Janssen Research & Development *

Clinical Protocol

Protocol Title
Subcutaneous Methotrexate, Oral Dexamethasone or Oral Montelukast for the Prevention of Infusion Related Reaction Associated with Amivantamab, an EGFR-MET bispecific antibody, Among Post-osimertinib Treated EGFRm NSCLC; SKIPPirr, a Phase 2 Study

Protocol 61186372NSC2005; Phase 2
Amendment 4

JNJ-61186372 (amivantamab)

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

Regulatory Agency Identifier Number:
IND: 146319
EudraCT Number: 2022-000974-25
EU Trial Number: 2023-506578-11

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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	**Country/Territory Affected**	**Date**
Amendment 4	All	21-Aug-2023
Amendment 3	All	27-Apr-2023
Amendment 2	All	12-Dec-2022
Amendment 1	All	29-Aug-2022
Original Protocol	All	29-Jun-2022

Amendment 4 (21-Aug-2023)

Overall Rationale for the Amendment: The overall rationale of this amendment is to add Cohort A2 with increased dose of dexamethasone based on emerging data, and also to incorporate new dose formulation for methotrexate due to supply issues. This amendment also serves to clarify some procedures related to VTE on the SoA, as well as to correct some errors, and add in EU CTR specific requirements.

The changes made to the clinical protocol 61186372NSC2005 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.7 Appendix 7: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis (Overall Design), 1.2 Schema 1.3. Schedule of Activities (SoA), 4.1. Overall Design, 6.1. Study Treatment(s) Administered Table and Suggested Order of Administration in Cohort A2 Table	Added Cohort A2: Oral Dexamethasone (8 mg) BID (16 mg total daily dose) on Cycle 1 Day -2 and -1, and 1 dose (8 mg) approximately 1 hour prior to the start of the infusion of IV amivantamab on C1D1	Emerging data suggest that extended administration of a higher dose of dexamethasone prevented IRR in participants receiving IV amivantamab.
6.1. Study Treatment(s) Administered Table	Added new dose formulation for methotrexate: 5mL/vials, 1mL/10mg	To incorporate new dose formulation for methotrexate due to supply issues
1.3. Schedule of Activities (SoA) 6.1. Study Treatment(s) Administered	Added footnote 'a' to the IV amivantamab in case if dose is missed and defined it in the table footnote as below: A missed dose is defined as failure to administer IV amivantamab within 1 day of the scheduled dosing date in Cycles 1 (except C1D1) and 2, or failure to administer IV amivantamab within 3 days of the scheduled dosing date in Cycle 3 and beyond. If a dose is missed, as defined above, it will not be made up. Administration may resume at the next planned	To provide a criterion to follow in case an IV amivantamab dose is missed.

Section Number and Name	Description of Change	Brief Rationale
	dosing date. If the first dose in Cycle 2 is delayed, then the dates of all subsequent doses must be maintained as originally scheduled based on Cycle 1 Day 1. All other assessments in SoA should be performed relative to actual IV amivantamab administration, not on the originally scheduled administration day.	
1.3. Schedule of Activities (SoA)	A new row for VTE prophylaxis was added in order to emphasize the recommended prophylactic dose anticoagulation during the first 4 months of treatment for participants receiving the combination of IV amivantamab and oral lazertinib.	To reinforce the VTE prophylaxis recommendation.
3. Objectives and Endpoints	Updated the language of the secondary objective in bold: To evaluate incidences and severity of individual IRR signs and symptoms **such as** chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, or fever.	To indicate this is not an all-inclusive list of all signs and symptoms associated with IRRs.
1.1. Synopsis (Overall Design), 4.1. Overall Design	Updated text that 'Up to 126 participants are planned to be treated with amivantamab and lazertinib in the study. For each cohort, the study will have 2 stages treating up to 16 participants (6 at stage 1 and 10 at stage 2) and an expansion stage that can treat up to 24 additional participants. First Cohort A will treat up to 6 participants in Stage 1. Then cohort B will be activated to treat up to 6 participants in Stage 1. Then cohort C will be activated to treat up to 6 participants in Stage 1. Cohort A2 will be then activated in Stage 1. If both Cohorts A and A2 have positive results in Stage 1, only one cohort with dexamethasone (Cohort A or A2) would move on to subsequent stages as determined by the SET. For	To adjust for the inclusion of Cohort A2, to allow for alternative sequential enrollment orders for operational optimization, and to delete redundant text not required by Simon's 2 stage design.

Section Number and Name	Description of Change	Brief Rationale
	Cohort A2 Stage 1, all cohorts in Stage 2 and expansion phase, the sequential enrollment will be maintained, however the order will be defined by SET considering data availability and other operational definitions. Added the following text: In the event of scheduling conflicts or screen failures at the end of cohort enrollment leading to an insufficient number of participants in a cohort, a previous cohort can be backfilled.	
1.3. Schedule of Activities (SoA [Background-Anti - Cancer Treatment Administration for IV Amivantamab]) 6.1. Study Treatment Administered Tables	Added the following text for the IV amivantamab (Cohorts A, A2, B, and C) dosage level: Based on positive study results in Stages 1 and 2, full dose may be administered on Cycle 1 Day 1 in expansion phase after consultation with the sponsor.	To provide flexibility to investigator on the expansion cohort, if the prophylactic regimen shows efficacy in the first 2 stages.
10.2. Appendix 2: Clinical Laboratory Tests	Added urinalysis.	Urinalysis was inadvertently excluded from Appendix 2 in the previous version of the protocol
1.3. Schedule of Activities (SoA [Hematology, Serum chemistry])	Deleted collection on Cycle 1 Day 2.	To correct an error
2.2 Background	Added reference	Reference to new data regarding dexamethasone as a prophylactic for IRR
2.2 Background	Added new text: in addition to an increased IV dose pre-infusion (20 mg IV)	To accurately describe the pre-infusion regimen and total dexamethasone dose used in PAPILLON trial.
5.2. Exclusion Criteria	Added a new exclusion criteria number 14: Participant previously enrolled in the Sponsor's studies 73841937NSC3003 (NCT04487080) or 61186372NSC3002 (NCT04988295).	To avoid bias on a key endpoint of other sponsor's studies.
5.2. Exclusion Criteria, 6.9.1. Prohibited or Restricted Concomitant Therapy/Drug Interaction	Added following, a new exclusion criteria number 10a; and text for prohibited restricted concomitant therapy: Participants who are taking systemic steroids, methotrexate or montelukast for other conditions are excluded (inhaled and/or nasal steroids are allowed), regardless of cohort assignment.	To reduce potential bias by limiting confounding factors for IRR prevention.

Section Number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria (Note)	Added following text: if there is no interference with the time between prophylactic treatment and Cycle 1 Day 1	To clarify the allowance of supportive care to meet eligibility criteria, but not to allow interference with dosing schedule.
6.9.1. Prohibited or Restricted Concomitant Therapy/Drug Interaction	Updated following text: potent inducer ~~or inhibitory~~ effects on CYP3A4/A5 activity ~~should be avoided. Drugs that are potent inhibitors of CYP3A4 activity~~ are prohibited and must have been discontinued for an appropriate period before administration of lazertinib. Drugs that are potent inhibitors of CYP3A4 activity are restricted and should be avoided, when possible, or used with caution. **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. substrates of P-gp, MRP4, BCRP, or OCT1 are not recommended and if necessary, should be used with caution. Concomitant use of CYP34A substrate drugs ~~must~~ should be ~~discontinued before administration of lazertinib.~~ avoided. If no other alternatives exist monitor participants more closely for adverse reactions. Guidance on CYP3A4 substrates that ~~are prohibited~~ require close monitoring.	Updated to align with currently available drug-drug interaction data.
7.1. Discontinuation of Study Treatment (Dexamethasone, Montelukast or Methotrexate)	Deleted the following text: ~~Additional participants will not be entered in the study.~~	To correct an error, participants need to be replaced for robust analysis.
1.1 Synopsis, 4.1 Overall Design 9.2 Sample Size Determination	Revised term “enroll” or “enrolled” to “treat” or “treated” throughout section. Revised term “Enroll” to “Treat”	To clarify that participants must be treated with amivantamab and lazertinib to be included into the primary analysis

Section Number and Name	Description of Change	Brief Rationale
	• Stage 1: ~~Enroll~~ Treat up to 6 participants. • Stage 2: ~~Enroll~~ Treat up to 10 additional participants.	
9.3 Populations for Analysis Sets	Revised Population "Enrolled" with description "All participants who sign the ICF" to Population "Screened".	To clarify that participants that sign the ICF are considered screened, not enrolled.
9.5. Interim Analysis	Updated that one interim analysis will occur after all participants from stage 1 complete Cycle 1 Day 1 and added the following text: Another interim analysis will take place after all participants from stage 2 complete Cycle 1 Day 1. Deleted the following text: ~~of dosing. Incidences of IRRs on Cycle 1 Day 1 will be assessed and if 4 or more of these 6 patients experience IRRs, enrollment to the cohort will be stopped.~~	To clarify that two interim analyses are planned. The deleted text is redundant. The content is covered in section 9.2 Sample size determination.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. Synopsis

Subcutaneous Methotrexate, Oral Dexamethasone or Oral Montelukast for the Prevention of Infusion Related Reaction Associated with Amivantamab, an EGFR-MET bispecific antibody, Among Post-osimertinib Treated EGFRm NSCLC; SKIPPirr, a Phase 2 Study

Amivantamab is a bispecific EGF receptor-directed and MET receptor-directed antibody with immune cell directing activity, which has received accelerated approval for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, after progression on or after platinum-based chemotherapy. Among patients with locally advanced or metastatic NSCLC (CHRYSALIS study) who received IV amivantamab, IRRs were reported in 66% of treated participants (Amivantamab-vmjw. Package insert. Janssen Biotech, Inc; 2021.), which are primarily limited to the first infusion on Cycle 1 Day 1, with dramatically reduced risk on subsequent infusions. The median time to onset was 1 hour after start of infusion, with the most common signs and symptoms of IRR including dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. Translational studies conducted to understand the underlying mechanisms contributing to amivantamab IRRs, failed to elucidate the underlying mechanism, but have ruled out cytokine release syndrome, mast cell degranulation, and complement-mediated etiologies for amivantamab-related IRRs, and the dramatically lowered risk after initial infusion is inconsistent with an IgE-mediated mechanism. Standard premedication with antihistamines, antipyretics, and glucocorticoids is recommended immediately prior to the IV amivantamab initial doses (Week 1, Days 1 and 2).

In general, systemic IRRs, including severe reactions, which occur with the introduction of a new protein therapeutic infusion are frequently observed but the mechanisms inducing the reactions are varied. There is emerging data to suggest that the addition of methotrexate, montelukast or oral dexamethasone to a premedication regimen can lower the signs and symptoms associated to infusion therapy, including the incidence of IRRs.

Infliximab, a monoclonal antibody targeting Tumor Necrosis Factor (TNF), is associated with early IRRs which are similar to amivantamab. Vermeire et al. 2007 found infliximab treated patients not taking concomitant Immunosuppressive (IS) therapy of either methotrexate (MTX) or azathioprine (AZA) more often experienced infusion reactions compared with patients taking concomitant IS treatment. There was no difference in infusion reactions between patients treated with AZA compared with patients receiving concomitant MTX. In addition, to infliximab, the anti-CD38 monoclonal antibody daratumumab is also associated with this type of IRR.

Other reports have suggested that premedication with montelukast, a leukotriene receptor antagonist known to reduce asthma attacks and allergic rhinitis, may reduce the IRR rate associated with monoclonal antibodies, and this observation was also reported by investigators in the phase 1/2 study that resulted in the initial approval of daratumumab.

Use of extended steroid pre-medications have also been utilized to reduce reactions to IV anti-cancer therapies such as pemetrexed and docetaxel and are now standard pre-medications for regimens including these agents.

The aim of this study is to determine whether premedication with dexamethasone, montelukast or methotrexate can act as a prophylaxis of amivantamab-related IRRs.

Amivantamab plus lazertinib is the background anti-cancer regimen in this protocol and is not the primary focus of this study. Lazertinib is a third-generation EGFR TKI approved in the Republic of Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. The combination of lazertinib plus IV amivantamab has been investigated in the CHRYSALIS study and is being further evaluated in the CHRYSALIS-2 study

where the incidence of IRR was 67% with the majority being grade 1 or 2 and a 9% incidence of grade ≥3 IRR. The safety profile of the combination was consistent with the individual components. Furthermore, the incidence of IRR with oral lazertinib plus IV amivantamab in CHRYSALIS-2 (67%) was similar to the incidence of IRR with IV amivantamab monotherapy previously (66%) suggesting that addition of oral lazertinib to IV amivantamab is not expected to impact the rate of IRRs associated with IV amivantamab.

BENEFIT-RISK ASSESSMENT

Combining amivantamab and lazertinib may lead to improved treatment outcomes through synergistic antiEGFR activity, prevention of EGFR- or MET-based resistance to a third-generation EGFR TKI, and potential recruitment of Fc-bearing immune cells in the antitumor response. Previous studies have shown robust and durable antitumor activity with favorable confirmed ORR, prolonged median duration of response, and high clinical benefit rate. IV amivantamab is FDA approved for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. Lazertinib is approved in the Republic of Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. At the time of the initiation of this study, the combination of oral lazertinib plus IV amivantamab is considered investigational for the treatment of lung cancer. Amivantamab given IV can cause IRRs and the incidence of IRR in the CHRYSALIS-2 study was 67% with the majority being grade 1 or 2 and a 9% incidence of grade ≥3 IRR. There is emerging data in amivantamab and other monoclonal antibodies to suggest that the addition of enhanced dexamethasone, methotrexate or montelukast to a premedication regimen can lower the signs and symptoms associated to infusion therapy, including the overall incidence of IRRs. These prophylactic regimens are being implemented to further optimize the benefit-risk profile for participants receiving treatment with IV amivantamab.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To separately assess the potential of dexamethasone, montelukast and methotrexate administration, prior to IV amivantamab infusion, to decrease the incidence and/or severity of first dose IRRs.	• Rate of IRRs occurring on Cycle 1 Day 1 following administration of oral lazertinib and IV amivantamab combination therapy, which is defined as IRR events with onset time within 24 hours of the start of the first amivantamab infusion and prior to the start of amivantamab infusion on Cycle 1 Day 2.
Secondary	
• To evaluate incidences and severity of individual IRR signs and symptoms such as chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, or fever.	• Rates and severity of these individual AEs during Cycle 1 Day 1. • Rates and severity of these individual AEs following subsequent administrations up to the end of the third cycle.
• To evaluate incidence and severity of IRR on subsequent cycles.	• Rates of IRR following subsequent administrations. • Severity of infusion-related reactions.
• To evaluate incidences non-IRR AEs.	• Incidence of other adverse events.
• To measure IV amivantamab infusion related times.	• Duration of infusion time for pre-amivantamab infusion medications, IV amivantamab infusion, and post-amivantamab infusion medications on C1D1. • Percent of participants completing amivantamab infusion within 4 hours on C1D1.
• To estimate the anti-tumor activity of IV amivantamab and oral lazertinib following pre-medication with study treatment	• Overall response rate (ORR) and duration of response (DOR) as determined by investigator, according to the Response Criteria in Solid Tumors (RECIST) v1.1.

Hypothesis

Through prophylactic treatment with methotrexate, montelukast, or dexamethasone pre-treatment, the incidence of IRRs on Cycle 1 Day 1 will be lower than 67%.

OVERALL DESIGN

This is a proof-of-concept, open-label, multicenter study in participants with EGFR exon 19 deletion or L858R mutated NSCLC who have progressed on or after prior osimertinib and on or after platinum chemotherapy, who may benefit from IV amivantamab + oral lazertinib combination therapy. In the study, all participants will receive standard prophylaxis with antihistamine, antipyretic, and glucocorticoid as used in clinical trials of amivantamab.

There are 4 cohorts in the study.

- Cohort A: Participants will be administered oral dexamethasone (4 mg) twice a day (8 mg total daily dose) on Day -1 (Cycle 1) prior to the first dose of oral lazertinib and IV amivantamab combination therapy.
- Cohort A2: Participants will be administered oral dexamethasone (8 mg) twice a day (16 mg total daily dose) on Day -2 and -1 (Cycle 1) and 8 mg approximately 1 hour prior to the start of the infusion of IV amivantamab on Cycle 1 Day 1.
- Cohort B: Participants will be administered oral montelukast (10 mg) in the morning on Days -4, -3, -2, -1, and C1D1 (5 doses total) prior to the first dose of oral lazertinib and IV amivantamab combination therapy.
- Cohort C: Participants will be administered a single dose of 25 mg SC methotrexate between Day -7 and Day -3 (Cycle 1) prior to the first dose of oral lazertinib and IV amivantamab combination therapy

Study treatments will be administered in addition to all other standard premedication.

Up to 126 participants are planned to be treated with amivantamab and lazertinib in the study. For each cohort, the study will have 2 stages treating up to 16 participants (6 at stage 1 and 10 at stage 2) and an expansion stage that can treat up to 24 additional participants. First cohort A will treat up to 6 participants in Stage 1. Then cohort B will be activated to treat up to 6 participants in Stage 1. Then cohort C will be activated to treat up to 6 participants in Stage 1. Cohort A2 will be then activated in Stage 1. In the event of scheduling conflicts or screen failures at the end of cohort enrollment leading to an insufficient number of participants in a cohort, a previous cohort can be backfilled.

A Study Evaluation Team (SET) will be commissioned for this study. After cohorts A, A2, B and C have each treated up to 6 participants, SET will evaluate individually which cohort(s) may move onto Stage 2 and this process will repeat for Stage 2 to select possible expansion phase cohorts. If both Cohorts A and A2 have positive results in Stage 1, only one cohort with dexamethasone (Cohort A or A2) would move on to subsequent stages as determined by the SET. For Cohort A2 Stage 1, all cohorts in Stage 2 and expansion phase, the sequential enrollment will be maintained, however the order will be defined by SET considering data availability and other operational definitions.

