 hours to the Medical Monitor. Events of rash and VTE should follow standard reporting guidelines.

8.4. Treatment of Overdose

There are no data on overdose from studies of amivantamab or lazertinib (refer to IB for each agent) or from studies of osimertinib (refer to local prescribing information[37]).

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

- Contact the Medical Monitor immediately.
- Closely monitor the participant for adverse events/serious adverse events, and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the study drug administration eCRF.

8.5. Pharmacokinetics

Serum samples will be used to evaluate the PK of amivantamab and plasma samples will be used to evaluate the PK of lazertinib. Serum or plasma collected for PK 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.

8.5.1. Evaluations

Serum samples will be collected from participants in Arm A for PK and immunogenicity assessments of amivantamab at the time points outlined in Table 2. Plasma samples will be collected from participants in Arm A for the evaluation of PK of lazertinib at the time points outlined in Table 2. The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Blood samples should not be collected from the same extremity in which the amivantamab infusion was administered.

Blood collected for PK may additionally be used to identify circulating metabolites and/or evaluate safety or efficacy aspects that address concerns arising during or after the study period.

8.5.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of amivantamab using a validated, specific, and sensitive enzyme-linked immunosorbent assay (ELISA) method by or under the supervision of the sponsor.

Plasma samples will be analyzed to determine concentrations of lazertinib using a validated liquid chromatography-tandem mass spectrometry method.

If required, some plasma and serum samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma and serum PK

samples may be stored for future analysis of other co-administered treatments, protein binding, and the metabolite profile.

8.5.3. Pharmacokinetic Parameters and Evaluations

Pharmacokinetic analysis of serum/plasma concentration data for amivantamab and lazertinib will be performed. Serum (amivantamab) and plasma (lazertinib) concentrations ~~and PK parameters~~ will be listed and summarized by sampling interval.

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

8.6. Pharmacogenomics

A pharmacogenomic blood sample will be collected from participants in Arm A to allow for assessment of GSTM-1 to understand correlation of genetic variants with PK, safety, tolerability and efficacy.

8.7. Biomarkers

Mandatory Tumor Biopsy Sample for Central Mutation Analysis

It is mandatory to provide an unstained tumor tissue sample obtained from the newly diagnosed, locally advanced, or metastatic NSCLC meeting criteria described in Inclusion Criterion no. 2 for each participant. This biopsy sample must be obtained before randomization. It will undergo central genetic analysis and other testing for biomarker analysis and to confirm EGFR status. If possible, the tumor tissue provided for central analysis should be from the same biopsy utilized for local testing and identification of Exon 19del or L858R. Biopsy samples taken from bone metastasis, fine needle aspiration (FNA), and cytology samples are unsuitable for testing and should not be provided. Samples may be collected from primary or metastatic tumor deposits but must not be taken from a previously irradiated lesion.

The tumor tissue sample must be unstained, formalin-fixed and paraffin-embedded (FFPE) and in a sufficient quantity to allow for central analysis of EGFR mutation status. Unstained FFPE tumor tissue blocks must be provided whenever possible. Alternatively, a minimum of 10 (up to 15 when available) re-cut unstained sections from FFPE tumor tissue block, presented on slides must be provided. Each section is to be 5 µm. Sites should ship the FFPE tumor sample to the sponsor-designated testing laboratory as soon as it is available. Please refer to the laboratory manual.

Blood Samples

Mandatory screening blood samples collected from all participants may undergo ctDNA and ddPCR analysis by the sponsor to evaluate pre-treatment mutational status of EGFR, MET, 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 time points specified in the Schedule of Activities for potential analysis of circulating biomarkers (eg, cytokines, growth factors) in samples taken prior to and after exposure to study treatment(s). Changes in circulating markers may be assessed in pre- and post-treatment samples and levels correlated with response to study treatments.

Additional biomarkers (eg, DNA, RNA, and protein) relevant to cancer and/or metabolism of study treatments may also be assessed in blood and tissue samples collected during the study to better understand the disease and mechanisms of response or resistance to study therapy.

Stopping Analysis

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

8.8. Immunogenicity Assessments

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

Antibodies to amivantamab will be evaluated in serum samples collected from all participants according to the Schedule of Activities. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

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

Serum samples will be used to evaluate the immunogenicity of anti-amivantamab 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.

Analytical Procedures

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

8.9. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The null hypothesis is that there is no difference of treatment effect in PFS between amivantamab and lazertinib combination and single agent osimertinib in participants with EGFR mutation (Exon 19del or Exon 21 L858R) positive, locally advanced or metastatic NSCLC. The alternative hypothesis is that, compared with single agent osimertinib, the amivantamab and lazertinib combination will prolong PFS.

9.2. Sample Size Determination

The primary objective of the study is to assess the efficacy of the combination of amivantamab and lazertinib, compared with single-agent osimertinib, as measured by PFS by BICR, in accordance with RECIST v1.1 guidelines. The sample size calculation was based on the assumption that the combination therapy will result in a 27% reduction in the risk of either progression or death over the single agent osimertinib therapy (an HR of 0.73, prolongs the median PFS from 19 months[35] to 26 months). A total of 450 PFS events in Arm A and Arm B will provide approximately 90% power to achieve a statistically significant difference between the 2 treatment arms with the stratified log-rank test (2-sided alpha 0.05).

Approximately 1000 eligible participants will be randomized in a 2:2:1 ratio to the three arms (Arm A: Arm B: Arm C). Assuming a 25-month recruitment period and an annual dropout rate of approximately 5%, 560 PFS events (approximately 450 events in Arm A and Arm B combined) are expected to occur approximately 42 months after the first participant is enrolled.

9.3. Populations for Analyses Sets

For purposes of analysis, the study populations are defined in Table 14.

Table 14: Populations for Analyses

Population	Description
Full Analysis Set	All randomized participants, classified according to their assigned treatment arm regardless of the actual treatment received.
Safety	Randomized participants who receive at least 1 dose of study treatment.
Pharmacokinetics	Randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline concentration measurement.[a]
Biomarkers	Randomized participants who receive at least 1 dose of study treatment and have at least 1 biomarker measurement.

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, which will be finalized prior to the interim analysis (Section 9.5), 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 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 number and percent. 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.

The hypothesis testing of primary efficacy endpoint and key secondary efficacy endpoint will be performed for the comparison between the combination of amivantamab and lazertinib therapy (Arm A) and single agent osimertinib (Arm B). The comparison of the combination of amivantamab and lazertinib therapy (Arm A) with the lazertinib monotherapy arm (Arm C) will also be performed to demonstrate the contribution of amivantamab to the activity of the combination using summary statistics of primary endpoint and secondary endpoints (PFS and OS) along with nominal p-values; there will be no hypothesis testing for this comparison.

9.4.2. Primary Endpoint

The primary efficacy endpoint of PFS is defined as the time from randomization until the date of objective disease progression or death, whichever comes first, based on BICR using RECIST v1.1. Participants who have not progressed or have not died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. If the participant progresses or dies after 2 or more missed disease assessments, the participant will be censored at the time of the last evaluable RECIST v1.1 assessment. If the participant has no evaluable visits or does not have baseline data, the participant will be censored at Day 1 unless the participant dies within 2 visits of baseline.

The treatment effect of the combination, compared with osimertinib, on PFS will be analyzed in the Full Analysis Set using the log-rank test stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent). The HR for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. The effect of the combination compared to lazertinib on PFS will be assessed using the same analysis methods.

9.4.3. Secondary Endpoints

Secondary endpoints will be analyzed using the Full Analysis Set.

Overall Survival

The secondary endpoint of OS is defined as the time from the date of randomization until the date of death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive. OS will be analyzed using the same methodology and model as for the analysis of PFS. To strongly control Type I error rate at 0.05 for the study, a hierarchical testing approach for the primary endpoint and key secondary endpoint will be used. The comparison between the combination and osimertinib for OS will be conducted only if PFS shows statistical significance. The analysis of OS will be conducted at 2 timepoints, based on the group sequential design with the O'Brian Fleming alpha spending approach:

- At the time of the final analysis of primary endpoint of PFS, when approximately 340 deaths overall (all treatment arms combined) are anticipated. With approximately 270 deaths in Arm A and Arm B combined, based on the O'Brian Fleming alpha spending approach, a 2-sided alpha of 0.0140 will be allocated to the interim analysis.
- Approximately 60 months after the first participant is enrolled, when 490 deaths overall (all treatment arms combined) are anticipated, with approximately 390 deaths from Arm A and Arm B combined.

Objective Response Rate

The ORR is defined as the proportion of participants who achieve either a complete response or PR, as defined by BICR using RECIST v1.1. ORR will be analyzed using a logistic regression stratified by mutation type (Exon 19del vs Exon 21 L858R) and race (Asian vs non-Asian) and history of brain metastasis (present vs absent). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% confidence intervals.

Duration of Response

Duration of response is defined as the time from the date of first documented response (CR or PR) until the date of documented progression or death, whichever comes first. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then his/her duration of response will use the PFS censoring time. 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.

Progression-free Survival After the First Subsequent Therapy

The PFS2 is defined as the time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first. Participants alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression. PFS2 will be analyzed using the same method as PFS.

Time to Symptomatic Progression

Time to symptomatic progression (TTSP) is defined as the time from randomization to documentation in the eCRF of any of the following (whichever occurs earlier): onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms or death, whichever comes first. The symptomatic progression can be reported before, after, or at the time radiographic disease progression is identified and should continue to be assessed after subsequent therapy has been initiated. The TTSP for a participant who does not experience any of these events will be censored on the date on which the participant was last known to be event free. The TTSP will be analyzed using similar methods as the analysis of PFS.

