**Janssen Pharmaceutical K.K.***

**Clinical Protocol**

**Protocol Title**
**A Phase 2, Open-label Study of Amivantamab in Subjects With Previously Treated Advanced or Metastatic Gastric or Esophageal Cancer**

**Protocol 61186372GIC2001; Phase 2**
**AMENDMENT 2**

**Amivantamab JNJ-61186372**

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

**Status:** Approved
**Date:** 16 August 2022
**Prepared by:** Janssen Pharmaceutical K.K
**EDMS number:** EDMS-RIM-208737, 3.0

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

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 2 | 16-Aug-2022 |
| Amendment 1 | 10-Nov-2021 |
| Original Protocol | 16-Apr-2021 |

## Amendment 2 (16 August 2022)

**Overall Rationale for the Amendment:** The overall purpose of the amendment is to allow for potential exploration of higher dose levels of amivantamab based on emerging data and per recommendation of the CTMT. Toxic epidermal necrolysis (TEN) is added in the suggested algorithm for management of rash. Additionally, some clarifications and corrections to the text are included.

The changes made to the clinical protocol 61186372GIC2001 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 10.9 Appendix 9: Protocol Amendment History.

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis - NUMBER OF PARTICIPANTS | A maximum of approximately **302** participants will be enrolled in the combined Phase 2a and Phase 2b populations, in the event the efficacy observed in both Phase 2a cohorts warrants full enrollment in their respective Phase 2b cohorts.<br>Approximately, 41 response evaluable participants will be enrolled in each of Phase 2a GC and EC arms (including extension cohort). The Phase 2b GC expansion or EC expansion cohorts will evaluate the antitumor activity of amivantamab in GC and EC patients, using biomarker selection. If activated, approximately 100 participants will be enrolled in each of the Phase 2b cohorts.<br>**If the CTMT recommends exploration of higher doses, approximately 20 response evaluable participants will be enrolled in each cohort of Phase 2a.** | To allow for the potential exploration of higher dose levels of Amivantamab based on emerging data and per recommendation of the CTMT. |
| 1.2. Schema - Figure 1 | Added below text in footnote:<br>If the CTMT recommends exploration of higher dose levels, approximately 20 response evaluable participants with expression of EGFR and/or cMet will be enrolled in each dose cohort. | To enable implementation/exploration of higher dose levels of amivantamab in Phase 2a. |
| 4.1. Overall Design | A maximum of approximately **302** participants will be enrolled in the combined Phase 2a and Phase 2b populations, in the event the efficacy observed in both Phase 2a cohorts warrants full enrollment in their respective Phase 2b cohorts.<br>**Based on emerging data, the CTMT may also recommend exploration of higher doses of amivantamab.** | To enable implementation/exploration of higher dose levels in Phase 2a. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.2. Sample Size Determination | **In each dose cohort of phase 2a, approximately 20 response evaluable participants will be additionally enrolled if the CTMT recommends exploration of higher doses. The probability to observe 4 or more response (ORR >= 20%) is 89% assuming ORR of 30%.** | To provide statistical rationale for sample size. |
| 9.5. Interim Analysis | An interim analysis was added in higher dose levels in Phase 2a. | To monitor the efficacy at higher dose levels in Phase 2a. |
| 4.3. Justification for Dose | Added rationale, safety review procedure for higher dose levels in Phase 2a. | To conduct safety review with close monitoring at higher dose levels in Phase 2a. |
| 6.1. Study Treatment Administered | Dosage Level(s)<br>Based on the participant's body weight at screening: 1,050 mg (if body weight is <80 kg) or 1400 mg (if body weight is ≥80 kg)<br>**Additional higher dosing, if recommended by the CTMT, will also be based on the participant's body weight: 1,750 mg (if body weight is <80 kg) or 2,100 mg (if body weight is ≥80 kg)**<br><br>Dosing Instructions<br>Amivantamab will be administered intravenously in 28 day cycles as follows:<br>· Cycle 1: Once weekly (with the first dose split over Day 1 [350 mg] and Day 2 [700 mg if body weight is <80 kg or 1,050 mg if body weight is ≥80 kg]). **For additional higher dosing, once weekly (with the first dose split over Day 1 [350 mg] and Day 2 [1.400 mg if body weight is <80 kg or 1,750 mg if body weight is ≥80 kg]).**<br>· Cycles 2+: Day 1 and 15 of each cycle | Defined potential higher dose level in Phase 2a. |
| 6.6. Dose Modification Guidance | Added dose modification criteria for amivantamab for the 1,750/2,100 mg dosing. | To provide guidance regarding dose modification for potential higher doses. |
| 5.1. Inclusion Criteria | Duration of contraception from the last dose was changed from 6 months to 3 months. | To align the management guidelines in the protocol with other studies within the amivantamab program. |
| 6.6.2. Rash related Adverse Events – Table 7 | Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN) are added in the suggested algorithm for management of rash. | To align the management guideline in the protocol with other studies within the amivantamab program and in accordance with health authority requests. |
| Synopsis - STATISTICAL METHODS | No hypothesis testing is planned in Phase 2a. Objective response rate (ORR) will be calculated for response evaluable population. **Other efficacy measurements will be also assessed.** | Clarification |
| 1.3. Schedule of Activities (SoA) - Table 1 | On the Demography line, x was added in pre-screening.<br><br>On the Demography line, added below text in note:<br><br>Note: In Pre-screening, only Age and gender will be collected. | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3. Schedule of Activities (SoA) - Table 1 | Footnote h was updated:<br><br>Phase 2a participants: Tumor biopsy at screening and C2D15 are mandatory. (must be collected even if the first disease assessment shows disease progression). Tumor biopsy sample after disease progression from the most recent treatment can replace the screening biopsy, if available. **For additional higher dosing, tumor biopsy at C2D15 is mandatory, if clinically feasible (It is not necessary for participants with one target lesion only.)** | To allow enrollment of participants for whom repeated biopsy is not clinically feasible. |
| 4.1.2. Treatment Phase | Added below text:<br><br>For additional higher dosing in Phase 2a, post-treatment biopsy at C2D15 will be mandatory, if clinically feasible. | To allow enrollment of participants for whom repeated biopsy is not clinically possible. |
| 6.1. Study Treatment Administered | Added below bold text:<br><br>Amivantamab will be administered intravenously using the escalating infusion rate regimen as specified in the IPPI. **At the discretion of the investigator, the infusion rate can be slower, but not faster than specified in the IPPI.** The product must be infused via a peripheral vein for all Cycle 1 doses; infusion via central line is allowed for subsequent dosing starting with the C2D1 dose. | Clarified dosing procedure. |
| 8.3.6. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events | Added below bold text:<br><br>An event such as disease progression, which is part of the natural course of the disease under study, does not need to be reported as an AE or SAE **term**. | Clarification |
| 10.3.5. Procedures | Modified below bold text:<br><br>Disease progression **does not need to be reported** as an adverse event or serious adverse event term. | Clarification |
| 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

A Phase 2, Open-label Study of Amivantamab in Subjects With Previously Treated Advanced or Metastatic Gastric or Esophageal Cancer

Amivantamab, also known as JNJ-61186372, is a low fucose, fully human immunoglobulin G1 (IgG1)-based bispecific antibody directed against the epidermal growth factor (EGF) and tyrosine-protein kinase mesenchymal epithelial transition (cMet) receptors, shows activity against tumors with overexpressed wild type EGF receptor (EGFR) and activation of the cMet pathway. By inhibiting EGFR and cMet signaling functions, amivantamab may disrupt these signaling pathways, thereby preventing tumor growth and progression. Furthermore, the presence of high levels of EGFR and cMet on the surface of tumor cells allow for targeting of these cells for destruction by immune effector cells, through antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis mechanisms.

**OBJECTIVES AND ENDPOINTS**

The primary objective is to investigate the activity of amivantamab in gastric cancer (GC) and esophageal cancer (EC) participants (Phase 2a) and to characterize the preliminary antitumor activity of amivantamab in selected GC and EC population (Phase 2b), based on Objective response rate by investigator (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1).

**Hypothesis**

Amivantamab will exhibit anti-tumor activity in participants with GC or EC expressing any level of EGFR, cMET, or both proteins.

**OVERALL DESIGN**

This is an open-label, multicenter, multi-arm Phase 2 interventional study in participants with previously treated advanced or unresectable GC or EC. Participants with gastric/gastroesophageal junction (GEJ) or EC who express varying degrees of EGFR, cMet, or both as determined by immunohistochemistry (IHC) locally or centrally will be enrolled in the Phase 2a cohorts. If activity is observed within Phase 2a cohorts, the corresponding Phase 2b expansion cohorts will be initiated.

The safety and conduct of the study will be monitored on an ongoing basis by the clinical trial management team (CTMT) in conjunction with the coordinating investigators.

The study will include a screening phase, a treatment phase, and a follow-up phase. Participants must complete screening procedures within 28 days before Cycle 1 Day 1 (C1D1). Imaging of disease sites will occur at regular intervals, as defined in the Schedule of Activities (Table 1), until documented objective clinical or radiographic disease progression or until the participant meets another criterion for discontinuation of study treatment.

The treatment phase for each participant will begin on C1D1 and continue as 28-day cycles until the end-of-treatment (EOT) visit, approximately 30 days after the last dose of study treatment. This study will be conducted in an outpatient setting. However, in-hospital observation, from C1D1 until Cycle 1 Day 8 (C1D8) is permitted during the Phase 2a cohorts to allow close monitoring, at the discretion of the investigator. Participants who discontinue study treatment for any reason will be followed for subsequent therapy, disease status (applicable only if participants discontinue treatment due to reasons other than progressive disease), and survival in the follow-up phase. The follow-up phase applies only to Phase 2b participants and starts after the EOT visit and continues until the end of study, death, lost to follow-up, or withdrawal of consent from participation in the study, whichever comes first. The end of study will occur after all participants have discontinued therapy with study treatment and have at least 6 months of follow-up or have discontinued from the study.

## NUMBER OF PARTICIPANTS

A maximum of approximately 302 participants will be enrolled in the combined Phase 2a and Phase 2b populations, in the event the efficacy observed in both Phase 2a cohorts warrants full enrollment in their respective Phase 2b cohorts.

Approximately, 41 response evaluable participants will be enrolled in each of Phase 2a GC and EC arms (including extension cohort). The Phase 2b GC expansion or EC expansion cohorts will evaluate the antitumor activity of amivantamab in GC and EC patients, using biomarker selection. If activated, approximately 100 participants will be enrolled in each of the Phase 2b cohorts.

If the CTMT recommends exploration of higher doses, approximately 20 response evaluable participants will be enrolled in each cohort of phase 2a.

## TREATMENT GROUPS AND DURATION

At study initiation, study treatment in Phase 2a cohorts will be administered in 28-day cycles, until disease progression or until the participant meets another criterion for discontinuation of study treatment.

### Description of study treatment

| | |
|---|---|
| **Dosage Level(s)** | Based on the participant's body weight at screening: 1,050 mg (if body weight is <80 kg) or 1400 mg (if body weight is ≥80 kg) |
| **Dosing Instructions** | Amivantamab will be administered intravenously in 28-day cycles as follows:<br>• Cycle 1: Once weekly (with the first dose split over Day 1 [350 mg] and Day 2 [700 mg if body weight is <80 kg or 1,050 mg if body weight is ≥80 kg]).<br>• Cycles 2+: Day 1 and 15 of each cycle |
| **IP Packaging and Labeling** | Study treatment will be provided in 7 mL glass vials, with 350 mg/vial |

As there are investigations ongoing assessing different amivantamab formulations and schedules, participants in Phase 2b cohorts may receive amivantamab according to a different schedule or route of administration. Any such change would only be made after approved protocol amendment.

## EFFICACY EVALUATIONS

Tumor response will be assessed by radiographic image assessments according to RECIST Version 1.1 guidelines, as defined in the Schedule of Activities.

## PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Blood samples will be collected from all participants receiving amivantamab for the measurement of serum amivantamab for pharmacokinetic (PK) analyses. Serum samples will be collected and analyzed for antibodies to amivantamab using a validated immunoassay. All samples collected for immune response analysis will also be evaluated for amivantamab serum concentration to ensure appropriate interpretation of immunogenicity data. Other immunogenicity analyses may be performed to further characterize any immune responses generated.

## PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Blood samples collected at screening and during the study may be evaluated for circulating tumor DNA (ctDNA) to evaluate molecular alterations to track response to treatment and understand mechanisms of resistance to amivantamab. Blood samples and tissue samples may also be evaluated for other biomarkers to evaluate molecular alterations and track response to amivantamab.

**SAFETY EVALUATIONS**

The safety of amivantamab will be assessed by physical examinations, Eastern Cooperative Oncology Group (ECOG) criteria for performance status, laboratory tests, vital signs, electrocardiograms, monitoring of adverse events (AEs), and concomitant medication usage.

**STATISTICAL METHODS**

No hypothesis testing is planned in Phase 2a. Objective response rate (ORR) will be calculated for response evaluable population. Other efficacy measurements will be also assessed.

The statistical hypothesis in Phase 2b is that amivantamab monotherapy will lead to ORR higher than 15% (ie, $H_0 \leq 15\%$ vs $H_a > 15\%$) in patients with GC or EC, selected on the basis of expression of EGFR, cMet, or both. This threshold is based on historical studies for approved third line (3L) regimens for GC (11.2%-13.6%) and efficacy of approved second line (2L) regimens for EC (approximately 15%).

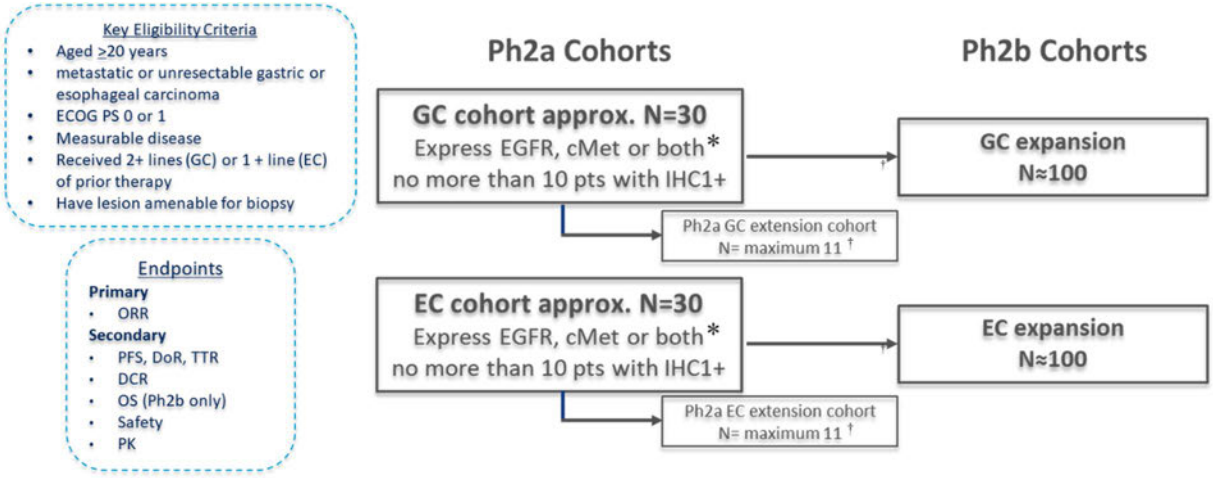
For Phase 2b part, a z test with normal approximation will be used to compare the ORR with 15%. An interim futility analysis is planned in each of subpopulation of GC and EC arm approximately 12 weeks after 50 participants received the first infusion. Multiplicity caused by subpopulation selection at the interim analysis will be controlled by closed testing procedure and weighted statistics. Details will be described in statistical analysis plan (SAP).