NUMBER OF PARTICIPANTS Up to 126 participants (n=6 in Stage 1 per cohort with an expansion option of up to 34 more participants added per cohort if there is evidence of reduced IRR rate).

TREATMENT GROUPS AND DURATION

EGFR exon 19 or L858R mutated advanced NSCLC with disease progression on or after osimertinib and doublet platinum chemotherapy and will proceed with the treatment of IV amivantamab + oral lazertinib as determined by investigator.

Description of Study treatments

Dexamethasone

Dexamethasone is a synthetic adrenocortical steroid available in oral and IV formulations for allergic states. IV dexamethasone (10 mg) is a standard premedication administered prior to all participants receiving IV amivantamab.

Montelukast

Montelukast, a highly selective leukotriene receptor antagonist, is an oral treatment for chronic asthma and prophylaxis and the prevention of exercise-induced bronchoconstriction.

Montelukast inhibits the mast cell mediated release of leukotrienes and may be used to reduce inflammation and bronchoconstriction.

Methotrexate

Methotrexate (MTX) is an anti-metabolite, commonly used in chemotherapy and immunosuppressant in auto-immune diseases; it may affect immune function.

EFFICACY EVALUATION

The primary objective is to separately assess the potential of dexamethasone, montelukast and methotrexate, administration, prior to IV amivantamab infusion, to decrease the incidence and/or severity of first dose IRRs. Investigator reported adverse events of IRR and associated symptoms and severity will be assessed. Investigator assessed tumor response and duration of response will be collected as secondary endpoints. Response assessment will be determined for all participants in accordance with RECIST v1.1. Disease will be assessed at baseline, 6 weeks (+1 week) after Cycle 1 Day 1 (ie, Day 42-Day 49) for the first assessment, and then every 6 (±1) weeks relative to Cycle 1 Day 1, until disease progression by imaging, start of new anti-cancer therapy, or withdrawal of consent. Scheduled disease assessments for participants who have completed 12 cycles and are clinically stable (both clinical symptoms and radiographical assessments), may be extended to 12-week intervals at the discretion of the investigator, after confirmation with medical monitor.

SAFETY EVALUATIONS

The safety of the study treatments (dexamethasone, montelukast, and methotrexate) and of the background anti-cancer therapy (IV amivantamab and oral lazertinib) will be assessed by physical examinations, clinical laboratory tests, vital signs, monitoring of adverse events (AEs), and concomitant medication usage.

STATISTICAL METHODS

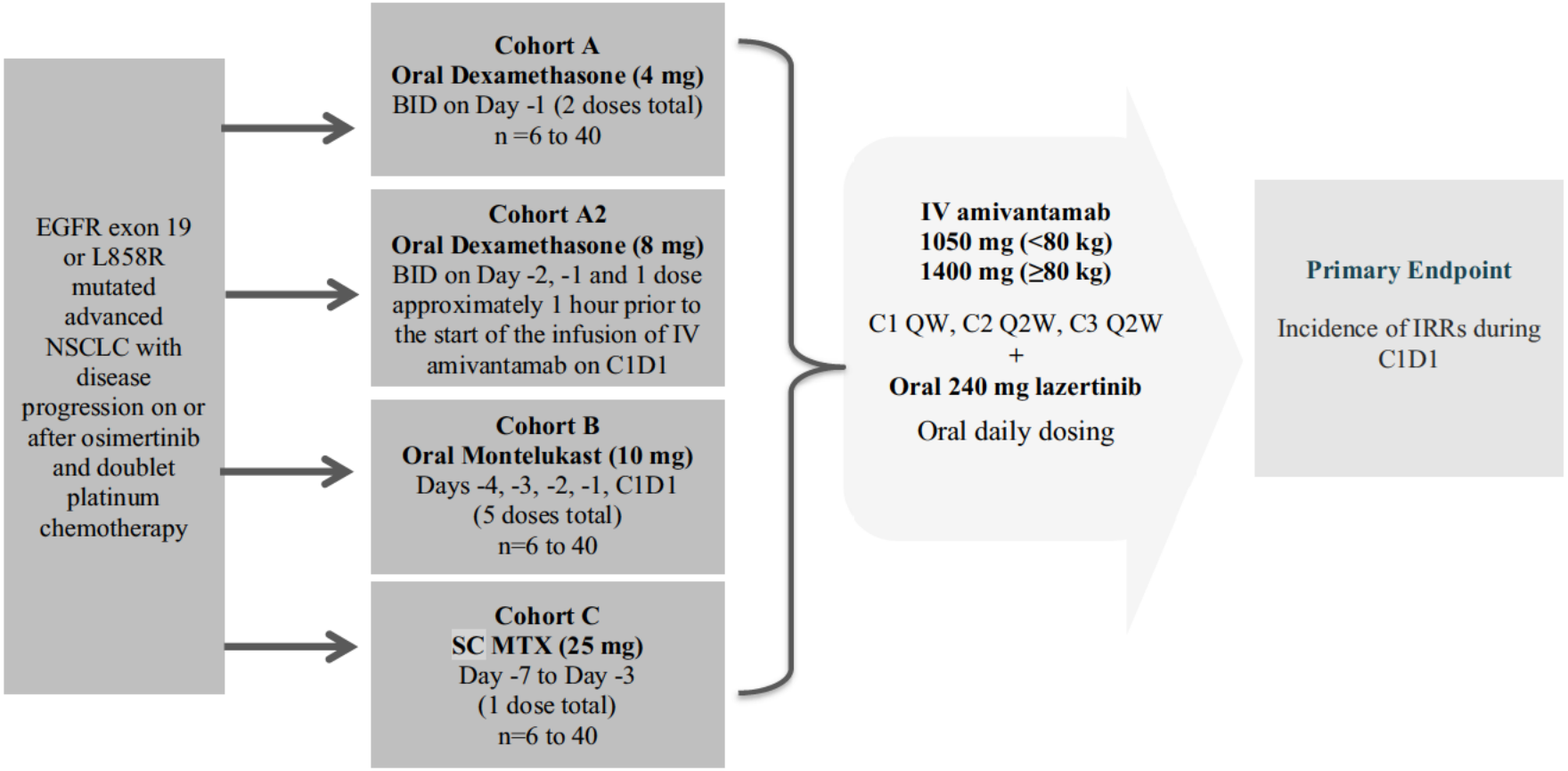
The null hypothesis that the true IRR rate is 0.67 or higher will be tested against a one-sided alternative for each prophylaxis treatment. Simon's two-stage design (Simon, 1989) will be used separately for each cohort. In the first stage, 6 participants will be accrued. If there are 4 or more participants with IRR out of these 6 participants, the cohort will be stopped. Otherwise, second stage of the cohort will be initiated with accrual of 10 additional participants for a total of 16. The null hypothesis will be rejected if 8 or less participants with IRR are observed in 16 participants; the cohort will be concluded to be promising in lowering IRR. The cohort can then be expanded by adding up to 24 additional participants (up to 40 participants total per expanded cohort) for a more precise estimation of the rate of IRR.

The Simon’s two-stage design yields a Type I error rate (one sided) of 0.04 and power of 0.8 when the true IRR rate is 0.34 (50% reduction in IRR).

1.2. Schema

Study Treatments: SC Methotrexate, PO Montelukast and PO Dexamethasone
Background Anti-Cancer Therapy: IV Amivantamab and PO Lazertinib

Figure 1: Schematic Overview of the Study



C1 Cycle 1; C2 Cycle 2; IRR infusion related reactions; Q2W every 2 weeks; NSCLC non small cell lung cancer; MTX methotrexate; SC subcutaneous

1.3. Schedule of Activities (SoA)

Study Period	Screening	Prophylaxis Administration					Treatment (28 days/cycle)									End of Study	Notes
							Cycle 1					Cycle 2		Cycle 3 (and all cycles thereafter)		Up to 30 days after last dose	
Cycle Day		-7 to -3 before C1D1	-4	-3	-2	-1	1	2	8	15	22	1	15	1	15		
Visit Window (Days)	-28 to -8	-7 to -3					-		±1	±2	±1	±1	±1	±3	±3	0	
Study Procedures: Assessments on dosing days should be performed prior to administration of study intervention treatment unless otherwise stated. Investigators must confirm that participants meet retreatment criteria prior to administration of study treatment.																	
Informed consent	X																Must be signed before any study related procedures. 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, provided the assessments fulfill the study requirements.
Inclusion/ exclusion criteria	X																Participants who fail to meet entry criteria and are screen failed may be rescreened if their condition changes but must sign a new informed consent form. Rescreening must be discussed with and approved by the Sponsor's medical monitor on a case by case basis.
Demography	X																Includes age, sex, ethnicity, and race.
Disease characteristics	X																Includes tumor type, date of initial diagnosis and metastatic disease, tumor stage at initial diagnosis, histology and EGFR mutation status, prior anticancer therapies (number and type of prior regimens, best response, and duration of therapy) and date of most recent disease progression.
Medical history	X																Includes relevant past medical diagnoses, and surgeries/procedures as well as current medical conditions with toxicity grade (including current cancer related symptoms). Include any planned surgeries.
ECOG performance status	X						X										
Duration of infusion time.							X	X	X	X	X	X	X	X	X		For pre amivantamab infusion medications, amivantamab infusion, and post amivantamab infusion medications
Time and Motion							X	X	X	X	X						

Study Period	Screening	Prophylaxis Administration					Treatment (28 days/cycle)									End of Study	Notes
							Cycle 1					Cycle 2		Cycle 3 (and all cycles thereafter)		Up to 30 days after last dose	
Cycle Day		-7 to -3 before C1D1	-4	-3	-2	-1	1	2	8	15	22	1	15	1	15		
Visit Window (Days)	-28 to -8	-7 to -3					-		±1	±2	±1	±1	±1	±3	±3	0	
STUDY TREATMENT ADMINISTRATION by Cohort																	
A: Oral Dexamethasone						X											Cohort A: Dexamethasone (4 mg) PO BID (8 mg total) Cycle 1 Day (1) Cohort A2: Dexamethasone (8 mg) PO BID (16 mg daily) on Cycle 1 Day 2, 1, and 1 dose (8 mg) approximately 1 hour prior to the start of the infusion of IV amivantamab on C1D1. Cohort B: montelukast (10 mg) PO QD for 5 days ending on C1D1. Cohort C: methotrexate (25mg) SC is administered only once anytime from 7 to 3 before C1D1
A2: Oral Dexamethasone (8 mg dosing)					X	X	X										
B: Montelukast			X	X	X	X	X										
C: Methotrexate		X															
BACKGROUND ANTI-CANCER TREATMENT ADMINISTRATION																	
Lazertinib							Once daily oral administration										
IV amivantamab[a]							X	X	X	X	X	X	X	X	X		Based on positive study results in Stage 1 and 2, full dose may be administered on Cycle 1 Day 1 in expansion phase after consultation with sponsor.
Concomitant medications	Continuous																Pre study therapies administered up to 28 days before first dose of lazertinib and IV amivantamab must be recorded at screening. Concomitant therapies must be recorded throughout the study beginning at screening and continuing until 30 days after the last dose of study treatment or oral lazertinib or IV amivantamab treatment, or until the end of study visit (whichever is later), or until the start of a subsequent systemic anti cancer therapy, if earlier. Concomitant therapies should also be recorded beyond 30 days after the last dose of study treatment or oral lazertinib or IV amivantamab in conjunction with the following situations: • Grade 3 or Grade 4 adverse events being followed per Section 8.3.1 • Adverse events reported after 30 days following the last dose of study drug, lazertinib or IV amivantamab if considered related to study drug, lazertinib or IV amivantamab, the sponsor must be notified.

Study Period	Screening	Prophylaxis Administration					Treatment (28 days/cycle)									End of Study	Notes
							Cycle 1					Cycle 2		Cycle 3 (and all cycles thereafter)		Up to 30 days after last dose	
Cycle Day		**-7 to -3 before C1D1**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**8**	**15**	**22**	**1**	**15**	**1**	**15**		
Visit Window (Days)	**-28 to -8**	**-7 to -3**					**-**		**±1**	**±2**	**±1**	**±1**	**±1**	**±3**	**±3**	**0**	
VTE prophylaxis							X					X		X(up the 4th month)			Prophylactic anticoagulation recommended during the first 4 months of combination therapy. Refer to NCCN Guidelines Version 1.2023 Cancer Associated Venous Thromboembolic Disease, Section VTE B for examples of prophylactic dose anticoagulants in ambulatory cancer patients (NCCN VTE Guidelines 2023) and protocol Section 6.6.5.
PRE-INFUSION MEDICATIONS																	
IV Dexamethasone (10 mg)							X	X									Dexamethasone (10 mg) IV 45 60 minutes prior to IV amivantamab (C1D1 and C1D2).
Diphenhydramine							X	X	X	X	X	X	X	X	X		Diphenhydramine (25 to 50 mg) or equivalent. IV 15 30 minutes prior to IV amivantamab (all cycles, all cohorts) or diphenhydramine (25 to 50 mg) or equivalent PO 30 60 minutes prior to IV amivantamab (all cycles, all cohorts).
Paracetamol or acetaminophen							X	X	X	X	X	X	X	X	X		Paracetamol (acetaminophen 650 to 1,000 mg) or equivalent IV 15 30 minutes prior to IV amivantamab (all cycles, all cohorts).
Treatment compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SAFETY ASSESSMENTS																	
Adverse events	Continuous																
Hematology	X						X		X	X	X	X	X	X	X	X	If performed within 3 days prior to the D1 dose of a cycle, the assessment does not have to be repeated at D1. See Appendix 2.
Serum chemistry	X						X		X	X	X	X	X	X	X	X	If performed within 3 days prior to the D1 dose of a cycle, the assessment does not have to be repeated at D1. See Section 6.6.2. and Appendix 2.
Coagulation	X						As clinically indicated										See Appendix 2.
Serology	X						As clinically indicated										HIV antibody, HBsAg, HBsAb (if needed), HBcAb, anti HCV antibody, HBV viral load (if needed) and HCV viral load (if needed)

Study Period	Screening	Prophylaxis Administration					Treatment (28 days/cycle)									End of Study	Notes
							Cycle 1					Cycle 2		Cycle 3 (and all cycles thereafter)		Up to 30 days after last dose	
Cycle Day		-7 to -3 before C1D1	-4	-3	-2	-1	1	2	8	15	22	1	15	1	15		
Visit Window (Days)	-28 to -8	-7 to -3					-		±1	±2	±1	±1	±1	±3	±3	0	
Urinalysis	X						As clinically indicated										See Appendix 2.
Pregnancy test	X						Within 72 hours of day 1 of each cycle and at End of Study and as clinically indicated, by urine or serum test, or required by local regulation, to establish the absence of pregnancy										Women of childbearing potential only. Serum test required at screening and urine or serum test within 72 hours prior to Day 1 of each cycle and at End of Study. See Appendix 2.
12 lead Electrocardiogram	X						X										If performed within 3 days prior to the C1D1 dose, the assessment does not have to be repeated at C1D1
Echocardiography/multi gated acquisition scan	X						6 weeks ±1 week (relative to C1D1) then as clinically indicated thereafter										
Vital signs	X						X	X	X	X	X	X	X	X	X	X	Vital signs should be measured within 30 minutes prior to IV amivantamab administration. On Cycle 1 Day 1, vital signs should also be measured 2 hours ±15 min after the IV amivantamab administration. For all visits, collect vital sign measurements ≤30 minutes before amivantamab infusion, at 30 minute intervals (±5 minutes) during each amivantamab infusion, and at the end of the infusion (±5 minutes).
Physical examination[b]	X						X					X		X		X	At all visits after the IV amivantamab administration, participants should be questioned for skin and eye symptoms, with physical examination as appropriate, and specialty referral as indicated.
Weight	X						X					X		X			Weight will be checked at baseline to determine amivantamab dose. Dose adjustments are not required for subsequent body weight changes.
ANTI-TUMOR ASSESSMENTS																	

Study Period	**Screening**	**Prophylaxis Administration**					**Treatment (28 days/cycle)**									**End of Study**	**Notes**
							Cycle 1					**Cycle 2**		**Cycle 3 (and all cycles thereafter)**		**Up to 30 days after last dose**	
Cycle Day		**-7 to -3 before C1D1**	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**8**	**15**	**22**	**1**	**15**	**1**	**15**		
Visit Window (Days)	**-28 to -8**	**-7 to -3**					**-**		±1	±2	±1	±1	±1	±3	±3	**0**	
Disease assessment/Tumor response evaluation	X						X										Disease assessments and evaluations as outlined in Section 8.1 (CT scan with contrast agent and/or MRI scan should be performed for all active disease sites documented at Screening, 6 weeks (+1 week) after Cycle 1 Day 1(ie, Day 42 Day 49) for the first assessment, and then every 6 (±1) weeks relative to Cycle 1 Day 1. Scheduled disease assessments for participants who have completed 12 cycles, and are clinically stable (both clinical symptoms and radiographical assessments), may be extended to 12 week intervals at the discretion of the investigator, after confirmation with Medical Monitor. Results will be recorded in the CRF. The same methodology should be used throughout the study. Tumor response evaluation will be assessed by the investigator according to RECIST v1.1. Results of the assessment should be available prior to the next scheduled dose.

C cycle; D day; ECOG Eastern Cooperative Oncology Group; EGFR epidermal growth factor receptor; min minute(s); IV intravenous; PO orally.