Intracranial Progression-Free Survival

Intracranial PFS is defined as the time from randomization until the date of objective intracranial disease progression or death, whichever comes first, based on BICR using RECIST v1.1 in participants who had a history of brain metastasis at screening in the full analysis set. Participants who have not progressed intracranially or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment. It will be analyzed using a similar method as the analysis of PFS.

Patient Reported Outcomes Analyses

Results for EORTC-QLQ-C30 and NSCLC-SAQ will be summarized for the full analysis set.

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

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

9.4.4. Exploratory Endpoints

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

9.4.5. Safety Analyses

All safety analyses will use the Safety Population.

Adverse Events

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

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

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. Changes from

baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

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

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline).

Electrocardiogram data will be summarized by ECG parameter. The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QT corrected according to Fridericia's formula (QTcF).

Vital Signs

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

LVEF Assessments

LVEF will be determined using either ECHO or MUGA scan. Descriptive statistics for LVEF and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.6. Other Analyses

An Independent Data Monitoring Committee (IDMC) will be established as noted in Committees Structure in Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

Pharmacokinetic Analyses

The PK analyses will use the PK Population (Table 14). For participants randomized to the combination of amivantamab and lazertinib, all plasma/serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or Statistical Analysis Software (SAS) dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the CSR.

Biomarkers Analyses

Biomarkers analyses will use the Biomarkers Population (Table 14). Each baseline tumor status will be evaluated by both tumor genetic analysis and ctDNA NGS analysis in order to characterize potential mechanisms of resistance to amivantamab in combination with lazertinib.

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

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

Immunogenicity Analyses

The incidence of anti-amivantamab antibodies will be summarized for all participants in the PK Population (Table 14). A listing of participants who are positive for antibodies to amivantamab will be provided. The maximum titers of antibodies to amivantamab will be summarized for participants who are positive for antibodies to amivantamab. Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Pharmacokinetic/Pharmacodynamic Analyses

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

9.5. Interim Analysis

A futility analysis based on PFS will be conducted when approximately 150 PFS events have occurred overall (all treatment arms combined). Futility will be assessed at this analysis and a nominal alpha of 0.00001 will be allocated to this analysis. The analysis method for primary efficacy endpoint described in Section 9.4.2 Primary Endpoints, will be used for the interim analysis. If the HR for combination versus osimertinib is ≥1.0, the study will be stopped for futility.

An interim analysis of PFS will be performed when approximately 350 PFS events have occurred overall (all treatment arms combined). With approximately 280 PFS events in Arm A and Arm B combined, based on the group sequential design with the O'Brian Fleming alpha spending

approach as implemented by the Lan-DeMets method, a 2-sided alpha of 0.0090 will be spent at the interim analysis. If there are 450 PFS events at the final analysis, the 2-sided alpha for the comparison between the combination and osimertinib will be 0.0472.

An interim analysis of OS will be conducted at the time of the final analysis for PFS, when approximately 340 deaths overall (all treatment arms combined) are anticipated. The key secondary endpoint of OS will be tested with a total 2-sided alpha of 0.05 only if statistical significance for PFS is achieved. With 270 deaths in Arm A and Arm B combined, based on the O'Brian Fleming alpha spending approach, a 2-sided alpha of 0.0140 will be allocated to the interim analysis. If there are 390 deaths at the OS final analysis, the 2-sided alpha for the comparison between the combination and osimertinib will be 0.0457.

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
ALT	alanine aminotransferase
Anti-HCV	hepatitis C virus antibody
ART	antiretroviral therapy
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BCRP	breast cancer resistance protein
BICR	blinded independent central review
CHF	congestive heart failure
CLIA	Clinical Laboratory Improvement Amendments
C_{min}	minimum plasma/serum concentration
CNS	central nervous system
CRO	Clinical Research Organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CYP	cytochrome P450
ddPCR	digital droplet polymerase chain reaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQol five-dimensional descriptive system (5-level version)
FDA	Food and Drug Administration
FFPE	formalin-fixed and paraffin-embedded
FSH	follicle stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HGF	hepatocyte growth factor
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board

IRR	infusion-related reaction
IV	intravenous
IWRS	interactive web response system
LLN	lower limit of normal
LTE	long-term extension
LVEF	left ventricular ejection fraction
MET	mesenchymal-epithelial transition
MRI	magnetic resonance imaging
MRP4	multi-drug resistance protein 4
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire
NYHA	New York Heart Association
OLE	open-label extension
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcomes
QT	uncorrected QT interval
QTc	corrected QT
QTcF	corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2CD	recommended Phase 2 combination dose
RP2D	recommended Phase 2 dose
SAC	Safety Assessment Committee
SAE	serious adverse event
SAP	statistical analysis plan
SIPPM	Site Investigational Product and Procedures Manual
SPF	skin protection factor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTSP	time to symptomatic progression
ULN	upper limit of normal
US	United States
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 International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

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

Protocol Amendments

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

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

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

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

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

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

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

Country Selection

This study will only be conducted in those countries/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 course of the study and for 1 year after completion of the study.

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

10.2.3. Informed Consent Process

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse

to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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

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

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

10.2.4. Recruitment Strategy

Enrollment is now complete; the last participant started study treatment on 19 May 2022.

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. ~~This~~ The informed consent also ~~addresses the~~ 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 and lazertinib, to understand the disease under investigation, to understand differential treatment responders, and to develop tests/assays related to amivantamab, lazertinib, and NSCLC. The research may begin at any time during the study or the post-study storage period.

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

10.2.7. Committees Structure

Independent Data Monitoring Committee (IDMC)

An IDMC will be established to monitor data on an ongoing basis. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. 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 amivantamab, lazertinib, or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish the goals of this study and will not use it for other purposes without the sponsor's prior written consent.

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

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there

will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose ~~the existence of, and~~ the interim results of~~,~~ clinical studies as required by law. The disclosure of the ~~final~~ 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

Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

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 will review 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 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 eDC tool. If corrections to an 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 adverse events and follow-up of adverse events; 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 should be identifiable.

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

The minimum source documentation requirements for Section 5.1 and Section 5.2 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 eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

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

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

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

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

10.2.15. Study and Site Start and Closure

First Act of Recruitment

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

Study Termination

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

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

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

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

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

10.3.1. Adverse Event Definitions and Classifications

Adverse Event

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

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*

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For amivantamab or lazertinib, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For osimertinib, the expectedness of an adverse event will be determined by whether or not it is listed in the local prescribing information.[37]

10.3.2. Attribution Definitions

Assessment of Causality

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

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

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

10.3.3. Severity Criteria

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to adverse event.

10.3.4. Special Reporting Situations

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

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

Participant-specific special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

10.3.5. Procedures

All Adverse Events

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

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

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

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

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

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

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

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

10.3.6. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.3.7. Product Quality Complaint Handling

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a

product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

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

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

Contacting Sponsor Regarding Product Quality

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

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

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

Definitions

Participants of Childbearing Potential (WOCBP)

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

Participants Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or 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 participants on HRT, the participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish to continue HRT during the study.
- **permanent absence of reproductive potential (for the purpose of this study)**
  - Has undergone a procedure that precludes reproductive potential.
  - Has a congenital abnormality that precludes reproductive potential.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant becomes sexually active where pregnancy can occur), a participant must begin 2 methods of contraception, including 1 highly effective method, as described throughout the inclusion criteria.

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

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

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

Pregnancy During the Study

Participants who become pregnant during the study will be withdrawn from the study treatment and followed for safety.

Examples of Contraceptives

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

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) 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) Multiple types of condoms should not be used together (due to risk of failure with friction).

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

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

Eastern Cooperative Oncology Group, Robert Comis M.D, Group Chair (Oken, 1982).[23]

10.6. Appendix 6: New York Heart Association Criteria

The following table presents the NYHA classification of cardiac disease:

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

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

10.7. Appendix 7: Clinical Laboratory Tests

The following tests will be performed by the local laboratory according to the Schedule of Activities (Table 1) during the main study, and according to Table 16 during the OLE Phase:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hemoglobin Platelet count	Absolute neutrophil count White blood cell (WBC) count with differential
Clinical Chemistry[a]	Magnesium Potassium Calcium Sodium Creatinine Albumin	Bilirubin (total, direct, and indirect) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase Lactic acid dehydrogenase (LDH)
Urinalysis[b]	*Dipstick* Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	
Coagulation[c]	Prothrombin time (PT)	Activated partial thromboplastin time (aPTT) International normalized ratio (INR)
Serology[d]	Anti-HIV antibody HBsAg, hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (Participants with a history of HBV are also required to have HBV DNA quantification.) Anti-HCV antibody (Participants with a history of HCV are required to have HCV RNA quantification.)	

a. At screening, direct and indirect bilirubin can be performed at the discretion of the Investigator. During the treatment period, if total bilirubin is normal, direct and indirect bilirubin is not required. If total bilirubin is abnormal, then direct or indirect bilirubin is required.
b. 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.
c. INR and aPTT are required. PT may be omitted if not routinely performed by the clinical laboratory.
d. Hepatitis B surface antibody is optional.