Safety data will be summarized for all participants who receive at least 1 dose of study treatment.

Data for PK, immunogenicity, and biomarkers will be summarized for participants who receive at least 1 dose of study treatment and provide an evaluable measurement for that endpoint at least once post-baseline.

## 1.2. Schema

**Figure 1: Schematic Overview of the Study**




*At least 20 participants with IHC2+ or higher and at least 10 participants with cMet expression will be enrolled.
†Participants without expression of EGFR and cMet
If the CTMT recommends exploration of higher dose levels, approximately 20 response evaluable participants with expression of EGFR and/or cMet will be enrolled in each dose cohort.

Abbreviations: cMET=tyrosine-protein kinase mesenchymal-epithelial transition; DCR=disease control rate; EC=esophageal cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; GC=gastric cancer; IHC=immunohistochemistry; OS=overall survival; PFS=progression-free survival; Ph=Phase; PK=pharmacokinetics.

## 1.3. Schedule of Activities (SoA)

**Table 1: Schedule of Activities for Study Procedures/Assessments**

| Phase | Screening | | Treatment (28 days/cycle) | | | | | | | | | EOT [j] | FU [i] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Period | Pre-screening | Full Screening | Cycle 1 | | | | | Cycle 2 | | Cycle 3+ | | Up to 30D After Last Dose | Q12W | |
| Day | Before full-screening | ≤28 days before C1D1 | 1 | 2 | 8 | 15 | 22 | 1 | 15 | 1 | 15 | -- | | |
| Visit Window (Days) | | | - | - | ±1 | ±1 | ±1 | ±1 | ±1 | ±3 | ±3 | +7 | ±14 | |
| **STUDY PROCEDURES**<br>Treatment cycles are 28 days in duration. Assessments during in-clinic dosing days should be performed prior to administration of study treatment unless otherwise stated. Starting with Cycle 2 Day 1: if a dose delay occurs, the sampling schedule (except disease assessments) should be delayed accordingly to ensure sampling relative to amivantamab dose administration. In Follow-up phase, collect data until the end of study unless the participant has died, is lost to follow-up, or has withdrawn consent. | | | | | | | | | | | | | | |
| ***SCREENING ASSESSMENTS*** | | | | | | | | | | | | | | |
| Informed consent | X | X | | | | | | | | | | | | Optional pre-screening ICF may be signed before completion of the prior therapy for tumor EGFR/cMet IHC characterization. Full study ICF must be signed before any study-related procedures. |
| Archival tissue[a] | X | | | | | | | | | | | | | |
| Inclusion/exclusion criteria[b] | | X | | | | | | | | | | | | Confirm all criteria are met before enrollment. If local IHC data is used for eligibility, collect tissue collection date and site (eg. primary organ, metastatic site), and details of antibodies used. |
| Demography | X | X | | | | | | | | | | | | Age, gender, ethnicity, race, history of smoking, and alcohol consumption.<br>Note: In pre-screening, only age and gender will be collected. |
| Disease characteristics[c] | | X | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | Includes relevant past medical diagnoses, and current medical conditions with toxicity grade (including current cancer-related symptoms). |
| 12-Lead ECG | | X | As clinically indicated | | | | | | | | | | | |
| ECOG performance status | | X | As clinically indicated | | | | | | | | | | | Any decline in ECOG performance status should be reported as an AE |
| Serology, Coagulation and Urinalysis | | X | As clinically indicated | | | | | | | | | | | Serology includes HIV, HBV, HCV. Perform urine microscopy if urinalysis abnormal. Refer to Section 8.2 for details. |
| Pregnancy test (serum or urine) | | X | As clinically indicated, according to local regulation requirements, or following the local practice of the center | | | | | | | | | | | For women of childbearing potential only screening test must be performed within 72 hours of first dose of study treatment |
| Hematology and Chemistry (up to 72h predose) | | X | X[l] | | X | X | X | X | X | X | X | X | | Results must be reviewed by the Investigator prior to each administration of amivantamab. Clinically significant abnormalities should be reported as AEs. |
| ***STUDY TREATMENT ADMINISTRATION*** | | | | | | | | | | | | | | |
| Amivantamab dosing[d] | | | X | X | X | X | X | X | X | X | X | | | |
| Concomitant medications[e] | | X | | | | | | | | | | | | |
| ***SAFETY ASSESSMENTS*** | | | | | | | | | | | | | | |
| Adverse events | | Continuous from the time full screening ICF is signed through 30 days after the last dose of study treatment (or >30 days, if considered related to study treatment) | | | | | | | | | | | | |

| Phase | Screening | | Treatment (28 days/cycle) | | | | | | | | | EOT [j] | FU [i] | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Period | Pre-screening | Full Screening | Cycle 1 | | | | | Cycle 2 | | Cycle 3+ | | Up to 30D After Last Dose | Q12W | |
| Day | Before full-screening | ≤28 days before C1D1 | 1 | 2 | 8 | 15 | 22 | 1 | 15 | 1 | 15 | -- | | |
| Visit Window (Days) | | | - | - | ±1 | ±1 | ±1 | ±1 | ±1 | ±3 | ±3 | +7 | ±14 | |
| Vital signs[f] | | X | X | X | X | X | X | X | X | X | X | X | | |
| Physical examination[g] | | X | X | | | | | X | | X | | X | | |
| ***EFFICACY ASSESSMENTS*** | | | | | | | | | | | | | | |
| CT/MRI tumor imaging[h] | | X[k] | 6 wks (+1 wk) for first assessment, then every 6 wks (±1 wk) for first 12 months then every 12 wks (±1 wk) relative to first dose | | | | | | | | | | | refer to Section 8.1 |
| Brain imaging | | X[k] | As clinically indicated | | | | | | | | | | | MRI preferred but CT with contrast is allowed if MRI is contraindicated |
| Survival and Subsequent anticancer therapies | | | | | | | | | | | | | X | Information may be collected via phone<br>Collect type of therapy, treatment start and stop date. |
| ***PHARMACODYNAMICS AND BIOMARKERS*** | | | | | | | | | | | | | | |
| Tumor Biopsy[h] | | X | | | | | | | X | | | X | | If the differential diagnosis between recurrence and fibrotic on the irradicated lesion makes possible, the biopsy may be conducted on the irradicated lesion. |
| ctDNA and biomarker | | X | | | | | | | X | | | X | | Blood sample for ctDNA and biomarker at EOT will be collected from participants with disease progression within 30 days of disease progression and before the next anticancer therapy in case the next anticancer therapy is planned. |

Abbreviations: AE=adverse event; C=Cycle; ctDNA=circulating tumor DNA; CT=computerized tomography; cMet=tyrosine-protein kinase mesenchymal-epithelial transition; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR= epidermal growth factor receptor; EOT=end-of-treatment; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; h=hour; ICF=informed consent form; IHC=Immunohistochemistry; IV=intravenous; MRI=magnetic resonance imaging; Q12W=every 12 weeks; wk(s)=week(s)

a. Archival tumor samples from the previous surgery or most recent biopsy may be submitted for molecular eligibility screening. Date of sample collection (ie. date of biopsy or surgery) and site of tissue collection (eg. primary organ, metastatic site) will also be collected.
b. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study treatment.
c. Tumor type (including Lauren classification [GC only] and primary lesion location), diagnosis date, prior anticancer therapies, date of disease progression, and HER2 expression status (if known).
d. A dose in Cycle 1 other than Day 1 and 2 in Cycle 1 can be delayed for 1 day and in Cycle 2 and beyond a dose delay is allowed 7 days. A planned dose must be skipped if amivantamab is not administered beyond 7-day. If a dose is delayed in Cycle 2 or beyond, then the dates of all subsequent doses must be maintained as originally scheduled based on first dose (ie. C1D1).
e. Record all prescription and over-the-counter treatments administered up to 28 days before the first dose through 30 days after the last dose of study treatment (or start of a subsequent systemic anticancer therapy, if earlier). For participants with Grade 3 or 4 AEs considered related to study treatment, record concomitant medications through the end of follow-up of that AE.
f. Heart rate, blood pressure, respiratory rate, temperature, and O2 saturation <30 min before amivantamab infusion, 30 min intervals (±5 minutes) during each amivantamab infusion, and at end of infusion (+5 minutes).

g. Screening will include, at a minimum, height, weight, general appearance, and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. On Day 1 of each cycle, body weight as well as directed physical examination of involved organs and other body systems will be performed as indicated, with clinically significant abnormalities reported as adverse events.
h. Whenever possible, nontarget lesions should be biopsied rather than target lesions. Biopsy of a target lesion is allowed for the pre-treatment sample, but baseline disease assessment must occur a minimum of 1 week after the biopsy procedure. The sponsor's medical monitor must give approval prior to the biopsy of a target lesion at baseline. During the study, biopsy of a target lesion is not allowed unless disease progression has occurred.
**Phase 2a participants:** Tumor biopsy at screening and C2D15 are mandatory. (must be collected even if the first disease assessment shows disease progression). Tumor biopsy sample after disease progression from the most recent treatment can replace the screening biopsy, if available. For additional higher dosing, tumor biopsy at C2D15 is mandatory, if clinically feasible (It is not necessary for participants with one target lesion only.)
**Phase 2b participants:** Tumor biopsy at screening is mandatory and on-treatment biopsy is optional.
**Phase 2a and 2b participants:** Post-progression biopsy (within 30 days of disease progression but before the next anticancer therapy) is requested if clinically feasible.
i. Applicable to participants in Phase 2b only by participant visit or call
j. If the initiation of the subsequent anticancer therapy is required prior to EOT, EOT must be completed prior to the initiation of the subsequent anticancer therapy.
k. If the imaging data is obtained within 28 days prior to the initiation of study treatment (C1D1), it is not necessary to repeat the imaging tests.
l. If performed within 72 hours of the first Amivantamab dose, the assessment does not have to be repeated for C1D1.

**Table 2: Sample Collection Times for Pharmacokinetics, Immunogenicity, and Pharmacodynamics for Amivantamab**

| Phase | Cycle | Cycle Day | Study Day | Visit Window (days) | Sample | Collection Window | Sample Collection | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Pharmaco kinetics | Pharmaco dynamics | Immunogenicity |
| Treatment Phase | Cycle 1 | D1 | D1 | -- | Before infusion | (<-2 hr) | X | X[b] | X |
| | | D1 | D1 | -- | End of Infusion (EOI)[a] | (+5 min) | X | | |
| | | D2 | D2 | -- | Before infusion | (<-2 hr) | X | X[b] | |
| | | D2 | D2 | -- | EOI[a] | (+5 min) | X | X[b] | |
| | | D2 | D2 | -- | EOI+2 hours | (±15 min) | X[b] | | |
| | | D3 | D3 | -- | EOI+24 hours | (±2 hr) | X[b] | | |
| | | D4 | D4 | -- | EOI+48 hours | (±2 hr) | X[b] | | |
| | | D5 | D5 | -- | EOI+72 hours | (±4 hr) | X[b] | | |
| | | D8 | D8 | ±1 | Before infusion | (<-2 hr) | X[b] | X[b] | |
| | | D15 | D15 | ±1 | Before infusion | (<-2 hr) | X | X[b] | |
| | | D15 | D15 | ±1 | EOI | (+5 min) | X | | |
| | Cycle 2 | D1 | D29 | ±1 | Before infusion | (<-2 hr) | X | X[b] | X |
| | | D1 | D29 | ±1 | EOI | (+5 min) | X | | |
| | | D1 | D29 | ±1 | EOI+2 hours | (±15 min) | X[b] | | |
| | | D2 | D30 | ±1 | EOI+24 hours | (±2 hr) | X[b] | | |
| | | D3 | D31 | ±1 | EOI+48 hours | (±2 hr) | X[b] | | |
| | | D4 | D32 | ±1 | EOI+72 hours | (±4 hr) | X[b] | | |
| | | D8 | D36 | ±1 | EOI+168 hours | (±4 hr) | X[b] | | |
| | | D15 | D43 | ±1 | Before infusion | (<-2 hr) | X | | |
| | Cycle 3 | D1 | D57 | ±3 | Before infusion | (<-2 hr) | X | | X |
| | | D15 | D71 | ±3 | Before infusion | (<-2 hr) | X | | |
| | Cycle 4 | D1 | D85 | ±3 | Before infusion | (<-2 hr) | X | | X |
| | | D1 | D85 | ±3 | EOI | (+5 min) | X | | |
| | | D15 | D99 | ±3 | Before infusion | (<-2 hr) | X | | |
| | Cycle 6, 8, 10, 12, 18, 24, and every 13 cycles | D1 | D113 | ±3 | Before infusion | (<-2 hr) | X | | |
| End-of-Treatment Visit | 30 Days After Last Dose | | | +7 | | | X[c] | | X[c] |

Abbreviations: C=Cycle; D=Day; EOI=end of infusion; h=hour; min=minutes; PK=pharmacokinetics; PD=pharmacodynamics.

a. The PK samples should be collected before infusion and EOI for both doses of amivantamab administered over 2 days (labelled as Predose and Postdose for C1D1, and Predose and EOI for C1D2).

b. The samples will be taken from at least 10 participants for each cancer type.

c. The PK and immunogenicity samples can be taken at any time during the end-of-treatment visit.

# 2. INTRODUCTION

Amivantamab, also known as JNJ-61186372, is a low fucose, fully human immunoglobulin G1 (IgG1)-based bispecific antibody directed against the EGF and tyrosine-protein kinase mesenchymal epithelial transition (cMet) receptors and shows activity against tumors with overexpressed wild type epidermal growth factor receptor (EGFR) and activation of the cMet pathway. By inhibiting EGFR and cMet signaling functions, amivantamab may disrupt these signaling pathways, thereby preventing tumor growth and progression, as demonstrated in preclinical models of tumors driven by activated EGFR or activated MET signaling, or simultaneous activation of either pathway. Furthermore, the presence of high levels of EGFR and cMet on the surface of tumor cells allow for targeting of these cells for destruction by immune effector cells, through antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis mechanisms.

For the most comprehensive nonclinical and clinical information regarding amivantamab, refer to the latest version of the Investigator's Brochure (IB) and Addenda for amivantamab.