[a] A missed dose is defined as failure to administer IV amivantamab within 1 day of the scheduled dosing date in Cycles 1 (except C1D1) and 2, or failure to administer IV amivantamab within 3 days of the scheduled dosing date in Cycle 3 and beyond. If a dose is missed, as defined above, it will not be made up. Administration may resume at the next planned dosing date. If the first dose in Cycle 2 is delayed, then the dates of all subsequent doses must be maintained as originally scheduled based on Cycle 1 Day 1. All other assessments in SoA should be performed relative to actual IV amivantamab administration, not on the originally scheduled administration day.

[b]For participants receiving the combination of amivantamab and lazertinib, evaluate for early signs and symptoms of venous thromboembolic (VTE). A focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed.

2. INTRODUCTION

For the most comprehensive nonclinical and clinical information regarding dexamethasone, montelukast and methotrexate refer to the product labeling. For the most comprehensive nonclinical and clinical information regarding IV amivantamab, and lazertinib refer to the latest version of the Investigator's Brochure (IB) and Addenda for IV amivantamab and oral lazertinib.

The term “study treatment” throughout the protocol, refers to study drug as defined in Section 6.1, Study Treatment(s) Administered.

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

2.1. Study Rationale

Systemic IRRs, including severe reactions, upon the introduction of a new protein therapeutic infusion are frequently observed but the mechanisms inducing the reactions are varied (Cáceres 2019; Matucci 2016). There is emerging data to suggest that the addition of methotrexate or montelukast to a premedication regimen can lower the signs and symptoms associated to infusion therapy, including incidence of IRRs.

Similar to amivantamab, infliximab also causes IRR, the etiology of which is unknown. Vermeire et al. 2007 found infliximab treated patients not taking concomitant Immunosuppressive (IS) therapy of either methotrexate (MTX) or azathioprine (AZA) more often experienced infusion reactions (40%) compared with patients taking concomitant IS treatment (16%; p 0.04). There was no difference in infusion reactions between patients treated with AZA (18%) compared with patients receiving concomitant MTX (14%; p NS).

Other reports have suggested that premedication with montelukast, a leukotriene receptor antagonist known to reduce asthma attacks and allergic rhinitis, may reduce the IRR rate associated with monoclonal antibodies, (Arora 2015; Lebel 2016; Lokhorst 2015; Moreau 2016; Quercia 2011) and this observation was also reported by investigators in the Phase 1/2 study that resulted in the initial approval of daratumumab. (Chari 2018) A multicenter, open-label treatment protocol provided early access to daratumumab for patients who had progressive MM after they received ≥3 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent or if they were refractory to both a proteasome inhibitor and an immunomodulatory agent. Patients received daratumumab 16 mg/kg weekly for 8 weeks, every other week for 16 weeks, and monthly until they developed disease progression, unacceptable toxicity, or 60 days after the drug gained US approval. Three hundred forty-eight patients were enrolled at 39 US sites between June and December 2015. Infusion reactions occurred in 56%, 2%, and 2% of patients during the first, second, and all subsequent infusions, respectively; respiratory symptoms (cough, dyspnea, throat irritation, nasal congestion) were common.

Sixty patients (17%) received montelukast 10 mg before at least 1 infusion. Of these, 50 patients (14%) at 2 study sites received montelukast before the first daratumumab infusion, 49 of whom

received montelukast on same day more than 30 minutes before daratumumab infusion. Based on those 50 patients, the IRR rates at first infusion were 38% and 59% (respiratory symptoms, 20% and 33%), respectively, in those who did or did not receive montelukast. Furthermore, the incidence of grade 3 or 4 IRRs was 2% and 9% in patients who did (n 60) or did not (n 298) receive montelukast, respectively. The median duration of the first daratumumab infusion was 6.7 hours (range, 1.0-10.7 hours) for the 50 patients who received montelukast before their first infusion versus 7.6 hours (range, 1.4-24.0 hours) for those who did not.

2.2. Background

Amivantamab given IV can cause IRRs. Amivantamab is a bispecific EGF receptor-directed and MET receptor-directed antibody FDA approved for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA -approved test, whose disease has progressed on or after platinum-based chemotherapy. Lazertinib is a potent, irreversible, and brain-penetrant third-generation EGFR TKI approved in the Republic of Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. The combination of oral lazertinib plus IV amivantamab has been investigated in the CHRYSALIS study where a total of 45 patients with EGFR exon 19 deletion- or L858R mutation-positive metastatic NSCLC who had progressed on prior osimertinib received the combination of IV amivantamab 1050/1400 mg (IV QW in C1; Q2W thereafter) plus oral lazertinib 240 mg (po QD). The incidence of IRR was 78%, and other common AEs included rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%) with the majority being grade 1-2. Treatment-related grade ≥3 AE occurred in 16% of patients, treatment-related discontinuations occurred in 4% and treatment-related dose reductions occurred in 18% of patients. At a median follow up of 11 months, an ORR of 36% was observed with a median duration of response of 9.6 months. (Bauml ASCO 2021).

The investigational regimen of oral lazertinib plus IV amivantamab is being further evaluated in Cohort A of the CHRYSALIS-2 study, where a total of 136 patients with EGFR exon 19 deletion -or L858R mutation-positive metastatic NSCLC who had progressed on prior osimertinib, and prior platinum-based chemotherapy received the same combination of oral lazertinib plus IV amivantamab. The incidence of IRR was 67% with the majority being grade 1 or 2 and a 9% incidence of grade ≥3 IRR. The safety profile was consistent with previously reported experience. Furthermore, the incidence of IRR with oral lazertinib plus IV amivantamab in CHRYSALIS-2 (67%) was similar to the incidence of IRR with IV amivantamab monotherapy (66%) suggesting that addition of oral lazertinib to IV amivantamab is not expected to impact the rate of IRRs associated with IV amivantamab. (Shu ESMO 2021).

More detailed information about the known and expected benefits and risks of dexamethasone, montelukast, and methotrexate may be found in the respective product labeling. More detailed information about the known and expected benefits and risks of lazertinib and IV amivantamab may be found in the respective IBs.

IV amivantamab can cause IRR; signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. Among 302 patients with locally advanced or metastatic NSCLC who received IV amivantamab at RP2D as a single-agent in the CHRYSALIS study, the most common (≥20%) adverse reactions were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritus. Patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued IV amivantamab due to IRR.

Studies conducted on a subset of patients to understand the underlying mechanisms contributing to IRRs failed to distinguish a pattern between patients with and without IRR. No correlation between IRR and cytokine release, mast cell degranulation, tumor lysis syndrome, or complement activation was observed; the underlying mechanism(s) of IRRs require further studies. (Park ESMO 2021)

Standard premedication with antihistamines, antipyretics, and glucocorticoids is recommended, including premedication with dexamethasone 10 mg IV required at IV amivantamab initial dose (Week 1, Days 1 and 2). IV amivantamab is also being investigated in combination with carboplatin-pemetrexed based chemotherapy in the PAPILLON study. In PAPILLON, the "enhanced steroid" premedication is aligned with the pemetrexed standard of care. In PAPILLON, for the carboplatin-pemetrexed based chemotherapy combination with IV amivantamab, dexamethasone 4 mg twice a day is to be administered orally (PO) the day prior to administration of pemetrexed/amivantamab (Cycle 1 Day -1), in addition to an increased IV dose pre-infusion (20 mg IV). It is hypothesized that this "enhanced steroid" use with oral pre-loading the day before the first IV amivantamab infusion may reduce the incidence of IV amivantamab associated IRRs.

IV amivantamab should be administered via a peripheral line on Week 1 and Week 2, given the high incidence of IRRs during initial treatment. IV amivantamab may be administered via central line for subsequent weeks. As a mitigation against the risk of IRRs, the initial dose of IV amivantamab (Cycle 1, Days 1 and 2), is administered as a split dose over 2 days (eg, Cycle 1 Day 1 [350 mg] and Cycle 1 Day 2 [remainder of dose]). During this initial dose, interruption of the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR. Patients should be monitored for any signs and symptoms of infusion reactions during IV amivantamab infusion in a setting where cardiopulmonary resuscitation medication and equipment are available, and the infusion should be interrupted if IRR is suspected and resumed at a reduced infusion rate for Grade 3 IRR or permanently discontinued for Grade ≥4 and recurrent Grade 3 IRR.

In an updated analysis by Park et al (Park ESMO 2021), among n 380 patients who received IV amivantamab at the RP2D, IRR was reported in 256 patients (67%) and was mostly grade 1 2 severity except for 8 patients (2%) who had Grade 3 events and 1 patient (0.3%) who had a Grade

4 event. The patient who had Grade 4 IRR received the C1D1 dose without implementation of IRR mitigation strategies. IRR typically occurred early; 98% of events occurred on C1D1, and only 5 events occurred past cycle 2. The predominance of Grade 2 IRR on C1D1 is consistent with guideline recommendation to hold infusion at first sign of IRR, even for Grade 1 events, in order to prevent more serious reactions. Even though the majority of IRRs are Grade 1/2, mostly limited to the first infusion, and manageable as described above, despite these measures, IRRs do remain frequent and are associated with a prolonged IV amivantamab infusion. Further measures to reduce the incidence of IRR are therefore desirable.

The observation by Vermeire et al that methotrexate may reduce infliximab associated infusion reactions supports the hypothesis that concomitant methotrexate treatment may reduce IRR associated with monoclonal antibodies. Other reports have suggested that premedication with montelukast, a leukotriene receptor antagonist known to reduce asthma attacks and allergic rhinitis, may reduce the IRR rate associated with monoclonal antibodies. (Arnett 1988; Elkayam 2005; Panayi 1978; Vermeire 2007). Use of extended steroid pre-medications have also been utilized to reduce reactions to IV anti-cancer therapies such as pemetrexed and docetaxel and are now standard pre-medications for regimens including these agents. Recent data from a single investigator practice suggests extended use of oral dexamethasone administered at 8 mg BID for 2 days prior to amivantamab infusion and on the day of infusion was able to prevent all IRRs in a small patient sample (Chan 2023). Together, this forms the basis for this current study dexamethasone, montelukast, or methotrexate for the reduction of IV amivantamab Infusion Related Reactions. Based on the diverse mechanisms by which dexamethasone, montelukast, and methotrexate are believed to reduce the incidence monoclonal antibody IRRs and the limited potential for clinical drug-drug interactions, administering dexamethasone, montelukast, and methotrexate together may be investigated in this study if administration of these agents alone prior to lazertinib and IV amivantamab treatment is associated with a reduced rate of IRR.

Please refer to Section 6.6.1 for Infusion-related Reactions.

2.3. Benefit-Risk Assessment

The study treatments are dexamethasone, montelukast, or methotrexate (see Section 6.1). IV amivantamab is FDA approved for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. Lazertinib is approved in the Republic of Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. At the time of the initiation of this study, the combination of oral lazertinib plus IV amivantamab is considered investigational for the treatment of lung cancer. The study drugs (dexamethasone, montelukast and methotrexate) that will be investigated in this study are to be given as pre-medication prior to the administration of this background investigational anti-cancer combination regimen of oral lazertinib plus IV amivantamab to assess the ability of the study drugs to decrease the incidence of IRRs with the anti-cancer treatment.

Dexamethasone

The safety risk information below is based on prolonged use of dexamethasone and the safety profile of a limited administration as described in this protocol has not been established. Risks associated with dexamethasone therapy may include, GI upset, headache, dizziness, insomnia, depression, anxiety, acne, bruising or infections.

More detailed information about the known and expected benefits and risks of dexamethasone, montelukast and methotrexate may be found in the respective product labeling.

Montelukast

The safety risk information below is based on prolonged use of montelukast and the safety profile of a limited administration as described in this protocol has not been established. Serious neuropsychiatric (NP) events have been reported with the chronic use of montelukast. The types of events reported were highly variable, and included, but were not limited to, agitation, aggression, depression, sleep disturbances, suicidal thoughts, and behavior (including suicide). The mechanisms underlying NP events associated with montelukast use are currently not well understood. Potential benefits and risks of montelukast should be discussed with patients and caregivers when montelukast is administered. Patients and/or caregivers should be advised to be alert for changes in behavior or new NP symptoms when taking montelukast. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, patients should be advised to discontinue montelukast and contact a healthcare provider immediately. The most frequently reported adverse reactions with montelukast include respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, and otitis.

Methotrexate

The safety risk information below is based on continuous use of methotrexate and the safety profile of a single, one-time dose of methotrexate has not been established.

Methotrexate should be used only by physicians whose knowledge and experience include the use of antimetabolite therapy. Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy.

1. Methotrexate has been reported to cause fetal death and/or congenital anomalies. Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women should not receive methotrexate.
2. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs).
3. Methotrexate causes hepatotoxicity, fibrosis, and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease.

4. Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible, and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.
5. Diarrhea and ulcerative stomatitis require interruption of therapy: otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.
6. Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
7. Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal methotrexate administration. Recovery has been reported with discontinuation of therapy.
8. Potentially fatal opportunistic infections, especially Pneumocystis carinii pneumonia, may occur with methotrexate therapy.

The most frequently reported adverse reactions with methotrexate injection include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

Background anti-cancer therapy with IV amivantamab plus oral lazertinib

The combination of oral lazertinib and IV amivantamab has been investigated in Cohort E of the CHRYSALIS study (n 45) and in Cohort A of the CHRYSALIS-2 study (n 136) in patients with patients with EGFR exon 19 deletion- or L858R mutation-positive advanced NSCLC who had progressed on prior osimertinib. In CHRYSALIS-2 the most common AEs (≥20%) included IRR, rash (acneiform dermatitis, rash), paronychia, stomatitis, hypoalbuminemia, vomiting, increased AST/ALT, and decreased appetite. A total of 37% of patients had treatment-related grade ≥3 AEs. Four patients (3%) had pneumonitis/ILD. The safety profile was consistent with previously reported experience with IV amivantamab plus oral lazertinib, and no new safety signals were identified. IV amivantamab plus oral lazertinib demonstrated antitumor activity in a population that progressed on both standard of care osimertinib and platinum chemotherapy and for whom there are no approved targeted therapy treatment options. (Shu ESMO 2021)

Prior to any IV amivantamab infusion, standard premedication with antihistamines, antipyretics, and glucocorticoids is recommended, including premedication with dexamethasone 10 mg IV required at initial IV amivantamab doses (Cycle 1, Days 1 and 2). This study will investigate "enhanced steroid" use in Cohort C with dexamethasone oral pre-loading the day before the first amivantamab dose to reduce the incidence of IV amivantamab associated IRRs.

At the 20 July 2022 Independent Data Monitoring Committee (IDMC) review of unblinded safety and efficacy data from another ongoing study of amivantamab and lazertinib combination therapy (73841937NSC3003), the IDMC confirmed a favorable benefit-risk assessment and therefore recommended continuation of the study. The IDMC also recommended that additional measures

be taken to mitigate an observed increase in venous thromboembolic (VTE) events for the combination that was primarily evident within the first 4 months of initiating therapy. Notably, based on the VTE search strategy used at the time of IDMC review, no Grade 5 VTE events were identified, and only 1 participant discontinued study treatment due to VTE events.

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

More detailed information about the known and expected benefits and risks of lazertinib and IV amivantamab may be found in the respective IBs.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To separately assess the potential of dexamethasone, montelukast and methotrexate administration, prior to IV amivantamab infusion, to decrease the incidence and/or severity of first dose IRRs.	• Rate of IRRs occurring on Cycle 1 Day 1 following administration of oral lazertinib and IV amivantamab combination therapy, which is defined as IRR events with onset time within 24 hours of the start of the first amivantamab infusion and prior to the start of amivantamab infusion on Cycle 1 Day 2.
Secondary	
• To evaluate incidences and severity of individual IRR signs and symptoms such as chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, or fever.	• Rates and severity of these individual AEs during Cycle 1 Day 1. • Rates and severity of these individual AEs following subsequent administrations up to the end of the third cycle.
• To evaluate incidence and severity of IRR on subsequent cycles.	• Rates of IRR following subsequent administrations. • Severity of infusion-related reactions.
• To evaluate incidences non-IRR AEs.	• Incidence of other adverse events.
• To measure IV amivantamab infusion related times.	• Duration of infusion time for pre-amivantamab infusion medications, IV amivantamab infusion, and post-amivantamab infusion medications on C1D1. • Percent of participants completing amivantamab infusion within 4 hours on C1D1.
• To estimate the anti-tumor activity of IV amivantamab and oral lazertinib following pre-medication with study treatment	• Overall response rate (ORR) and duration of response (DOR) as determined by investigator, according to the Response Criteria in Solid Tumors (RECIST) v1.1.

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

HYPOTHESIS

Through prophylactic treatment with enhanced dexamethasone, montelukast, or methotrexate pre-treatment, the incidence of IV amivantamab IRRs on Cycle 1 Day 1 will be lower than 67%.

4. STUDY DESIGN

4.1. Overall Design

This is a proof-of-concept open-label, multicenter study in participants with EGFR Exon 19 deletion or L858R mutated NSCLC who have progressed on or after osimertinib, and on or after platinum-based chemotherapy, who may benefit from oral lazertinib and IV amivantamab combination therapy. In the study, all participants will receive standard prophylaxis with antihistamine, antipyretic, and glucocorticoid as used in clinical trials of amivantamab and lazertinib.

IRRs with IV amivantamab treatment typically occur early. Among 380 participants who received IV amivantamab at the RP2D, 98% of events occurred on C1D1, and only 5 events occurred past cycle 2 (Park ESMO 2021). There are four cohorts in the study.

Cohort A: Participants will be administered oral dexamethasone (4 mg) twice a day (8 mg total daily dose) on Day -1 (Cycle 1) prior to oral lazertinib and IV amivantamab combination therapy in addition to all other standard premedication.

Cohort A2: Participants will be administered oral dexamethasone (8 mg) twice a day (16 mg total daily dose) on Day -2 and -1 (Cycle 1) and 8 mg approximately one hour prior to the start of the infusion of IV amivantamab on Cycle 1 Day 1.