10.8. Appendix 8: Prohibited and Restricted Medications and Therapies That Induce, Inhibit, or Are Substrates of CYP3A4/5

Lazertinib is considered unlikely to cause clinically significant drug interactions through induction or inhibition of cytochrome P450 (CYP) enzyme activity. Strong inducers of CYP3A4 may reduce the exposure of study drugs when concomitantly administered. Strong inducers of CYP3A4, including those listed below are prohibited and should be discontinued for an appropriate period before starting study treatment regimens that include lazertinib or osimertinib.

Although the potential effect of CYP3A4/5 inhibition on exposure is thought to be low at clinically relevant concentrations, to ensure patient safety, medications with known strong inhibitory effects are restricted but can be used with caution when there is no alternative. Use of medications that are substrates of CYP3A4/5 or CYP1A2 is also restricted and should be avoided, when possible, or used with caution. These restricted substances should be identified during screening and discontinued for an appropriate period before starting study treatment. They may then be restarted as appropriate and used with caution once study treatment has been started.

Listing of Prohibited Medications and Therapies That Are Strong Inducers of CYP3A4/5

Prohibited Medications	Withdrawal Period Before Starting Study Treatment
Medications Inducing CYP3A4/5	
Phenytoin, rifampicin, St. John's Wort, carbamazepine, primidone, griseofulvin, barbiturates, troglitazone, pioglitazone, oxcarbazepine, nevirapine, efavirenz, rifabutin	3 weeks
Phenobarbitone	5 weeks

Listing of Restricted Medications and Therapies That Are Strong Inhibitors of CYP3A4/5 or Substrates of CYP3A4/5 or CYP1A2

Restricted Medications	Withdrawal Period Before Starting Study Treatment
Medications Inhibiting CYP3A4/5	
Ketoconazole, itraconazole, indinavir, saquinavir, nelfinavir, atazanavir, amprenavir, fosamprenavir, troleandomycin, telithromycin, fluconazole, nefazodone, cimetidine, aprepitant, miconazole, fluvoxamine	1 week
Amiodarone	27 weeks
Erythromycin, clarithromycin, verapamil, ritonavir, diltiazem	2 weeks
Medications That Are Substrates of CYP3A4	
Abemaciclib, ABT-384, alfentanil, almorexant, alpha-dihydroergocryptine, atazanavir, avanafil, avapritinib, brecanavir, buspirone, casopitant, conivaptan, darifenacin, darunavir, dronedarone, ebastine, elvitegravir, everolimus, ibrutinib, ivacaftor, lomitapide, lopinavir, lovastatin, maraviroc, midazolam, midostaurin, naloxegol, nisoldipine, paritaprevir, saquinavir, simeprevir, simvastatin, sirolimus, tacrolimus, tilidine, tipranavir, triazolam, vardenafil, voclosporin, zanubrutinib	1 Day
Medications That Are Substrates of CYP1A2	
Agomelatine, alosetron, duloxetine, melatonin, pirfenidone, ramelteon, selegiline, tacrine, tasimelteon, tizanidine	1 Day

This listing is not intended to be exhaustive, and a similar restriction will apply to other agents known to strongly induce or inhibit CYP3A4/5 activity, or that are substrates of CYP3A4/5 or

CYP1A2. Appropriate medical judgment is required, and any of these medications should be utilized, if clinically indicated, for the treatment of adverse events. The Medical Monitor can be contacted with any questions.

10.9. Appendix 9: Substrates of P-glycoprotein (P-gp), multi-drug resistance protein 4 (MRP4), and Breast Cancer Resistance Protein (BCRP): Exercise Caution

Transporter	Substrates
P-gp	Dabigatran etexilate Digoxin Fexofenadine Loperamide Quinidine Talinolol Vinblastine
BCRP	Rosuvastatin Sulfasalazine Coumestrol Daidzein Dantrolene Estrone-3-sulfate Genistein Prazosin
MRP4	acyclovir ritonavir adefovir tenofovir furosemide, hydrochlorothiazide ceftizoxime cefazolin methotrexate 6-mercaptopurine, 6-thioguanine topotecan olmesartan para-methoxy-N-ethylamphetamine

Source: References[20,38]

10.10. Appendix 10: Liver Event Follow-Up and Rechallenge Criteria

Liver Event Follow-Up Requirements

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

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

Rechallenge Criteria

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

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

10.11. Appendix 11: Cockcroft-Gault Formula for Estimated Creatinine Clearance

Cockcroft-Gault Formula for Estimated Creatinine Clearance for Adults

$$eCrCl = \frac{(140 - Age) \times Mass\ (Kilograms) \times [0.85\ if\ female]}{72 \times Serum\ Creatinine\ (in\ mg/dL)}$$

OR

$$eCrCl = \frac{(140 - Age) \times Mass\ (Kilograms) \times Constant}{Serum\ Creatinine\ (in\ \mu mol/L)}$$

Where Constant 1.23 for men and 1.04 for women

Reference: http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

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

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

Medications known to prolong QT interval or induce Torsades de Pointes

Restricted drugs	**Washout period prior to study treatment**
anagrelide, ciprofloxacin, clarithromycin, cocaine (only medical use), domperidone, droperidol, erythromycin, ibutilide, levofloxacin, ondansetron, papaverine HCl (intra-coronary), procainamide, quinidine, sulpiride, sultopride, terlipressin, thioridazine	2 days
chlorpromazine, cilostazol, disopyramide, dofetilide, dronedarone, ibogaine, levosulpiride, moxifloxacin, sotalol	4 days
citalopram, escitalopram, flecainide, fluconazole, levomepromazine (ethotrimeprazine), roxithromycin, sevoflurane	1 week
methadone, pimozide, terodiline	2 weeks
azithromycin, donepezil, propofol	15 days
halofantrine, pentamidine	2 months
haloperidol	4 months
amiodarone, chloroquine	10 months

Medications that may prolong QT interval or induce Torsades de pointes

Restricted drugs	**Washout period prior to study treatment**
apomorphine, benperidol, clotiapine, dexmedetomidine, dolasetron, eliglustat, encorafenib, gemifloxacin, granisetron, hydrocodone-ER, isradipine, melperone, nicardipine, ofloxacin, oxytocin, perflutren lipid microspheres, pilsicainide, primaquine phosphate, prothipendyl, risperidone, saquinavir, telavancin, tetrabenazine, tiapride, tolterodine, tramadol, tropisetron, vardenafil	2 days
alfuzosin, clozapine, cyamemazine (cyamepromazine), deutetrabenazine, dextromethorphan/quinidine, ezogabine (retigabine), lacidipine, lopinavir/ritonavir, mifepristone, moexipril/HCTZ, pasireotide, perphenazine, promethazine, telithromycin, venlafaxine	4 days
asenapine, atomoxetine, betrixaban, felbamate, imipramine (melipramine), ketanserin, nortriptyline, paliperidone, pipamperone, trimipramine, valbenazine, zotepine, zuclopenthixol (zuclopentixol, oral)	1 week
buprenorphine, delamanid, desipramine, iloperidone, lithium, maprotiline, mirabegron, mirtazapine, palonosetron, rilpivirine, tacrolimus, tizanidine	2 weeks
aripiprazole, clomipramine, efavirenz, memantine	3 weeks
artemether/lumefantrine, sertindole	1 month
fingolimod, flupentixol, pimavanserin	1.5 months
zuclopenthixol (zuclopentixol, IM injection)	3.5 months
artenimol/piperaquine	6 months
clofazimine	12 months
nusinersen	15 months
bedaquiline	28 months

10.13. Appendix 13: Anticipated Events

An anticipated event is an adverse event (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 15 will be considered anticipated events: The review of anticipated events was stopped after the database lock associated with the primary endpoint of the study.

Table 15: 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

Reporting of Anticipated Events

All AEs will be recorded in the electronic case report form (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. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

Safety Assessment Committee (SAC)

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

The review of anticipated events was stopped after the database lock associated with the primary endpoint of the study..

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.

10.14. Appendix 14: Open-Label Extension Phase

The purpose of the OLE Phase is to collect data of clinical relevance/importance while reducing protocol-required visit procedures and assessments and the burden on participants after the primary PFS analysis and unblinding. Data collected during this phase will be limited to those procedures and assessments specified in Table 16.

The OLE Phase will begin after approval of Amendment 4 by health authorities of countries/territories in which this study is being conducted at the time of transition, and by study site ECs/IRBs.

During the OLE Phase:

- Participants in Arm A (amivantamab + lazertinib) will continue to receive the open-label study treatment they are currently receiving at the time of transition to the OLE Phase and until the discontinuation criteria described in Section 7.1 are met, or until the end of the OLE Phase and/or transition to the LTE Phase.
- Participants in Arm B (osimertinib) and Arm C (lazertinib) will continue to receive (in an unblinded manner) the study treatment they are currently receiving at the time of transition to the OLE Phase and until the discontinuation criteria described in Section 7.1 are met, or until the end of the OLE Phase and/or transition to the LTE Phase. Only active treatment will be provided. Placebo will not be provided.
- Participants who have already discontinued study treatment and are in the Follow-up Phase in the main study will continue Follow-up as specified in the Schedule of Activities for the OLE Phase (Table 16).

10.14.1. Eligibility Criteria

All participants who remain in the study are eligible to transfer to the OLE Phase. Informed consent must be obtained.

10.14.2. Study Treatment Administration

Study treatment should continue as specified in Section 6.1. In the OLE Phase, there will be no placebo. Osimertinib can be provided as either over-encapsulated or non-over-encapsulated active medication. Study Procedures

All participants in the OLE Phase should follow the Schedule of Activities for the OLE Phase (Table 16).

