Janssen Pharmaceutical K.K.*

Statistical Analysis Plan

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

Protocol 61186372GIC2001; Phase 2

JNJ-61186372 (Amivantamab)

*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.

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	25 Nov 2021	Not Applicable	Initial release
2	11 Aug 2023	Refer to the Table below	Refer to the Table below

Amendments below are listed.

Amendment 1 (11 Aug 2023)

Summary of key changes: Protocol Amendment 3 was performed to allow higher dose if CTMT recommended. The SAP has been updated to align with protocol language and analyze per dose group.

Sections	Description of Changes	Rationale
Section 1.2	Update description for potential new dose if recommended by CTMT, eligibility criteria and EOT assessment.	Per changes in Protocol Amend 3.
Section 3. Sample Size Determination	Added the target sample size for higher dose if CTMT recommended.	Per changes in Protocol Amend 3 to allow higher dose if CTMT recommend.
Section 4. Populations (Analysis sets) for analysis	Add Enrolled sets.	To analyze number of subjects included in each analysis sets.
Section 5.3.3 Analysis Methods	Add best response analysis and the minimum duration of SD.	To understand the activity of amivantamab for this population, the best response analysis is added.
Section 5.6.1 Extent of Exposure	Add sentence to clarify to summarize both prior and during infusion.	To summarize exposure related events both prior and during infusion.
Section 5.6.2 Compliance of Disease evaluation	Add analysis for missing assessment due to COVID.	To assess the impact of COVID to the study result.
Section 5.7.6 Definition of subgroups	Add new subgroup for EGFR, cMET (0+/1+, ≥2+), prior ramucirumab use and prior anti HER2 therapy use.	To investigate the relationship between biomarker expression and efficacy as well as prior therapy used.
Section 5.8.1 Clinical trial management team.	Add interim futility analysis for higher dose.	To align with Protocol Amend 3.
Section 6.1 Appendix 2. Demographics and baseline Characteristics.	Add analysis for prior fluoropyrimidine agent use, prior platinum agent use, prior ramucirumab use, prior anti HER2 therapy use.	To summarize distribution of prior therapy more detail.

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the Phase 2 study of amivantamab in subjects with previously treated advanced or metastatic gastric cancer (GC) or esophageal cancer (EC). The SAP is to be interpreted in conjunction with the protocol. This SAP covers the planned analysis for the clinical study report (CSR).

1.1. Objectives and Endpoints

Following objectives and end points are defined as per the protocol v3.0 (16 August 2022):

Objectives	Endpoints
Primary	
• To investigate the activity of amivantamab in gastric cancer (GC) and esophageal cancer (EC) participants (Phase 2a) • 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 • Explore the relationship between serum PK and pharmacodynamic (PD) markers (eg, soluble EGFR and cMet) • Determine whether amivantamab can impact the anti-tumor immune response or microenvironment	

1.2. Study 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.

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. Details of CTMT are described in Section 5.8.1.

The study will include a Screening phase, a Treatment phase, and a Follow-up phase (Phase 2b only). 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. Pretreatment 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.

The treatment phase for a 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. 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.

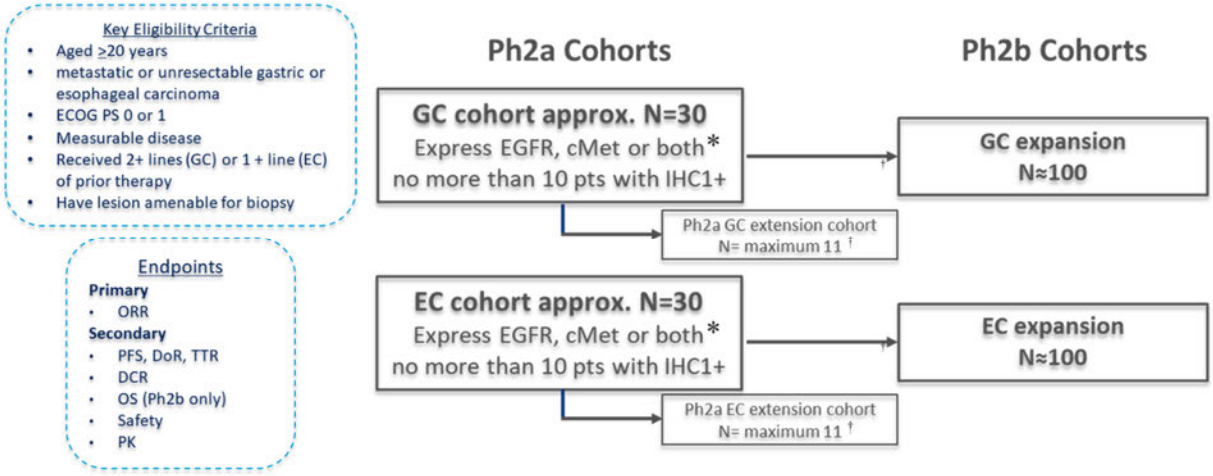
The follow up Phase is scheduled only in Phase 2b. Participants who discontinue study treatment will be followed for subsequent therapy, disease status (applicable only if participants discontinuing treatment due to reasons other than progressive disease, to confirm disease progression date), and survival 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.