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

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

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

## 2.1. Background

### 2.1.1. Gastric and Esophageal Cancer

**Gastric Cancer**

Cancer is a leading cause of death worldwide. Gastric cancer (GC) is the fifth most common cancer worldwide and over 1 million new cases were reported worldwide in 2018. (Ferlay 2018) Gastric cancer is highly prevalent in Asian countries accounting for approximately 75% of new cases in 2018 and is the third (male)/fourth (female) most prevalent cancer in Japan. (Ferlay 2018) Majority of patients exhibit adenocarcinoma histology. The treatment regimen depends on the type of cancer (eg, histology), the stage of the cancer at diagnosis, and the presence of molecular biomarkers (eg, human epidermal growth factor receptor 2 (HER2) amplification, Programmed death-ligand 1 expression, and microsatellite instability). Treatment commonly includes surgery and chemotherapy. In patients with metastatic disease, National Comprehensive Cancer Network (NCCN) guidelines recommend HER2, programmed death-ligand 1, and microsatellite instability testing. (NCCN Guidelines 2020) Likewise Japanese gastric cancer association guidelines recommend HER2 testing prior to the initiation of initial systemic chemotherapy. (Japanese gastric cancer treatment guidelines 2018) The first line treatment generally includes fluoropyrimidine+cisplatin or oxaliplatin±trastuzumab (depending on HER2 status). The combination therapy with S-1 is also recommended in Japan. (Japanese gastric cancer treatment

guidelines 2018) The observed overall response rate for the guideline-recommended initial treatment ranged between 35% to 68% (Bang 2010; Kurokawa 2014) with the median progression-free survival (mPFS) of approximately 6 months. (Bang 2010; Kurokawa 2014; Koizumi 2008; Ohtsu 2011; Yamada 2015; Yoon 2016) Available treatment options after first line treatment are limited. The NCCN recommendations are chemotherapy as a single agent, ramucirumab+paclitaxel, immune checkpoint inhibitor, or fluorouracil+irinotecan. Similar to NCCN guidelines, the recommended second line (2L) and third line (3L) treatments are ramucirumab+paclitaxel (2L), nivolumab (3L), or irinotecan (3L) per the Japanese guidelines. (Japanese gastric cancer treatment guidelines 2018) The reported overall response rate from the Phase 3 studies for 2L and 3L treatments are limited to 11% to 28% with the mPFS of 1.6 to 4.4 months. (Wilke 2014; Hironaka 2013; Kang 2017) Furthermore, 5-year survival rate is only 7.0% and the median overall survival (OS) merely exceeds a year among stage IV patients. (Gastric Cancer [Type of Cancer] 2020)

**Esophageal Cancer**

Esophageal cancer (EC) is the eighth most common cancer worldwide and ranked sixth among all cancers in mortality in 2018. (Ferlay 2018) Similar to GC, EC is highly prevalent in Asian countries accounting for over 75% of new cases in 2018. (Ferlay 2018) Squamous cell carcinoma and adenocarcinoma are 2 major histologies of primary ECs. However, predominant EC histology varies between geographical regions. The predominant histology observed among the Caucasian population is adenocarcinoma whereas squamous histology predominates Asian countries. (Chen 2017) Treatment commonly includes surgery, radiation therapy, chemoradiation therapy, and chemotherapy. The NCCN guideline recommendations for the first line therapies are identical to GC regimens due to the nature of histological similarities. (NCCN Guidelines 2020) Clinical data of esophageal squamous cell carcinoma, which is the predominant histology in Asian countries, are limited to mostly Phase 2 studies. The reported overall response rate of chemotherapy as a single agent is 15%~40%. The recommended regimen in Japan for the first line treatment is considered fluorouracil+cisplatin. (Vijayaraghavan 2020, Waddell 2013, Wang 2007, Wilke 2014, Xu 2016, Yamada 2015, Yano 2003, Yoon 2016). The overall response rate and mPFS from 2 phase 2 studies of this combination were reported to be 35% to 35.9% and 3.5 to 6.2 months, respectively. (Muro 2004; Kato 2011) There are no recommended 2L treatments per Japanese guidelines and single agent chemotherapy is often used with the reported mPFS of 1.5 to 3.9 months. (Muro 2004; Kato 2011; Kudo 2017) A recent Phase 3 study evaluating pembrolizumab versus chemotherapy in patients with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus as 2L therapy (KEYNOTE-181) had led to the regulatory approval in Japan for the patients with PD-1 combined positive score ≥10. Even with this targeted therapy, observed overall response rate and mPFS are limited to 17% and 1.5 months, respectively. (Kudo 2017)

### 2.1.2. Role of EGFR and cMet in Gastric and Esophageal Cancer

Receptor tyrosine kinases (RTK) are involved in the regulation of many processes in mammalian development, cell function, and tissue homeostasis. Dysregulation of RTKs has been implicated

in the development of numerous human cancers, and various RTKs are targets for both approved and experimental anticancer therapies.

Epidermal growth factor receptor, an RTK in the HER family, is normally expressed in tissues of epithelial, mesenchymal, and neuronal origin. Binding of any of its 7 ligands, including EGF, induces diverse cellular responses, including differentiation, proliferation, migration, and survival. (Olayioye 2000) cMet is also an RTK, expressed in normal epithelial cells (Prat 1991), with a role in growth and homeostasis, including embryonic development, angiogenesis, and wound healing. (Sattler 2011) cMet is activated by a single specific ligand, hepatocyte growth factor, also known as scatter factor.

Overexpression and mutations of the EGFR and cMet receptors have been linked to tumorigenesis and malignancy, as well as poor prognosis in several types of cancer. (Birchmeier 2003; Hyner 2005; Yano 2003) It is reported that approximately 25% and 50% of GC patients express EGFR or cMet, respectively. (Fuse 2016) Likewise approximately 60% to 70% and 45% to 70% of EC patients express EGFR or cMet, respectively. (Hanawa 2006; Gibault 2005) The expression of EGFR or cMet has been implicated as a poor prognostic factor in GC (Aydin 2014; Gao 2013; Galizia 2007; Atmaca 2012; Fuse 2016) and EC (Wang 2007; Brand 2011; Ozawa 2015). Furthermore, co-expression of EGFR and cMet has been reported to have significantly worse OS in squamous cell carcinoma of esophagus. (Xu 2016)

Despite numerous agents targeting EGFR (including anti-EGFR antibodies and EGFR tyrosine kinase inhibitors [TKIs]) having been used as a standard of care for many cancers, including colorectal cancer, non-small cell lung cancer (NSCLC), and head and neck cancer, no EGFR-directed therapy is available for gastric or ECs. Previous studies have failed to show efficacy of cetuximab and panitumumab, anti-EGFR antibodies, for the treatment of GC or gefitinib, EGFR tyrosine kinase inhibitor, in EC in non-biomarker selected population. (Lordick 2013; Waddell 2013; Dutton 2014) A more recent study evaluating nimotuzumab, anti-EGFR antibody, in combination with irinotecan for GC patients with EGFR expression has also been shown to be unsuccessful. (Satoh 2015) The clinical experience of cMet-targeted therapy is less extensive. The studies evaluating the efficacy of rilotumumab or onartuzumab, anti-cMet antibodies, in GC failed to show clinical benefit. However, post-hoc retrospective analysis of these studies has implicated clinical benefit in an EGFR or cMet overexpressing population, implying the clinical activity of anti-EGFR and anti-cMet treatments in the subset of GC or EC population. (Iveson 2014; Satoh 2015)

### 2.1.3. Clinical Studies of Amivantamab

The safety and efficacy of amivantamab as a monotherapy has been previously described in patients with NSCLC in the first-in-human Phase 1 CHRYSALIS study (Study 61186372EDI1001). Study 61186372EDI1001 includes both a dose-escalation phase (Part 1: subjects with advanced NSCLC) and a dose-expansion phase (Part 2: subjects with advanced EGFR-mutated or cMET-mutated NSCLC, after standard of care therapy). Part 1 of the study includes a chemotherapy combination arm for participants with advanced NSCLC who are eligible for treatment with standard of care carboplatin and pemetrexed. Part 2 of the study includes

expansion cohorts for amivantamab monotherapy in populations with unmet clinical need, including NSCLC characterized by the following: 1) Cohort C: EGFR resistance mutations (eg, C797S and others) and previous treatment with a third-generation EGFR TKI; 2) Cohort D: EGFR Exon 20ins disease and no previous treatment with an EGFR TKI with known activity in Exon 20ins disease; 3) Cohort MET-1: EGFR mutation with MET mutation or amplification of ≥3 copy number and previous treatment with any EGFR TKI; and 4) Cohort MET-2: Primary MET Exon 14 skipping mutation. Study 61186372EDI1001 also carried out initial safety and efficacy exploration of amivantamab in combination with lazertinib, a 3rd generation EGFR TKI, as well as amivantamab with carboplatin and pemetrexed chemotherapy combination. Please refer to IB for further details regarding the experience with amivantamab in these combinations.

Based on early activity observed within the EFGR Exon20ins population, amivantamab was awarded Breakthrough Therapy Designation by the United States Food and Drug administration (FDA) and China Center for Drug Evaluation for the treatment of patients with EGFR Exon20ins NSCLC, after progression on prior platinum-based chemotherapy.

In November 2020, the first biologic license application was submitted to United States (US) FDA for the treatment of patients with EGFR Exon20ins NSCLC after prior progression on platinum-based chemotherapy and is currently under review. Additional global regulatory submissions are ongoing.

## 2.2. Study Rationale

Gastric and ECs have been known to express EGFR and cMet and the expression of these proteins have corelated with poor prognosis. Although many agents targeting EGFR are part of standard of care for many tumor types, no anti-EGFR or anti-cMet therapy has been approved in GC or EC. As a bispecific duobody capable of engaging the extracellular domains of both EGFR and cMet receptors, amivantamab has a unique mechanism of action that suggests it has the potential to control EGFR-expressed and/or cMet-expressed GC and EC patients. Amivantamab has demonstrated in vitro and in vivo pre-clinical activities against tumors with the EGFR or cMet amplified GC and EC models (Vijayaraghavan 2020). Furthermore, clinical experience of amivantamab in NSCLC has shown clinical benefit against broad-spectrum of EGFR and cMet aberrations, including EGFR protein overexpression and cMet amplifications.

This study aims to evaluate the clinical activity of amivantamab as a monotherapy in GC (including GEJ cancer) and EC patients who had received at least 2 prior lines (GC/GEJ participants) or at least 1 prior line (EC participants) of standard therapy. The Phase 2a cohorts will initially investigate the anti-tumor activity of amivantamab in participants with documented expression of either EGFR, cMet, or both as evaluated by immunohistochemistry (IHC). Approximately 30 participants with any expression level of EGFR, cMet, or both proteins will be enrolled in each of the Phase 2a cohort. However, based on the prior experiences investigating anti-EGFR and anti-cMet antibodies in gastroesophageal cancers, at least 20 participants expressing IHC 2+ or higher (defined as participants expressing EGFR IHC 2+ or above and/or cMet IHC 2+ or above) will be enrolled. The clinical trial management team (CTMT) may allow additional enrollment in Phase 2a cohorts to achieve this minimal enrollment. Moreover, at least 10 participants expressing any

level of cMet protein will be enrolled in each of Phase 2a cohort to better characterize the contribution of cMet in amivantamab activity. If activity is demonstrated in the Phase 2a cohorts, Phase 2a extension cohorts investigating participants without expression of EGFR and cMet, may open for enrollment upon agreement with the CTMT. The Phase 2b cohorts will investigate the clinical activity of amivantamab in selected patient population based on the Phase 2a data.

## 2.3. Benefit-risk Assessment

### 2.3.1. Risks for Study Participation

The safety and tolerability of amivantamab monotherapy was shown in the Phase 1 Study 61186372EDI1001 (Section 2.1.3) in NSCLC patients. Amivantamab was generally well tolerated without any occurrence of dose limiting toxicities (DLTs). However, given that the available clinical data are limited to NSCLC participants, unforeseen safety risks associated with the study treatments are possible in GC or EC participants. This study protocol includes the following elements to mitigate risks for study participants:

- The CTMT in conjunction with the coordinating investigator will review the safety and conduct of Phase 2a periodically.
- Participants will be monitored closely for safety throughout the study (refer to Section 8.2), per the scheduled assessments outlined in the Schedule of Activities (Table 1).
- Dose modification guidance is provided to manage toxicities that occur during the study (refer to Section 6.5 and Section 6.6), including specific guidance for infusion-related reactions (IRRs), rash, interstitial lung disease (ILD), liver test abnormalities, or paronychia.

Amivantamab is generally safe and well tolerated based on the data mentioned above.

### 2.3.2. Benefits for Study Participation

Although many agents targeting EGFR have been approved and are part of standard of care for many tumor types, no anti-EGFR or anti-cMet therapy has been approved in GC or EC. Amivantamab has demonstrated significant activity as monotherapy for the treatment of NSCLC, receiving Breakthrough Therapy Designation by the US FDA and China Center for Drug Evaluation, based on an overall response rate of 41% in subjects with EGFR Exon20ins disease, after prior treatment with platinum-based chemotherapy. Consistent with the unique mechanism of action of amivantamab, activity was observed in subjects with diverse EGFR mutations, as well as in subjects with amplification of MET and overexpressed EGFR.

It is anticipated that using this therapeutic targeted approach with amivantamab as a single agent in either advanced GC (including GEJ cancer) or EC participants may provide benefit to these participants.

### 2.3.3. Benefit-risk Assessment for Study Participation

Considering the measures taken to minimize risk to participants of this study (refer to Section 2.3.1), the potential risks of amivantamab are justified by the anticipated benefits that may be afforded to participants with advanced GC or EC (refer to Section 2.3.2). More detailed

information about the known and expected benefits and risks of amivantamab may be found in the IB and Addenda for amivantamab.

# 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To investigate the activity of amivantamab in gastric cancer (GC) and esophageal cancer (EC) participants (Phase 2a)<br>• To characterize the preliminary antitumor activity of amivantamab in selected GC and EC population (Phase 2b) | • Objective response rate, as determined by investigator, according to the Response Criteria in Solid Tumors (RECIST) Version 1.1. |
| **Secondary** | |
| • To assess additional measures of clinical benefits with amivantamab | • Disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), and overall survival (OS; Phase 2b only). |
| • To confirm the safety of amivantamab in participants with gastric or esophageal cancers (ECs) | • Adverse events defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 in participants treated with amivantamab |
| • To assess the pharmacokinetics (PK) and immunogenicity of amivantamab following multiple intravenous dose administrations | • Serum PK parameters including but not limited to maximum serum concentration ($C_{max}$), time to reach the maximum serum concentration ($T_{max}$), area under the curve $(AUC)_{(t1-t2)}$, $AUC_{tau}$, plasma/serum concentration immediately prior the next study treatment administration ($C_{trough}$), and accumulation ratio; incidence of anti-amivantamab antibodies |
| **Exploratory** | |
| • Explore biomarkers predictive of clinical response and resistance to amivantamab in blood and tumor tissue<br>• Explore the relationship between serum PK and pharmacodynamic (PD) markers (eg, soluble EGFR and cMet)<br>• Determine whether amivantamab can impact the anti-tumor immune response or microenvironment | |

Refer to Section 8, STUDY ASSESSMENTS AND PROCEDURES for evaluations related to endpoints.

## HYPOTHESIS

Amivantamab will exhibit anti-tumor activity in participants with GC or EC expressing any level of EGFR, cMET, or both proteins.

# 4. STUDY DESIGN

## 4.1. Overall Design

This is an open-label, multicenter, multi-arm Phase 2 interventional study in participants with previously treated advanced or unresectable GC or EC who are 20 years or older (or the legal age of consent in the jurisdiction in which the study is taking place). The participants with gastric/GEJ

or EC who express varying degrees of EGFR, cMet, or both as determined by IHC locally or centrally will be enrolled in the GC cohort or EC cohort. If activity is demonstrated in the Phase 2a cohorts, Phase 2a extension cohorts investigating participants without expression of EGFR and cMet, may open for enrollment upon agreement with the CTMT. If activity is observed within the Phase 2a cohorts, the corresponding Phase 2b GC or EC expansion cohorts will be initiated to evaluate the antitumor activity of amivantamab in selected GC and EC participants based upon the prospective assessment of IHC during Phase 2a (schematic overview is Section 1.2).