Laboratory tests should be conducted by a local laboratory as specified in the Schedule of Activities for the OLE Phase (Table 16). The investigator should review the laboratory report, document this review, record only clinically significant abnormalities or changes in the adverse event eCRF along with documentation of the corresponding laboratory value in the eCRF. Additional follow-up monitoring as specified in the Schedule of Activities in Table 16 should be performed. Pregnancy reporting should continue as described in Section 8.3.5. A positive pregnancy test should be reported via the adverse event/serious adverse event process (see

Section 8.3.5 and Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

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

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

- Dosing, including pre-infusion and post-infusion medications
- Investigator-assessed disease assessment by RECIST v1.1
- Tumor response by blinded independent central review (BICR) according to RECIST v1.1.
- Survival data
- Symptomatic progression (until final OS analysis)
- Subsequent anticancer therapy
- PROs (treatment phase: predose every 2 cycles continuing with the next odd-numbered cycle): EQ-5D-5L, EORT-QLQ-C30, NSCLC-SAQ, PGIS, and PGIC (continue for 1 year after end of treatment, reducing the data collection frequency from every 3 months to every 6 months after end of treatment
- All adverse events (including serious adverse events and adverse events of special interest)
- Laboratory test results related to adverse events
- Vital sign values related to adverse events and for Arm A, vitals related to amivantamab administration.
- Concomitant medications
- Biomarkers

Table 16: Schedule of Activities in the Open Label Extension Phase (All Arms, Unless Otherwise Indicated)

Phase		Treatment Phase	End of Treatment Visit[a]	Follow-Up (Visit or Call)
Study Procedure	**Comment**	**Subject Continuing on Previously Received Study Treatment on a 28 day cycle (±2days)**	**30 (±7) Days After Last Dose of Study Treatment**	**Q12 (±2) Weeks From the Last Dose of OLE Study Treatment**
Screening				
Informed consent (ICF)	All Subjects must sign the updated ICF.	X		
Hematology/Chemistry (Appendix 7)	Laboratory assessments must be reviewed by the Investigator prior to study treatment. Report only clinically significant abnormalities as adverse events, along with documentation of the corresponding abnormal lab in the eCRF.	X	X	
Pregnancy test	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).	X A serum or urine pregnancy test is required within 72 hours before the first dose of each treatment cycle. 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 center.	X A final pregnancy test, serum or urine, is required at the End of Treatment visit at least 30 days after the last dose of study treatment.	
Efficacy Assessments				
CT or MRI tumor imaging[b]		X		
Brain MRI[c]		X		
Symptomatic progression events		Collect continuously (including during the Follow up Phase)		
Survival/disease status				X
Subsequent anticancer therapy				X

Table 16: Schedule of Activities in the Open Label Extension Phase (All Arms, Unless Otherwise Indicated)

Phase		Treatment Phase	End of Treatment Visit[a]	Follow-Up (Visit or Call)
Study Procedure	**Comment**	**Subject Continuing on Previously Received Study Treatment on a 28 day cycle (±2days)**	**30 (±7) Days After Last Dose of Study Treatment**	**Q12 (±2) Weeks From the Last Dose of OLE Study Treatment**
Safety Assessments Report only clinically significant abnormalities as an adverse event in the eCRF.				
Vital signs[d]	Arm A: Days 1 and 15 ≤30 min before infusion of amivantamab, ~30 min intervals (±5 min) during each infusion, and at end of infusion (+5 min) All Arm A infusion administration vitals must be recorded in eCRF Arm B/C: Day 1 All non infusion vitals must be reviewed by the Investigator prior to study treatment. Report only clinically significant abnormalities as adverse events. along with documentation of the corresponding abnormal value in the eCRF.	X		
Physical examination Symptom directed exams[e]; Weight at Day 1 of each cycle	All Arms	X	X	
Adverse events (serious or non serious)		Collect continuously from ICF through 30 days after the last dose of study treatment (>30 days for a serious adverse event if considered related to study treatment)		
Concomitant medications		Collect continuously from ICF through 30 days after the last dose of study treatment (or start of subsequent anticancer therapy) Concomitant medications administered >30 days after the last dose of study treatment in conjunction with serious adverse events considered related to study treatment must continue to be collected until resolution of event or start of subsequent therapy.		
Study Treatment				
Arm A: IV amivantamab (open label)		X (on Days 1 and 15)		
Arm A: oral lazertinib (open label)[f]		X		
Arms B/C: oral osimertinib or lazertinib (open label)		X		
All arms: record oral study treatment compliance		X		
Patient-Reported Outcomes (Should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses)				
EQ 5D 5L, EORT QLQ C30, NSCLC SAQ (predose every 2 cycles continuing with the next odd numbered cycle)		X	X	X (up to 1 year after EOT)[g]
PGIS (predose every 2 cycles continuing with the next odd numbered cycle)		X	X	
PGIC (predose every 2 cycles continuing with the next odd numbered cycle)		X	X	

Table 16: Schedule of Activities in the Open Label Extension Phase (All Arms, Unless Otherwise Indicated)

Phase		Treatment Phase	End of Treatment Visit[a]	Follow-Up (Visit or Call)
Study Procedure	**Comment**	**Subject Continuing on Previously Received Study Treatment on a 28 day cycle (±2days)**	**30 (±7) Days After Last Dose of Study Treatment**	**Q12 (±2) Weeks From the Last Dose of OLE Study Treatment**
Biomarkers				
Tumor biopsy			Post progression biopsy, if medically feasible, within 30 days of PD; obtain before next anticancer therapy	
ctDNA (predose) Blood sample			Blood sample within 30 days of PD; obtain before next anticancer therapy	
ddPCR (predose) Blood sample (After C7, sample can be collected on day of disease assessment or with the next safety laboratory assessment.)		Collect at each disease assessment	Blood sample within 30 days of PD; obtain before next anticancer therapy	
Exploratory biomarkers Serum sample			X	

AE adverse event; BICR blinded independent central review; CT computerized tomography; D# Day #; eCRF electronic case report form; EORTC QLQ C30 European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EOT end of treatment; EQ 5D 5L EuroQol five dimensional descriptive system (5 level version); ICF informed consent form; IV intravenous; MRI magnetic resonance imaging; NSCLC SAQ Non Small Cell Lung Cancer Symptom Assessment Questionnaire; OLE open label extension; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; Q every; SAE serious adverse event; VTE venous thromboembolic.

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 anti cancer therapy is to be initiated.

b. CT/MRI tumor imaging: Disease assessment of the chest, abdomen, pelvis, and any other disease location every 8 weeks (±1 week) for the first 30 months and then 12 weeks (±1 week). Timing of imaging is relative to randomization. Continue imaging until disease progression is confirmed by BICR. Submit images to central vendor per Imaging Manual until BICR confirmed disease progression. For participants who discontinue treatment prior to disease progression, tumor imaging should continue until BICR confirmed disease progression. If participant begins a new cancer therapy before BICR confirmed disease progression, obtain tumor imaging before the new therapy. If a participant receives study treatment beyond disease progression, continue disease assessments as per the schedule of assessments. See Section 8.1.1 for further details.

c. Brain MRI: Participants with a history of brain metastasis at Screening will undergo postbaseline brain MRI every 8 weeks (±1 week) for the first 30 months and then every 12 weeks (±1 week); participants with no history of brain metastasis at Screening will undergo postbaseline surveillance brain MRI every 24 weeks (±1 week). Timing is relative to randomization. Continue imaging until disease progression is confirmed by BICR. Submit images to central vendor per Imaging Manual until BICR confirmed disease progression. For participants who discontinue treatment prior to disease progression, tumor imaging should continue until BICR confirmed disease progression. If participant begins a new cancer therapy before BICR confirmed disease progression, obtain tumor imaging before the new therapy. If a participant receives study treatment beyond disease progression, continue disease assessments as per the schedule of assessments. Repeat imaging can be obtained at any time as clinically indicated. See Section 8.1.1 for further details.

d. Vital signs include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation.

e. Evaluate for early signs and symptoms of VTE. A focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed.

f. Study participants who permanently discontinue amivantamab and continue open label lazertinib can follow the visit schedule for Arms B/C.

g. Continue data collection for 1 year after end of treatment, reducing data collection frequency from every 3 months to every 6 months.

10.15. Appendix 15: Long-Term Extension Phase

The purpose of the LTE Phase is to continue providing participants access to study treatment while further reducing protocol-required visit procedures and assessments, and burden on participants after the final analysis for overall survival is complete. Investigators should monitor and assess each participant's disease status (response, progression, survival) and safety according to routine standard practice and local label requirements. The LTE Phase will begin after the final analysis for overall survival and will continue until the discontinuation criteria described in Section 7.1 are met, or until 4 years after local marketing authorization is obtained for the studied indication, whichever occurs first. After notification from the sponsor, participants that remain in the study at the conclusion of the OLE Phase will be provided with the option to transfer to 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 serious adverse event 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 serious adverse events are planned for the LTE Phase.

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

Participants entering the LTE Phase will continue to receive the study treatment they were receiving at the end of the OLE Phase. The sponsor will continue to provide study drugs until the discontinuation criteria described in Section 7.1 are met, or until 4 years after local marketing authorization is obtained for the studied indication, whichever occurs first. Study treatment dispensation and accountability will be performed via IWRS.