Cohort B: Participants will be administered oral montelukast (10 mg) in the morning on Days -4, -3, -2, -1, and C1D1 (5 doses total) prior to oral lazertinib and IV amivantamab combination therapy.

Cohort C: Participants will be administered a single dose of 25 mg subcutaneous (SC) methotrexate on any day between Days -7 and Day -3 (Cycle 1) prior to oral lazertinib and IV amivantamab combination therapy.

Study treatments will be administered in addition to all other standard premedication (See Section 1.3, Schedule of Activities and Section 6.1, Suggested Order of Administration).

Up to 126 participants are planned to be treated with amivantamab and lazertinib in the study. For each cohort, the study will have 2 stages treating up to 16 participants (6 at stage 1 and 10 at stage 2) and an expansion stage that can treat up to 24 additional participants. First Cohort A will treat up to 6 participants in Stage 1. Then Cohort B will be activated to treat up to 6 participants in Stage 1. Then Cohort C will be activated to treat up to 6 participants in Stage 1.Cohort A2 will be then activated in Stage 1. If both Cohorts A and A2 have positive results in Stage 1, only one cohort with dexamethasone (Cohort A or A2) would move on to subsequent stages as determined by the SET. For Cohort A2 Stage 1, all cohorts in Stage 2 and expansion phase, the sequential enrollment

will be maintained, however the order will be defined by SET considering data availability and other operational definitions.

In the event of scheduling conflicts or screen failures at the end of cohort enrollment leading to an insufficient number of participants in a cohort, a previous cohort can be backfilled. If a stop decision can be made within a cohort before reaching the planned sample size, which is 6 for Stage 1 and 10 additional participants for Stage 2, the enrollment into this cohort will be closed and the enrollment for the next cohort will start. (see Section 9.2, Sample Size Determination).

A Study Evaluation Team will be commissioned for this study. The Study Evaluation Team will evaluate which cohort(s) may move onto Stage 2 and this process will be repeated on Stage 2 to select possible expansion phase cohorts. Refer to Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema (Figure 1).

4.2. Scientific Rationale for Study Design

4.2.1. Study-Specific Ethical Design Considerations

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

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 Japanese Red Cross (The Japanese Red Cross Society 2018) and American Red Cross (American Red Cross 2020).

4.3. 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 due to progressive disease or has not prematurely discontinued the study for another reason (Section 7) by the end of the study. If death occurs for any other reason than progressive disease, the participant's status will be categorized as early withdrawal.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before administration of oral lazertinib and IV amivantamab. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

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

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

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Participant must have advanced or metastatic NSCLC

3. Progressed on or after prior treatment with osimertinib and platinum-based chemotherapy. Prior use of first-or-second generation EGFR TKI is allowed if administered prior to osimertinib.

4. Previously identified EGFR-mutated NSCLC (EGFR Exon19 deletion or L858R) (identified locally in a Clinical Laboratory Improvement Amendments [CLIA]-certified laboratory [or equivalent])

5. ECOG performance status grade of 0 or 1 (Attachment 1).

6. Participant must have organ and bone marrow function as follows:

    a) Hemoglobin ≥9 g/dL
    b) ANC ≥1.5 x 10^9/L
    c) Platelets ≥75 x 10^9/L
    d) AST and ALT ≤3 x ULN
    e) Total bilirubin ≤1.5 x ULN; participants with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits.
    f) Have an estimated glomerular filtration rate (eGFR), based on the Modified Diet in Renal Disease (MDRD) 4-variable formula (see Attachment 5), of >30 mL/min.

Sex and Contraceptive/Barrier Requirements

7. Male or female (according to their reproductive organs and functions assigned by chromosomal complement at birth).

8. A female participant using oral contraceptives must use an additional barrier contraceptive method (details in Appendix 5: Contraceptive and Barrier Guidance).

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

    a. Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months); permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise, be incapable of pregnancy.

    b. Of childbearing potential and practicing at least 1 highly effective method(s) of birth control consistent with local regulations regarding the use of birth control methods for participants participating in clinical studies, as described below:

        - Practicing true abstinence (when this is in line with the preferred and usual lifestyle of the participant), which is defined as refraining from heterosexual intercourse during the entire period of the study, including up to 6 months after the last dose of dexamethasone, montelukast, methotrexate, lazertinib or IV amivantamab is given. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not considered an acceptable contraceptive method.

        - Have a sole partner who is vasectomized.

        - Practicing 2 methods of contraception, including one highly effective method (ie, established use of oral, intravaginal, transdermal, injected or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine system [IUS], tubal ligation procedures as consistent with local regulations), AND, a second method, (eg, condom with spermicidal foam/gel/film/cream/suppository or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository).

        - Participants must agree to continue contraception throughout the study and continuing through 6 months after the last dose of dexamethasone, montelukast, methotrexate, lazertinib or IV amivantamab.

    Note: If the childbearing potential changes after start of the study (eg, woman who is not heterosexually active becomes active, premenarchal woman experiences menarche) the woman must begin a method of birth control, including 1 highly effective method, as described above.

10. Criterion modified per Amendment-3

10.1. A female participant of childbearing potential must have a negative serum (b-human chorionic gonadotropin [b-hCG]) at screening (within 72 hours of the first dose of study treatment administration) and must agree to further serum or urine pregnancy tests during the study prior to Day 1 of each cycle and at End of Study.

11. A female must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 6 months after receiving the last dose of study drug, oral lazertinib and IV amivantamab. Female participants should consider preservation of eggs prior to study treatment as anti-cancer treatments may impair fertility.

12. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for 3 months after receiving the last dose of study treatment, oral lazertinib and IV amivantamab.

13. If the male participant's partner is a female of childbearing potential, the male participant must use condom with or without spermicide and the female partner of the male participant must also be practicing a highly effective method of contraception (see Appendix 6: Contraceptive and Barrier Guidance). A male participant who is vasectomized must still use a condom (with or without spermicide), but the partner is not required to use contraception.

14. A male participant must agree not to donate sperm for the purposes of reproduction during the study and for 3 months after receiving the last dose of IV amivantamab or lazertinib or study treatment (whichever comes last). Male participants should consider preservation of sperm prior to study treatment as anti-cancer treatments may impair fertility.

15. A male participant must agree not to plan to father a child while enrolled in this study or within 3 months after the last dose of IV amivantamab or lazertinib or study treatment (whichever comes last).

Informed Consent

16. Criterion 16 modified per Amendment-3

16.1. Each participant, or legally authorized representative, where allowed, must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

5.2. Exclusion Criteria

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

Medical Conditions

1. Participant has uncontrolled inter-current illness, including but not limited to:

    - Active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week prior to study treatment] or diagnosed or suspected viral infection)

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

        - No detectable viral load (ie, <50 copies/mL) at screening
        - CD4+ count >300 cells/mm^3 at screening
        - No acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of screening.

        Receiving highly active antiretroviral therapy (HAART). Any changes in HAART due to resistance/progression should occur at least 3 months prior to screening. A change in HAART due to toxicity is allowed up to 4 weeks prior to screening.

        Note: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment). Poorly controlled (persistent) hypertension: systolic blood pressure >180 mm Hg; diastolic blood pressure >100 mm Hg,

        - Uncontrolled diabetes
        - 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
        - Any ophthalmologic condition that is either clinically unstable or requires treatment
        - Psychiatric illness/social situation that would limit compliance with study requirements.
        - 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

- Participant has at screening positive hepatitis B (hepatitis B virus [HBV]) surface antigen (HbsAg)

  Note: Participant 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) a 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.

- Participant has at screening positive hepatitis C 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.

2. 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 first dose of study drug or any of the following within 6 months prior to the first dose of study drug: myocardial infarction, unstable angina, stroke, transient ischemic attack, uncontrolled hypertension, or clinically significant cardiac arrythmia. Clinically nonsignificant thrombosis, such as nonobstructive catheter--associated clots, are not exclusionary.
   - Prolonged QT interval corrected with Fridericia's formula (QTcF) >470 msec
   - Congestive heart failure (CHF), defined as New York Heart Association (NYHA) class III-IV or hospitalization for CHF (any NYHA class; refer to Appendix: New York Heart Association Criteria) within 6 months of study Day 1. (Attachment 4)

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

4. Prior treatment with antiPD-1 or antiPD-L1 antibody within 6 weeks of planned first dose of study treatment or immune-mediated rash from checkpoint inhibitors that has not resolved prior to enrollment.

5. Participant has symptomatic brain metastases. A participant with asymptomatic or previously treated and stable brain metastases may participate in this study. Participants who have completed definitive therapy, are not on steroids, and have a stable clinical status for at least 2 weeks prior to study treatment are allowed. If brain metastases are diagnosed on Screening imaging, the participant may be enrolled, or rescreened for eligibility, after definitive treatment if above criteria are met.

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

7. Prior treatment with amivantamab or lazertinib.

8. Criterion modified per Amendment-3

8.1 Contraindications, allergies, hypersensitivity, or intolerance to lazertinib, IV amivantamab, dexamethasone, montelukast, methotrexate or their excipients.

9. An invasive operative procedure with entry into a body cavity or major surgery (eg, requiring general anesthesia), other than placement of vascular access or percutaneous tumor biopsy, within 4 weeks or without complete recovery before Cycle 1 Day 1. Thoracentesis, if needed and/or clinically indicated, and percutaneous biopsy for tumor tissue sample, if needed, may be done less than 4 weeks prior to Cycle 1 Day 1, as long as the participant has adequately recovered from the procedure prior to the first dose of study treatment in the clinical judgement of the investigator.

Concomitant Therapy

10. Disallowed therapies as noted in Section 6.9, Prior and Concomitant Therapy must be discontinued at least 3 weeks or 5 half-lives, whichever is shorter, before the first dose of study treatment. [See Section 6.9.1] for guidance on drugs that are prohibited and required washout periods].

    a. Participants who are taking systemic steroids, methotrexate, or montelukast for other conditions are excluded (inhaled and/or nasal steroids are allowed), regardless of cohort assignment.

Prior/Concurrent Clinical Study Experience

11. Received an investigational treatment (including investigational vaccines, but not including anticancer therapy) or used an invasive investigational medical device within 6 weeks before the planned first dose of study treatment.

12. Participant with a significant genetic predisposition to venous thromboembolic events (VTE, such as Factor V Leiden).

13. Participant with a prior history of VTE and who are not on appropriate therapeutic anticoagulation as per the NCCN guidelines or local guidelines.

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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and that the participant continues to meet criteria prior to dosing on Cycle 1 Day1. On Cycle 1 Day 1, the participant's condition should be consistent with their baseline, and the participant should have taken regular prescribed medication(s), unless instructed otherwise by the study physician. If a participant's clinical status changes (including any available laboratory results or

receipt of additional medical records) after screening but before the first dose of study treatment is given such that the participant no longer meets all eligibility criteria, supportive treatment may be administered, if necessary, so that eligibility criteria can be met and laboratory test(s) may be repeated once, to determine if the participant qualifies for the study, if there is no interference with the time between prophylactic treatment and Cycle 1 Day 1. If enrollment criteria are not met after further evaluation, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.9, Prior and Concomitant Therapy 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).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

The screening and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copies 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 enrolled into the study, the date seen and age at initial informed consent will be used. Participants who are determined to be eligible for the study due to changes in their condition after initially failing screening must sign a new ICF. Rescreening must be discussed with and approved by the Sponsor's medical monitor on a case-by-case basis.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Participants who are rescreened will be assigned a new participant number.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Dexamethasone
Montelukast
Methotrexate
Lazertinib
Amivantamab

Authorization status in the EU/EEA:
<table><tr><td>Authorized</td><td>Dexamethasone
Montelukast
Methotrexate
Amivantamab</td></tr><tr><td>Unauthorized</td><td>Lazertinib</td></tr></table>The authorized IMPs will not be used in accordance with the terms of their marketing authorization.</td></tr>
<tr><td>Auxiliary Medicinal Product(s) (AxMP)</td><td>None

Authorization status in the EU/EEA:
<table><tr><td>Authorized</td><td>Not applicable</td></tr><tr><td>Unauthorized</td><td>Not applicable</td></tr></table></td></tr>
</table>

Study treatment administration must be captured in the source documents, and the case report form (CRF). Investigational Study Materials (ISM) Dispensing, Accountability, and Reconciliation Log

The study treatments, dexamethasone, montelukast, and methotrexate, will be investigated prior to administration of the background anti-cancer combination regimen of oral lazertinib plus IV amivantamab to assess the incidence of IRRs.

Oral dexamethasone, montelukast, and methotrexate, will be provided under the responsibility of the sponsor. Dexamethasone for injection will be locally sourced and not provided by the sponsor. Refer to the product labeling for a list of excipients.

Background Anti-Cancer Regimen

Oral lazertinib and IV amivantamab, will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients. The combination of IV amivantamab plus oral lazertinib is currently being evaluated in two ongoing phase 3 studies, and additional phase 1/2 studies.

For a definition of oral lazertinib and IV amivantamab overdose, refer to Section 6.8, Treatment of Overdose.

A missed dose is defined as failure to administer IV amivantamab within 1 day of the scheduled dosing date in Cycles 1 (except C1D1) and 2, or failure to administer IV amivantamab within 3 days of the scheduled dosing date in Cycle 3 and beyond. If a dose is missed, as defined above, it will not be made up. Administration may resume at the next planned dosing date. If the first dose in Cycle 2 is delayed, then the dates of all subsequent doses must be maintained as originally scheduled based on Cycle 1 Day 1. All other assessments in SoA should be performed relative to actual IV amivantamab administration, not on the originally scheduled administration day.

Group/Arm Name	**Dexamethasone (Cohort A)**	**Dexamethasone (Cohort A2)**	**Montelukast (Cohort B)**	**Methotrexate (Cohort C)**	**Lazertinib (Cohorts A, A2, B, and C)**	**IV Amivantamab (Cohorts A, A2, B, and C)**
Treatment Name	Dexamethasone **Study Treatment**	Dexamethasone **Study Treatment**	Montelukast **Study Treatment**	Methotrexate **Study Treatment**	Lazertinib **Background Anti-Cancer Regimen**	IV Amivantamab **Background Anti-Cancer Regimen**
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Vial	Tablet	Vial
Unit Dose Strength(s)	4 mg per tablet	4 mg per tablet	10 mg per tablet	25 mg/mL 2mL/vial and 10 mg/mL 5 mL/vial	80 mg per tablet	350 mg/vial with concentration 50 mg/mL in a 7 mL vial.

Group/Arm Name	Dexamethasone (Cohort A)	Dexamethasone (Cohort A2)	Montelukast (Cohort B)	Methotrexate (Cohort C)	Lazertinib (Cohorts A, A2, B, and C)	IV Amivantamab (Cohorts A, A2, B, and C)
Dosage Level(s)	4 mg oral twice a day (8 mg total daily dose) on Cycle 1 Day -1. May be taken without regard to food or meals.	8 mg oral twice a day (16 mg total daily dose) on Cycle 1 Day -2 and -1, and 8 mg approximately1 hour prior to the start of the infusion of IV amivantamab on Cycle 1 Day 1. May be taken without regard to food or meals.	10 mg oral in the morning on days -4, -3, -2, -1 and C1D1 (5 doses total). may be taken without regard to food or meals.	2mL/vial 1 mL/25mg or 5mL vials, 1mL/10mg subcutaneous, single-dose, between D-7 and D-3 before Cycle 1.	Oral 240 mg once daily	1050 mg (for participants <80 kg) or 1400 mg (for participants ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Initial dose of IV amivantamab (Cycle 1, Days 1 and 2), is administered as a split dose over 2 days (eg, Cycle 1 Day 1 [350 mg] and Cycle 1 Day 2 [remainder of dose]). Based on positive study results in Stages 1 and 2, full dose may be administered on Cycle 1 Day 1 in expansion phase after consultation with the sponsor.
Route of Administration	Oral	Oral	Oral	SC Injection	Oral	IV infusion diluted to final volume of 250 mL in 5% dextrose or 0.9% sodium chloride
Use	Experimental	Experimental	Experimental	Experimental	Background treatment	Background treatment
Investigational Medicinal Product (IMP)	Yes	Yes	Yes	Yes	Yes	Yes

Group/Arm Name	Dexamethasone (Cohort A)	Dexamethasone (Cohort A2)	Montelukast (Cohort B)	Methotrexate (Cohort C)	Lazertinib (Cohorts A, A2, B, and C)	IV Amivantamab (Cohorts A, A2, B, and C)
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	depending on regional requirements, dexamethasone may be sourced centrally or locally	depending on regional requirements, dexamethasone may be sourced centrally or locally	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	Bulk. 4 mg tablets Not Child resistant	Bulk. 4 mg tablets Not Child resistant	Bulk. 10 mg tablets Not Child resistant	Bulk. 2mL/vial. Or Bulk. 5mL/vial. Not Child resistant	Bulk. 80 mg tablets Not Child resistant	Bulk. 350 mg/vial with concentration 50 mg/mL in a 7 mL vial. Not Child resistant
Delivery Instructions	Do not crush tablets	Do not crush tablets	Do not crush tablets	2mL/vial. Administer 1mL/25mg SC in the abdomen or the thigh. Or 5mL/vial: Administer 1mL/10mg SC in the abdomen or thigh.	Do not crush tablets	For IV administration. Do not mix or dilute with other drugs. Required preinfusion medications (a corticosteroid, an antihistamine, and an antipyretic) must be administered as described in Section 1.3

Group/Arm Name	Dexamethasone (Cohort A)	Dexamethasone (Cohort A2)	Montelukast (Cohort B)	Methotrexate (Cohort C)	Lazertinib (Cohorts A, A2, B, and C)	IV Amivantamab (Cohorts A, A2, B, and C)
Food/Fasting Requirement	May be taken without regard to food or meals.	May be taken without regard to food or meals.	May be taken without regard to food or meals.	N/A	May be taken without regard to food or meals.	N/A
Current/Former Name(s) or Alias(es) (Not an all-inclusive list of Former or Alias names)	Decadron (dexamethasone)	Decadron (dexamethasone)	Singulair (montelukast)	Rasuvo (methotrexate)	Laclaza (lazertinib)	Rybrevant (IV amivantamab)

Suggested Order of Administration in Cohort A

Medication	Dose	Route of Administration	Recommended Dosing Window
Study Treatment	Dexamethasone 4 mg twice a day (8 mg total daily dose)	Oral	1 day before the first amivantamab infusion in Cycle 1
Glucocorticoid	Days 1 and 2 of Cycle 1: Dexamethasone 10 mg	IV	Start 60 90 minutes before amivantamab infusion
Antipyretic	Paracetamol (acetaminophen) 650 to 1000 mg (or equivalent)*	IV or oral	Start 15 30 minutes before amivantamab infusion
Antihistamine	Diphenhydramine 25 mg or equivalent*	IV or oral	
Background anti cancer treatment	Lazertinib 240 mg	Oral	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
Background anti cancer treatment	Amivantamab	IV	1050 mg (for participants <80 kg) or 1400 mg (for participants ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Initial dose of IV amivantamab (Cycle 1, Days 1 and 2), is administered as a split dose over 2 days (eg, Cycle 1 Day 1 [350 mg] and Cycle 1 Day 2 [remainder of dose]). Based on positive study results in Stages 1 and 2, full dose may be administered on Cycle 1 Day 1 in expansion phase after consultation with the sponsor.