A maximum of approximately 302 participants will be enrolled in the combined Phase 2a and Phase 2b populations, in the event the efficacy observed in both Phase 2a cohorts warrants full enrollment in their respective Phase 2b cohorts. Approximately, 30 response evaluable participants will be enrolled in each of Phase 2a GC and EC arm. However, based on the prior experiences investigating anti-EGFR and anti-cMet antibodies in gastroesophageal cancers, at least 20 participants expressing IHC 2+ or higher (defined as participants expressing EGFR IHC 2+ or above or cMet IHC 2+ or above) will be enrolled. Moreover, at least 10 participants expressing any level of cMet protein (IHC1+ or above) will be enrolled in each Phase 2a cohort to better characterize the contribution of cMet in amivantamab activity. The CTMT may allow additional enrollment in the Phase 2a cohorts to achieve this minimal enrollment, if these criteria aren't met in the initial 30 evaluable subjects. If activity is demonstrated in the Phase 2a cohorts, Phase 2a expansion cohorts investigating a maximum of 11 participants without any expression of EGFR and cMet, may open for enrollment upon agreement with the CTMT. The CTMT will assess the data and may recommend additional participants to be enrolled for further characterization if 2 or more responses are observed in each of Phase 2a GC or EC extension cohorts. Based on emerging data, the CTMT may also recommend exploration of higher doses of amivantamab. The Phase 2b GC expansion or EC expansion cohorts will evaluate the antitumor activity of amivantamab in GC and EC patients, using biomarker selection based upon Phase 2a results. If activated, approximately 100 participants will be enrolled in each of the Phase 2b cohorts.

The safety and conduct of the study will be monitored by the CTMT in conjunction with the coordinating investigators. In general, the CTMT will monitor the conduct of the study and review study data in an ongoing basis. The CTMT may recommend and decide on modifications in the study conduct which may include, but are not restricted to, changes in (1) study treatment administration dose/schedule, (2) patient population based on the emerging biomarker data, (3) allowing further enrollment or terminate enrollment of a specific subpopulation to better characterize the specific population (eg, enrollment of IHC 2+/3+ or EGFR and cMet double positive population), (4) opening of Phase 2a extension cohorts and (5)-PK or biomarker sampling times. All decisions made by the CTMT will be documented in a CTMT decision document. The Independent Ethics Committee/Institutional Review Board (IEC/IRB) will be notified for all CTMT decisions, if required. The recommendations of the CTMT may be instituted by the study team, pending protocol amendment, as long as they are consistent with the benefit-risk and fall within the populations already reviewed and approved by the health authority (HA) and local IRBs. All the CTMT documentation will be maintained in the sponsor's study master file and, as applicable, in the investigator's study files. If unexpected safety findings are identified, the CTMT

will assess the safety data in a prompt manner. The study will include a screening phase (Section 4.1.1), a treatment phase (Section 4.1.2), and a follow-up phase (Section 4.1.3).

### 4.1.1. Screening Phase (Pre- and Full Screening)

The participant must sign an informed consent form (ICF) at the beginning of the full screening phase, before the first study-related activity is conducted. During the full screening period, participants will be evaluated for eligibility for study participation. Participants must complete all screening procedures within 28 days of C1D1. Pre-treatment biopsy will be collected for all participants in Phase 2a and Phase 2b. The tumor IHC result regardless of the local or central must be obtained and confirmed for the eligibility prior to C1D1. If the central tumor IHC is used for the eligibility prior to the initiation of the study treatment and the central results are not completed during the screening period, the screening period can be extended by 14 days. However, all other assessments must still meet timing criteria relative to C1D1 or must be repeated.

If an assessment was performed as part of the participant's routine clinical evaluation and not specifically for this study, it needs not be repeated after signed ICF has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to C1D1.

An optional pre-screening period with corresponding ICF is offered to facilitate molecular characterization of archived tumor biopsy sample, prior to signing of full study ICF. The participant may sign pre-screening ICF and submit archival sample before completion of the previous therapy. If IHC assay is performed locally, enrollment should be considered with reference to the scoring criteria used in the central IHC assay.

If there is a discrepancy between the local and central IHC assay, the study treatment may be continued at the investigator discretion.

### 4.1.2. Treatment Phase

The treatment phase for a participant will begin on C1D1 and continue as 28-day cycles until the EOT visit, approximately 30 days after the last dose of study treatment. If the initiation of the subsequent anticancer therapy is required prior to EOT, EOT must be completed prior to the initiation of the subsequent anticancer therapy. This study will be conducted in an outpatient setting. However, in-hospital observation, from C1D1 until C1D8 is permitted in the Phase 2a (including Phase 2a extension cohorts) to allow close monitoring at the discretion of the investigator. Study treatment will continue until documented clinical or radiographic (RECIST Version 1.1) disease progression or until the participant meets another criterion for discontinuation of study treatment.

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

At each study visit during the treatment phase, participants will undergo safety evaluations, including physical examinations and assessment of adverse events (AEs), vital signs, concomitant medication usage, and clinical laboratory parameters. Participants will also have blood samples drawn for assessment of PK and immunogenicity parameters and for biomarker evaluations, at selected visits. Post-treatment biopsy, circulating tumor DNA (ctDNA), and biomarker at C2D15 as well as per the Schedule of Activities (Section 1.3) will be collected on C2D15 (±1 day) from all participants in Phase 2a. For additional higher dosing in Phase 2a, post-treatment biopsy at C2D15 will be mandatory, if clinically feasible.

### 4.1.3. Follow-up Phase (Applicable to Phase 2b Only)

Participants who discontinue study treatment will be followed for subsequent therapy, disease status (applicable only if participants discontinuing treatment due to reasons other than progressive disease, to confirm disease progression date), and survival in the follow-up phase. This phase starts from the EOT visit assessment will be done every 12 weeks (±14 days) after the last dose of study treatment or disease progression (whichever occurs first) and continues until the end of study, death, lost to follow-up, or withdrawal of consent from participation in the study, whichever comes first. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died, the date and cause of death will be collected and documented on the electronic case report form (eCRF). Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF.

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

## 4.2. Scientific Rationale for Study Design

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

This is an open-label non-randomized study; therefore, no blinding or randomization is applied.

**Clinical Pharmacology Assessments**

Serum samples will be collected and analyzed for amivantamab concentrations, and estimation of basic PK parameters from this concentration-time data will be performed and reported. Immunogenicity (antibodies to amivantamab, also termed anti-drug antibody) will be evaluated for potential impact on PK. Pharmacokinetic profiles and parameters will be assessed relative to clinical safety, efficacy, pharmacokinetic (PD) (soluble EGFR and cMet), and exploratory biomarker data, as available.

**Biomarker Collection**

In Phase 2a: Pre-treatment tumor samples will be assessed by IHC for EGFR and Met expression levels on the tumor. On-treatment tumor samples in Phase 2a and, if collected in Phase 2b, will be assessed for changes in the expression of markers of pathway inhibition including, but not limited to, EGFR and MET. Tissue samples collected may be tested by next-generation sequencing or another methodology to identify genetic alterations which may predict response or resistance to

amivantamab. These include, but are not limited to, mutations, insertions, or amplification of the EGFR and MET genes and other genes of interest. Tumor tissue may also be evaluated for additional biomarkers (DNA, RNA, and/or protein) relevant to GC or EC or the mechanism of action of amivantamab, including immune cell activity.

Circulating tumor DNA from screening blood samples will be analyzed to characterize baseline EGFR and cMet mutational status. Biomarker samples (tumor and blood) will be collected to evaluate the mechanism of action of amivantamab, to help explain inter-participant variability in clinical outcomes, and to help identify population subgroups that respond to amivantamab. The goal of the biomarker analyses is to evaluate the drug-clinical response relationship and mechanisms of resistance to amivantamab.

In addition, blood samples may be evaluated for biomarkers (DNA, RNA, and/or protein) which may be related to amivantamab response.

### 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 blood donation and American Red Cross. (Japanese Red Cross Society; American Red Cross)

## 4.3. Justification for Dose

Amivantamab was generally well tolerated in a Phase 1 study (Study 61186372EDI1001) up to the dose of 1750 mg, with no dose limiting toxicities reported during dose escalation and no maximum tolerated dose identified in lung cancer participants. Based on the totality of exposure, safety, and efficacy data, the recommended Phase 2 dose was determined to be 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, administered by IV infusion in 28 day cycles: once weekly in Cycle 1 (with a split dose on Days 12), and then every 2 weeks in subsequent cycles. The recommended Phase 2 dose achieved a complete soluble target saturation throughout dosing for the EGFR and cMet in the lung cancer participants. The observed safety profile of amivantamab is consistent with EGFR and cMet inhibition and majority of treatment emergent adverse events (TEAEs) were Grade 1 to 2 in severity. Therefore, administering the same dosing regimen to GC or EC participants is considered appropriate.

Based on observed PK, safety, and efficacy data, the CTMT may recommend exploration of higher dosing of amivantamab. In the monotherapy dose escalation of amivantamab in Study 61186372EDI1001, doses up to 1,750 mg were assessed. In this study, participants who received

1,750 mg had a body weight (BW) <80 kg, and the observed exposure was similar to model-estimated exposures achieved with weight-based dosing of 1,750 mg/2,100 mg for participants weighing <80 kg and ≥80 kg, respectively. At the maximum assessed dose, there were no dose-limiting toxicities (DLTs) observed, and a maximum tolerated dose (MTD) was not established.

The need for exploration of higher dose levels, and which dose(s) to assess, will be dependent upon the clinical activity observed at the current dose (1,050 mg [BW<80 kg]/1,400 mg [BW≥80 kg]), exposure-response data, and safety data. Based upon these data, the CTMT may recommend exploration of the following doses: 1,750 mg [body weight < 80 kg]/2,100 mg [body weight ≥ 80 kg]. For evaluation of potential higher doses, the CTMT will convene after 3 subjects have completed 1 cycle of treatment, to review safety and tolerability. Based on the data reviewed, the CTMT may recommend continuation of the cohort to approximately 20 response evaluable participants. Safety will be closely monitored for all study participants, with ongoing review of safety during regularly scheduled CTMT meetings.

## 4.4. End of Study Definition

**End of Study Definition**

The end of study will occur after all participants have discontinued therapy with study treatment and have at least 6 months of follow-up or have discontinued from the study. The data cutoff for the clinical study report (CSR) will be 6 months after the first dose of last participant in the Phase 2b. Participants on-treatment at the time of analysis will continue to receive study treatment and those who are in follow-up will continue to be followed.

**Study Completion Definition**

Phase 2a: A participant will be considered to have completed the study if:

- The participant has died
- The participant has met all of the following:
    - Documented radiographic disease progression
    - Completed the EOT assessment
    - Completed protocol-required AE follow-up
- Note: In case a subsequent therapy is initiated without documented radiographic disease progression, then it will be considered the study completion.

Phase 2b: A participant will be considered to have completed the study if the participant died before the EOT.

# 5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before administration of the study treatment. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

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

## 5.1. Inclusion Criteria

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

1. Participant must be ≥20 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Criterion modified per Amendment 1:

   2.1. Participant tumor must express either EGFR, cMet, or both as determined by either local or central IHC assay (IHC 1+ or above). A copy of the de-identified pathology report, or equivalent information, for IHC analysis must be submitted during the screening period if local IHC test was used for the eligibility determination.

   Phase 2a extension cohorts: Participant tumor must lack expression of EGFR and MET as determined by either local or central IHC assessment. A copy of the de-identified pathology report, or equivalent information, for IHC analysis must be submitted during the screening period if local IHC test was used for the eligibility determination.

3. Participant must have histologically or cytologically confirmed gastric (including GEJ) or EC that is locally advanced, unresectable, or metastatic, and not eligible for curative treatment.

   **Gastric or GEJ Cancer Only**

   a. Must be refractory or ineligible to at least 2 prior lines of standard of care systemic therapy. Prior therapies must include fluoropyrimidine- and platinum-based chemotherapy. Participants with known HER2 expression must have had HER2-targeting therapy as part of the prior therapy.

   b. In case of progression within 24 weeks of prior adjuvant or neoadjuvant chemotherapy, this therapy will be considered as 1 prior line of systemic therapy for the purpose of meeting the eligibility criteria.

   **Esophageal Cancer Only**

   a. Must be refractory or intolerant to at least 1 prior line of systemic therapy. Prior therapies must include fluoropyrimidine-, and platinum-based chemotherapy (including chemoradiation therapy given as stage IV setting).

   b. Participant who underwent a radical resection in conjunction with chemotherapy including neo-adjuvant/adjuvant therapy or chemoradiation

(including participants who underwent chemoradiation, if residual tumor exists, followed by salvage surgery) whose recurrence was confirmed by imaging within 24 weeks after the last dose of chemotherapy will be considered as having received 1 line of prior systemic therapy for the purpose of meeting the eligibility criteria.

Note: If prior combination therapy discontinued due to an AE, and then one of the agents continued, this is considered to be "1 prior line" and not "2 prior lines." The change in dosage form (IV administration, oral administration) or dose reduction without progression is considered to be "1 prior line" and not "2 prior lines."

4. Participant must have measurable disease according to RECIST Version 1.1. If only one measurable lesion exists, it may be used for the screening biopsy if the baseline tumor assessment scans are performed ≥7 days after the biopsy.

5. Participant must have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (refer to Section 10.5, Appendix 5: Eastern Cooperative Oncology Group (ECOG) Performance Status).

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

    a. Hemoglobin ≥8 g/dL

    b. Absolute neutrophil count ≥1500/mm$^3$, without use of granulocyte colony stimulating factor (G-CSF) within 10 days prior to the date of the test

    c. Platelets ≥75,000/mm$^3$

    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3×upper limit of normal (ULN). If liver metastases are present, ≤5×ULN

    e. Total bilirubin ≤1.5×ULN (participants with Gilbert's syndrome can enroll if direct bilirubin is within normal limits)

    f. Calculated or measured glomerular filtration rate ≥40 mL/min using the Modified Diet in Renal Disease (MDRD) equation (refer to Section 10.7, Appendix 7: MDRD formula for eGFR)

7. Participant must have a tumor lesion amenable for biopsy and agree to protocol-defined mandatory biopsies.

8. A woman of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study treatment.

9. Criterion modified per Amendment 2:

    9.1 A female participant must be as defined in Section 10.4, Appendix 4: Contraceptive and Barrier Guidance) either of the following:

a. Not of childbearing potential

b. Of childbearing potential and

- practicing true abstinence;
- or have a sole partner who is vasectomized;
- or practicing at least 1 highly effective user independent method of contraception (see Section 10.4, Appendix 4: Contraceptive and Barrier Guidance).

Participant must agree to continue the above throughout the study and for 3 months after the last dose of study treatment.

Note: If a woman becomes of childbearing potential after start of the study the woman must comply with point (b.) as described above.

10. Criterion modified per Amendment 2:

10.1 A female participant must not be pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study treatment (enrollment is not permitted even if a woman who is breast-feeding stops breast-feeding).

11. Criterion modified per Amendment 2:

11.1 A male participant must wear a condom (with or without spermicidal foam/gel/film/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 3 months after receiving the last dose of study treatment. His female partner, if of childbearing potential, must also be practicing a highly effective method of contraception (see Section 10.4, Appendix 4: Contraceptive and Barrier Guidance).

If the male participant is vasectomized, he still must wear a condom (with or without spermicidal foam/gel/film/cream/suppository), but his female partner is not required to use contraception.

12. Criterion modified per Amendment 2:

12.1 A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 3 months after receiving the last dose of study treatment.

13. Criterion modified per Amendment 2:

13.1 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 study treatment.