10.15.1. Eligibility Criteria

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

10.15.2. Study Treatment Administration

Study treatment should continue as specified in Section 6. In the LTE Phase, osimertinib can be provided as either over-encapsulated or non-over-encapsulated active medication. There will be no placebo.

10.15.3. Study Procedures

All participants in the LTE Phase should follow the Schedule of Activities for the LTE Phase (Table 17).

Participants in the LTE Phase should be followed up for disease assessment and safety per local practice and follow the local label(s). No efficacy data will be collected. Only serious adverse events will be collected via the serious adverse event form per the serious adverse event 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. Other procedures and safety

assessments may be performed per local practice.

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

Table 17: 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)
Study Procedure	**Comment**	**Subject Continuing on Previously Received Study Treatment on a 28 day cycle (±2days)**	**30 (±7) Days After Last Dose of Study Treatment**	**Q12 (±2) Weeks From the Last Dose of LTE Study Treatment**
Pregnancy test	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).	X As clinically indicated, according to local regulation requirements, or following the local practice of the center.	X	
Efficacy Assessments: All participants continuing in the LTE Phase should be followed up for disease assessment per the local practice and following the local label(s).				
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).				
Adverse events (serious)	Collect continuously from ICF through 30 days after the last dose of study treatment (>30 days for a serious adverse event if considered related to study treatment)			
Study Treatment				
Arm A: IV amivantamab (open label)		X (on Days 1 and 15)		
Arm A: oral lazertinib (open label)[b]		X		
Arms B/C: oral osimertinib or lazertinib (open label)		X		
All arms: record oral study treatment compliance		X		

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 anti cancer therapy is to be initiated.

b. Study participants who permanently discontinue amivantamab and continue open label lazertinib can follow the visit schedule for Arms B/C.

10.16. Appendix 16: Protocol Amendment History

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

Amendment 3 (22 August 2022)

Overall Rationale for the Amendment: To implement the adverse event of special interest of venous thromboembolic (VTE) events, as well as associated measures for monitoring and prophylaxis of these events, and to align the protocol with the information provided in Investigator's Brochure for the safety of the participants. This amendment also serves to provide clarity on the schedule of assessments and visits, timing of pharmacokinetic (PK) sampling, the reporting of symptomatic progression during the follow up period, and the documentation of ophthalmology examination results and how to report overdose in the electronic case report form (eCRF).

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (Table 1)	Added notes in computerized tomography (CT) or magnetic resonance imaging (MRI) tumor imaging and brain MRI to indicate that images should be submitted to central vendor per Imaging Manual until blinded independent central review (BICR) confirmed disease progression. Text was added to clarify that if the participant begins a new cancer therapy before BICR disease progression, tumor imaging should be obtained before the new therapy and if a participant receives study treatment beyond disease progression, disease assessments should be continued as scheduled.	To clarify the information about timing of imaging and submission to central vendor.
4.1.3. Follow-up Phase	Added a note that tumor imaging should continue per schedule of activities until PD is confirmed by BICR review for participants who discontinue study treatment prior to BICR confirmed disease progression.	
1.3. Schedule of Activities (Table 1)	Cells were merged to remove the text that the follow-up visit or call for CT or MRI tumor imaging and brain MRI at Q12W applies only to participants who discontinue study treatment and have not had radiographic progression confirmed by BICR. Corresponding footnote c was deleted.	To clarify the information about the follow-up visits for CT or MRI tumor imaging and brain MRI.
	In study treatment Arm A: oral lazertinib, a new footnote e was added to indicate that study participants who permanently discontinue amivantamab and continue open label lazertinib can follow the visit schedule for Arms B/C if the discontinuation occurs after Cycle 1.	To provide clarification on visit schedule for the participants who permanently discontinue amivantamab and continue lazertinib.
1.3. Schedule of Activities (Table 2)	Footnote d was edited as 'If an amivantamab dose is skipped on a visit where PK collection was required, the pre-dose sample should be collected. When amivantamab is restarted, the pre and postdose/postinfusion sampling should occur at the next dose administration. Subsequent PK sampling should occur per Schedule of Activities (SoA)'.	To provide clarification on collection of sample for PK when an amivantamab dose is skipped.

Section Number and Name	Description of Change	Brief Rationale
	A new footnote e was added stating with the exception of the end-of-treatment pregnancy test for women 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 anti-cancer therapy is to be initiated.	To provide more clarity and for consistency about the end of treatment procedures.
1.3. Schedule of Activities (Table 1)	Row and a footnote d added for prophylactic-dose anticoagulation during the first 4 months of treatment.	To implement the adverse event of special interest of VTE events, as well as associated measures for monitoring and prophylaxis of these events.
2.6.1. Risks for Study Participation; 8.3.7. Adverse Events of Special Interest	Text was updated to include VTE events, a new adverse event of special interest and other adverse events which require specific management guidelines.	
2.6.3. Benefit-Risk Assessment for Study Participation	Text was updated to include information about Independent Data Monitoring Committee (IDMC), who have reviewed both the unblinded safety and efficacy data of 1038 randomized participants on the study and confirmed a favorable risk-benefit assessments, therefore recommended continuation of the study conduct. In addition, the text was also added to mitigate an observed increase in VTE events in Arm A.	
6.6.1. Withholding Treatment	In Table 7 and Table 8, a new footnote d was added to provide dosing guidance for VTE events.	
6.6.3.12. Venous Thromboembolic Events	A new section was added to provide guidance on management of VTE events.	
8.2.1. Physical Examinations; 1.3. Schedule of Activities (Table 1)	A new footnote c to Table 1 was added to include VTE related text and text related to additional guidance was added for detection of VTE through physical examination.	
11. References	References added for VTE text.	
4.1.2. Treatment Phase	Text in bold was added and strikethrough was deleted Continuation of study treatment after disease progression **is** ~~may be~~ allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believes the participant is deriving clinical benefit.	To provide clarification on study treatment administration and associated visits and procedures.
4.1.2. Treatment Phase	Text was added to indicate that the participants continuing treatment after progression will continue within the Treatment phase of the study and comply with associated visits and procedures, including scheduled disease assessments, until the termination of study treatment.	
4.2. Scientific Rationale for Study Design	Text was updated to indicate that the pharmacogenomic samples will be collected to test for null or non-null glutathione S-transferase Mu-1 (GSTM-1) genotype for participants in Arm A on Cycle 1 Day 1.	To align the text with Schedule of Activities.

Section Number and Name	Description of Change	Brief Rationale
6.1.1. Amivantamab	Text was added to indicate that skipped doses should be avoided when feasible.	To provide insight into the approach for amivantamab dose skipping.
6.6.1. Withholding Treatment	Text in bold was added and strikethrough was deleted If study treatment is withheld for more than 28 days, **consider a dose reduction per Table 9 or 10 when** ~~consult with the Medical Monitor before~~ restarting study treatment. In general, if both are to be continued, lazertinib should be restarted **at least 7-14 days** prior to the next infusion of amivantamab **to ensure stability on monotherapy,** ~~or consult with the Medical Monitor.~~	To provide clarity on how doses should be held or modified in the case of adverse events.
	In Table 7, 'If 2 consecutive doses of amivantamab are withheld, consult the Medical Monitor before restarting' was deleted for Grade 2 events. In Table 7 and Table 8, a new footnote d added also included text to specify that study treatment initially held for stable, treated pulmonary embolism and deep vein thrombosis ≤Grade 3 can be resumed at the discretion of the investigator.	
6.6.2 Dose Reduction	Text in strikethrough was deleted. Amivantamab may be restarted, ~~after consultation with the Medical Monitor,~~ if the symptoms have improved and treatment with the combination is thought to be in the participant's best interest**. If 2 consecutive doses of amivantamab are withheld, please consult the medical monitor.** Re-escalation of study treatment after a ~~prior~~ dose reduction is allowed if determined to be in the best interest of the participant ~~after consultation with the Medical Monitor~~.	
6.6.3.2. Rash-Related Adverse Events	Dose adjustment and management of severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis was added to Table 12. Grade 3 and Grade 4 rash events were segregated and discontinuation of amivantamab for Grade 4 rash was added. Footnote b was updated to indicate that if amivantamab must be withheld due to toxicity for 2 consecutive doses, the Medical Monitor should be consulted before restarting for infusion guidance.	To clarify for safety of the participants.
7.1. Discontinuation of Study Treatment; 8.1.1. Disease Assessments	Text in bold was added and strikethrough was deleted. Participants who discontinue study treatment for any reason should have the End of Treatment assessments, document any subsequent therapy in the electronic data capture (eDC) and continue to be	To avoid redundant text

Section Number and Name	Description of Change	Brief Rationale
	followed up ~~for survival every 12 weeks (±14 days) and symptomatic progression~~ in accordance with the Follow-up phase.	
	Text was added to indicate that the participant's study treatment should be discontinued in case of disease progression that requires a new systemic anti-cancer treatment at the discretion of the treating investigator.	To clarify for the safety of participants and align with clinical practice.
8.1.1. Disease Assessments	Text in bold was added and strikethrough was deleted. Participants with contraindications to intravenous (IV) CT and MRI contrast may be able to undergo non-IV contrast CT exams of the chest abdomen and pelvis **with proper documentation of medical contraindication** ~~after consultation with the Medical Monitor.~~ Contraindications to the CT scan with IV contrast that develop postbaseline require **investigator discretion** ~~consultation with the Medical Monitor.~~	To provide guidance on the management of participants who develop a contraindication to IV contrast while on study.
8.1.2. Symptomatic Progression	Text was updated to indicate that if symptomatic progression is not reported prior to treatment discontinuation, continued assessment is required during the follow up period even after subsequent therapy is initiated.	To clarify about assessments required in participants with no symptomatic progression prior to treatment discontinuation.
8.2.5. Ophthalmologic Assessment	Text was updated to indicate that ophthalmology examination results should be recorded on the procedures page in the database.	To provide clarification on data entry practices.
8.4 Treatment of Overdose	Text was updated to indicate that the quantity of the excess dose as well as the duration of the overdosing should be documented in the **study drug administration** eCRF.	
Section 10.10 Appendix 10: Liver Event Follow-up and Rechallenge Criteria	Text was updated indicate that blood samples for unscheduled PK analysis at timepoints when liver chemistry is assessed should be drawn **for Arm A participants.**	To limit blood sampling to Arm A participants.
Throughout the protocol	Minor formatting changes were made.	Minor errors were noted.