*required premedication for amivantamab

Suggested Order of Administration in Cohort A2

Medication	Dose	Route of Administration	Recommended Dosing Window
Study Treatment	Dexamethasone 8 mg twice a day (16 mg total daily dose) on Cycle 1 Days 2 and 1 and 8 mg approximately one hour prior to start of the infusion of IV amivantamab on Cycle 1 Day 1	Oral	2 days before the first amivantamab infusion in Cycle 1 C1D1 oral dose 60 90 minutes before strat of first amivantamab infusion
Glucocorticoid	Days 1 and 2 of Cycle 1: Dexamethasone 10 mg	IV	Start 60 90 minutes before amivantamab infusion
Antipyretic	Paracetamol (acetaminophen) 650 to 1000 mg (or equivalent)*	IV or oral	Start 15 30 minutes before amivantamab infusion
Antihistamine	Diphenhydramine 25 mg or equivalent*	IV or oral	
Background anti cancer treatment	Lazertinib 240 mg	Oral	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
Background anti cancer treatment	Amivantamab	IV	1050 mg (for participants <80 kg) or 1400 mg (for participants ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Initial dose of IV amivantamab (Cycle 1, Days 1 and 2), is administered as a split dose over 2 days (eg, Cycle 1 Day 1 [350 mg] and Cycle 1 Day 2 [remainder of dose]).

			Based on positive study results in Stages 1 and 2, full dose may be administered on Cycle 1 Day 1 in expansion phase after consultation with the sponsor.

Suggested Order of Administration in Cohort B

Medication	Dose	Route of Administration	Recommended Dosing Window
Study Treatment	Montelukast 10 mg	Oral	Montelukast taken in the morning on days -4, -3, -2, -1 and C1D1 (5 doses total). Montelukast should be taken at approximately the same time each day, approximately 24 hours apart, if possible
Glucocorticoid	Days 1 and 2 of Cycle 1: Dexamethasone 10 mg	IV	Start 60-90 minutes before amivantamab infusion
Antipyretic	Paracetamol (acetaminophen) 650 to 1000 mg (or equivalent)*	IV or oral	Start 15-30 minutes before amivantamab infusion
Antihistamine	Diphenhydramine 25 mg or equivalent*	IV or oral	
Background anti-cancer treatment	Lazertinib 240 mg	Oral	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
Background anti-cancer treatment	Amivantamab	IV	1050 mg (for participants <80 kg) or 1400 mg (for participants ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Initial dose of IV amivantamab (Cycle 1, Days 1 and 2), is administered as a split dose over 2 days (eg, Cycle 1 Day 1 [350 mg] and Cycle 1 Day 2 [remainder of dose]). Based on positive study results in Stages 1 and 2, full dose may be administered on Cycle 1 Day 1 in expansion phase after consultation with the sponsor.

*required premedication for amivantamab

Suggested Order of Administration in Cohort C

Medication	Dose	Route of Administration	Recommended Dosing Window
Study treatment	Methotrexate 25 mg	SC	Single dose on any day between Days 7 and Day 3 (Cycle 1) prior to oral Lazertinib and IV amivantamab combination therapy.
Glucocorticoid	Days 1 and 2 of Cycle 1: Dexamethasone 10 mg	IV	Start 60 90 minutes before amivantamab infusion
Antipyretic	Paracetamol (acetaminophen) 650650 to 1000 mg (or equivalent)*	IV or oral	Start 15 30 minutes before amivantamab infusion
Antihistamine	Diphenhydramine 25 mg or equivalent*	IV	

Background anti cancer treatment	Lazertinib 240 mg	Oral	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
Background anti cancer treatment	Amivantamab	IV	1050 mg (for participants <80 kg) or 1400 mg (for participants ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. Initial dose of IV amivantamab (Cycle 1, Days 1 and 2), is administered as a split dose over 2 days (eg, Cycle 1 Day 1 [350 mg] and Cycle 1 Day 2 [remainder of dose]). Based on positive study results in Stages 1 and 2, full dose may be administered on Cycle 1 Day 1 in expansion phase after consultation with the sponsor.

*required premedication for amivantamab

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study treatments (dexamethasone, montelukast, methotrexate) and background anticancer therapy (oral lazertinib, and IV amivantamab) must be stored at controlled temperatures according to the requirements on the drug product label and protected from light prior to use.

Refer to the Site Investigational Product Procedures Manual (SIPPM) for additional guidance on dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab received at the site is inventoried and accounted for throughout the study. The dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab administered to the participant must be documented on the Investigational Study Materials (ISM) Dispensing, Accountability, and Reconciliation Log. All dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab will be stored and disposed of according to the SIPPM. Study site personnel must not combine contents of the dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab containers.

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

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

Dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab will be supplied only to participants participating in the study. Returned dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab must not be dispensed again, even to the same participant. Dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab 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 dexamethasone, montelukast, methotrexate, lazertinib, and IV amivantamab are provided in the SIPPM.

6.3. Assignment to Study Intervention

Treatment Allocation

Procedures for Randomization

Not Applicable

6.4. Blinding, Masking

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

6.5. Treatment Compliance

The study personnel at the study site will account for all dexamethasone, montelukast, methotrexate, dispensed and for appropriate return or destruction, if approved by the sponsor. The certificates of delivery, return, and/or destruction should be signed and filed in the Investigator Site File.

Dexamethasone, montelukast, methotrexate, are to be prescribed only by the principal investigator or a qualified physician listed as a sub investigator. Dexamethasone, montelukast, methotrexate, may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing. Methotrexate will be administered as a single dose of 25 mg SC between Day -7 and Day -3 (Cycle 1) prior to oral lazertinib and IV amivantamab combination therapy by qualified study site personnel and the details of administration will be recorded in the electronic case report form (eCRF) (including date, start, and stop times of the participant visit and volume administered). Dispensing of all dexamethasone, montelukast, methotrexate, must also be recorded in the participant's source documents.

6.5.1. IV Amivantamab and Oral Lazertinib Treatment Compliance

The study personnel at the study site will account for all oral lazertinib and IV amivantamab dispensed and for appropriate return or destruction, if approved by the sponsor. The certificates of delivery, return, and/or destruction should be signed and filed in the Investigator Site File.

Oral lazertinib and IV amivantamab are to be prescribed only by the principal investigator or a qualified physician listed as a subinvestigator. Oral lazertinib, and IV amivantamab may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing. IV amivantamab will be administered as an IV infusion by qualified study site personnel and the details of each administration will be recorded in the electronic case report form (eCRF) (including date, start, and stop times of the IV infusion and volume infused). Dispensing of all oral lazertinib, and IV amivantamab must also be recorded in the participant's source documents.

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

6.6. Dose Modification

Dose modifications are not allowed for study treatments dexamethasone, montelukast or methotrexate,

Adverse Events of Clinical Interest

Dexamethasone

Not Applicable.

Montelukast

The safety risk information is based on prolonged use of montelukast, and the safety profile of a limited administration as described in this protocol has not been established. Neuropsychiatric events have been reported in participants receiving montelukast. These events have been noted in adults, teenagers, and younger participants, and include among others: anxiety, depression, aggressiveness, agitation, attention, and memory impairment, sleeping disorders (insomnia, somnambulism, dream anomalies), seizures, paresthesia, hypoesthesia, as well as suicidal thoughts and behavior. (Farah 2018)

Methotrexate

Participants should be monitored for bone marrow, liver, lung and kidney toxicities as described in the Schedule of Assessments following the single dose of methotrexate.

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

When dose modification is required, modification should occur as listed below. (Table 1)

If the experienced toxicity is felt to be attributable to either IV amivantamab or oral lazertinib, then the dose of the responsible agent should be preferentially modified.

Table 1: Dose Modifications for Oral lazertinib and IV amivantamab

Combination dosing level	Dose of oral lazertinib (mg)	Dose of IV amivantamab (mg) IV (dose <80 kg/dose ≥ 80kg)
1	240	1050/1400
2	160	1050/1400
3	160	700/1050
4	80	700/1050
5	Discontinue	1050/1400

If holding of oral lazertinib or IV amivantamab is considered clinically indicated, the decision to hold oral lazertinib or IV amivantamab dosing should be guided by the experienced toxicity and the likelihood of either treatment contributing to the toxicity, based upon the safety profile of both treatments (Refer to the respective IBs or consult with the Sponsor).

If both treatments are held, and are to be restarted, oral lazertinib should be restarted first and dosed for approximately 7 days prior to the next infusion of IV amivantamab.

Treatment of Infusion-related Reactions

Participants who experience early symptoms of IRRs, manifesting as, but not limited to, chills, nausea, dyspnea, flushing, chest discomfort, vomiting, or any other symptoms during the time of the infusion, should have their infusions interrupted, if indicated, and the symptoms managed according to the recommendations provided in Table 2. With the initial dose of IV amivantamab (Cycle 1, Days 1 and 2), interruption of the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR. All NCI-CTCAE Grade 3 or 4 infusion-related reactions should be reported within 24 hours to the Sponsor.

Table 2: Management of Infusion-related Reactions

Toxicity Grade*	Treatment	Premedication at all subsequent dosing
Grade 1 or 2 **Grade 1:** Mild reaction	• Interrupt IV amivantamab infusion if IRR is suspected and monitor participant until reaction symptoms resolve. • Resume the infusion at 50% of the infusion rate at which the reaction occurred. • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated. • Include corticosteroid with premedications for subsequent dose.	Antihistamine, antipyretic, and glucocorticoid
Grade 2: Mild to moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment		Antihistamine, antipyretic, and glucocorticoid Consider meperidine if participant experiences chills and rigors.
Grade 3 Severe reaction Grade 3: prolonged (ie, not rapidly responsive to		Based on severity of symptoms, consider permanent discontinuation of IV amivantamab. Discussion with Sponsor

Toxicity Grade*	Treatment	Premedication at all subsequent dosing
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)	• Interrupt IV amivantamab infusion and administer supportive care medications. Monitor participant until reaction symptoms resolve. • Resume the infusion at 50% of the infusion rate at which the reaction occurred. • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated. • Include corticosteroid with premedications for subsequent dose. For recurrent Grade 3, permanently discontinue IV amivantamab.	required before continuing with subsequent dosing.
Grade 4: life-threatening; pressor or ventilator support indicated	Permanently discontinue IV amivantamab	
General	**Prophylactic medications** (after initial event) may be used as described in the IV amivantamab product label. Appropriate personnel and appropriate resuscitation equipment should be available in or near the infusion room and a physician should be readily available during the infusion of IV amivantamab	

*Per NCI CTCAE Version 4.03

6.6.1. Infusion-related Reactions

Infusion-related reactions have been observed during treatment with other monoclonal anti-EGFR antibodies. The severity of infusion reactions has been variable. Refer to Summary of Data and Guidance for Investigators in the current version of the IV amivantamab Investigator's Brochure.

Signs and symptoms of IRR include chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, and fever.

During the IV amivantamab infusion, participants should be clinically monitored at regular intervals (including an assessment prior to the start of infusion). The monitoring should include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation measurements. Participants must remain at the infusion center for monitoring for at least 2 hours after the end of the first dose of IV amivantamab (Cycle 1 Day 1), and at least 1 hour after Cycle 1 Day 2, after which time, vital signs should be obtained (See SOA).

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

Pre-infusion Medications for IV amivantamab

Required pre-infusion medications (a corticosteroid, an antihistamine, and an antipyretic) must be administered as described in Section 6.1 (Suggested Order of Administration) and Section 1.3 (Schedule of Activities).

6.6.2. Liver Chemistry Abnormalities

Liver chemistry stopping criteria have been established to provide safety to the participants and to better assess the etiology of a liver event during the development of new investigational products. Liver chemistry should be monitored as part of serum chemistry laboratory tests according to the Schedule of Activities (Section 1.3) and Appendix 2: Clinical Laboratory Test. The liver chemistry stopping criteria include any of the following:

1. ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) and bilirubin ≥2×ULN (if baseline was normal; ≥2 x baseline if baseline was abnormal) (>35% direct bilirubin) (AST or ALT ≥3×ULN [if baseline was normal; ≥3×baseline if baseline was abnormal] and INR >1.5, if INR measured).
   a) Exception to the bilirubin elevation is made if the participant has Gilbert's disease and the elevated bilirubin is predominantly unconjugated.
   b) This event, if confirmed upon repeat, should be reported as an SAE.
2. ALT or AST >5×ULN (if baseline was normal; ≥5×baseline if baseline was abnormal) for 2 weeks or ALT or AST >8×ULN (if baseline was normal; ≥8×baseline if baseline was abnormal).
3. ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) if associated with the appearance or worsening of symptoms of liver injury, hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.
4. Persistent elevation of ALT or AST ≥3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal) for ≥4 weeks. The sponsor's medical monitor should be consulted for participants with baseline ALT and/or AST near 3×ULN (if baseline was normal; ≥3×baseline if baseline was abnormal).

Liver chemistry should be repeated within 1 to 3 days. If any of the chemistry stopping criteria are confirmed upon repeat, then assessments listed below should be conducted. If no alternative etiology of liver toxicity is identified, oral lazertinib and IV amivantamab treatment should be permanently discontinued.

Liver Event Follow-up Requirements

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

- Monitor liver chemistries (ALT, AST, ALP, bilirubin, and INR), creatinine phosphokinase, and lactate dehydrogenase, 1 to 2 times per week until resolution, stabilization, or return to participant's baseline values.

- Monitor clinical condition closely.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, or known hepatotoxins.
- Record alcohol use in the eCRF.
- Check the viral hepatitis serology as appropriate and include:

  Hepatitis A immunoglobulin M (IgM) antibody

  Hepatitis B surface antigen and Hepatitis B core antibody (IgM)

  Hepatitis C ribonucleic acid (RNA)

  Hepatitis E IgM antibody

  Cytomegalovirus IgM antibody

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

Resumption of oral lazertinib and IV amivantamab administration may be considered if the following criteria are met:

- Drug-related hepatotoxicity has been excluded.
- A reversible underlying cause not associated with oral lazertinib and IV amivantamab (eg, alcohol use or concomitant medication) is clearly identified and agreed upon in consultation with sponsor's medical monitor.
- Liver chemistry abnormalities have resolved, or values have returned to baseline.

6.6.3. 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 oral lazertinib and IV amivantamab combination, 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 combination therapy,** 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: either a topical antibiotic (clindamycin, mupirocin, or fusidic acid) on sun-exposed skin, or an oral antibiotic (such as doxycycline 100 mg once daily, minocycline 100 mg once daily, or cephalexin 500 mg once daily).

  A topical corticosteroid of medium to low potency twice daily on the face and chest (such as alclometasone 0.05% or desonide 0.05% cream) may also be considered.

Reactive Management Recommendations

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

- 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, refer to the following recommendations:

Reactive Management Recommendations for Pruritic Lesions:

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).
- For skin fissures, use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is recommended.
- For xerosis, fragrance-free moisturizing creams or sprays are recommended.
- For desquamation, emollients and mild soap are recommended.
- After the rash is controlled, consider gradually tapering the antibiotic.

A suggested algorithm for stepwise management of rash is provided in Table 3.

Table 3: 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 oral lazertinib and IV amivantamab
2	• Initiate reactive management as above • Reassess after 2 weeks	• Initiate supportive care management. • Reassess after 2 weeks; if rash does not improve, consider [IV amivantamab] 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 (20 30 mg/day) • Reassess after 2 weeks • Consider dermatology consultation and manage rash per recommendation	• Withhold oral lazertinib and IV amivantamab and initiate supportive care management. • Upon recovery to ≤ Grade 2, resume IV amivantamab at reduced dose. • After consultation with the Medical Monitor may restart oral lazertinib at current dose level or consider dose reduction of oral lazertinib • If no improvement within 2 weeks, permanently discontinue treatment
4	• 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 (20 30 mg/day) • Reassess after 2 weeks • Consider dermatology consultation and manage rash per recommendation	• Permanently discontinue IV amivantamab and hold oral lazertinib. • Consider restarting oral lazertinib per investigator assessment of causality, once resolved.
Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN)	• Consult dermatologist and manage rash per recommendation	• Permanently discontinue IV amivantamab and hold oral lazertinib • Consider restarting oral 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 IV amivantamab must be withheld due to toxicity for 2 consecutive doses, then oral lazertinib and IV amivantamab cannot be restarted without consultation from the Medical Monitor. Participants considered by the investigator and sponsor to be benefiting from treatment may be continued, potentially at a lower dose upon satisfactory resolution of the toxicity.
c. Resolution defined as: ≤Grade 1 non-hematologic toxicity or back to baseline.
d. For example, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream.