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

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

## 5.2. Exclusion Criteria

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

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

    a. Diabetes

    b. Ongoing or active bacterial infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week before enrollment]), symptomatic viral infection, or any other clinically significant infection

    c. Active bleeding diathesis

    d. Psychiatric illness/social situation that would limit compliance with study requirements

2. Participant has had prior chemotherapy, targeted cancer therapy, immunotherapy, or treatment with an investigational anticancer agent within 2 weeks or 4 half-lives whichever is longer or had radiation therapy within 4 weeks before the first administration of study treatment. For agents with long half-lives, the maximum required time since last dose is 28 days. Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less, (except for alopecia or post-radiation skin changes [any grade], Grade ≤2 peripheral neuropathy, and Grade ≤2 hypothyroidism stable on hormone replacement).

3. Participant has untreated brain metastases (a participant with definitively, locally treated metastases who is clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to the first administration of study treatment is eligible), history of leptomeningeal disease or spinal cord compression that has not been treated definitively with surgery or radiation. If brain metastases are diagnosed on screening imaging, the participant may be rescreened for eligibility after definitive treatment.

4. Participant has a history of (non-infectious) ILD/pneumonitis that required steroids, or has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening. GEJ or Esophageal cancer participants with history of radiation

pneumonitis (defined as radiographically stable for 3 months prior to enrollment without need of any treatment) may be enrolled.

5. Participant has an active malignancy (ie, progressing or requiring treatment change in the last 12 months) other than the disease being treated under study. The only allowed exceptions are:

   a. Non-muscle invasive bladder cancer treated within the last 24 months that is considered completely cured.
   b. Skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured.
   c. Non-invasive cervical cancer treated within the last 24 months that is considered completely cured.
   d. Localized prostate cancer (N0M0):
      - With a Gleason score of 6, treated within the last 24 months or untreated and under surveillance,
      - With a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence,
      - Or history of localized prostate cancer and receiving androgen deprivation therapy and considered to have a very low risk of recurrence.
   e. Breast cancer:
      - adequately treated lobular carcinoma in situ or ductal carcinoma in situ,
      - or history of localized breast cancer and receiving antihormonal agents and considered to have a very low risk of recurrence.
   f. Malignancy that is considered cured with minimal risk of recurrence.
   g. Phase 2a participants only: Participants with another malignancy may enroll if any systematic treatment is considered not to become necessary by the investigator for at least 6 months after the enrollment.

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

   a. Diagnosis of deep vein thrombosis or pulmonary embolism within 4 weeks prior to the first dose of study treatment or any of the following within 6 months prior to the first dose of study treatment: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated clots, are not exclusionary.
   b. Prolonged QTcF interval >480 msec or clinically significant cardiac arrhythmia or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate).

Note: Participants with cardiac pacemakers who are clinically stable are eligible.

c. Uncontrolled (persistent) hypertension: systolic blood pressure >180 mm Hg; diastolic blood pressure >100 mm Hg

d. Congestive heart failure defined as New York Heart Association (NYHA) class III-IV or Hospitalization for congestive heart failure (any NYHA class) (refer to Section 10.6, Appendix 6: New York Heart Association Criteria) within 6 months of study enrollment

e. Pericarditis/clinically significant pericardial effusion

f. Myocarditis

7. Participant has known allergies, hypersensitivity, or intolerance to excipients of amivantamab (refer to the IB).

8. Participant has received study treatment (including investigational vaccines) within 6 weeks before enrollment except for the anticancer therapy described in the Exclusion Criterion No. 2.

9. Participant has, or will have, any of the following:

a. An invasive operative procedure with entry into a body cavity, within 4 weeks or without complete recovery before C1D1. Thoracentesis, if needed, and percutaneous biopsy for baseline tumor tissue sample may be done less than 4 weeks prior to C1D1, 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

b. Significant traumatic injury within 3 weeks before the start of C1D1 (unless all wounds must be fully healed prior to Day 1)

c. Expected major surgery while the investigational agent is being administered or within 6 months after the last dose of study treatment

10. Participant has at screening:

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

Note: Participants with a prior history of HBV demonstrated by positive hepatitis B core antibody are eligible if they have at screening 1) a negative HBsAg and 2) 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.

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

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.

c. Other clinically active infectious or non-infectious liver disease

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

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

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

12. Participant has received prior EGFR or cMet-directed therapies.

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

**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening and that the participant continues to meet criteria prior to dosing on C1D1. On C1D1, 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 status changes (including laboratory results or receipt of additional medical records) after Screening but before the first dose of study treatment is given such that he or she no longer meets all eligibility criteria, 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 enrollment criteria are not met after further evaluation, the participant should be excluded from participation in the study. 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. The required source documentation to support meeting the enrollment criteria are noted in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations.

## 5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, 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).

### 5.3.1. Activity

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

## 5.4. Screen Failures

**Participant Identification, Enrollment, and Screening Logs**

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

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number that is different from the initial screening.

# 6. STUDY TREATMENT AND CONCOMITANT THERAPY

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

## 6.1. Study Treatment Administered

Study treatment administration must be captured in the source documents and the electronic case report form (eCRF).

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

The initial dosage of amivantamab will be based on the participant's body weight at screening: 1,050 mg (if body weight is <80 kg) or 1,400 mg (if body weight is ≥80 kg). Additional higher dosing, if recommended by the CTMT, will also be based on the participant's body weight: 1,750 mg (if body weight is <80 kg) or 2,100 mg (if body weight is ≥80 kg). Qualified site personnel will administer amivantamab as an IV infusion in 28-day cycles as follows:

Cycle 1: Once weekly (with the first dose split over Day 1 [350 mg] and Day 2 [700 mg if body weight is <80 kg or 1,050 mg if body weight is ≥80 kg]). For additional higher dosing, once weekly (with the first dose split over Day 1 [350 mg] and Day 2 [1.400 mg if body weight is <80 kg or 1,750 mg if body weight is ≥80 kg]).

Cycles 2+: Days 1 and 15 of each cycle

Amivantamab will be administered intravenously using the escalating infusion rate regimen as specified in the IPPI. At the discretion of the investigator, the infusion rate can be slower, but not faster than specified in the IPPI. The product must be infused via a peripheral vein for all Cycle 1 doses; infusion via central line is allowed for subsequent dosing starting with the C2D1 dose.

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

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

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

Dose and administration schedule may be adjusted based on CTMT recommendations during Phase 2a part.

As there are investigations ongoing assessing different amivantamab formulations and schedules, participants in Phase 2b cohorts may receive amivantamab according to a different schedule or route of administration. Any such change would only be made after approved protocol amendment.

## 6.2. Preparation/Handling/Storage/Accountability

### Preparation/Handling/Storage

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

### Accountability

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

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

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

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

## 6.3. Measures to Minimize Bias: Randomization and Blinding

### Treatment Allocation

#### *Procedures for Randomization*

Randomization will not be used in this study. Participants will be assigned to treatment in the order in which they qualify for this study.

### Blinding

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

## 6.4. Study Treatment Compliance

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

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

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

## 6.5. Dose Delay Guidance

In instances where treatment delay is indicated, treatment with amivantamab may be delayed until recovery of toxicity to a level allowing continuation of therapy. A participant for whom treatment was delayed should be assessed at least weekly to ensure adequate supportive care is being administered and to assess for improvement of toxicity. For majority of clinically significant toxicities dose delay and dose modifications should occur as per the guidelines described below (Section 6.6). If dose delay is continued for more than 28 days, consult with the medical monitor before restarting study treatment.

## 6.6. Dose Modification Guidance

Any dose/dosage adjustment should be overseen by medically qualified study site personnel (principal or sub-investigator unless an immediate safety risk appears to be present). The following guidance should be followed for dose delay and modification of the amivantamab based on the toxicity grade of AEs other than IRRs (Section 6.6.1), rash (Section 6.6.2), paronychia (Section 6.6.3), liver chemistry abnormalities (Section 6.6.4), and pulmonary toxicity (Section 6.6.5). When possible, the medical monitor should be notified prior to dose modifications.

**Table 3: Guidance for Amivantamab Dose Delay and Modification for Toxicities (Other Than Rash, Paronychia, Infusion-related Reaction, or Pulmonary Toxicity)**

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

a. Per Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
b. For all toxicities, consider supportive care according to protocol or local standards (if no protocol guidance provided), as appropriate.
c. Resolution defined as: Grade ≤1 or back to baseline.
d. If dose delay occurs for more than 1 cycle, contact the medical monitor to discuss retreatment.

In case a dose modification is necessary, the study treatment will be administered as follows:

**Table 4: Dose Modification for Amivantamab (1050mg/1400mg starting dose)**

| Dosage Level | Amivantamab | |
|---|---|---|
| | Participant <80 kg | Participant ≥80 kg |
| 0 (starting dose) | 1050 mg Q2W | 1400 mg Q2W |
| -1 | 700 mg Q2W | 1050 mg Q2W |
| -2 | 350 mg Q2W | 700 mg Q2W |
| -3 | Discontinue | Discontinue |
| Q2W=every 2 weeks (eg, Day 1 and Day 15 of each 28-day cycle) | | |

If the CTMT recommends exploration of higher doses of amivantamab and a dose modification is necessary, the study treatment will be administered as follows:

**Table 5: Dose Modification for Amivantamab (1750mg/2100mg starting dose)***

| Dosage Level | Amivantamab | |
|---|---|---|
| | Participant <80 kg | Participant ≥80 kg |
| 0 (starting dose) | 1750 mg Q2W | 2100 mg Q2W |
| -1 | 1400 mg Q2W | 1750 mg Q2W |
| -2 | 1050 mg Q2W | 1400 mg Q2W |
| -3 | Discontinue | Discontinue |

*Will be explored per CTMT recommendation
Q2W=every 2 weeks (eg, Day 1 and Day 15 of each 28-day cycle)

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

### 6.6.1. Infusion-related Reactions

Infusion-related reactions have been commonly observed during treatment with amivantamab, predominantly with the first exposure on C1D1, and typically within the first 90 minutes of the infusion. The majority of IRRs are Grade 1 or 2. Refer to Summary of Data and Guidance for Investigators in the current version of the IB for amivantamab. The guidelines described here are related to the safe administration of amivantamab during initial dosing.

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

Particularly with the initial dose (C1D1 and C1D2), participants should be educated on 1) the likelihood of experiencing an IRR with the initial dose, 2) the symptoms to anticipate (which include chills, dyspnea, chest discomfort, fever, flushing, among others), 3) that they should alert nursing staff if they experience these symptoms, and 4) that the experience of an IRR will not preclude further therapy with amivantamab. Participants must be monitored closely for early signs and symptoms indicative of an acute IRR. Even with mild symptoms, the study treatment infusion should be interrupted immediately when the initial dose is administered (ie, C1D1 or C1D2), as described in the tables below, to prevent more serious grade IRRs from occurring. Trained clinical personnel should be prepared to intervene in the event of IRRs. Resources necessary for resuscitation (ie, agents such as epinephrine, aerosolized bronchodilator, IV antihistamines, IV corticosteroids; medical equipment such as oxygen, airway management equipment including suction, and a defibrillator) must be readily available.

**Prevention of Infusion-related Reactions**

Required prophylaxis for IRRs is described in Section 6.8.1.

**Treatment of Infusion-related Reactions**

Participants who experience early symptoms of IRRs, manifesting as fever, chills, rigors, bronchospasm, headache, rash, pruritus, arthralgia, hypo- or hypertension or other symptoms, must have their amivantamab infusion interrupted, if indicated, and the symptoms managed according to the recommendations provided in Table 6. With the initial dose of amivantamab (C1D1 and C1D2), interrupting the infusion should be considered even with mild symptoms to prevent more severe manifestations of IRR. All Grade 3 or 4 IRRs should be reported within 24 hours to the medical monitor.

**Table 6: Management of Infusion-related Reactions**

| Toxicity Grade* | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>Mild reaction | Monitor participant as medically indicated until recovery from symptoms. If occurring with initial dose (ie, C1D1 or C1D2), consider early infusion interruption to prevent more severe symptoms. | Antihistamine, antipyretic, and glucocorticoid, as per Table 8. |
| **Grade 2**<br>Mild to moderate reaction; therapy or infusion interrupted but responds promptly to symptomatic treatment | **Interrupt infusion**<br>If clinically indicated, start IV fluids; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol (acetaminophen) 650 to 1,000 mg; consider corticosteroids and bronchodilator therapy; monitor participant closely until recovery from symptoms<br><br>**First interruption for infusion-related reaction: Restart infusion at 50% of the rate at the time of interruption**: if no further evidence of infusion-related reaction after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely.<br><br>**Second interruption for infusion-related reaction:** Stop and consider discontinuation of further study treatment at that visit; administer diphenhydramine 50 mg IV or equivalent and monitor participant until resolution of symptoms. The amount of study treatment infused must be recorded in the eCRF. If continuing administration after the second interruption, restart infusion at 50% of the rate at the time of the second interruption. If no further evidence of infusion-related reaction after 30 minutes, the rate may be increased to 100% of the infusion rate at the time of interruption; monitor participant closely. | Antihistamine, antipyretic, and glucocorticoid, as per Table 8.<br><br>Consider meperidine if participant experiences chills and rigors. |
| **Grade 3 or 4**<br>Severe reaction<br><br>Grade 3: prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)<br><br>Grade 4: life-threatening; pressor or ventilator support indicated | Stop infusion<br>Start IV saline infusion; recommend bronchodilators, supplemental oxygen; epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed (other drugs as appropriate).<br><br>Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids), as appropriate. | Based on severity of symptoms, consider permanent discontinuation of study treatment. Consultation with Medical Monitor required before continuing with subsequent dosing. |

eCRF=electronic case report form; IRR=infusion-related reaction; IV=intravenous.
*Per National Cancer Institute - Common Terminology Criteria for Adverse Events Version 5.0

### 6.6.2. Rash-related Adverse Events

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

***Prophylaxis Recommendations***

The prophylactic regimen can be managed according to local practice and guidelines; however, 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. Ultraviolet A light can penetrate glass; therefore, sunscreen should also be worn indoors and in vehicles if exposed to direct sunlight. Recommended active sunscreen ingredients are zinc oxide and/or titanium dioxide.
- Apply alcohol-free emollient cream or ointments (eg, glycerin, cetomacrogol, or ceramide-based cream) or skin moisturizer on dry areas of the body. These topical agents can be applied on a daily basis starting on Day 1 and more often as needed. Ideal time for application is after bathing. Creams and ointments are preferred over gels, lotions and oils.

***Reactive Management Recommendations***

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

- Consider consultation with a dermatologist, especially if the rash is Grade 3, atypical in appearance or distribution, or does not improve within 2 weeks (for Grade 2 rash).
- Initiate a topical corticosteroid (cream or ointment) twice daily

  Examples to use for face: betamethasone valerate 0.05%, hydrocortisone valerate 0.2%, or desonide 0.05%

  Examples to use for body: betamethasone valerate 0.1%, triamcinolone acetonide 0.1%
- If not already initiated for prophylaxis, initiate systemic antibiotic (such as doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily), or increase the dosing if already administered.
- If an associated skin infection is suspected, obtain bacterial and fungal cultures followed by adjustment of antibiotic or antifungal therapy, based upon culture and susceptibility determination.
- For skin fissures, use of Monsel's solution (ferric subsulfate solution), silver nitrate, 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 7.