Amendment 2 (23 September 2021)

Overall Rationale for the Amendment: To provide clarity on tumor imaging and brain imaging assessments, provide additional information on amivantamab infusion, provide additional information on infusion-related reactions, add information for paresthesia management, provide revised guidance on initiation and course of corticosteroid therapy for Grades 2 to 4 pneumonitis, provide clarity on computed tomography (CT) and magnetic resonance imaging (MRI) assessments required at end of treatment, and align with the latest protocol template.

The new text is captured in **bold text**, and deleted text as strike-through, wherever applicable.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis (Study Treatment Groups and Duration); 4.1.2. Treatment Phase	The term 'radiographic' was deleted with respect to disease progression.	To provide clarity that progression is not limited to imaging.
1.3. Schedule of Activities (Table 1)	• Deleted the following statement from CT or MRI tumor imaging assessment: If participant begins a new cancer therapy before disease progression, obtain tumor imaging before the new therapy. • Clarified that disease assessment should be performed until disease progression is confirmed by blinded independent central review (BICR). • Indicated that CT or MRI imaging assessment and brain MRI assessment should be performed in follow-up phase. • The following footnote c was added in Table 1: Only applies to participants who discontinue study treatment and have not had radiographic disease progression confirmed by BICR.	To provide clarity on tumor imaging and brain imaging assessments.
	Added full term of BICR in Table 1 footnote.	To define the full term of abbreviation mentioned in Table 1.
	Added reference to Section 8.1.1. to CT or MRI tumor imaging and brain MRI assessment.	To provide additional information.
	The phrase 'collect continuously from randomization (including during the Follow-up Phase)' was replaced with 'X' under the treatment column of Table 1 and the phrase was mentioned along with the assessment (of symptomatic progression events).	To provide clarity, phrase moved to different column in Table 1.
	The following statement was modified for prestudy and concomitant medications as: Collect continuously from ICF through 30 days after the last dose of study treatment (or start of subsequent anticancer therapy)**.**~~, if earlier~~ **Concomitant medications administered** >30 days after the last dose of study treatment in conjunction with serious adverse events considered related to study treatment~~,~~ **must continue to be collected** until resolution of event or start of subsequent therapy).	To provide clarity on collection of concomitant medications.
	The following text was modified from 'X (x4 visits/calls)' to 'X (Up to 1 year after EOT)' for EuroQol five-dimensional descriptive system (5-level version), European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30, Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire outcomes at follow-up visit.	To indicate that patient reported outcomes should be collected up to 1 year after EOT.
1.3. Schedule of Activities (Table 2 - Footnote d)	The following footnote was added: Contact the Medical Monitor for pharmacokinetic guidance if treatment is held.	To clarify the timing for pharmacokinetic (PK) sample collection.
2.4. Amivantamab and Lazertinib Combination	The following text was modified as : After ~~7~~ **18** months of follow-up, the median duration of response was not estimable **with 16 of 20 subjects remaining on therapy without progression**.	To clarify the duration and subject count with which the median duration of response was not estimable.

Section Number and Name	Description of Change	Brief Rationale
4.1.2. Treatment Phase	Specified that study treatment should be continued until documented disease progression is confirmed by BICR.	To provide clarity on continuation of study treatment in case of disease progression.
5.1. Inclusion Criteria (#11)	The criterion was modified to include 'Of child-bearing potential and practicing true abstinence during the entire period of the study, including up to 6 months after the last dose of study treatment is given'.T	To align with the study requirement.
5.2. Exclusion Criteria (#1)	The following criteria was modified as: Participant has received any prior systemic treatment **at any time** for locally advanced **Stage III** or metastatic **Stage IV** disease (adjuvant or neoadjuvant therapy for ~~early stage~~ **Stage I or II** disease is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease.	To specify the exact disease stage for participant selection.
6.1. Study Treatments Administered	The following text was added: All cycles are 28 days and each study visit must be scheduled based on date of Cycle 1 Day 1. The site should not re-adjust visit schedule based on treatment interruptions or delays.	To provide guidance on study cycle duration and visit scheduling.
6.1.1. Amivantamab	• Added that the infusion rate of amivantamab can be slower but not faster than specified in the investigational product preparation instructions (IPPI) at the discretion of the investigator. • Specified that amivantamab must be administered as described in the IPPI; deleted the term 'prior to infusion'. • Added the following text: The administration set IV line will be primed with diluent prior to the initiation of each IV bag of diluted amivantamab as described in the IPPI.	To provide additional information on amivantamab infusion.
6.2. Preparation/ Handling/Storage/ Accountability	Added the term 'study treatment' in the following statement as follows: Study treatment must be handled in strict accordance with the protocol and the container label, and **study treatment** must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions.	To provide clarity as the statement seemed incomplete.
6.3. Measures to Minimize Bias: Randomization and Blinding	The following statement was added: Participants who have undergone treatment for metastatic brain lesions, including a complete resection must be stratified as brain metastasis present.	To define the participants with presence of brain metastasis.
6.5.2. Amivantamab Pre-infusion and Post-infusion Medications (Table 5)	Replaced 'Optional Pre-Infusion Medications' with 'Optional Additional Pre-Infusion Medications'.	To indicate the optional pre-infusion medications as supplementary to required medications.
	Separated and indicated intravenous (IV) and oral route of administration against corresponding dosing windows.	To provide better clarity.
6.5.2. Amivantamab Pre-infusion and Post-infusion	The footnote f was modified as follows: Optional Pre-Infusion glucocorticoid may be administered by IV **push** or oral route.	To clarify that method of administration should not be

Section Number and Name	Description of Change	Brief Rationale
Medications (Table 5-footnote f)		an IV infusion but an IV push.
6.5.2. Amivantamab Pre-infusion and Post-infusion Medications (Table 6)	Added 'or equivalent' alongside paracetamol.	To expand the optional post-infusion medication dose of antipyretic.
6.6.1. Withholding Treatment	Added the term 'clinically significant' for Grade 3 or higher toxicity.	To indicate an exception for hematologic Grade 3 toxicities.
6.6.1. Withholding Treatment	Included 'rash' and reference to 'Section 6.6.3.2' in addition to reference for guidance of IRR management.	To indicate section reference for rash management.
6.6.1. Withholding Treatment (Table 7 and Table 8)	Specified considering dose reduction in case of Grade 2 toxicities witnessed in Arms A, B, and C.	To allow participants to start treatment at a reduced dose.
6.6.2. Dose Reduction	• Specified that lazertinib can be preferentially reduced if toxicity is considered related to lazertinib alone. A footnote 'a' explaining the same was added in Table 9. • Specified that escalation of lazertinib dose is applicable for Arm A. • Added the term 'Recommended' in Table 9 title.	To allow flexibility in dosing if toxicity is experienced.
6.6.3. Dose Modifications and Management of Specific Adverse Events	Added reference to Tables 7, 8, 9, and 10 for dose modifications in case of toxicities defined in Section 6.6.3.	To cross refer to tables for dose modifications for toxicities.
6.6.3.1. Infusion-Related Reactions (Arm A only) – Table 11	Added that guidance for Grade 2 interruptions should be followed if infusion is interrupted for Grade 1 infusion-related reactions.	To provide guidance in case of infusion interruption.
	Added 'H1 and H2 antagonist and antiemetic' to the list of medications for Grade 2 infusion-related reactions.	To provide additional medications.
	Specified that participant with Grade 4 infusion-related reaction should not be re-challenged.	To exclude the participant with Grade 4 infusion-related reaction.
6.6.3.2. Rash-Related Adverse Events	The following modifications were made: …~~either~~ **both** a topical antibiotic (clindamycin, mupirocin, or fusidic acid) on sun exposed skin, ~~or~~ **and** an oral antibiotic…	To indicate that oral antibiotic should be strongly considered as prophylaxis.
	Added the term 'strongly'.	To indicate that consultation with dermatologist should be a must in case of Grade 3 rash or Grade 2 rash which does not improve within 2 weeks.
	The following text was modified as: After the rash is controlled, consider ~~gradually tapering the antibiotic~~ **de-escalating broad spectrum antibiotic and continuing or resuming prophylactic antibiotics.**	To clearly indicate the steps to be performed after the rash is controlled.
	Added reference to Table 7 and Table 9.	To provide clarity to the sites.
	Added 'or consider dose reduction' for Grade 2 rash.	To clarify that study treatment dose can be reduced in case of Grade 2 rash.