The primary efficacy endpoint is objective response rate (ORR). Objective response rate is defined as the proportion of participants who achieve either complete response (CR) or partial response (PR), determined by investigator assessment using RECIST Version 1.1. Confirmation of investigator-assessed ORR may be performed through IRC in the Phase 2b.

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

A diagram of the study design is provided in Figure 1, as follows:

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.

Blinding

This is an open-label study.

2. 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 ≤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%). The interim analysis with subpopulation selection is planned in Phase 2b, so multiplicity caused by subpopulation selection will be controlled by closed testing procedure and weighted statistics.

3. 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.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

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: • Receive at least 1 dose of study treatment • Met all eligibility criteria for the study • 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
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

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.

5. STATISTICAL ANALYSES

5.1. General Considerations

Unless otherwise specified, the phases (Phase 2a or 2b), cohort (GC or EC) and dose regimen (if applicable) will be analyzed separately. The efficacy analysis will be performed by IHC subgroups (≥2+, 1+, 0+, not available).

5.1.1. Visit Windows

The study will consist of 3 phases: a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will start up to 28 days before randomization. The Treatment Phase will extend from Cycle 1 Day 1 to until the end-of-treatment (EOT) visit, approximately 30 days after discontinuation of study treatment. Scheduled visits within each cycle will have a window up to ±1 day as per SoA in study protocol (except C1D1 and C1D2 with no window and C3 and after with ±3 day window).

Visit windowing will be based on cycles. Unless otherwise specified, data to be analyzed or presented over time will be presented by cycle, day and time point (as appropriate) that are recorded in CRF.

5.1.2. Pooling Algorithm for Analysis Centers

There will be no pooling of centers for analyses.

5.1.3. Study Day/Relative Day

Study day or relative day is defined as:

- Reference date (Day 1) = first dose date of amivantamab.
- Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; assessment date – reference date for assessment performed before the reference date.

There is no 'Day 0'. First dose date will be the date of starting amivantamab.

5.1.4. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study drug administration (including time if time is available). If the first administration date is missing or the administration is not done, then the baseline measurement is the closest non-missing measurement taken on or prior to the corresponding visit date.

For IHC, EGFR and cMET, the data by centrally performed IHC assay will be used. The tissue samples obtained at full screening visit will be used as baseline, if available.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants who received study intervention
- Participants who terminated study prematurely
- Participants who completed the study
- Reason for termination of study
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention

The number of participants who discontinued treatment by cycle with reported reasons will also be provide.

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely

5.3. Primary Endpoint(s) Analysis

Overall response rate (ORR) as per RECIST v.1.1 as evaluated by the investigator.

5.3.1. Definition of Endpoint(s)

ORR is defined as the proportion of subjects achieved either a confirmed CR or PR based on RECIST v. 1.1. among Response Evaluable Population.

5.3.2. Estimand

Estimand Scientific Question of Interest: What is the overall response rate under receiving amivantamab monotherapy in patients with EGFR mutation or cMET expressed GC or EC?