**Table 7: Suggested Algorithm for Management of Rash**

| Grade[a] | Management | Dose Adjustment[b,c] |
|---|---|---|
| 1 | • Initiate reactive management as above<br>• Reassess after 2 weeks | • Continue current dose of study treatment |
| 2 | • Initiate reactive management as above<br>• Reassess after 2 weeks | • Continue current dose of study treatment |
| 3 or 4 | • Initiate reactive management as above<br>• Start moderate strength topical corticosteroids[d] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days<br>• Consider low doses of acitretin or isotretinoin (20-30 mg/day)<br>• Reassess after 2 weeks<br>• Consider dermatology consultation and manage rash per recommendation | • Temporarily dose delay of study treatment until rash improves to ≤Grade 2<br>• For guidance on dose delay of study treatment and dose modification, refer to Table 3 and Table 4. For additional higher dosing, refer to Table 5. |
| Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN) | • Consult dermatologist and manage rash per recommendation. | • Permanently discontinue amivantamab |

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

### Scalp Rash

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

- A topical steroid shampoo (eg, clobetasol 0.05%), or an anti-dandruff shampoo with anti-inflammatory, antibacterial, and antifungal properties (eg, ketoconazole, selenium sulfide [Selsun®], zinc pyrithione [Head and Shoulders®], or Ciclopirox). These shampoos should be used twice/week, massaging into scalp, leaving on for 2 to5 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.

### 6.6.3. Paronychia

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

***Prophylaxis Recommendations***

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

***Reactive Management Recommendations***

Grade 1 paronychia:

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

Grade 2 or 3 paronychia:

- In addition to the guidance for Grade 1 paronychia above:

  Apply topical antibiotic/antifungal agent (eg, mupirocin, fusidic acid, clotrimazole, or miconazole) twice daily.

  Initiate oral antibiotic for at least 14 days (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily).

  Consult a dermatologist or podiatrist.

### 6.6.4. Liver Chemistry Abnormalities

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

a) ALT or AST ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) (or ALT ≥3×ULN and international normalized ratio [INR] >1.5, if INR measured).

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

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

In the event abnormalities of liver function tests require the dose delay of study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. If the liver function test criteria either a) or b) above are met, etiology of the liver chemistry abnormality should be investigated, as described below. If no alternative etiology of liver toxicity is identified, study treatment should be permanently discontinued.

**Liver Event Follow-up Requirements**

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

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

  Hepatitis A IgM antibody

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

  Hepatitis C RNA

  Hepatitis E IgM antibody

  Cytomegalovirus IgM antibody

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

**Rechallenge Criteria**

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

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

### 6.6.5. Pulmonary Toxicity

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

- Detailed focused history reviewing respiratory status and exercise tolerance.
- Focused physical exam including full assessment of vital signs (with pulse oximetry).
- Unscheduled radiological assessment, including chest x-ray or CT scan (high-resolution CT is preferred).

Documentation of ILD/pneumonitis of any grade should prompt withholding study treatment and contacting the medical monitor. For symptomatic pneumonitis (Grade 2 and above), treatment with steroids should be initiated in addition to withholding of study treatment. Confirmation of ILD/pneumonitis of any grade should prompt discontinuation of study treatment and should be reported as an SAE (see Section 8.3.1). If the ILD/pneumonitis is attributed to prior radiation, participant can restart after discussion with the sponsor's medical monitor. Pertinent radiological images and reports should be submitted to the sponsor.

## 6.7. Treatment of Overdose

There are no data on overdose from studies of amivantamab.

In the event of an overdose, 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.

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

## 6.8. Concomitant Therapy

Concomitant therapies administered up to 28 days before first dose of study treatment must be recorded at screening and continued until 30 days after the last dose of study treatment or start of subsequent anticancer therapy, whichever is first. Concomitant therapies should also be recorded beyond 30 days only in conjunction with SAEs considered related to study treatment. For

participants with Grade 3 or 4 AEs considered related to study treatment, record concomitant medications through the end of follow-up of that AE.

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

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

### 6.8.1. Amivantamab Pre-infusion and Post-infusion Medications

#### 6.8.1.1. Amivantamab Pre-infusion Medications

Required and optional amivantamab pre-infusion medications for IRRs are summarized in Table 8.

**Table 8: Amivantamab Pre-infusion Medications**

| Medication | Dose | Route of Administration | Recommended Dosing Window Before Infusion | Cycle/Day |
|---|---|---|---|---|
| **Required Pre-infusion Medications[a,b]** | | | | |
| Glucocorticoid | Dexamethasone (10 mg) or Methylprednisolone (40 mg) | IV | 45 to 60 minutes | C1D1<br>C1D2 |
| Antihistamine[d] | Diphenhydramine (25 to 50 mg) or equivalent | IV | 15 to 30 minutes | All |
| | | Oral | 30 to 60 minutes | |
| Antipyretic[d] | Paracetamol (acetaminophen 650 to 1,000 mg) or equivalent | IV | 15 to 30 minutes | All |
| | | Oral | 30 to 60 minutes | |
| **Optional Pre-infusion Medications[a]** | | | | |
| Glucocorticoid[c,d] | Dexamethasone (10 mg)<br>Methylprednisolone (40 mg) | IV | 45 to 60 minutes | C1D8 and beyond |
| | | Oral | 60 to 90 minutes | |
| $H_2$ antagonist | Ranitidine (50 mg) or equivalent | IV | 15 to 30 minutes | Any |
| Antiemetic[d] | Ondansetron (16 mg) or equivalent<br>Ondansetron (8 mg) or equivalent | IV<br>Oral | 15 to 30 minutes<br>15 to 30 minutes | Any |

C Cycle; D Day X; IV intravenous.

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

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

c. Beginning with C1D8, optional predose steroids may be administered if clinically indicated for participants who experienced an infusion related reaction on C1D1 or C1D2.

d. Either IV or oral route is selected for antihistamine, antipyretic, glucocorticoid and antiemetic medications.

#### 6.8.1.2. Amivantamab Post-infusion Medications

Optional amivantamab post-infusion medications may be prescribed and continued for up to 48 hours after the infusion if clinically indicated, at the discretion of the investigator as described in Table 9.

**Table 9: Amivantamab Post-infusion Medications**

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

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

### 6.8.2. Prohibited or Restricted Medications and Therapies

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

- Any chemotherapy, systemic anticancer therapy, or experimental therapy (other than study treatments). Hormonal treatments as specified in exclusion 5 are allowed.
- Radiotherapy to tumor lesions being assessed for tumor response prior to radiographic progression
- Use of live or live attenuated vaccines is prohibited. COVID-19 vaccine is not considered as live or live attenuated vaccines but the administration of COVID-19 vaccine should be avoided on the same day of study drug administration.
- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.

## 7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Treatment

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study treatment
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study treatment
- The participant becomes pregnant (refer to Section 10.4, Appendix 4: Contraceptive and Barrier Guidance).

- Noncompliance with study treatment or procedure requirements
- Documented radiographic (RECIST, Version 1.1) disease progression, unless treatment beyond disease progression has been approved by the medical monitor
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the judgement of the investigator
- The participant receives concurrent (non-protocol) anticancer treatment

If a participant discontinues study treatment for any reason, then the EOT assessments should be obtained according to the Schedule of Activities and follow-up visits should continue after study treatment is discontinued. If the initiation of the subsequent anticancer therapy is required prior to EOT, EOT must be completed prior to the initiation of the subsequent anticancer therapy. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant. Additional participants will not be entered in the study.

## 7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

**Withdrawal of Consent**

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

### 7.2.1. Withdrawal From the Use of Research Samples

**Withdrawal From the Use of Samples in Future Research**

The participant may withdraw consent for use of samples for research (refer to Long-term Retention of Samples for Additional Future Research in Section 10.2, Appendix 2: Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

## 7.3. Lost to Follow-up

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

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

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

# 8. STUDY ASSESSMENTS AND PROCEDURES

**Overview**

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of the measurements applicable to this study.

The total blood volume collected for the study will be approximately 25 mL (screening), 105 mL (Cycle 1), 75 mL (Cycle 2), and 30 mL (for each cycle beyond Cycle 3 and EOT).

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

**Sample Collection and Handling**

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

Refer to the Schedule of Activities (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. 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
- IB
- IPPI and SIPPM
- Laboratory manual and kits
- NCI-Common Terminology Criteria for Adverse Events (CTCAE) Version 5
- RECIST guidelines Version 1.1
- Electronic data capture (eDC) manual
- Sample ICF
- Wallet cards
- Study treatment

## 8.1. Efficacy Assessments

### 8.1.1. Disease Assessments

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

Computerized tomography scan of the chest (including the supraclavicular region), abdomen, pelvis, and any other disease location(s), if clinically indicated, should be performed with an IV contrast agent. Participants not able to undergo CT scans with IV contrast (eg, due to allergy or renal insufficiency) may have non-contrast CT of the thorax and MRI of the abdomen and pelvis with IV contrast at baseline and during the study if approved by the sponsor. Contraindications to the CT scan with IV contrast that develop post-baseline should be discussed with the medical monitor. Identical methodology should be used for disease assessment at baseline and throughout the course of the study to characterize each identified and reported lesion to document disease status. Techniques other than CT or MRI may be used based upon investigator's judgement, local standard of care, and RECIST Version 1.1 guidelines for the use of these alternative techniques.

The baseline disease assessments should be performed as close as possible to the start of treatment, but no more than 28 days prior to the first dose. Subsequent assessments should be performed at 6 weeks (+1 week) after initiation of study treatment administration, then every 6 weeks (±1 week) for the first 12 months and then every 12 weeks (±1 week) until objective radiographic disease progression. Timing for each disease assessment is relative to the first dose of study treatment administration, regardless of dose modifications, and will continue until disease progression. If an

assessment is performed outside of the scheduled visit and the participant has not progressed, every attempt should be made to perform the subsequent assessment at their scheduled visit timepoint. Any other site at which new disease is suspected should also be imaged.

If a participant achieves partial response (PR) or complete response (CR), every effort should be made to confirm the response after, but as close to, 4 weeks of entering PR or CR instead of predefined 6 weeks. Response may also be assessed by an Independent Review Committee (IRC) for the central confirmation.

If the investigator is in doubt as to whether progression has occurred, particularly with response to nontarget lesions or the appearance of a new lesion, treatment should be continued until the next scheduled assessment (or sooner if clinically indicated) and reassess the participant's status. If the repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression. To achieve "unequivocal progression" on the basis of nontarget lesions, there must be an overall substantial worsening in nontarget lesions such that, even in the presence of stable disease or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression. 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 eCRF and documented in the source documents. Every effort should be made to document radiographic progression even after discontinuation of treatment for symptomatic deterioration, but prior to subsequent therapy, if possible. For participants who discontinue study treatment due to toxicity or a reason other than objective progressive disease, tumor assessments should be continued per schedule until radiographic progressive disease is documented.

Participants will have brain MRI scan (CT scan with contrast may also be used to determine the presence of brain lesions if MRI is contraindicated) at screening to identify any untreated brain metastases (Exclusion criterion #3). Brain scan is not required with every subsequent disease assessment, regardless of history of prior brain metastases, and should be performed if clinically indicated, according to local guidelines and practices.

If a participant is deriving clinical benefit and treatment beyond documented disease progression is approved by the sponsor's medical monitor, disease assessments will continue as scheduled and the investigator and the Medical Monitor will review clinical benefit after each disease assessment.

## 8.2. Safety Assessments

Details regarding the CTMT are provided in Committees Structure in Section 10.2, Appendix 2: 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 Section 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

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

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (see Section 1.3).

### 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 scale.

### 8.2.2. Vital Signs

Vital sign measurements will include the following assessments as indicated in the Schedule of Activities (Table 1):

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

Blood pressure and 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 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

Triplicate electrocardiograms (ECGs), performed locally, will be collected at screening to determine the eligibility. 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.

Three individual ECG tracings should be obtained as closely as possible in succession, but approximately 2 minutes apart. The clinical investigator will review the ECG, including ECG morphology, for immediate management. The results, including measurement of heart rate, QRS axis, and intervals for PR, uncorrected QT interval (QT), QRS, RR, and QTcF will be entered into the eCRF. Abnormalities at screening should be included in the medical history.

QTcF is calculated using the Fridericia's formula: QTcF QT/(RR)^0.33.

### 8.2.4. ECOG Performance Status

Eastern Cooperative Oncology Group performance status score will be evaluated during the screening phase to determine the eligibility. Any decline in ECOG performance status score should be reported as an AE.

### 8.2.5. Clinical Safety Laboratory Assessments

Clinical laboratory assessments will be performed locally. Clinical laboratory tests will be performed as noted in Table 10.

**Table 10: Clinical laboratory assessments**

| Laboratory Assessments | Parameters | |
|---|---|---|
| Hematology | Hemoglobin<br>Platelet count | Absolute neutrophil count<br>White blood cell (WBCs) absolute count with differential |
| Clinical Chemistry | Alkaline phosphatase<br>Creatinine<br>Aspartate aminotransferase<br>Alanine aminotransferase<br>Gamma-glutamyl transferase<br>Bilirubin (total, direct, indirect)<br>Lactic acid dehydrogenase<br>Albumin | Total protein<br>Blood urea nitrogen<br>Magnesium<br>Phosphorus<br>Sodium<br>Potassium<br>Calcium |
| Coagulation (screening only) | Prothrombin time (in seconds)<br>Activated partial thromboplastin time | International normalized ratio |
| Urinalysis (screening only) | Dipstick<br>Specific gravity<br>pH<br>Glucose<br>Protein<br>Blood<br>Ketones<br>Bilirubin<br>Urobilinogen<br>Nitrite<br>Leukocyte esterase | Sediment (if dipstick result is abnormal)<br>Red blood cells<br>WBCs<br>Epithelial cells<br>Crystals<br>Casts<br>Bacteria |
| Serology | Anti- human immunodeficiency virus (anti-HIV) antibody<br>hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb)<br>(Participants with a history of hepatitis B virus (HBV) are also required to have HBV DNA quantification.)<br>Anti- hepatitis C virus (anti-HCV) antibody<br>(Participants with a history of HCV are required to have HCV RNA quantification.) | |

The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

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

### 8.2.6. Pregnancy Testing

Serum or urine pregnancy testing will be performed at screening (72 hours before the first dose of study treatment administration) and as clinically indicated, according to local regulation requirements, or following the local practice of the center during the treatment period for women of childbearing potential only. At other times, additional serum or urine pregnancy tests may be performed, at investigator's decision.

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

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

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

Further details on AEs, SAEs, and PQC can be found in Section 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

### 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 completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

**Serious Adverse Events**

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

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported. 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 SAE Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study

site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

### 8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

**Solicited Adverse Events**

Solicited AEs are predefined local (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 Section 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

### 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. The investigator (or sponsor where required) must report suspected unexpected serious adverse reactions to the appropriate 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.

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

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

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

An event such as disease progression, which is part of the natural course of the disease under study, does not need to be reported as an AE or SAE term. In this circumstance, death due to disease progression should be recorded on appropriate case report forms (such as the Death or study treatment disposition eCRF page). However, disease progression must be reported as an SAE term if the event was accelerated or greater in severity than expected for the participant, or if the investigator considers there to be a causal relationship between the event and the study treatment, protocol design, or protocol procedures.

### 8.3.7. Adverse Events of Special Interest

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

## 8.4. Pharmacokinetics

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

### 8.4.1. Evaluations

Blood samples will be collected for measurement of serum amivantamab for PK analyses. The PK profile of amivantamab will be based on serum concentration data obtained from the timepoints surrounding the first and fifth dose administrations collected from at least 10 participants in each cancer type in Phase 2a. Blood samples for sparse PK will also be obtained following all other dose administrations from participants in Phase 2a and 2b, prior to the start of the infusion and following the end of the infusion, from all the participants. Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

### 8.4.2. Analytical Procedures

**Pharmacokinetics**

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

In addition, serum PK samples may be stored for future analysis of other co-administered treatments.