Section Number and Name	Description of Change	Brief Rationale
	Changed the duration of rash reassessment in Table 12 from 'after 2 weeks' to 'weekly' for Grade 3 or 4 rash.	To increase the frequency of rash assessment for Grade 3 or 4 rash.
	Added the following treatment options for atypical scalp rash and associated infection, • Topical Acetic acid 0.25% solution irrigation • Fluocinonide 0.05% lotion.	To include additional treatment options for atypical scalp rash and associated infection.
6.6.3.6. Pulmonary Toxicity	Information on suspected pulmonary toxicity was updated.	To maintain consistency in prevention, monitoring, and management of pulmonary toxicity guidelines across program-wide protocols.
	The following text was added: 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.	To provide revised guidance on initiation and course of corticosteroid therapy for Grades 2 to 4 pneumonitis.
6.6.3.11. Paresthesia	A section on dose modification and management of paresthesia was added.	To provide guidance on management of paresthesia.
7.1. Discontinuation of Study Treatment	• Deleted the statements pertaining to end of treatment assessments in case of treatment discontinuation. • Added reference to section for guidance on study drug discontinuation. • Added the following statement: Participants who discontinue study treatment for any reason should have the End of Treatment assessments and continue to be followed up for survival every 12 weeks (±14 days) and symptomatic progression in accordance with the Follow-up phase (Section 4.1.3).	To provide clarity on assessments required at end of treatment.
8.1.1. Disease Assessments	The following statement was modified as follows: Post randomization disease assessments will occur every 8 weeks (±1 week) for the first 30 months, and then every 12 weeks (±1 week) **relative to randomization** until disease progression **is confirmed by BICR, even if a participant discontinues treatment prior to progression or receives another systemic anti-cancer therapy.**	To clarify the period and condition for performing post-randomization disease assessments.
	• Added information related to requirement of CT and MRI examinations. • Section was modified to include requirements and period for performing disease assessments.	To provide clarity on assessments required in the study.
8.1.2. Symptomatic Progression	The following text was added: If symptomatic progression is not reported prior to treatment discontinuation, continued assessment is required even after subsequent therapy is initiated.	To clarify the requirement of continued assessment when symptomatic progression is not reported.
9.4.3. Secondary Endpoints	Added reporting timing for symptomatic progression.	To further clarify that participants don't need to have radiographic progression in order to report symptomatic progression.

Section Number and Name	Description of Change	Brief Rationale
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Bilateral tubal ligation was added to the list of permitted contraceptives and the bullet was modified as follows: **Tubal closure** (**eg,** bilateral tubal occlusion, **bilateral tubal ligation**).	To align with the recommendation from the Women's Health Group and updates in the latest protocol template.
10.7. Appendix 7: Clinical Laboratory Tests	Corrected 'direct and direct bilirubin' to 'direct and **in**direct bilirubin' in footnote a.	To rectify the error.
Throughout the protocol	Minor formatting changes were made.	Minor errors were noted.

Amendment 1 (22 April 2021)

Overall Rationale for the Amendment: The overall rationale for this amendment is to make clarifications to study procedures based on investigator and health authority feedback.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities – Table 1	End of Treatment Visit: Footnote b was added. The With the exception of pregnancy testing, the End-of-Treatment Visit assessments may be performed less than 30 days after last dose of study treatment if subsequent anticancer therapy is planned before then.	To limit the confounding of treatment effects potentially introduced by subsequent anticancer therapy, and to allow flexibility in study conduct.
	Pregnancy test: Serum pregnancy testing is required at Screening and within 72 hours before the first dose of Cycle 1. Pregnancy testing (serum or urine) is required within 72 hours before the first dose of each subsequent treatment cycle (previously only required per local regulation). Text was added to reiterate that a final serum or urine pregnancy test is required as part of the End of Treatment Visit at least 30 days after the last dose of study treatment.	Requirements for pregnancy testing were clarified to reduce the possibility that pregnant women receive study treatment and to ensure that pregnancy is detected in women who received treatment.
5.1. Inclusion Criteria	Criterion 10 was revised to: 1) Remove urine pregnancy test as an option for the Screening test and test 72 hours before the first dose of study treatment; 2) Add that participants must agree to additional pregnancy testing during the study.	To help ensure only the intended target population is enrolled. Tightening pregnancy testing requirements further limits the possibility that pregnant women may be exposed to study treatment.
	Criterion 11b was revised to specify that women of childbearing potential must be practicing 2 methods of contraception, one of which must be a highly effective user independent method. Previously, 2 methods of highly effective contraception were required. Reference to abstinence and a vasectomized partner were deleted.	To clarify the requirement for contraception and reduce the burden on participants regarding use of highly effective methods of contraception. Deleted reference to abstinence and vasectomized subjects was redundant with Appendix 4.
10.4, Appendix 4, Contraceptive Guidance	Text was revised for women who gain childbearing potential during the study to require that they begin contraception with 2 methods of contraception, including 1 highly effective method.	To align text with requirements for contraception described in Inclusion Criterion 11b.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities – Table 1	ECHO or MUGA: Timeframe for collection (up to 72 hours prior to study visit) was added.	To provide flexibility and help ensure compliance with required study procedures.
	Randomization: start study treatment within 3 days or 72 hours of randomization.	To help ensure compliance with required study procedures by quantifying the amount of time that can elapse between randomization and C1D1.
	ddPCR: Text was added: (After C7, sample can be collected on day of disease assessment or with the next safety laboratory assessment.)	To help ensure compliance with required study procedures by allowing flexibility in sample collection, which may increase the number of participants with samples for analysis.
1.3. Schedule of Activities – Table 1; 8.6. Pharmacogenomics	Pharmacogenomic testing for GSTM-1: Text was added that assessment is only for Arm A and specifies that the sample must be collected on C1D1. Text stating that samples may be collected anytime during the study was deleted.	To reduce blood collection for participants who are not subsequently randomized to Arm A.
1.3. Schedule of Activities – Table 1; 6.6.1. Withholding Treatment	For Arm A: IV amivantamab, text was added that starting with C2, infusions delayed >7 days cannot be made up. The delayed dose should be skipped, and the participant dosed at the next scheduled visit.	To reduce the possibility that consecutive doses of amivantamab are administered <7 days apart.
1.3. Schedule of Activities – Table 2	Text was added for amivantamab serum PK sample collection that the end of infusion sample occurs within a 0-15 min window.	Specific collection window may limit error in PK analysis.
	Footnote “a” regarding PK sample collection for lazertinib at 4h postdose was expanded to state that if amivantamab infusion goes beyond 5 hours, then the lazertinib 4h postdose sample should still be collected within the 3-5h window.	Additional guidance on sample collection requirements may limit error in PK analysis.
1.3. Schedule of Activities – Table 2 (footnote “c”) 8.5.1. Evaluations	Text was added to specify that post-infusion PK blood samples should not be collected from the same extremity in which the amivantamab infusion was administered.	To help ensure that PK blood samples accurately reflect circulating amivantamab levels.
6.1.1. Amivantamab	Text was added to clarify that amivantamab dose is based on the participant’s body weight at Screening and will remain the same for the duration of treatment.	Reducing intra-participant variability in amivantamab exposure may improve assessment of treatment effect.
5.1. Inclusion Criteria	Criterion 2 was revised to require that participants have newly diagnosed, locally advanced or metastatic NSCLC that is treatment naïve and not amenable to curative therapy that includes surgical resection or chemoradiation.	Detail added to help ensure that only the intended study population is enrolled.
	Criterion 3 was revised to clarify that EGFR mutation must be demonstrated in tumor meeting the criteria described in Inclusion Criterion no. 2. Text made redundant following revision to Inclusion Criterion no. 2 was deleted.	To help ensure only the intended target population is enrolled by clarifying that assessment reflects participants’ current disease state.

Section Number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Criterion 4 was revised to clarify that submission of tissue from tumor meeting criteria described in Inclusion Criterion no. 2 is mandatory. Text made redundant following revision to Inclusion Criterion no. 2 was deleted.	To help ensure only the intended target population is enrolled by clarifying that assessment reflects participants' current disease state.
	Criterion 7 was revised to: 1) Require creatinine clearance measurement >45 mL/min (units corrected) for all participants (bullet 6); 2) Add a requirement for urine culture to rule out urinary tract infection for participants with urinalysis positive for bacteria and leukocytes (bullet 7).	To help ensure only the intended target population is enrolled by clarifying requirements for demonstration of adequate organ function.
5.2. Exclusion Criteria	Criterion 1 was revised to clarify that prior adjuvant or neoadjuvant therapy must have been administered for early stage disease.	To help ensure only the intended target population is enrolled.
	Criterion 2 was revised to clarify that assessment of participants with brain metastases will occur at the time of randomization, not Screening.	To help ensure only the intended target population is enrolled. Assessment closer to the start of treatment allows for a more accurate description of participants' baseline disease characteristics.
	Criterion 4 was revised to specify that participants with untreated spinal cord compression are excluded and to describe requirements for participants with prior definitive surgery or radiation treatment and stable neurologic status.	To help ensure only the intended target population is enrolled.
	Criterion 7 was revised to limit exclusions for ophthalmologic conditions to those that are clinically unstable (bullet 7).	To help ensure only the intended target population is enrolled.
	Criterion 8 was revised to add that both prior and concurrent malignancy is exclusionary. Consultation with the Medical Monitor was added as a requirement before the criterion can be satisfied by any of the specified exceptions. Exception "e" pertaining to breast cancer was revised to clarify that lobular carcinoma in situ or ductal carcinoma in situ must be considered completely cured. History of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence was removed as an exception. Exception "f" was revised to require that the participant has undergone curative therapy and is considered cured after 5 years with no evidence of recurrence since initiation of that therapy.	To help ensure only the intended target population is enrolled.
	Criterion 9 was revised to: 1) clarify the meaning of non-exclusionary thrombosis (bullet 1); 2) clarify that pericardial effusion considered due to the disease under study is not exclusionary if clinically stable at Screening (bullet 6); 3) set the lower limit for LVEF at <50% or below the LLN per institutional guidelines (bullet 7).	To help ensure only the intended target population is enrolled.