Study intervention: amivantamab monotherapy

Population: participants with previously treated advanced or metastatic GC or EC expressing EGFR and/or MET

Variable: overall response; a confirmed CR or PR, determined by investigator assessment using RECIST Version 1.1

Summary Measure (Population-level summary): ORR

Intercurrent event:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use response, regardless of whether or not study treatment discontinuation had occurred
Subsequent anticancer therapy	**While-on-treatment policy strategy:** Response after this intercurrent event will not be included

5.3.3. Analysis Methods

Phase 2a

There will be no formal hypothesis testing. ORR will be calculated for response evaluable population descriptively. The 95% confidence interval will also be calculated by Clopper-Pearson method.

The posterior probability of ORR >22.5% will also be evaluated based on beta distribution. Let θ be the distribution of ORR following beta distribution and the non-informative beta distribution θ_0 will be used as a prior.

$$\theta_0 \sim Beta(1,1)$$

When n_1 of responder and n_2 of non-responder are observed, the posterior distribution follows beta distribution

$$\theta \sim Beta(1+n_1, 1+n_2)$$

The Pr (ORR >22.5%) will be derived from following formula.

$$\int_{0.225}^{1} p(\theta|n_1, n_2)d\theta$$

The ORR, 95% confidence interval and Pr (ORR >22.5%) will be calculated for IHC subgroup variant 2 defined in Section 5.7.6.

The best overall response (BOR) will also be summarized. The minimum duration for BOR of SD is 6 weeks from the baseline.

Phase 2b

A z test with normal approximation (i.e, continuous correction) will be used to compare the ORR with 15%. An interim futility analysis is planned in each of GC and EC arm approximately 12 weeks after 50 participants receive the first infusion. If both IHC 2+/3+ and IHC 1+ populations are included in Phase 2b, based on posterior probability, IDMC will make a recommendation whether both populations, only IHC 2+/3+ subpopulation or neither of them should continue the study. To control multiplicity caused by this subpopulation selection at the interim analysis, closed testing procedure and weighted statistics proposed by Jenkins (2011) et al will be applied.

Let p_1^1 and p_1^2 be 1 sided p-value for overall population and IHC 2+/3+ subpopulation from participants at IA (i.e, first $n_1 = 50$ participants) and $p_1^{1,2}$ be p-value for intersection hypothesis corresponding with p_1^1 and p_1^2,which is adjusted by Simes test as

$$\mathrm{p}_1^{1,2} = \min\left[2\min\{\mathrm{p}_1^1, \mathrm{p}_1^2\}, \max\{\mathrm{p}_1^1, \mathrm{p}_1^2\}\right]$$

Let p_2 be p-value from participants only after IA (i.e, later $n_2 = 50$ participants) in selected population at IA (either overall or IHC 2+/3+ subpopulation). The weighted test statistics will be applied to calculate p value. If overall population is selected at IA and both of p value derived from test statistics below are less than 0.025, the null hypothesis will be rejected.

$$\frac{\sqrt{n_1}}{\sqrt{n_1+n_2}}\Phi^{-1}(1-p_1^1) + \frac{\sqrt{n_2}}{\sqrt{n_1+n_2}}\Phi^{-1}(1-p_2)$$

$$\frac{\sqrt{n_1}}{\sqrt{n_1+n_2}}\Phi^{-1}\left(1-p_1^{1,2}\right) + \frac{\sqrt{n_2}}{\sqrt{n_1+n_2}}\Phi^{-1}(1-p_2)$$

If 2+/3+ subpopulation is selected at IA and both of p value derived from test statistics below are less than 0.025, the null hypothesis will be rejected.

$$\frac{\sqrt{n_1}}{\sqrt{n_1+n_2}}\Phi^{-1}(1-p_1^2) + \frac{\sqrt{n_2}}{\sqrt{n_1+n_2}}\Phi^{-1}(1-p_2)$$

$$\frac{\sqrt{n_1}}{\sqrt{n_1+n_2}}\Phi^{-1}\left(1-p_1^{1,2}\right) + \frac{\sqrt{n_2}}{\sqrt{n_1+n_2}}\Phi^{-1}(1-p_2)$$

In the preceding formulas, Φ is the cumulative distribution function of the standard normal distribution.

The ORR and its 95% confidence interval (CI) will also be calculated. The 95% CI will be derived by grid search of threshold when 2 sided p-value is 0.05.

The best overall response (BOR) will also be summarized. The minimum duration for BOR of SD is 6 weeks from the baseline.

5.3.4. Sensitivity Analysis

No sensitivity analysis is planned.