### 8.4.3. Pharmacokinetic Parameters and Evaluations

The primary PK endpoints include, but are not limited to maximum serum concentration ($C_{max}$), $T_{max}$, $AUC_{(t1-t2)}$ (eg, $AUC_{Day1-8}$), $AUC_{tau}$, plasma/serum concentration immediately prior the next study treatment administration ($C_{trough}$), $t_{1/2}$, CL, steady state volume of distribution ($V_{SS}$), and accumulation ratio. Population PK modeling may be performed to assess the potential effect of intrinsic factors and extrinsic on the PK of amivanatamab.

## 8.5. Pharmacogenomics

Pharmacogenomics are not evaluated in this study.

## 8.6. Biomarkers

Collected tumor tissue samples will be used to evaluate the tumor surface levels of EGFR and cMET protein expression by centrally performed IHC assay to determine the patient eligibility, although documentation of previously performed local IHC results may be submitted for the purposes of demonstrating eligibility for study conduct. All statistical and biomarker analysis, however, will utilize the results of the centrally performed IHC results, based on the statistical analysis plan. Tumor tissue collected at screening may also be analyzed by tumor next-generation sequencing to evaluate molecular alterations and track response to treatment. Tumor samples collected post-treatment and post-progression may also be evaluated by IHC and next-generation sequencing to track response to amivantamab. Tissues may also be used to determine biomarkers relevant to GC/EC and/or analyzed to confirm ctDNA results.

Screening blood samples from all participants will undergo ctDNA analysis to evaluate pre-treatment mutational status of EGFR, cMet, and other key oncogenes to characterize the tumor. Additional blood samples will be collected during the study and may be evaluated for ctDNA to assess changes in the levels or types of genetic alterations observed over time and to monitor for the emergence of potential markers of resistance to amivantamab.

Blood samples will also be collected at time points specified in the Schedule of Activities (Table 2) and may be analyzed for circulating factors relevant to disease biology (eg, hepatocyte growth factor).

Blood samples will also be collected from at least 10 participants in each cancer type at selected time points to analyze PD markers (eg, soluble EGFR and cMet) in samples taken prior to and

after exposure to amivantamab, to explore whether the complete soluble target saturation throughout the dosing was attained.

For the provision of biopsy tissue samples, fresh or formalin-fixed, paraffin-embedded (FFPE) tissue samples are requested and will be evaluated for biomarkers (DNA, RNA, and/or protein) relevant to cancer.

**Stopping Analysis**

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

**Additional Collections**

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

## 8.7. Immunogenicity Assessments

Serum samples will be collected for immunogenicity assessments of amivantamab (anti-drug antibodies to amivantamab). The detection and characterization of antibodies to amivantamab will be performed using a validated immunoassay method by or under the supervision of the sponsor.

Serum samples will be screened for antibodies binding to amivantamab and serum titer will be determined from positive samples. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. All samples collected for immune response analysis will also be evaluated for amivantamab serum concentration to ensure appropriate interpretation of immunogenicity data. Other immunogenicity analyses may be performed to further characterize any immune responses generated.

## 8.8. Medical Resource Utilization and Health Economics

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

# 9. STATISTICAL CONSIDERATIONS

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

## 9.1. Statistical Hypotheses

No hypothesis is planned to be tested in Phase 2a.

The statistical hypothesis in Phase 2b is that amivantamab monotherapy will lead to objective response rate (ORR) higher than 15% (ie, $H_0 \leq 15\%$ vs $H_a > 15\%$) in patients with GC or EC, selected on the basis of expression of EGFR, cMET, or both. This threshold is based on historical studies for approved 3L regimens for GC (11.2%-13.6%) and reported efficacy of approved 2L regimens for EC (approximately 15%).

## 9.2. Sample Size Determination

In Phase 2a, approximately 30 response evaluable participants with tumors expressing either EGFR, cMet, or both, as determined by central IHC, will be enrolled in GC and EC cohorts. Twenty participants will be enrolled for IHC 2+/3+ that will provide approximately 90% probability to observe the posterior probability of (ORR >22.5%) ≥40% (which is similar with ORR ≥20%) assuming ORR is 30% for the subpopulation. By enrolling 10 participants with IHC 1+, the probability to observe the posterior probability (ORR >22.5%) ≥40% is 80%.

Upon agreement with CTMT, a maximum of 11 participants may be enrolled in each Phase 2a extension cohort. Enrollment will halt if no response or stable disease of 6 weeks or more is observed among the first 6 participants for futility in each of the Phase 2a extension cohorts. If 2 or more responses are observed in each of Phase 2a extension cohorts, CTMT will assess the data and may recommend additional participants to be enrolled for further characterization.

In each dose cohort of phase 2a, approximately 20 response evaluable participants will be additionally enrolled if the CTMT recommends exploration of higher doses. The probability to observe 4 or more response (ORR > 20%) is 89% assuming ORR of 30%.

In Phase 2b cohorts, approximately 100 participants will be enrolled in each of GC and EC expansion cohort. The eligible participants will be decided based on the results in Phase 2a part. Assuming an overall ORR of 30% for amivantamab, 100 participants in Phase 2b part will provide approximately 90% power to reject the null hypothesis, 15% ORR, using 2-side z test at alpha 0.05.

## 9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| All Enrolled | All participants who are assigned with study treatment. |
| All Treated | All participants who take at least 1 dose of study treatment |
| Response evaluable | All participants who satisfy the following criteria:<br>• Receive at least 1 dose of study treatment<br>• Met all eligibility criteria for the study<br>• Had a baseline and at least 1 post-baseline efficacy disease assessments, or have disease progression/death due to disease progression prior to the first post-baseline disease assessment |
| Safety | All participants who take at least 1 dose of study treatment |

| Population | Description |
|---|---|
| Pharmacokinetics | All participants who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline measurement |
| Immunogenicity | All participants who receive at least 1 dose of study treatment and have at least 1 evaluable post-baseline measurement |
| Biomarker | All participants who receive at least 1 dose of study treatment and have at least 1 biomarker measurement |

## 9.4. Statistical Analyses

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

### 9.4.1. General Considerations

All continuous variables will be summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables will be summarized with number and percent. The Kaplan-Meier product limit method will be used to estimate the time-to-event variables including median survival time. Unless otherwise specified, the phases, arm and dose regimen will be analyzed separately.

Analyses of ORR and disease control rate (DCR) will be performed on the response evaluable population. The other efficacy analyses will be performed on all treated population. The central IHC data will be used for the statistical analysis purposes.

At the end of Phase 2a part, CTMT will review the result and determine which subpopulations and dose to be included in the Phase 2b part (see Appendix 2, Section 10.2.6: Committees Structure).

### 9.4.2. Primary Endpoint

#### 9.4.2.1. Objective Response Rate

Primary Estimand

- Population: participants with GC or EC expressing EGFR and/or MET
- Variable: overall response; CR or PR
- Study drug: amivantamab monotherapy
- Intercurrent event: subsequent anticancer therapy. The while-on-treatment policy: Response after this intercurrent event will not be included.
- Summary: ORR

The primary efficacy measure is ORR. Objective response rate is defined as the proportion of participants who achieve either CR or PR, determined by investigator assessment using RECIST

Version 1.1. Confirmation of investigator-assessed ORR may be performed through IRC in the Phase 2b.

For Phase 2a part, there will be no formal hypothesis testing. ORR will be calculated for response evaluable population descriptively.

For Phase 2b part, a z test with normal approximation will be used to compare the ORR with 15%. Multiplicity caused by subpopulation selection at the interim analysis (see section 9.5) will be controlled by closed testing procedure and weighted statistics. More detail will be described in SAP. The ORR and its 95% confidence interval (CI) will also be calculated.

### 9.4.3. Secondary Endpoints

#### 9.4.3.1. Disease Control Rate

Disease control rate is defined as the percentage of participants achieving complete or partial response or stable disease for at least 6 weeks as defined by RECIST Version1.1. The DCR and its 95% CI with Clopper-Pearson method will also be calculated.

#### 9.4.3.2. Duration of Response

Duration of Response (DoR) is defined as the time from the date of first documented response (CR or PR) until the date of documented progression or death, whichever comes first. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then his/her duration of response will use the PFS censoring time. A Kaplan-Meier plot and median DoR with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented. Confirmation of investigator-assessed DoR may be performed through IRC in the Phase 2b.

#### 9.4.3.3. Time to Response

Time to Response (TTR) is defined as the time from the date of first amivantamab administration to the date of achieving objective response (CR or PR) by investigator assessment using RECIST Version 1.1 among patients who achieve objective response. TTR will be analyzed using the same methodology as for the analysis of DoR.

#### 9.4.3.4. Progression-free Survival

Progression-free survival is defined as the time from first dose until the date of objective disease progression or death (by any cause in the absence of progression), whichever comes first, based on investigator assessment using RECIST Version 1.1. Participants who have not progressed or have not died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST Version 1.1 assessment. PFS will be analyzed using the same methodology as for the analysis of DoR.

#### 9.4.3.5. Overall Survival

Overall survival is defined as the time from the date of first dose until the date of death due to any cause. Any participant not known to have died at the time of analysis will be censored based on

the last recorded date on which the participant was known to be alive. OS will be analyzed using the same methodology as for the analysis of DoR.

### 9.4.4. Safety Analyses

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

**Adverse Events**

The verbatim terms used in the eCRF 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 treatment through the day of last dose plus 30 days or until the start of subsequent anticancer therapy, if earlier, is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

**Clinical Laboratory Tests**

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

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

**Vital Signs**

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

### 9.4.5. Other Analyses

**Pharmacokinetic Analyses**

The PK analyses will use the PK population. Serum amivantamab concentrations will be summarized for each cancer type and overall population in tables of mean, SD, median, and range over time, as appropriate. PK parameters will be estimated for individuals and descriptive statistics will be calculated for each cancer type and overall population.

Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study treatment; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

**Pharmacokinetic/Pharmacodynamic Analyses**

The exposure-response relationship between amivantamab exposure and key efficacy and safety parameters may be explored if the data allow. In addition, the relationship may be characterized using an exposure-response model. Details will be provided in an analysis plan and detailed results may be reported separately from the CSR.

**Immunogenicity Analyses**

The incidence of anti-amivantamab antibodies will be summarized for immunogenicity population.

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

**Pharmacodynamic and Biomarker Analyses**

The biomarker analyses will use the biomarker population. Analyses are planned to explore PD and other biomarkers that may be indicative of the mechanisms of action of the drug or predictive of efficacy as well as the potential mechanisms of resistance to amivantamab.

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

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

## 9.5. Interim Analysis

If the CTMT recommends exploration of higher doses in each cohort of phase 2a, an interim futility analysis is planned for the participants receiving the higher dose, when 10 response evaluable participants have radiographic assessment. The enrollment may halt if the number of participants with objective response (ie, CR or PR) is 1 or less. CTMT will make a decision considering all other aspects of study data such as safety, PK and other efficacy endpoints.

In Phase 2b, an interim futility analysis is planned in each of GC and EC arm approximately 12 weeks after 50 participants receive the first infusion. The interim futility analyses will be based on the best response rate for each subpopulation (for example, IHC 2+/3+ and IHC 1+) selected at the end of Phase 2a and prespecified before initiating Phase 2b). The enrollment of each subpopulation may be terminated for futility if the posterior probability (ORR >22.5%) is <40%. Specific details will be provided in the data review committee Charter and interim analysis plan.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Abbreviations

| | |
|---|---|
| 2L | second line |
| 3L | third line |
| AEs | adverse events |
| ALT | alanine aminotransferase |
| AUC | area under the curve |
| ART | antiretroviral therapy |
| AST | aspartate aminotransferase |
| CI | confidence interval |
| cMet | tyrosine-protein kinase mesenchymal-epithelial transition |
| COVID-19 | Coronovirus disease 2019 |
| CR | complete response |
| CSR | clinical study report |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMT | clinical trial management team |
| ctDNA | circulating tumor deoxyribonucleic acid |
| C | Cycle |
| D | Day |
| DCR | disease control rate |
| DoR | duration of response |
| EC | esophageal cancer |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| eDC | electronic data capture |
| EGF | Epidermal growth factor |
| EGFR | epidermal growth factor receptor |
| EOT | end-of-treatment |
| FSH | follicle stimulating hormone |
| GC | gastric cancer |
| GCP | Good Clinical Practice |
| GEJ | gastroesophageal junction |
| HA | Health authority |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HER | human epidermal growth factor receptor |
| HGF | hepatocyte growth factor |
| HIV | human immunodeficiency virus |
| HRT | hormonal replacement therapy |
| IB | investigator's brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IgG1 | immunoglobulin G1 |
| IHC | Immunohistochemistry |
| ILD | interstitial lung disease |
| INR | international normalized ratio |
| IPPI | Investigational Product Preparation Instructions |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |
| IRR | infusion-related reaction |
| IV | intravenous |

| | |
|---|---|
| mPFS | median progression-free survival |
| MRI | magnetic resonance imaging |
| NCCN | National Comprehensive Cancer Network |
| NCI-CTCAE | National Cancer Institute - Common Terminology Criteria for Adverse Events |
| NSCLC | non-small cell lung cancer |
| NYHA | New York Heart Association |
| ORR | objective response rate |
| OS | overall survival |
| PD | Pharmacodynamic |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PQC | product quality complaint |
| PR | partial response |
| RTK | Receptor tyrosine kinases |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | serious adverse event |
| SAP | Statistical analysis plan |
| Scr | Screening |
| SD | standard deviation |
| SIPPM | Site Investigational Product and Procedures Manual |
| SPF | Skin protection factor |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TEN | Toxic epidermal necrolysis |
| TKI | tyrosine kinase inhibitor |
| $T_{max}$ | time to reach the maximum plasma/serum concentration |
| TTR | Time to Response |
| ULN | upper limit of normal |
| US | United States |
| WBC | White blood cells |

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

### 10.2.1. Regulatory and Ethical Considerations

**Investigator Responsibilities**

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

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

**Protocol Amendments**

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

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

**Regulatory Approval/Notification**

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

**Required Prestudy Documentation**

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

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

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

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

**Independent Ethics Committee or Institutional Review Board**

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

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

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

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

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

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

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

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

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

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

**Country Selection**

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

**Other Ethical Considerations**

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

### 10.2.2. Financial Disclosure

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

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

### 10.2.3. Informed Consent Process

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

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

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

### 10.2.4. Data Protection

**Privacy of Personal Data**

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

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

The informed consent obtained from the participant 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.

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.

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

### 10.2.5. Long-term Retention of Samples for Additional Future Research

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

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

### 10.2.6. Committees Structure

**Clinical Trial Management Team**

The safety and conduct of the study will be monitored by the CTMT established by the sponsor in conjunction with the coordinating investigator. The CTMT will consist of coordinating investigator(s) or their designee(s), the sponsor's medical monitor, the Safety Management Team Chair, one of the sponsor's clinical pharmacologists or their designees, and additional sponsor staff as appropriate. The sponsor's statistician or biomarker scientist will be consulted when the CTMT determines it is necessary. In general, the CTMT will monitor the conduct of the study and review study data in an ongoing basis. The CTMT may recommend and decide on modifications in the study conduct which may include, but are not restricted to, changes in (1) study treatment administration dose/schedule, (2) participant population based on the emerging biomarker data, (3) allowing further enrollment of or terminate enrollment of a specific subpopulation to better characterize the specific population (eg, enrollment of IHC 2+/3+ or EGFR and cMET double positive population), (4) opening of Phase 2a extension cohorts, and (5) PK or biomarker sampling times. All decisions made by the CTMT will be documented in a CTMT decision document. The IRB/IEC will be notified for all CTMT decisions, if required. The recommendations may be instituted by the CTMT, pending protocol amendment, as long as they are consistent with the benefit-risk and populations already reviewed and approved by the HA and local IRBs. All the CTMT documentation will be maintained in the sponsor's study master file and, as appropriate, in the investigator's study files. If unexpected safety findings are identified, the CTMT will assess the safety data in a prompt manner.