Scalp Rash

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

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

- Initiation of a systemic antibiotic (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily) may also be used to treat acute scalp infection.

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

6.6.4. Pulmonary Toxicity

Participants with NSCLC are at risk of multiple adverse events affecting pulmonary function, including disease progression, pulmonary embolus, infectious pneumonias, and more rarely, drug related Interstitial lung disease (ILD)/pneumonitis. Participant respiratory status should be assessed at every visit; any clinically significant change in respiratory status, including a change in radiographic lung images, should prompt immediate investigation into the etiology in accordance with local practice/guidelines to institute appropriate treatments and to rule out early ILD/pneumonitis. If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pulmonary adverse event is observed, including ILD/pneumonitis, oral lazertinib and IV amivantamab should be withheld, and appropriate treatment management should be promptly initiated.

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion, which may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible, and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and careful investigation.

Oral lazertinib and IV amivantamab can cause ILD/pneumonitis. Participants with a medical history of ILD, drug induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD have not been studied. As of June 2021, 2 fatal events of pneumonitis have been reported in 351 (0.6%) participants treated with the combination of oral lazertinib and IV amivantamab. Participants should be monitored for symptoms indicative of ILD/pneumonitis (eg, dyspnea, cough, fever). If symptoms develop, interrupt treatment with amivantamab pending evaluation of these symptoms for suspected ILD and initiate appropriate treatment as necessary. Discontinue amivantamab in participants with confirmed ILD.

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 examination, including full assessment of vital signs (with pulse oximetry)
- Unscheduled radiological assessment, including 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

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

6.6.5. Venous Thromboembolic Events

Participants with NSCLC are at risk of developing complications, including VTE events. Investigators should closely monitor all participants receiving the combination of amivantamab and lazertinib 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.

All study participants receiving the combination of amivantamab and lazertinib are recommended to receive prophylactic-dose anticoagulation as per local guidelines during the first 4 months of combination therapy. Vitamin K antagonists are not recommended due to numerous drug interactions. The benefit-risk assessment for participants to tolerate prophylactic-dose anticoagulation is at the discretion of the treating investigator. Notably, prophylactic-dose anticoagulation has been found to be safe and effective in multiple prior studies (Carrier 2019, Rutjes 2020).

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 treatment can be resumed at the discretion of the investigator. In the case of a recurrent VTE whilst on therapeutic anticoagulation therapy, the combination of amivantamab and lazertinib should be permanently discontinued. Participants may continue to receive treatment with either amivantamab or lazertinib (but not both) at the discretion of the treating investigator. For participants that have experienced VTE, if symptoms persist or in case of worsening VTE, further imaging studies (which may include doppler studies) should be performed to assess the resolution of the event with corrective measures, as per the investigator's discretion.

6.7. Continued Access to Lazertinib and IV Amivantamab After the End of the Study

At the end of their participation in the study, participants who have completed the main part of the study (Section 4.3 End of Study Definition) and are benefiting from the IV amivantamab and oral

lazertinib, as determined by their investigator, will be able to receive continued access via post-study independent requests from their investigators.

All serious adverse events that occur while the participant is receiving IV amivantamab and/or oral lazertinib and within 30 days after the last dose of IV amivantamab and/or oral lazertinib or until the start of subsequent anti-cancer therapy, if earlier, will be collected and reported to the sponsor. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of oral lazertinib and IV amivantamab, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Please refer to Section 8.3 for the details.

Pregnancy reporting should continue as described in Section 8.3.5.

In instances where the investigator feels a participant may continue to receive clinical benefit from further treatment with IV amivantamab and oral lazertinib after documented disease progression (eg, new CNS disease), the case must be discussed with the sponsor's medical monitor, who in conjunction with the investigator, will determine if treatment beyond RECIST v1.1 defined progression is indicated. If the participant is treated beyond documented disease progression, disease assessments will continue according to the schedule in Section 1.3, and the investigator and sponsor medical monitor will review clinical benefit after each disease assessment.

6.8. Treatment of Overdose

In the event of an overdose of study treatment (dexamethasone, montelukast, methotrexate) or background anticancer therapy (oral lazertinib and IV amivantamab), the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Montelukast

No specific information is available on the treatment of overdosage with montelukast. In the event of overdose, it is reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

Methotrexate

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the

serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin. In cases of massive overdosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall 1996). In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported.

IV Amivantamab and/or Oral Lazertinib

There are no data on overdose from studies of amivantamab or lazertinib (refer to IB for each agent).

6.9. Prior and Concomitant Therapy

Pre-study therapies administered up to 28 days before first dose of oral lazertinib and IV amivantamab must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning at screening and continuing until 30 days after the last dose of oral lazertinib or IV amivantamab treatment, or until the end of study visit (whichever is later), or until the start of a subsequent systemic anti-cancer therapy, if earlier. Concomitant therapies should also be recorded beyond 30 days after the last dose of oral lazertinib or IV amivantamab in conjunction with the following situations.

- Grade 3 or Grade 4 adverse events being followed per Section 8.3.1
- Adverse events reported after 30 days following the last dose of study drug, oral lazertinib or IV amivantamab if considered related to study drug, oral lazertinib or IV amivantamab, the sponsor must be notified.

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

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

6.9.1. Prohibited or Restricted Concomitant Therapy/DRUG INTERACTIONS

Disallowed therapies must be discontinued at least 3 weeks or 5 half-lives, whichever is shorter, before the first dose of study treatment (dexamethasone, montelukast or methotrexate).

To avoid study bias, participants who are taking systemic steroids, methotrexate, or montelukast for other conditions are excluded (inhaled and/or nasal steroids are allowed), regardless of cohort assignment.

Methotrexate

Methotrexate is contraindicated in pregnancy, alcoholism or liver disease, immunodeficiency syndromes, preexisting blood dyscrasias, and hypersensitivity to methotrexate (MTX).

NSAIDs, salicylates, TMP, penicillin, warfarin, valproate, proton pump inhibitors, cyclosporin, cisplatin increases the risk of MTX toxicity in the blood; aminoglycosides, neomycin, probenecid reduces the absorption of MTX.

Drug Interactions:

- Aspirin, NSAIDs, and steroids: concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity.
- Proton pump inhibitors: concomitant use may elevate and prolong serum methotrexate levels and cause increased toxicity.
- Oral antibiotics
- Hepatotoxins
- Theophylline
- Folic acid and antifolates
- Mercaptopurine
- Nitrous oxide

The most significant and serious interactions are with NSAIDs and proton pump inhibitors (PPIs) since these are very common therapeutic choices.

As methotrexate is highly plasma protein bound, any drug that displaces methotrexate from proteins can increase its blood levels.

Montelukast

Montelukast is contraindicated in participant with a history of hypersensitivity to the drug or its components. For participants with phenylketonuria (PKU), caution should be exercised with phenylalanine-containing formulations.

Oral lazertinib and IV amivantamab

Prohibited Medications and Therapies

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

- Any chemotherapy, anti-cancer therapy (other than oral lazertinib and IV amivantamab), or experimental therapy.
- Concomitant use of medications, herbal supplements and/or ingestions of foods with known potent inducer effects on CYP3A4/A5 activity are prohibited and must have been discontinued for an appropriate period before administration of lazertinib. Drugs that are potent inhibitors of CYP3A4 activity are restricted and should be avoided, when possible, or used with caution. Guidance on drugs that are prohibited, require close monitoring and washout periods is given in Attachment 2.

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.

- Lazertinib is an inhibitor of P-glycoprotein (P-gp), multi-drug resistance protein 4 (MRP4), Breast Cancer Resistance Protein (BCRP), and Organic Cation Transporter 1 (OCT1). Therefore, concomitant administration of medications, herbal supplements and/or ingestions of foods with that are substrates of P-gp, MRP4, BCRP, or OCT1 are not recommended and if necessary, should be used with caution. A list of substrates of P-gp, MRP4, and BCRP is provided in Attachment 3.
- Lazertinib has the potential for reversible and time dependent inhibition of CYP3A4. Concomitant use of CYP34A substrate drugs should be avoided. If no other alternatives exist monitor participants more closely for adverse reactions. Guidance on CYP3A4 substrates that require close monitoring (Attachment 2 require close monitoring).

7. DISCONTINUATION OF DEXAMETHASONE, MONTELUKAST, METHOTREXATE, ORAL LAZERTINIB, AND IV AMIVANTAMAB AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment (Dexamethasone, Montelukast or Methotrexate)

A participant's dexamethasone, montelukast or methotrexate treatment must be discontinued if:

- The participant withdraws consent to receive dexamethasone, montelukast or methotrexate
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue dexamethasone, montelukast or methotrexate
- The participant becomes pregnant (refer to Section 10.5, Appendix 5: Contraceptive and Barrier Guidance)
- Noncompliance with study drug administration or procedure requirements.

Participants refusing the assigned study treatment will withdraw from study and will not be eligible to receive IV amivantamab and oral lazertinib in this study. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant.

7.2. Discontinuation of Anti-cancer Background Regimen (Oral lazertinib, and IV amivantamab

Study treatment will continue until disease progression or until early discontinuation criteria are met. A participant's oral lazertinib, and IV amivantamab treatment must be discontinued if:

- The participant withdraws consent to receive oral lazertinib and IV amivantamab
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue oral lazertinib and IV amivantamab
- The participant becomes pregnant (refer to Section 10.5, Appendix 5: Contraceptive and Barrier Guidance)
- Noncompliance with study drug administration or procedure requirements.

If a participant discontinues oral lazertinib and IV amivantamab for any reason, then the EOS assessments should be obtained according to the Schedule of Activities. Lazertinib, and IV amivantamab assigned to the participant who discontinued oral lazertinib, and IV amivantamab may not be assigned to another participant. Additional participants will not be entered in the study.

In instances where the investigator feels a participant may continue to receive clinical benefit from further treatment with IV amivantamab and oral lazertinib after documented disease progression (eg, new CNS disease), the case must be discussed with the sponsor’s medical monitor, who in conjunction with the investigator, will determine if treatment beyond RECIST v1.1 defined progression is indicated. If the participant is treated beyond documented disease progression,

disease assessments will continue according to the schedule in Section 1.3, and the investigator and sponsor medical monitor will review clinical benefit after each disease assessment.

7.3. 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
- Noncompliance with dexamethasone, montelukast or methotrexate administration.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent [or assent] 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.

7.3.1. Withdrawal From the Use of Research Samples

Not Applicable

7.4. Lost to Follow-up

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

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

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

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

The total blood volume to be collected from each participant depends upon the duration of participation and the required blood volume for local laboratory assessments, but through 3 cycles of treatment and the End of Study visit, the total amount of blood drawn from each participant for the study is approximately 115 mL (110 mL for safety and 5 mL for pregnancy testing [women only]). Depending on country-specific regulations, volume requirements at local laboratories, and availability of blood collection tubes, the total blood volume may vary (see Table 4).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 4: Volume of Blood to be Collected From Each Participant Through Cycle 3

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post treatment assessments)			
Hematology	5 mL	10	50 mL
Serum chemistry	5 mL	10	50 mL
Serology (HIV, hepatitis)[b]	5 mL	1	5 mL
Serum β hCG pregnancy tests	5 mL	1	5 mL
Coagulation (PT/APTT)[b]	5 mL	1	5 mL
Approximate Total			115 mL

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Additional coagulation and serology tests may be performed as clinically indicated
Note: An indwelling intravenous cannula may be used for blood sample collection.
β hCG Human chorionic gonadotropin, PT Prothrombin time, APTT activated prothrombin test time

Sample Collection and Handling

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

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

Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Clinical protocol

- IBs for lazertinib and IV amivantamab and product labeling for dexamethasone, montelukast and methotrexate,
- IPPI and SIPPM
- NCI-CTCAE, Version 5.0
- Electronic data capture (eDC) manual
- Sample ICF

8.1. Study Assessments

The objective of this study is to assess prophylaxis efficiency of dexamethasone, montelukast or methotrexate prior to oral lazertinib, and IV amivantamab infusion to reduce first-dose IRRs. The primary endpoint is rate of IRRs occurring on Cycle 1 Day 1 following administration of oral lazertinib and IV amivantamab combination therapy. Signs and symptoms of IRR include: chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, and fever. Investigator reported adverse events of IRR and associated symptoms and severity will be assessed (see Section 3, Objectives and Endpoints).

During the IV amivantamab infusion, participants should be clinically monitored at regular intervals (including an assessment prior to the start of infusion). Vital signs should be measured within 30 minutes prior to IV amivantamab administration. On Cycle 1 Day 1, vital signs should also be measured 2 hours ±15 min after the IV amivantamab administration. The monitoring should include pulse/heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation measurements. Participants must remain at the infusion center for monitoring for at least 2 hours after the end of the first dose of IV amivantamab (Cycle 1 Day 1), after which time, vital signs should be obtained (See Vital Signs row in SOA).

Secondary endpoints are rates and severity of individual AEs associated with IRR signs and symptoms (chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, fever) as defined by the NCI CTCAE Criteria, Version 5.0 during Cycle 1 Day 1, rates and severity of these AEs on subsequent administrations up to 3 months, severity of infusion-related reactions, incidence of other AEs, and median duration of infusion time for pre-amivantamab infusion medications, IV amivantamab infusion, post-amivantamab infusion medications, investigator assessed tumor response and duration of response.

Disease Assessments and Evaluation of Tumor Response

Disease assessments will be performed as scheduled regardless of any dose modifications, according to the Schedule of Activities (Section 1.3). More frequent radiological assessments are allowed, if clinically indicated. CT scans of the disease location(s) should be performed with an IV contrast agent. Participants not able to undergo CT scans with IV contrast (eg, due to allergy or renal insufficiency) may have non-contrast CT of the thorax and MRI scan of the abdomen and pelvis with IV contrast at baseline and during the study, if approved by the sponsor. Contraindications to the CT scan with IV contrast that develop post-baseline should be discussed with the sponsor medical monitor. MRI should be used to evaluate sites of disease that cannot be

adequately imaged using CT (eg, brain). Brain MRI is not required at Screening unless clinically indicated (eg, prior brain metastases or suspicion of brain metastases). Subsequent brain imaging is allowed per local practice for surveillance. Identical methodology (CT scan with contrast agent and/or MRI) should be used for disease assessment at baseline, and throughout the course of the study, to characterize each identified and reported lesion to document disease status. Techniques other than CT or MRI may be used, based upon investigator judgment, local standard of care, and RECIST v1.1 guidelines for the use of these alternative techniques. For example, bone scintigraphy may be used to identify bone lesions at Screening or new bone lesions during treatment, but bone lesions will not be considered target lesions. Sites will be required to retain digital copies of radiological images (eg CT, MRI) used for disease assessments for potential independent review. Assessment of responses for solid tumors will be performed according to RECIST v1.1 criteria. RECIST assessments at baseline should be representative of all areas involved with metastases. At any time, disease progression is clinically suspected, tumor assessments should be performed. Irradiated or partially excised lesions will generally be considered not measurable at baseline and may be followed as non-target lesions, except for a lesion that has progressed following local radiation or surgery, provided the investigator and sponsor medical monitor agree it is measurable and will not confound the efficacy evaluation. Additionally, a lesion that was biopsied during Screening should only be assessed as a target lesion if a post-biopsy CT confirms that it still meets measurability criteria and is amenable to accurate and reproducible measurement. Tumor response will be reported by the investigator in the CRF. The following response criteria (according to RECIST v1.1) are acceptable: complete response, partial response, stable disease, progressive disease, unevaluable. A response of partial response or complete response must be confirmed by repeat assessments ≥4 weeks from the initial observation. For a response to qualify as stable disease, follow-up measurements must have met the stable disease criteria at least once at a minimum interval not less than 6 weeks after the first dose of study agent. If symptomatic deterioration (on the basis of global deterioration of health status) is recorded as the basis for determining disease progression, then the clinical findings used to make the determination must be specified in the CRF and documented in the source documents. Every effort should be made to document radiographic progression even after discontinuation of treatment for symptomatic deterioration, but prior to subsequent therapy, if possible.

Response assessment will be determined for all participants in accordance with RECIST v1.1. Disease will be assessed at baseline, 6 weeks (+1 week) after Cycle 1 Day 1 (ie, Day 42-Day 49) for the first assessment, and then every 6 (±1) weeks relative to Cycle 1 Day 1, until disease progression by imaging, start of new anti-cancer therapy, or withdrawal of consent. Scheduled disease assessments for participants who have completed 12 cycles and are clinically stable (both clinical symptoms and radiographical assessments), may be extended to 12-week intervals at the discretion of the investigator, after confirmation with Medical Monitor.

8.2. Safety Assessments

Details regarding the Study Evaluation Team are provided in Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

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

8.2.1. Physical Examinations

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

On Day 1 of each cycle, directed physical examinations of involved organs and other body systems, as indicated, will be performed and participant body weight will be obtained using a calibrated scale. At all visits (per SoA) after the IV amivantamab administration, participants should be questioned for skin and eye symptoms, with physical examination as appropriate, and specialty referral as indicated. In addition, participants receiving the combination of amivantamab and lazertinib should similarly be questioned for signs and symptoms of VTE events, and a focused physical examination of extremities and evaluation of respiratory status (including pulse oximetry) should be performed, particularly during the first 4 months of assigned therapy. Any changes from baseline should prompt consideration for further diagnostic evaluation, including unscheduled CT exam or lower-extremity Doppler evaluation.