5.3.5. Supplementary Analysis

5.3.5.1. ORR for All Treated Population

The supplementary analysis will be performed for All Treated Population in the same manner with primary estimand.

5.3.5.2. ORR determined by Independent Review Committee IRC (Phase 2b only)

If tumor response is assessed by independent review committee (IRC) in Phase 2b, the supplementary analysis will be performed using the ORR determined by IRC in the same manner with the primary estimand.

5.4. Secondary Endpoints Analysis

Following secondary endpoints analysis is planned to be performed.

For disease control rate (DCR), duration of response (DoR) and progression free survival (PFS), if tumor response is assessed by IRC in Phase 2b, the analysis will also be performed using the response determined by IRC. The estimands is the same as the one using response determined by investigator described below with only the variable changing to the one determined by IRC.

5.4.1. Disease Control Rate

5.4.1.1. Definition

Disease control rate is defined as the percentage of participants achieving CR, PR or stable disease for at least 6 weeks determined by investigator assessment using RECIST Version 1.1.

5.4.1.2. Estimand(s)

Estimand Scientific Question of Interest: What is the DCR under receiving amivantamab monotherapy in patients with EGFR mutation or cMET expressed GC or EC?

Study intervention: amivantamab monotherapy

Population: participants with previously treated advanced or metastatic GC or EC expressing EGFR and/or MET

Variable: disease control; CR, PR or stable disease for at least 6 weeks, determined by investigator assessment using RECIST Version 1.1

Summary Measure (Population-level summary): DCR

Intercurrent event:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use response, regardless of whether or not study treatment discontinuation had occurred
Subsequent anticancer therapy	**While-on-treatment policy strategy:** Response after this intercurrent event will not be included

5.4.1.3. Analysis Methods

The DCR and its 95% CI with Clopper-Pearson method will also be calculated.

5.4.2. Duration of Response

5.4.2.1. Definition

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. This analysis only includes participants who achieve CR or PR.

Key censoring rules for DoR are summarized below.

Situation	Date of Censoring
No evaluable baseline or postbaseline disease assessment	Censored at the date of initial amivantamab administration
No documented disease progression or death	Censored at the date of last evaluable disease assessment using RECIST Version 1.1
Receive subsequent therapy	Censored at the date of last evaluable disease assessment using RECIST Version 1.1 before the start of subsequent therapy
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visits. However, if an adequate image-based response assigned as CR, PR, or stable disease is obtained after 2 or more consecutive missed/unevaluable disease assessments, then the tumor response assessment will not be excluded from the analysis as long as no other censoring events have occurred.

*If no evaluable disease assessment before the consecutive missed/unevaluable visits, participants will be censored at the date of initial amivantamab administration.

5.4.2.2. Estimand(s)

Estimand Scientific Question of Interest: How long the response will be kept under receiving amivantamab monotherapy after CR or PR is observed in patients with EGFR mutation or MET expressed GC or EC?

Study intervention: amivantamab monotherapy

Population: participants with previously treated advanced or metastatic GC or EC expressing EGFR and/or MET who achieve CR or PR during amivantamab administration before receiving subsequent anticancer therapy

Variable: DoR

Summary Measure (Population-level summary): Median DoR

Intercurrent event:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use response, regardless of whether or not study treatment discontinuation had occurred
Subsequent anticancer therapy	**Hypothetical strategy:** Response after this intercurrent event will not be included
Death	**Composite strategy:** death being a component of the variable

5.4.2.3. Analysis Methods

A Kaplan-Meier plot and median DoR with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented. A swim lane plot for responders will also be presented.

5.4.3. Time to Response

5.4.3.1. Definition

Time to response 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. This analysis only includes participants who achieve CR or PR.

5.4.3.2. Estimand(s)

Estimand Scientific Question of Interest: How long it will take to achieve CR or PR under receiving amivantamab monotherapy in patients with EGFR mutation or cMET expressed GC or EC?

Study intervention: amivantamab monotherapy

Population: participants with previously treated advanced or metastatic GC or EC expressing EGFR and/or MET achieve CR or PR during amivantamab administration before receiving subsequent anticancer therapy

Variable: Time to Response

Summary Measure (Population-level summary): Median time to response

Intercurrent event:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use response, regardless of whether or not study treatment discontinuation had occurred

5.4.3.3. Analysis Methods

A Kaplan-Meier plot and median time to response with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented.