At the end of Phase 2a part, CTMT will review the results and determine which subpopulations and dose to be included in the Phase 2b part. In general, Phase 2b will be initiated if a Phase 2a population (or subset of Phase 2a populations) achieves posterior probability (ORR >22.5%) ≥40% (which is similar with ORR ≥20%). All available data (eg, efficacy, safety, and biomarker data) will be assessed to determine whether enrollment in a given subpopulation should continue. More details will be described in the CTMT charter.

### 10.2.7. Publication Policy/Dissemination of Clinical Study Data

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

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

The results of the study will be reported in a CSR 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 any analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

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 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 International Committee of Medical Journal Editors 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.

### 10.2.8. Data Quality Assurance

**Data Quality Assurance/Quality Control**

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

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

### 10.2.9. 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 eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

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

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

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

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

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

### 10.2.10. 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 medication; treatment receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

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

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

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

### 10.2.11. Monitoring

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

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

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

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

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

### 10.2.12. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be

respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

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

### 10.2.13. Record Retention

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

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

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

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

### 10.2.14. 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 HA, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

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

### 10.3.1. Adverse Event Definitions and Classifications

**Adverse Event**

An 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 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 Event and Serious Adverse Event Information, for time of last AE recording).

**Serious Adverse Event**

An SAE based on ICH and Europeon Union (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 judgement 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 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 amivantamab, the expectedness of an AE will be determined by whether or not it is listed in the IB.

### 10.3.2. Attribution Definitions

**Assessment of Causality**

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

**Related**

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

**Not Related**

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

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

### 10.3.3. Severity Criteria

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. Any AE or SAE not listed in the NCI-CTCAE, Version 5 will be graded according to the investigator clinical judgment by using the standard grades as follows:

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

### 10.3.4. Special Reporting Situations

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

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

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

### 10.3.5. Procedures

**All Adverse Events**

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

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

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number

**Serious Adverse Events**

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

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

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. 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 or Phase 2a participants during C1D1 until C1D8)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the treatment period.

Disease progression does not need to be reported as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Adverse Event Definitions and Classifications in Section 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the eCRF, 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.

### 10.3.6. Product Quality Complaint Handling

**Definition**

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

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

**Procedures**

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

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

### 10.3.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.3, Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

**Definitions**

***Woman of Childbearing Potential***

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

***Woman Not of Childbearing Potential***

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

Note: If the childbearing potential changes after start of the study or the risk of pregnancy changes, a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

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

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

## Examples of Contraceptives

**1. HIGHLY EFFECTIVE METHODS** *(Failure rate of <1% per year when used consistently and correctly.)*

**1.1. USER INDEPENDENT - Highly Effective Methods.**

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation [b,d]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner
  *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*

**1.2. USER DEPENDENT - Highly Effective Methods**

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [b]
  - oral
  - intravaginal[d]
  - transdermal[d]
  - injectable[d]
- Progestogen-only hormone contraception associated with inhibition of ovulation [b, d]
  - 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.)*

**2. NOT HIGHLY EFFECTIVE METHODS** *(Failure rate of >1% per year)*

- **USER DEPENDENT and NOT considered to be (highly) effective methods.** Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Male or female[d] condom with or without spermicide [c, d]
- Cap[d], diaphragm, or sponge[d] with spermicide
- A combination of male condom with either cap[d], diaphragm, or sponge[d] with spermicide (double-barrier methods) [c]
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus-interruptus)
- Spermicides alone
- Lactational amenorrhea method (LAM)

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

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

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

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

## 10.6. Appendix 6: New York Heart Association Criteria

The following table presents the NYHA classification of cardiac disease:

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

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

## 10.7. Appendix 7: 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)

## 10.8. Appendix 8: Study Conduct During a Natural Disaster

**GUIDANCE ON STUDY CONDUCT DURING CORONOVIRUS DISEASE 2019 (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, self-isolation/quarantine by participants and study site personnel; travel restrictions/limited-access to public places, including hospitals; study site personnel being reassigned to critical tasks.

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

Scheduled visits that cannot be conducted in person at the study site 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 via COVID-19 pandemic 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-related" in the eCRF.

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

## 10.9. Appendix 9: Protocol Amendment History

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

### Amendment 1 (10 November 2021)

**Overall Rationale for the Amendment:** The overall reason for the amendment is addition of time to response (TTR) as a secondary endpoint, update to require skin protection factor (SPF) ≥30 for participants with sun exposure as part of the rash prophylaxis guidance, correction of PK, clarification of dose delay criteria, Additionally, some changes for the clarification and some corrections were made.

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 3. Objectives and Endpoints<br><br>9.4.3.3. Time to Response | Time to response (TTR) was added.<br><br>Section added. | To add a secondary endpoint. |
| 5.3.1 Activity<br><br>6.6.2. Rash related Adverse Events - Prophylaxis Recommendations | Following update was made:<br>Use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥~~15~~ **30**.<br><br>Use broad-spectrum sunscreen with an SPF of ≥~~15~~ **30** and reapply as necessary. | To align the updated management guideline in protocol within the amivantamab program. |
| 1.3. Schedule of Activities (SoA) – Table 2 | Updated the collection window as below:<br>C1D15 EOI: ~~±2 hr~~ **+5 min**<br>C2D1 EOI:~~±2 hr~~ **+5 min**<br>C2D8 EOI+168 hours:~~< 2 hr~~ **± 4 hr**<br>C4D1 EOI: ~~±2 hr~~ **+5 min** | The error was corrected. |
| 1.3. Schedule of Activities (SoA) – Table 1 | Footnote d was updated:<br>d. ~~Any missed doses should be discussed with the medical monitor prior to redosing.~~ **A dose in Cycle 1 other than Day 1 and 2 in Cycle 1 can be delayed for 1 day and in Cycle 2 and beyond a dose delay is allowed 7 days. A planned dose must be skipped if amivantamab is not administered beyond 7-day.** If a dose is delayed in Cycle 2 or beyond, then the dates of all subsequent doses must be maintained as originally scheduled based on first dose (ie. C1D1). | Clarified the dose delay window and actions to be taken if out of the window. |
| 6.5. Dose Delay Guidance | The text 'withhold dosing' was changed to 'dose delay'. | To clarify the definition. |
| Throughout 6.6. Dose Modification Guidance | The text 'interruption' was changed to 'dose delay'.<br><br>The text 'withhold' or 'hold' was changed to 'delay' or 'dose delay'.<br><br>The text 'reduction' was changed to 'modification'. | To clarify the definition. |
| 1.3. Schedule of Activities (SoA) – Table 1 | Updated the pre-screening window from '-28 of C1D1' to 'before full-screening'. | The description was corrected because pre-screening may be performed over 28 days prior to C1D1. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3. Schedule of Activities (SoA) – Table 1 | Updated the EOT window from '30D After Last Dose' to 'Up to 30D After Last Dose'. | The description was clarified. |
| 1.3. Schedule of Activities (SoA) – Table 1 | Note was added in the tumor biopsy as below:<br>If the differential diagnosis between recurrence and fibrotic on the irradicated lesion makes possible, the biopsy may be conducted on the irradicated lesion. | To clarify biopsy from irradiated lesion. |
| 1.3. Schedule of Activities (SoA) – Table 1 | Note was added in the ctDNA and biomarker as below:<br>Blood sample for ctDNA and biomarker at EOT will be collected from participants with disease progression within 30 days of disease progression and before the next anticancer therapy in case the next anticancer therapy is planned. | To clarify the timing of blood sample for ctDNA and biomarker at EOT. |
| 1.3. Schedule of Activities (SoA) – Table 1 | Footnote j was added:<br>j. If the initiation of the subsequent anticancer therapy is required prior to EOT, EOT must be completed prior to the initiation of the subsequent anticancer therapy. | Considered the possibility of starting the next anticancer therapy immediately after treatment discontinuation. |
| 1.3. Schedule of Activities (SoA) – Table 1 | Footnote k was added:<br>k. If the imaging data is obtained within 28 days prior to the initiation of study treatment (C1D1), it is not necessary to repeat the imaging tests. | It was considered that an imaging test would be available within 28 days prior to C1D1. |
| 1.3. Schedule of Activities (SoA) – Table 1 | Footnote l was added:<br>l. If performed within 72 hours of the first Amivantamab dose, the assessment does not have to be repeated for C1D1. | The description was clarified. |
| 4.1. Overall Design | Section updated as below:<br>This is an open-label, multicenter, multi-arm Phase 2 interventional study in participants with previously treated advanced or unresectable GC or EC who are 20 years or older (or the legal age of consent in the jurisdiction in which the study is taking place). ~~Japanese~~ **The** participants with gastric/GEJ or EC who express varying degrees of EGFR, cMet, or both as determined by IHC locally or centrally will be enrolled in the GC cohort or EC cohort. | To update in consideration of the possibility of expansion of countries. |
| 4.1.1. Screening Phase (Pre- and Full Screening) | Section updated as below:<br>The participant must sign an informed consent form (ICF) at the beginning of the full screening phase, before the first study-related activity is conducted. During the full screening period, participants will be evaluated for eligibility for study participation. Participants must complete all screening procedures within 28 days of C1D1. Pre treatment biopsy will be collected for all participants in Phase 2a and Phase 2b. **The tumor IHC result regardless of the local or central must be obtained and confirmed for the eligibility prior to C1D1. If the central tumor IHC is used for the eligibility prior to the initiation of the study treatment and the central results are not completed during the screening** | To clarify that IHC result (EGFR or cMet) will be confirmed positive during the screening period regardless of local or central pathology results. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | **period, the screening period can be extended by 14 days.** ~~The screening period can be extended by 14 days if reporting of central tumor IHC results are not completed within the 28 day screening period.~~ However, all other assessments must still meet timing criteria relative to C1D1 or must be repeated. | |
| 4.1.1. Screening Phase (Pre- and Full Screening) | Following description was added:<br>If an assessment was performed as part of the participant's routine clinical evaluation and not specifically for this study, it needs not be repeated after signed ICF has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to C1D1. | To clarify that an assessment, if had be performed routinely, do not need to be repeated in screening. |
| 4.1.1. Screening Phase (Pre- and Full Screening) | Following description was added:<br>If IHC assay is performed locally, enrollment should be considered with reference to the scoring criteria used in the central IHC assay. | To clarify the IHC scoring criteria for local IHC assay. |
| 4.1.1. Screening Phase (Pre- and Full Screening) | Following description was added:<br>If there is a discrepancy between the local and central IHC assay, the study treatment may be continued at the investigator discretion. | To clarify that subjects enrolled with a positive local result can continue the study even if the central pathology results are different from the local results. |
| 4.1.2. Treatment Phase | Addition of the text in bold:<br>The treatment phase for a participant will begin on C1D1 and continue as 28 day cycles until the EOT visit, approximately 30 days after the last dose of study treatment. **If the initiation of the subsequent anticancer therapy is required prior to EOT, EOT must be completed prior to the initiation of the subsequent anticancer therapy.** | Considered the possibility of starting the next anticancer therapy immediately after treatment discontinuation. |
| 4.1.2. Treatment Phase | Post-treatment biopsy, circulating tumor DNA (ctDNA), and biomarker at C2D15 as well as per the Schedule of Activities (Section 1.3) will be collected on C2D15 (~~±1 week~~ **±1 day**) from all participants in Phase 2a. | To align the visit window with other blood drawing on C2D15. |
| 4.4. End of Study Definition | Study completion definition was added. | To clarify the definition. |
| 5.1. Inclusion Criteria | Inclusion criterion 2. Addition of the following text:<br>Participant tumor must express either EGFR, cMet, or both as determined by either local or central IHC assay (IHC 1+ or above). A copy of the de-identified pathology report**, or equivalent information,** for IHC analysis must be submitted during the screening period if local IHC test was used for the eligibility determination.<br><br>Phase 2a extension cohorts: Participant tumor must lack expression of EGFR and MET as determined by either local or central IHC assessment. A copy of the de-identified pathology report**, or equivalent information,** for IHC analysis must be submitted during the screening period if local IHC test was | Added text because IHC results may not be included in pathology reports. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | used for the eligibility determination. | |
| 5.4. Screen Failures | Following change was made:<br>Rescreened participants should be assigned ~~the same~~ **a new** participant number ~~as for~~ **that is different from** the initial screening. | Correction was made. |
| 6.6.4. Liver Chemistry Abnormalities | Following change was made:<br>In the event abnormalities of liver function tests require the dose delay of study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. ~~Etiology~~**If the liver function test criteria either a) or b) above are met, etiology** of the liver chemistry abnormality should be investigated, as described below. If no alternative etiology of liver toxicity is identified, study treatment should be permanently discontinued. | To clarify the definition. |
| 6.8.1.1. Amivantamab Pre-infusion Medications – Table 7<br>6.8.1.2. Amivantamab Post-infusion Medications – Table 8 | Footnote d was added:<br>d. Either IV or oral route is selected for antihistamine, antipyretic, glucocorticoid and antiemetic medications.<br><br>Footnote b was added:<br>b. Either IV or oral route is selected for antiemetic medications. | To clarify the description. |
| 6.8.2. Prohibited or Restricted Medications and Therapies | Addition of the text in bold:<br>• Use of live or live attenuated vaccines is prohibited. **COVID-19 vaccine is not considered as live or live attenuated vaccines but the administration of COVID-19 vaccine should be avoided on the same day of study drug administration.** | To clarify COVID-19 vaccination. |
| 7.1. Discontinuation of Study Treatment | Addition of the text in bold:<br>If a participant discontinues study treatment for any reason, then the EOT assessments should be obtained according to the Schedule of Activities and follow-up visits should continue after study treatment is discontinued. **If the initiation of the subsequent anticancer therapy is required prior to EOT, EOT must be completed prior to the initiation of the subsequent anticancer therapy.** Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant. Additional participants will not be entered in the study. | Considered the possibility of starting the next anticancer therapy immediately after treatment discontinuation. |
| 8.2.3. Electrocardiograms | Following description was deleted:<br>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. | To clarify the order of procedures are not specified. |
| 9.3. Populations for Analysis Sets | 'All enrolled' population was added.<br><br>Following change was made in 'Response | To clarify and correct the definition. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | evaluable' population:<br>All participants who satisfy the following criteria:<br>• Receive at least 1 dose of study treatment<br>• ~~At~~**Met all eligibility criteria for the study**<br>• **Had a baseline and at** least ~~2~~**1** post-baseline efficacy disease assessments, or ~~discontinued treatment for any reason, or~~ have disease progression/death **due to disease progression** prior to the ~~second~~**first** post-baseline disease assessment | |
| 10.4. Appendix 4: Contraceptive and Barrier Guidance | Addition of the text in bold:<br>*Woman Not of Childbearing Potential*<br>• permanently sterile: permanent sterilization methods include hysterectomy, bilateral salpingectomy, **bilateral tubal occlusion/ligation procedures,** and bilateral oophorectomy. | To align with other programs of Amivantamab. |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. | Minor errors were noted. |

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## INVESTIGATOR AGREEMENT

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

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

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K

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 course of 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 | 16-Aug-2022 06:06:55 (GMT) | Document Approval |