Section Number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Criterion 11 was revised to delete reference to CYP3A4/5 inhibitors for consistency with changes to Appendix 8.	To help protect participant safety by aligning study conduct with current understanding of the interaction between study treatment and potential concomitant medication.
	Criterion 19 was revised to: 1) remove reference to general anesthesia as an example characteristic feature of major surgery; 2) move the assessment of traumatic injury status from the time the ICF is signed to randomization.	To help ensure only the intended target population is enrolled.
	The NOTE at the end of the section was revised to clarify that investigators must ensure that all participants continue to meet entry criteria through randomization.	To help ensure only the intended target population is randomized and receives study treatment.
10.8. Appendix 8: Prohibited and Restricted Medications	Guidance for the use of concomitant medications that induce, inhibit, or are substrates of CYP3A4/5 was revised. The listings of medications that induce or inhibit CYP3A4/5 were revised to identify prohibited and restricted medications.	To help protect participant safety by aligning study conduct with current understanding of the interaction between study treatment and potential concomitant medication.
6.5.4. Prohibited or Restricted Medications and Therapies 6.6.3.9. Diarrhea	Clarification was added that strong inhibitors of CYP3A4 are restricted and should be avoided, when possible, or used with caution.	To help protect participant safety by aligning study conduct with current understanding of the interaction between study treatment and potential concomitant medication.
6.6.3.8. Liver Chemistry Abnormalities	Item b) was revised. Elevations of ALT or AST ≥3x (for participants with baseline values in the normal range) with other symptoms suggestive of drug induced liver injury, including new onset eosinophilia (>5%), should be reported as serious adverse events.	To improve guidance for reporting of hepatic serious adverse events.
6.5.2. Amivantamab Pre-infusion and Post-infusion Medications	Table 5, footnotes d, e, and f were added, and the Route of Administration column revised for required and optional pre-infusion medications.	Guidance was added to align with local practice and local availability of pre-infusion medications.
6.5.3.2. Radiotherapy	Text was added to provide guidance for study treatment interruption and scheduling of radiotherapy relative to study treatment.	Guidance was added to minimize interruption of study treatment for participants requiring concomitant radiotherapy.
6.5.3.1. Supportive Care	The section heading changed from “Symptomatic Treatment” to “Supportive Care”. Osteoclast inhibitors were added to the examples of supportive care. Reference to concomitant medications for the symptomatic treatment of related toxicities was deleted.	Indication for supportive care may extend beyond management of treatment-related toxicities.
6.6.1. Withholding Treatment 6.6.2. Dose Reduction	Guidance for restarting study treatment at the current dose level was changed to be based on withheld study treatment up to 28 days for all arms (previously 21 days for Arms B and C).	To facilitate study conduct by aligning dose withholding guidance for all arms.

Section Number and Name	Description of Change	Brief Rationale
6.6.1. Withholding Treatment	Guidance for restarting both agents in Arm A was revised to require consultation with the Medical Monitor if both agents are to be restarted and if lazertinib is not planned to be restarted before amivantamab. Requirement for 7 days of lazertinib dosing before restarting amivantamab was deleted. Consultation with the Medical Monitor is required if amivantamab is withheld for 2 or more consecutive doses.	To ensure participant safety by clarifying guidance for restarting study drug in Arm A.
	Table 7, Table 8: The option to dose reduce study treatment was added for Grade 2 toxicities.	To provide investigators additional flexibility to adjust study treatment.
6.3. Measures to Minimize Bias: Randomization and Blinding	Text regarding recommended interaction between the investigator and sponsor before breaking the treatment code was deleted.	To facilitate study conduct by clarifying that the investigator alone is responsible for breaking the treatment code.
6.6.3.1. Infusion-Related Reactions (Arm A only)	Table 11: The third column heading was revised to reflect that the specified information includes premedication at subsequent dosing as well as other action to be taken.	Clarification of table content.
6.6.3.7. Cardiac Adverse Events	Expanded guidance was provided for retreatment at a reduced dose for instances of QTcF prolongation. Repeat triplicate ECG is required before restarting treatment. If retreatment is indicated, Arms B and C should be dose reduced to Dose Level 2, and lazertinib in Arm A should be dose reduced to Dose Level 3.	To facilitate study conduct by providing specific guidance for retreatment and to further protect participant safety.
7.1. Discontinuation of Study Treatment	Clarification was added that any of the listed reasons is sufficient to require discontinuation of study treatment. An additional reason for study treatment discontinuation based on investigator discretion was added (bullet 6).	To facilitate study conduct by clarifying guidance for treatment discontinuation.
8.7. Biomarkers (Mandatory Tumor Biopsy Sample for Central Mutation Analysis)	Text was revised to specify that the tumor tissue sample must be collected from the newly diagnosed, locally advanced or metastatic NSCLC tumor meeting criteria described in Inclusion Criterion no. 2 before randomization occurs. Previously, tissue could be obtained before start of treatment. Fine needle aspiration (FNA) was added as an unacceptable source of material for mutation testing.	To facilitate study conduct by clarifying requirements for collection of tissue samples.
10.12. Appendix 12: Medications With Potential for QT Interval Prolongation	Table headings were changed from “Contraindicated drugs” to "Restricted drugs” and from “Washout period prior to randomization” to “Washout period prior to study treatment”.	To facilitate study conduct by aligning the washout period for certain prestudy medications relative to study treatment.
6.6.1. Withholding Treatment	Clarification was added that all modifications, not only withheld doses, to study treatment should be recorded in the eCRF. Extraneous text related to withholding or discontinuing study treatment was deleted.	To facilitate study conduct by ensuring that all clinically relevant data are collected and to improve readability.
8.1.1. Disease Assessments	Reference to the latest Imaging Site Manual was added. Additional text was added to requirements for CT and MRI oral and IV contrast agents.	To facilitate study conduct by ensuring that diagnostic imaging assessments are adequate to evaluate study endpoints.

Section Number and Name	Description of Change	Brief Rationale
10.7. Appendix 7: Clinical Laboratory Tests	For Protocol-Required Safety Laboratory Assessments (Urinalysis) specific assays to be performed in case of abnormal dipstick results were deleted. Footnotes a-d were added to the table.	To allow flexibility and align procedures with local clinical laboratory practice.
2.3. Lazertinib: A Third-Generation EGFR TKI	Lazertinib safety data were updated per the current IB. Redundant text regarding drug related serious TEAEs was deleted, and reference to the current IB was added.	To direct readers to the latest source of background information and improve readability.
2.4. Amivantamab and Lazertinib Combination	Text was updated to present current information consistent with the updated IB and the new reference, Cho 2020.	To provide investigators with current information related to combination treatment.
9.3. Populations for Analyses Sets	The Patient Reported Outcomes population was deleted. Description of the Biomarker Population was modified so as not to require at least 1 disease assessment.	Patient reported outcomes analyses will use the Full Analysis Set, as for other efficacy endpoints. Not all biomarker analyses will require disease assessment.
6.7. Continued Access to Study Intervention	Section added to describe the sponsor's commitment to provide participants with continued access to investigational drug after study closure if it is found to be effective treatment.	To state the conditions for continued access to investigational treatment to be provided by the sponsor.
9.4.3. Secondary Endpoints; 9.4.6. Other Analyses (Patient-Reported Outcomes Analyses)	The description of Patient Reported Outcomes analyses for EORTC-QLQ-C30 and NSCLC-SAQ was moved from Section 9.4.6 to Section 9.4.3. The analysis population to be used was changed to the Full Analysis Population.	To position the description of patient-reported outcomes analyses with other secondary endpoints, as defined in study objectives.
10.2.3. Appendix 10: Informed Consent Process	Text describing a scenario when prior consent of the participant is not possible has been deleted.	The described situation is inappropriate for this study with a 28-day screening period.
3. Objectives and Endpoints	PK objectives were clarified to specify that plasma lazertinib concentrations and serum anti-amivantamab antibodies will be assessed.	Text aligned with planned PK and immunogenicity evaluations.
6.6.1. Withholding Treatment	Extraneous text related to withholding or discontinuing study treatment was deleted.	To improve readability.
11. References	Reference 4, Cho 2020, was added. In-text citations were updated accordingly.	To direct investigators to relevant emerging information.
	References to the amivantamab and lazertinib IBs were updated to the latest editions.	To direct readers to the latest source of background information.
COVID-19 Appendix	The stand-alone COVID-19 appendix was updated to Version 2. Text was added to specify that subjects will not be excluded from the study for having received non-live vaccines that are either approved or authorized for emergency use (eg, COVID-19) by local health authorities. The provision allowing remote consenting for study screening was deleted.	To provide additional guidance to investigators regarding COVID-19 vaccine use.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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INVESTIGATOR AGREEMENT

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

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

Signature

User	Date	Reason
PPD	14-Nov-2023 14:24:10 (GMT)	Document Approval