5.4.4. Progression-free Survival

5.4.4.1. Definition

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.

Key censoring rules for PFS are summarized below.

Situation	Date of Censoring
No evaluable baseline or postbaseline disease assessment	Censored at the date of initial amivantamab administration
No documented disease progression or death	Censored at the date of last evaluable disease assessment using RECIST Version 1.1
Receive subsequent therapy	Censored at the date of last evaluable disease assessment using RECIST Version 1.1 before the start of subsequent therapy
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visits. However, if an adequate image-based response assigned as CR, PR, or stable disease is obtained after 2 or more consecutive missed/unevaluable disease assessments, then the tumor response assessment will not be excluded from the analysis as long as no other censoring events have occurred.

*If no evaluable disease assessment before the consecutive missed/unevaluable visits, participants will be censored at the date of initial amivantamab administration.

5.4.4.2. Estimand(s)

Estimand Scientific Question of Interest: How long amivantamab monotherapy can prevent disease progression in patients with EGFR mutation or MET expressed GC or EC?

Study intervention: amivantamab monotherapy

Population: participants with previously treated advanced or metastatic GC or EC expressing EGFR and/or MET

Variable: PFS

Summary Measure (Population-level summary): Median PFS

Intercurrent event:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use response, regardless of whether or not study treatment discontinuation had occurred
Subsequent anticancer therapy	**Hypothetical strategy:** Observation after this intercurrent event will not be included
Death	**Composite strategy:** death being a component of the variable

5.4.4.3. Analysis Methods

A Kaplan-Meier plot and median PFS with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented.

5.4.5. Overall Survival (Phase 2b only)

5.4.5.1. Definition

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.

Key censoring rules for OS are summarized below.

Situation	Date of Censoring
No documented death	Censored at the date of last recorded date on which the participant was known to be alive

5.4.5.2. Estimand(s)

Estimand Scientific Question of Interest: How long participants with EGFR mutation or MET expressed GC or EC can survive by receiving amivantamab monotherapy

Study intervention: amivantamab monotherapy

Population: participants with previously treated advanced or metastatic GC or EC expressing EGFR and/or MET

Variable: OS

Summary Measure (Population-level summary): Median survival time

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use time to death, regardless of whether or not study treatment discontinuation had occurred
Subsequent anticancer therapy	**Treatment Policy strategy:** use time to death, regardless of whether or not started subsequent anticancer therapies

5.4.5.3. Analysis Methods

A Kaplan-Meier plot and median OS with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

5.5.1. ORR by IHC result at pre-screening

The exploratory analysis will be performed by using central IHC result at pre-screening in the same manner with primary estimand. The concordance of IHC result between pre-screening and screening will also be summarized.

5.5.2. ORR by local IHC result

The exploratory analysis will be performed by using local IHC result at screening in the same manner with primary estimand. The concordance between central and local IHC result will also be summarized.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

5.6.1. Extent of Exposure

All the exposure information will be summarized based on safety analysis set. Study treatment duration is defined as (date of last dose of study intervention – date of first dose of intervention) +1. Descriptive statistics for duration of study intervention will be presented in months.

The total number of administration cycles of amivantamab received for each participant will be summarized by descriptive statistics. Cumulative duration of amivantamab will be provided by

cycle (≥1 cycle, ≥2 cycles, …). Total number of amivantamab infusion and the total dose of amivantamab for each participant will be summarized by descriptive statistics.

The relative dose intensity (%) defined as the ratio of total received dose versus total prescribed dose will be summarized by descriptive statistics.

The number (%) of participants with a dose modification prior to infusion (such as dose reduction, dose not administrated and cycle delay) and its reason will be summarized. A dose modification during infusion (such as infusion abort, infusion interruption and infusion rate decrease) will also be summarized.

5.6.2. Compliance of Disease Evaluation

Tumor assessment will occur at regular intervals, as defined per SoA in study protocol. Descriptive statistics will be provided for imaging assessments separately for the All Treated Population for:

- Number of participants missed at least 1 scheduled disease evaluation
- Number of participants missed 2 or more consecutive scheduled disease evaluation
- Number of missed scheduled disease evaluation per participant

The missing assessments due to COVID-19 will also be summarized.