8.2.2. Vital Signs

Vital sign measurements will include the following assessments as indicated in the Schedule of Activities. Vital signs should be measured within 30 minutes prior to IV amivantamab administration. On Cycle 1 Day 1, vital signs should also be measured 2 hours ±15 min after the IV amivantamab administration. For all visits, collect vital sign measurements ≤30 minutes before amivantamab infusion, at 30-minute intervals (±5 minutes) during each amivantamab infusion, and at the end of the infusion (±5 minutes) (See SOA).

Temperature, pulse/heart rate, respiratory rate, O2 saturation, blood pressure will be assessed.

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. Only a single ECG tracing is required unless the result is both abnormal and clinically significant.

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.

If the first ECG tracing is abnormal and clinically significant, triplicate ECGs are required. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

The study will also include the following analysis according to the time points provided in the SoA: urinalysis, Echocardiography/multigated acquisition scan.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

8.2.5. Pregnancy Testing

Serum pregnancy testing will be performed at screening (within 72 hours prior to the first study treatment administration) and as clinically indicated for women of childbearing potential only.

A negative serum or urine pregnancy test is required within 72 hours before Day 1 of each cycle, at the End of Study visit, and 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.

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

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

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

Further details on AEs, SAEs, and PQCs can be found in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug or IV amivantamab and/or oral lazertinib or until the start of subsequent anti-cancer therapy, if earlier.

Serious Adverse Events

All SAEs, as well as PQCs, 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 oral lazertinib and IV amivantamab, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

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

Unsolicited Adverse Events

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

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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or

PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

8.3.5. Pregnancy

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

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 an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments or disease related. 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 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: 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 events. Additional information will be collected for these events (see Section 6.6). 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. Pharmacokinetics

Not Applicable

8.5. Pharmacodynamics

Not Applicable

8.6. Genetics and Pharmacogenomics

Not Applicable

8.7. Biomarkers

Not Applicable

8.8. Immunogenicity Assessments

Not Applicable

8.9. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The primary hypothesis of this study is that through prophylactic treatment with dexamethasone, methotrexate or montelukast, the incidence of IV amivantamab IRRs on Cycle 1 Day 1 will be lower than 67%.

In this study, the null hypothesis that the true IRR rate is 0.67 or higher will be tested against a one-sided alternative for each prophylaxis cohort.

9.2. Sample Size Determination

Simon's two-stage design (Simon, 1989) will be used separately for each cohort. Details of the design are below.

- Stage 1: Treat up to 6 participants

  If the number of participants with IRR $\geq$ 4 (out of 6), the cohort stops at Stage 1.

Otherwise, move on to Stage 2.

- Stage 2: Treat up to 10 additional participants

  Reject the null hypothesis in that cohort if the number of participants with IRR ≤ 8 (out of 16), the cohort will be declared promising in lowering IRR.

Each cohort can be expanded by adding up to 24 additional participants (up to 40 participants total per expanded cohort).

For each cohort, the Simon's two-stage design was identified as optimal on minimizing the expected number of participants through PASS 15 given the following assumptions:

- The IRR is 67% without prophylaxis treatment (null hypothesis) and true IRR rate is 34%
- One-sided type-I error controlled within 0.05 and the target power of 80%.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF
Randomized	Not Applicable
Treated Set	All participants who take at least 1 cycle of oral lazertinib and IV amivantamab combination therapy preceded by prophylaxis treatment for the given cohort.

9.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Detailed specifics and algorithms will be provided in the Statistical Analysis Plan.

9.4.1. General Considerations

Data will be summarized using descriptive statistics. Categorical values will be summarized using the number of observations and percentages as appropriate. Where appropriate, two-sided exact 95% confidence intervals will be provided. Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate.

9.4.2. Primary Endpoint

The primary endpoint is the Rate of IRRs occurring on Cycle 1 Day 1 following administration of oral lazertinib and IV amivantamab combination therapy. Primary analysis of IRR rate will be performed after the last participant receives the first infusion or at the end of study, whichever comes first. Treated participant population will be used for primary analysis. IRR rate along with 95% confidence interval will be estimated for the cohorts that have moved to second stage of the trial.

9.4.3. Secondary Endpoints

Secondary endpoints are rates and severity of individual AE signs and symptoms of IRR (chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, fever) occurring on Cycle 1 Day 1, and on subsequent administrations of IV amivantamab for up to 3 months, the severity of infusion-related reactions, incidence of other adverse events, rates of IRR following subsequent administrations, median duration of infusion time for pre-amivantamab infusion medications, IV amivantamab infusion, and post-amivantamab infusion medications and investigator assessed ORR and duration of response.

The secondary endpoint of IRR rate on subsequent administrations of IV amivantamab will be analyzed similarly to the primary endpoint using treated participant population. Infusion time will be summarized descriptively.

Final analysis of secondary endpoints will be conducted after last participant completes last scheduled study assessment.

Disease Assessments and Evaluation of Tumor Response

The secondary endpoint of ORR with confirmed best overall responses will be performed approximately 12 weeks after the last participant receives the first infusion or at the end of study, whichever comes first. Due to the limited number of participants and the nature of this study, all anti-tumor analyses are considered descriptive. ORR is defined as the proportion of participants who achieve either a complete (CR) or partial response (PR) as defined by investigator assessment using RECIST v1.1. Observed ORR along with their two-sided exact 95% CIs will be presented for each cohort as appropriate.

Duration of response will be estimated using the Kaplan-Meier method and calculated as time from initial response of CR or PR to progressive disease (PD) or death due to underlying disease, whichever comes first, only for participants who achieve CR or PR.

9.4.4. Safety Analyses

All participants who received at least one cycle of IV amivantamab and oral lazertinib combination therapy preceded by prophylaxis treatment will be included in the safety analysis.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study treatments (dexamethasone, montelukast or methotrexate) or background anti-cancer therapy (oral lazertinib and IV amivantamab) through the day of last dose plus 30 days is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by system organ class, preferred term, worst grade experienced by the participant.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

Electrocardiogram data will only be collected at screening visit and as clinically indicated thereafter. No analysis is planned for this data.

Vital Signs

The percentage of participants with vital signs values (including temperature, pulse/heart rate, respiratory rate, and blood pressure [systolic and diastolic]) supine beyond clinically important limits will be summarized and abnormal changes from baseline will be reported as adverse events.

Physical Examinations

Abnormal changes from baseline in physical examination findings will be reported as adverse events.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9.4.5. Other Analyses

A Study Evaluation Team (SET) will be established as noted in Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

9.5. Interim Analysis

The study has two stages for each cohort using Simon's 2-stage optimal design to assess the primary endpoint of incidence of IRRs. One interim analysis will occur after all participants from stage 1 complete Cycle 1 Day 1.

Another interim analysis will take place after all participants from stage 2 complete Cycle 1 Day 1.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANA	antinuclear antibody
AST	aspartate aminotransferase
BCRP	Breast Cancer Resistance Protein
cMet	tyrosine-protein kinase mesenchymal epithelial transition
CNS	central nervous system
CRF	case report form(s) (paper or electronic as appropriate for this study)
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
FDA	Food and Drug administration
GCP	Good Clinical Practice
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HBsAb	hepatitis B surface antibody
HBcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB(s)	investigator brochure(s)
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	immunoglobulin M
ILD	interstitial lung disease
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
IRR(s)	infusion-related reaction(s)
ISM	investigational study materials
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition
MRP	multi-drug resistance protein 4
MTX	methotrexate
NCI	National Cancer Institute
NP	neuropsychiatric
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
PCC	protocol clarification communication
P-gp	P-glycoprotein
PKU	phenylketonuria
PO	orally
PPI	proton pump inhibitors
PQC(s)	product quality complaint(s)
RA	rheumatoid arthritis

RP2D	recommended Phase 2 dose
SAE(s)	serious adverse event(s)
SET	study evaluation team
SIPPM	Site Investigational Product Procedures Manual
SoA	schedule of activities
TEN	toxic epidermal necrolysis
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
VTE	venous thromboembolic

10.2. Appendix 2: Clinical Laboratory Tests

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

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Hemoglobin	White Blood Cell (WBC) count: Neutrophils (ANC)
Clinical Chemistry	Sodium Potassium Chloride Creatinine Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase	Total bilirubin Alkaline phosphatase Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Albumin
	Potential Hy's Law case (ALT or AST ≥3 x ULN and Tbili ≥2 x ULN) reporting requirements are defined in Section 8.3.1.	
• Other Screening Tests	• Serum pregnancy testing at screening and within 72 hours prior to the first administration of study treatment for women of childbearing potential only. Additional serum or urine pregnancy tests may be performed, prior to Day 1 of each cycle and at the End of Study, and 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. • Serology Human immunodeficiency virus antibody. HbsAg and antibody to hepatitis B virus (HBV) core antigen (antiHBc). Antibody to hepatitis B virus surface (antiHBs) performed if HBsAg is positive. Hepatitis B core and/or hepatitis B surface antibody: if positive, further testing (deoxyribonucleic acid [DNA] by polymerase chain reaction) to rule out active disease or chronic carrier. Hepatitis C virus (HCV) antibody: if positive for HCV, further testing (by ribonucleic acid [RNA] polymerase chain reaction) should be performed to rule out active infection. Clinical and laboratory signs of active HBV/HCV infection should be closely monitored for participants who have history of HBV/HCV infection during study treatment. • Coagulation PT / INR prothrombin time APTT (activated partial thromboplastin time) • Urinalysis	

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

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

Protocol Clarification Communications

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

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

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

Protocol Amendments

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

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment or background anti-cancer treatments

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Country/Territory Selection

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

Other Ethical Considerations

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

10.3.2. Financial Disclosure

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

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

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent

should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants 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 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 the participant'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 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 is obtained.

10.3.4. Recruitment Strategy

Various resources will be developed to support trial awareness and provide information and education to potential participants about the trial and clinical trials in general. Materials may include informational brochures, advertisements, study guides, provider referral materials, advocacy outreach and diversity resources.

10.3.5. 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 includes 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 consent also addresses the 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. 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.

10.3.6. Committees Structure

SET Evaluation Team

A SET Evaluation Team will be established to monitor data at a regular interval. 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 SET Evaluation Team will make recommendations regarding the continuation of the study.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding IV amivantamab and oral 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 research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to

accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of IV amivantamab and oral 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 analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

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

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

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the 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.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

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

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study.

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

10.3.9. Case Report Form Completion

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

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

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

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

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

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

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant and prophylactic medication; treatment receipt/dispensing/return/destruction records; study treatment, oral lazertinib and IV amivantamab administration information; and date of study completion and reason for early discontinuation of oral lazertinib and IV amivantamab 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, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

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

10.3.11. Monitoring

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

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

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

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

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

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

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

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

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

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

Serious Adverse Event

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

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*.

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

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study treatment, lazertinib or IV amivantamab 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 AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For IV amivantamab and oral lazertinib, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study treatment, lazertinib or IV amivantamab is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment, lazertinib or IV amivantamab administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment, lazertinib or IV amivantamab administration and the AE.

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

10.4.3. Severity Criteria

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

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

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

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

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

10.4.4. Special Reporting Situations

Safety events of interest on dexamethasone, montelukast, methotrexate, lazertinib, or IV amivantamab in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of dexamethasone, montelukast, methotrexate, lazertinib, or IV amivantamab
- Suspected abuse/misuse of dexamethasone, montelukast, methotrexate, lazertinib, or IV amivantamab
- Accidental or occupational exposure to dexamethasone, montelukast, methotrexate, lazertinib, or IV amivantamab
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without participant exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to dexamethasone, montelukast, methotrexate, lazertinib, or IV amivantamab from breastfeeding.

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

10.4.5. Procedures

All Adverse Events

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

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

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

Serious Adverse Events

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

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

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

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

Expected progression of disease should not be considered or reported as an adverse event (or serious adverse event).

However, if determined by the investigator to be more likely related to the study treatment, lazertinib or IV amivantamab than being expected from the underlying disease, the treatment-invoked progression (ie, the treatment--invoked signs/symptoms of such progression) should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 10.4: Adverse Events, Serious Adverse Events, Product Quality

Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Death that is attributed by the investigator explicitly to progression of disease should not be considered nor reported as an adverse event (or serious adverse event).

However, if determined by the investigator to be more likely related to the study treatment, lazertinib or IV amivantamab than being expected from the underlying disease, the treatment-invoked death due to progression should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 10.4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form).

Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure, should be documented on the appropriate eCRF forms (eg, the Clinical Progression form).

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

10.4.6. Product Quality Complaint Handling

Definition

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

Procedures

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

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

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

  Has congenital abnormalities resulting in sterility.

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

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

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

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

Examples of Contraceptives

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

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

10.6. Appendix 6: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING COVID-19 PANDEMIC

It is recognized that the COVID-19 pandemic may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study treatment will be followed.

If, as a result of the COVID-19 pandemic scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow up. Modifications to protocol-required assessments may be permitted using the examples contained in this appendix, after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatments and withdrawal from the study should be documented with the prefix "[COVID-19 pandemic]-related" in the CRF.

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

10.7. Appendix 7: Protocol Amendment History

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

All Protocol Amendments

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 3	All	27-Apr-2023
Amendment 2	All	12-Dec-2022
Amendment 1	All	29-Aug-2022
Original Protocol	All	29-Jun-2022

Amendment 3 (27 April 2023)

Overall Rationale for the Amendment: The overall purpose of this protocol amendment is to incorporate changes that were recommended by health authorities in response to the Urgent Safety Measure (VTE risk with combination of amivantamab and lazertinib) released on July 22,2022. This amendment also serves to provide clarity on the schedule of assessments, objectives, and study procedures.

The changes made to the clinical protocol 61186372NSC2005 as part of Protocol Amendment 3 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.7 Appendix 7: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
6.5.5. Venous Thromboembolic Events	The following text was added: If a VTE event is diagnosed, the participant should be treated with treatment-dose anticoagulation as per local guidelines. Vitamin K antagonists are not recommended because of numerous drug interactions. For VTE events associated with clinical instability (eg, respiratory failure or cardiac dysfunction) in participants receiving the combination of amivantamab and lazertinib, study treatment should be held until the patient recovers from the event. Thereafter, the treatment can be resumed at the discretion of the investigator. In the case of a recurrent VTE whilst on therapeutic anticoagulation therapy, the combination of amivantamab and lazertinib should be permanently discontinued. Participants may continue to receive treatment with either amivantamab or lazertinib (but not both) at the discretion of the treating investigator. For participants that have experienced VTE, if symptoms persist or in case of worsening VTE, further imaging studies (which may include doppler studies) should be performed to assess the resolution of the event with corrective measures, as per the investigator's discretion. The following text was deleted: ~~After completion of the duration of treatment for active VTE events, the investigator may consider~~	To clarify and align with the VTE risk mitigation and management.

Section Number and Name	Description of Change	Brief Rationale
	~~continuing treatment-dose anticoagulation or transition to prophylactic-dose anticoagulation while continuing the combination of amivantamab and lazertinib. Dose modification is not required for a VTE event.~~	
5.2. Exclusion Criteria	New criteria added per Amendment-3: 12. Participant with a significant genetic predisposition to venous thromboembolic events (VTE; such as Factor V Leiden). 13. Participant with a prior history of VTE and who are not on appropriate therapeutic anticoagulation as per the NCCN guidelines or local guidelines.	To clarify and align with the VTE risk mitigation and management.
Title Page	The title was updated from: ~~Evaluation of Amivantamab Infusion Related Reaction Mitigation~~ to: Subcutaneous Methotrexate, Oral Dexamethasone or Oral Montelukast for the Prevention of Infusion Related Reaction Associated with Amivantamab, an EGFR-MET bispecific antibody, Among Post-osimertinib Treated EGFRm NSCLC ; SKIPPirr, a Phase 2 Study	To reflect the trial objective on the protocol title.
1.1. Synopsis (Objectives and Endpoints; Efficacy Evaluation) 3. Objectives and Endpoints	The following text was removed: IRR, when amivantamab is given in combination with oral lazertinib, to reduce	To correct errors.
1.1. Synopsis (Hypothesis) 3. Objectives and Endpoints (Hypothesis) 9.1 Statistical Hypotheses	The following text was updated from reduced by half, from 67% to 34% to lower than 67%.	
1.2 Schema	The term C1D-1 was replaced by Day-1.	
1.3 SoA (Visit Window)	The visit window for Screening was updated to -28 to -8	
1.3 SoA (Duration of infusion time row)	The duration of infusion time collection is not applicable prior to C1D1, therefore removed from the prophylaxis administration visit.	
1.3 SoA (Weight)	The weight assessment is marked at Screening.	
2.1. Study Rationale	The following text was deleted: The IRR rates at first infusion were 38% and 59% (respiratory symptoms, 20% and 33%), respectively, in those who did or did not receive montelukast. The text in secondary endpoints was updated from	

Section Number and Name	Description of Change	Brief Rationale
3. Objectives and Endpoints 5.4. Screen Failures 6.1. Study Treatment(s) Administered Table	'3 months' to 'the end of the third cycle' and Median time to complete was updated to Duration of infusion time The term randomized was updated to enrolled. All references to (single dose) auto injectors were deleted and replaced with 2mL/vial where applicable for column 'Methotrexate (Cohort C). The dosage level for 'Methotrexate (Cohort C) was replaced from ~~Administer SC in the abdomen or the thigh~~ to 1 ml/25mg subcutaneous, single-dose, between D-7 and D-3 before Cycle 1.	
1.1. Synopsis (Efficacy Evaluation) 8.1 Study Assessments (Disease Assessments and Evaluation of Tumor Response) 1.3. SoA (Disease assessment/Tumor response evaluation)	The following text was deleted: ~~Subjects who permanently discontinue treatment for any reason other than radiological disease progression or withdrawal of consent will continue disease assessments per the protocol schedule until radiological progression is confirmed, or new anti-cancer therapy begins, whichever comes first.~~ The following text was deleted: ~~For subjects who discontinue treatment prior to disease progression, radiological assessments should continue to be performed as per the protocol schedule until disease progression is documented. If a discontinued subject begins a new cancer therapy prior to progression, disease assessment should occur prior to initiation of the new therapy.~~	To exclude procedures after end of study and to align with Schedule of Assessments.
1.3. SoA (Inclusion/ exclusion criteria row)	The following text was added: Rescreening must be discussed with and approved by the Sponsor's medical monitor on a case-by-case basis.	To clarify procedures related to inclusion/exclusion criteria.
1.3 SoA (Medical history row) 1.3. SoA (Time and Motion row) 1.3. SoA (Safety Assessments: Hematology Serum Chemistry Coagulation Urinalysis Pregnancy test) 1.3. SoA (Diphenhydramine and paracetamol / acetaminophen) 1.3. SoA Vital signs	The following text was added: Include any planned surgeries. The line item for 'Time and Motion' was added. The following text was added to the column 'Notes': See Appendix 2. The pre-infusion medications diphenhydramine and paracetamol/acetaminophen are marked for Cycle 1, Days 8, 15, and 22. The vital signs are marked for Cycle 2 Day 15 and Cycle 3 (and all cycles thereafter) Day 15. The following text was deleted:	To clarify requirements in medical history - including planned surgeries while on study treatment. To evaluate duration of patient care. To clarify required assessments. To correct an error as diphenydramine and paracetamol/acetominphen are to be used as pre-infusion medication in all amivantamab infusions. To correct an error as vital signs are to be assessed on all visits per this study.