5.6.3. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention 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. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by the phases (Phase 2a or 2b) and cohort (GC or EC).

The incidence (%) of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term (PT), by toxicity grade, and by relationship to study drug administration.

5.6.3.1. Treatment Emergent Adverse Events

An overview of TEAEs reported through the study will be provided. The overview will include summaries of participants with TEAEs, with TEAEs related to study intervention, with TEAEs of maximum toxicity grade of 1 to 5, Serious TEAEs, TEAEs leading to discontinuation of study intervention, and deaths due to TEAE.

5.6.3.1.1. All TEAEs

- Incidence (%) of TEAEs by SOC and PT

5.6.3.1.2. Toxicity Grade 3 or higher TEAEs

- Incidence (%) of toxicity grade 3 or higher TEAEs by SOC and PT

5.6.3.1.3. Study Drug-Related TEAEs

- Incidence (%) of TEAEs by relationship to study treatment, and by SOC and PT
- Incidence (%) of TEAEs with toxicity grade 3 or higher by relationship to study treatment, and by SOC and PT
- Incidence (%) of TEAEs leading to study treatment interruption/dose reduction by relationship to study treatment, and by SOC and PT
- Incidence (%) of TEAEs leading to study treatment discontinuation by relationship to study treatment, and by SOC and PT

5.6.3.1.4. Serious TEAEs

- Incidence (%) of serious TEAEs by SOC and PT
- Incidence (%) of serious TEAEs by toxicity grade, and by SOC and PT
- Incidence (%) of serious TEAEs by relationship to study treatment, and by SOC and PT
- Listing of participants with any serious TEAEs

5.6.3.1.5. TEAEs Leading to Study Drug Interruption/Dose Reduction/Dose Delay

Incidence (%) of TEAEs leading to study treatment reduction and dose delay will be summarized respectively by SOC and PT. The summaries will be presented for all toxicity grades and for toxicity grade 3 or higher. In addition, the summary by relationship will be presented.

5.6.3.1.6. TEAEs Leading to Discontinuation of Study drug

Incidence (%) of TEAEs leading to study treatment discontinuation will be summarized by SOC and PT. The summaries will be presented by all toxicity grades and toxicity grade 3 or higher. In addition, the summary by relationship will be presented. The AEs leading to discontinuation of study treatment are based on AEs recorded in the AE CRF page with an action taken of drug withdrawal for any study drug.

5.6.3.2. Adverse Events of Special Interest

Adverse events of special interest are pneumonitis/interstitial lung disease (ILD), rash, and infusion-related-reaction (IRR). The MedDRA preferred terms associated with each of these categories are identified in Appendix 6 Adverse Events of Special Interest. Additional information will be collected for these events.

Treatment-emergent adverse events of special interest will be included for analysis. Incidence (%) for the following AEs will be provided for each AE of special interest as appropriate:

- TEAEs by PT
- TEAEs by toxicity grade
- TEAEs of toxicity grade 3 or higher by PT
- Serious TEAEs by PT
- TEAEs by relationship to study intervention
- Serious TEAEs by PT
- Serious TEAEs by relationship to study intervention
- TEAEs leading to study intervention discontinuation by PT
- TEAEs leading to study intervention discontinuation by relationship to study intervention
- TEAEs leading to death by PT

Additional analyses will be provided based on information collected in CRF.

Pneumonitis/ILD

For participants with pneumonitis/ILD, frequency tabulation will be provided for:

- Symptom (fever, dry cough, productive cough, dyspnea, chest pain, other)
- Pleural effusion present at the time of the pneumonitis/ILD (yes/no)

Relative onset day (since Day 1) of pneumonitis/ILD will be summarized by descriptive statistics (N, mean, standard deviation, median, and range).

All information related to pneumonitis/ILD collected in CRF page will be presented in listing.

Rash

Relative onset day (since Day 1), duration, and time between onset and the preceding infusion administration will be summarized for rash by descriptive statistics (N, mean, standard deviation, median, and range) in days.

IRR

Incidence (%) of IRR leading to infusion modification (infusion interrupted, infusion rate decreased, and infusion aborted) will be presented.

Relative onset day (since Day 1), and duration will be summarized for IRR by descriptive statistics (N, mean, standard deviation, median, and range) in days.