Section Number and Name	Description of Change	Brief Rationale
8. Study Assessments and Procedures (Sample Collection and Handling)	~~Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.~~	To correct an error as this study is using local labs.
8.1. Study Assessments 1.3 SoA (Vital signs) 8.2.2. Vital Signs	The following text was added: (See Vital Signs row in SOA) The following text was added: For all visits, collect vital sign measurements ≤30 minutes before amivantamab infusion, at 30-minute intervals (±5 minutes) during each amivantamab infusion, and at the end of the infusion (±5 minutes). (See SOA).	To clarify study procedures related to vital signs.
10.2.Appendix 2: Clinical Laboratory Tests (Clinical Chemistry)	Serum glutamic-oxaloacetic was replaced by Serum ***glutamic-pyruvic transaminase*** The term direct/indirect was deleted.	To correct an error and to clarify study procedures.
1.3. SoA (Serology)	The following text was added to the column 'Notes': HIV antibody, HBsAg, HBsAb, HBcAb, anti-HCV antibody, HBV viral load (if needed) and HCV viral load (if needed).	To clarify study procedures related to serology tests.
1.3. SoA (Pregnancy test)	The following text was added: Within 72 hours of day 1 of each cycle and at End of Study The text in bold was updated to the column 'Notes': Serum test required at screening **and urine or serum test** within 72 hours prior **to each IV amivantamab infusion and at End of Study.**	To clarify study procedures related to pregnancy tests.
1.3. SoA (Chest X-ray) 6.5.4. Pulmonary Toxicity 8.1. Study Assessments 8.2.3. Electrocardiograms	The row for Chest X-ray was deleted The text '~~chest X-ray~~' was deleted.	To align with the latest safety guidance for amivantamab plus lazertinib.
2.2. Background	The text was modified as: the infusion should be interrupted if IRR is suspected and resumed at a reduced infusion rate for Grade 3 IRR or permanently discontinued for Grade ≥**4** and recurrent Grade 3 IRR	To correct an error regarding when the infusion rate should be reduced versus having the infusion permanently discontinued based on IRR grade.
2.2.1. Benefit-Risk Assessment	Pregnant women ~~with psoriasis or rheumatoid arthritis~~ was deleted.	To clarify the study procedures regarding treatment received by pregnant woman.
3. Objectives and Endpoints	The text in bold was added to primary endpoints: Rate of IRRs occurring on Cycle 1 Day 1 following administration of oral lazertinib and IV amivantamab combination therapy, **which is defined as IRR events with onset time within 24**	To clarify the primary endpoint timeframe.

Section Number and Name	Description of Change	Brief Rationale
	hours of the start of the first amivantamab infusion and prior to the start of amivantamab infusion on Cycle 1 Day 2. A new secondary objective was added: To evaluate incidence and severity of IRR on subsequent cycles. And the following endpoints were updated from non-IRR AEs secondary objective to the newly added secondary objective: -Rates of IRR following subsequent administrations. -Severity of infusion-related reactions.	To clarify a secondary objective and related endpoints.
4.1. Overall Design	The following text was added: Up to 126 patients could be enrolled in the study. The study will have 2 stages and an expansion cohort of that will enroll up to 24 additional patients. The following text was deleted and updated to ~~After cohorts A, B and C have each completed Stage 1, the Study Evaluation Team will evaluate which cohort(s) may move onto Stage 2 and this process will repeat for Stage 2~~ Similarly in Stage 2, the selected cohorts (if more than one) will be enrolled sequentially as well. If a stop decision can be made within a cohort before reaching the planned sample size, which is 6 for Stage 1 and 10 additional patients for Stage 2, the enrollment into this cohort will be closed and the enrollment for the next cohort will start. The following text was added: The Study Evaluation Team will evaluate which cohort(s) may move onto Stage 2 and this process will be repeated on Stage 2 to select expansion phase cohorts.	To clarify study enrollment.
4.3. End of Study Definition (Study Completion Definition)	The following text in bold was added: A participant will be considered to have completed the study if he or she has died before the end of the study **due to progressive disease** or has not prematurely discontinued the study for another reason (Section 7) by the end of the study. **If death occurs for any other reason, than progressive disease, the participant's status will be categorized as early withdrawal.**	To clarify end of study.
5.1. Inclusion Criteria	The criterion 10 was updated and text in bold was added as: 10. **Criterion modified perAmendment-3** 10.1. A female participant of childbearing potential must have a negative serum (b-human chorionic gonadotropin [b-hCG]) at screening (within 72 hours of the first dose of study treatment administration) and must agree to further serum or urine pregnancy tests during the	To clarify the timing and frequency of pregnancy test.

Section Number and Name	Description of Change	Brief Rationale
8.2.5. Pregnancy Testing	study **prior to each** IV **amivantamab infusion and at End of Study.** The following text was deleted: ~~Additional serum or urine pregnancy tests may be performed.~~ and updated to: A negative serum or urine pregnancy test is required within 72 hours before Day 1 of each cycle, at the End of Study visit	
5.1. Inclusion Criteria	The criterion 16 was updated and text in bold was added as: 16. **Criterion 16 modified per Amendment-3** 16.1. Each participant, **or legally authorized representative, where allowed,** must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.	For clarification and consistency with other sections of protocol regarding the ICF procedure.
5.2. Exclusion Criteria	The criterion 8 was updated and text in bold was added as: 8. **Criterion modified per Amendment-3** 8.1. Contraindications, allergies, hypersensitivity, or intolerance to oral lazertinib, IV amivantamab, dexamethasone, montelukast, methotrexate or their excipients. ~~Methotrexate is contraindicated in pregnancy, alcoholism or liver disease, immunodeficiency syndromes, preexisting blood dyscrasias, and hypersensitivity to methotrexate.~~	For clarification on exclusion criteria for drug interactions section.
5.4. Screen Failures	The following texts were added: Rescreening must be discussed with and approved by the Sponsor's medical monitor on a case-by-case basis.	To clarify rescreening procedure.
6.1. Study Treatment(s) Administered	The following text was added to the row 'Current/Former Name(s) or Alias (es) as: (Not an all-inclusive list of Former or Alias names).	For clarification of study drug names.
6.5.1. Infusion-related Reactions	The text in bold was updated in the following sentence: Subjects must remain at the infusion center for monitoring for at least **2 hours** ~~1 hour~~ after the end of the first dose of IV amivantamab (Cycle 1 Day ~~2~~**1**), **and at least 1 hour after Cycle 1 Day 2**, after which time, vital signs should be obtained **(See SOA)**.	To clarify study procedures related to post infusion monitoring.
6.5.2. Liver Chemistry Abnormalities	The following text was deleted: ~~including bilirubin fractions,~~	To align with the latest safety guidance for amivantamab plus lazertinib.
6.7. Treatment of Overdose (IV Amivantamab and/or Oral Lazertinib	The following text was updated to: There are no data on overdose from studies of amivantamab or lazertinib (refer to IB for each agent). from: ~~No clinical studies have been conducted to assess a toxic threshold for IV amivantamab. Doses up to 1,750 mg have been assessed without~~	To clarify and align with the latest safety guidance for amivantamab plus lazertinib.

Section Number and Name	Description of Change	Brief Rationale
	~~identification of a maximum tolerated dose (MTD). In the event of an overdose, stop amivantamab, undertake general supportive measures until clinical toxicity has diminished or resolved.~~ ~~Lazertinib: There is no specific antidote designed for lazertinib overdose. In the event of an acute overdose, close monitoring and supportive care should be provided.~~	
7.2. Discontinuation of Anti-cancer Background Regimen (Oral lazertinib, and IV amivantamab)	The following text was added: Study treatment will continue until disease progression or until early discontinuation criteria are met. The text in bold was updated in the following sentence: If a participant discontinues lazertinib and IV amivantamab for any reason ~~before the EOS visit~~, then the ~~end of treatment~~ **EOS** ~~and post-treatment~~ assessments should be obtained according to the Schedule of Activities ~~and follow-up visits should continue after study treatment is discontinued~~.	For clarification of treatment duration. To clarify study procedures and align the text with Schedule of Activities
8. Study Assessments and Procedures (Overview) 8. Study Assessments and Procedures Table 4	The following text in bold w added: The total blood volume **to be collected from each participant depends upon the duration of participation and the required blood volume for local laboratory assessments, but through 3 cycles of treatment and the End of Study visit, the total amount of blood drawn from each participant** for the study is approximately **115** mL (1**10** mL for safety and 5 mL for pregnancy testing [women only]). **Depending on country-specific regulations, volume requirements at local laboratories, and availability of blood collection tubes, the total blood volume may vary (see** Table 4). The title of the Table 4 was updated in bold: Volume of Blood to be Collected From Each Participant **Through Cycle 3** Serology and B HCG were made standalone tests, Footnote b was deleted: ~~Serum chemistry includes serology (HIV, hepatitis) and serum b-hCG pregnancy tests~~ Footnote c was updated to b The term PTT was updated to APTT Superscript for chemistry was removed and superscript for serology and coagulation was updated.	To clarify the total volume of blood to be collected. To correct an error.
8.2.3. Electrocardiograms	The following text was added: Only a single ECG tracing is required unless the result is both abnormal and clinically significant and If the first ECG tracing is abnormal and clinically significant, triplicate ECGs are required.	To align with the latest safety guidance for amivantamab plus lazertinib.

Section Number and Name	Description of Change	Brief Rationale
8.3.5. Pregnancy 10.2. Appendix 2: Clinical Laboratory Tests (Other Screening Tests)	The following text in bold was added: Any participant who becomes pregnant during the study must **discontinue further study treatment and complete End of Study assessments.** The following text was added:prior to each amivantamab IV infusion and at the End of Study	To clarify the study procedure for participants who become pregnant.
8.3.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	The following text in bold was added: All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments **or disease related. 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 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).**	To clarify the reporting procedure related to events related to PD.
8.8. ~~Health Economics OR~~ Medical Resource Utilization and Health Economics	~~N/A~~ was deleted, and the following text was added: Time and motion studies will evaluate participant chair time, treatment room time, duration of treatment administration, and active HCP time for drug preparation, treatment administration, and post-treatment monitoring.	To clarify study assessments.
9.2. Sample Size Determination	The text in bold was added: For each cohort, the Simon's two-stage design **was identified as optimal on minimizing the expected number of subjects through PASS 15 given the following assumptions:** • **The IRR is 67% without prophylaxis treatment (null hypothesis) and true IRR rate is 34%** • **One-sided type-I error controlled within 0.05 and the target power of 80%.** and the following text was deleted: ~~yields a Type I error rate (one sided) of 0.04 and power of 0.8 when the true IRR rate is 0.34 (50% reduction in IRR). Under null hypothesis, expected sample size of the trial (for each cohort) is estimated to be 9.1 and probability of early stopping is estimated to be 0.687.~~	To provide clarification on sample size calculation.
9.4.4. Safety Analyses	The following text in bold was added:	For clarification.

Section Number and Name	Description of Change	Brief Rationale
	All subjects who received at least one cycle of **IV amivantamab** and **oral** lazertinib combination therapy preceded by prophylaxis treatment will be included in the safety analysis.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 2 (12 December 2022)

Overall Rationale for the Amendment:

The overall rationale for the amendment is to add regulatory agency identifier numbers.

The changes made to the clinical protocol 61186372NSC2005 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.7 Appendix 7: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Title page	Added the EudraCT and IND numbers	To add regulatory agency identifier numbers.
Throughout	Updated "country" to "country/territory"	To align with current template

Amendment 1 (29 August 2022)

Overall Rationale for the Amendment: To implement guidance related to participant safety and dose modification for rash-related adverse events. This amendment also serves to implement safety measures related to venous thromboembolic events (VTEs).

The changes made to the clinical protocol 61186372NSC2005 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Venous thromboembolic (VTE)-related footnote "a" for physical examination and recommendation of prophylactic-dose anticoagulation during the first 4 months of amivantamab and lazertinib treatment were added.	To implement safety measures related to VTE.
2.3. Benefit-Risk Assessment	The rationale for and aims of the VTE-related safety measures were added.	
6.5.5. Venous Thromboembolic Events	A new section to provide guidance on management of VTE events was added.	
8.2.1. Physical Examinations	Additional guidance for detection of VTE through physical examination was added.	
8.3.7. Adverse Events of Special Interest	VTE was added to the list of AEs of special interest. It was noted that events of VTE should follow standard reporting guidelines.	
11. References	Three new references (Carrier 2019, NCCN 2022, and Rutjes 2020) were added to the list of references to support VTE-related information.	
6.5.3. Rash-related Adverse Events	The suggested algorithm for management of Grade 4 rash was modified in Table 3.	To provide specific guidance for rash-related (including TEN)

Section Number and Name	Description of Change	Brief Rationale
	Management of severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN) was added to Table 3.	adverse events and clarify for the safety of participants.
10.4.3. Severity Criteria	The following text was removed: Any AE will be graded as per the above. Should an AE become fatal or have a fatal outcome, the original grade is not changed but "fatal" shall be reported as an outcome. Only in the following cases a Grade 5 event is to be reported: • Death NOS: only for deaths due to unknown reason (pending follow-up information; if further information becomes available this should be adapted as adequate) • Sudden death: a sudden (defined as instantaneous or within 1 hour of the onset of symptoms) cessation of life that cannot be attributed to a CTCAE term.	To ensure all Grade 5 events are captured.
5.4. Screen Failures	The participant number assignment requirement for rescreened participants was removed.	To facilitate study operation.
10.1. Appendix 1: Abbreviations and Definitions	Abbreviations of Independent Data Monitoring Committee, TEN, and VTE were added to the abbreviation list.	To include minor updates.
Throughout the protocol	Minor formatting changes were made.	Minor errors were noted.

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ATTACHMENTS

Attachment 1: Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, 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).

Attachment 2: Listing of Prohibited or Restricted Medications and Therapies for Lazertinib

Medications Inhibiting CYP3A4/5	
Contraindicated Drugs	**Withdrawal Period Prior To Lazertinib start**
ketoconazole, itraconazole, indinavir, 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 Inducing CYP3A4/5	
Contraindicated drugs	**Withdrawal Period Prior To Lazertinib start**
phenytoin, rifampicin, St. John's Wort, carbamazepine, primidone, griseofulvin, barbiturates, troglitazone, pioglitazone, oxcarbazepine, nevirapine, efavirenz, rifabutin	3 weeks
Phenobarbitone	5 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, paritaprevir4, saquinavir, simeprevir, simvastatin, sirolimus, tacrolimus, tilidine3, tipranavir, triazolam, vardenafil, voclosporin, zanubrutinib	1 day

This listing is not intended to be exhaustive, and a similar restriction will apply to other agents known to induce or inhibit CYP3A4/5 activity. Appropriate medical judgment is required, and any of these medications should be utilized, if clinically indicated, for the treatment of adverse events. Please contact the medical monitor with any questions.

Attachment 3: Substrates of P-glycoprotein (P-gp), Multi-drug Resistance Protein 4 (MRP4), and Breast Cancer Resistance Protein (BCRP)

Transporter	Substrates
P gp	Dabigatran etexilate Digoxin Fexofenadine Loperamide Auinidine 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

Attachment 4: New York Heart Association Criteria

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

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

Classification of Functional Capacity and Objective Assessment. Available at http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes of Heart Failure UCM 306328 Article.jsp Accessed 18 March 2019.

Attachment 5: MDRD formula for eGFR

Modified Diet in Renal Disease Formula

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

eGFR (MDRD) mL/min per 1.73 m^2 = 175 x [standardized S_{Cr} (mg/dL)]$^{-1.154}$ x age$^{-0.203}$ x $1.212_{\text{if black}}$ x $0.742_{\text{if female}}$

Creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4.

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

Alternatively, for standardized serum creatinine (S_{Cr}) in **µmol/L**, the estimated glomerular filtration rate (eGFR) is:

eGFR (MDRD) mL/min per 1.73 m^2 30,849 x [standardized S_{Cr} (µmol)/L)] $^{1.154}$) x age $^{0.203}$ x $1.212_{\text{if black}}$ x $0.742_{\text{if female}}$

Sources: Levey (2006)

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

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

Signature

User	Date	Reason
PPD	21-Aug-2023 16:49:55 (GMT)	Document Approval