5.6.3.3. Deaths

5.6.3.3.1. Death Due to TEAEs

The number of participants who died due to TEAEs will be summarized by preferred term and relationship to study treatment. The TEAEs included in this table are AEs with outcome of death or toxicity grade of 5 recorded in the AE CRF page within 30 days of the last dose or until the start of subsequent anticancer therapy (if earlier).

A listing of participants who died due to TEAE will be provided.

5.6.3.3.2. All Deaths

A summary of all death and cause of death will be tabulated. Specifically, the number of participants who died during the study will be summarized. The primary cause of death collected on the death information CRF page will be reported.

The similar summaries will be presented for participants who died within 30 days of last study drug dose.

5.6.4. Additional Safety Assessments (if applicable)

5.6.4.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points. Change from baseline over time will be summarized and displayed. Plots for selected laboratory tests change over time may be provided.

NCI-CTCAE version 5.0 will be used to derive toxicity grades for clinical laboratory tests when applicable. Shift tables from baseline to worst value on treatment (from treatment start to 30 days after last dose date or until the start of subsequent anti-cancer therapy, whichever is later) will be provided. The worst toxicity grade during the treatment will be tabulated.

An eDISH plot of peak ALT/ AST versus peak BILI will be provided along with a listing of participants who had ALT/ AST values > 3xULN (Upper Limit of Normal) or BILI values > 2xULN.

Laboratory criteria for potential Hy's Law cases are defined as:

- Peak aminotransaminases (AT, either ALT or AST) of >3xULN;
- Total bilirubin ≥2xULN;
- Alkaline phosphatase (ALK-P) <2xULN prior to or on the same date of the first occurrence of total bilirubin ≥2x ULN;

Note: data from all the on-treatment (postbaseline) visits are combined to check the above laboratory criteria.

- All potential Hy's Law cases based on the laboratory criteria will be presented.

5.6.4.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, respiratory rate, oxygen saturation, pulse/heart rate, blood pressure (systolic and diastolic), as well as weight from physical examination will be summarized at each scheduled timepoint. Change from baseline will be summarized over time. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Post baseline physical examination findings were collected as AEs, and therefore will not be summarized.

For criteria that do not include an increase or decrease from baseline:

- Treatment-Emargent will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

5.6.4.3. Electrocardiogram

Triplicate electrocardiograms (ECG) will be performed at Screening to determine the eligibility. Post baseline measurement may be collected as clinically indicated. Since there is no scheduled timepoint for ECG, ECG will not be summarized.

A listing of clinically relevant ECG abnormalities will be provided.

5.6.5. ECOG Performance Status

Eastern Cooperative Oncology Group performance status score will be evaluated during the screening phase to determine the eligibility. Post baseline measurement may be collected as clinically indicated. Baseline ECOG performance status will be summarized (see Appendix 2).

5.7. Other Analyses

5.7.1. Pharmacokinetics

Serum samples will be collected for PK and immunogenicity assessments of amivantamab. Sampling timepoints are outlined in Table 2 of study protocol.

PK analyses will be performed on the PK Population, defined as participants who received at least 1 dose of a study treatment and have at least 1 evaluable postbaseline concentration measurement. Participants or samples 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).

Concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize amivantamab concentrations at each sampling time point and for each PK parameter of amivantamab. PK data may be displayed graphically, such as mean +/- SD PK concentrations over time by study intervention.

Amivantamab concentrations will be presented based on the following baseline body weight categories at each time point:

- <80 kg
- ≥ 80 kg

All participants and samples excluded from the analysis will be clearly documented.

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

5.7.2. Immunogenicity

The incidence (%) of antibodies to Amivantamab will be summarized based on Immunogenicity Population, defined as all participants who receive at least 1 dose of study intervention and have appropriate samples for detection of antibodies to Amivantamab (ie, participants with at least 1 sample obtained after their first dose of Amivantamab).

A listing of participants who are positive for antibodies to Amivantamab will be provided. The maximum titers of antibodies to Amivantamab will be summarized for participants who are positive for antibodies to Amivantamab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

5.7.3. Pharmacodynamics (PD)/Biomarkers

Analyses are planned to explore PD and other biomarkers that may be indicative of the mechanisms of action of the study intervention or predictive of efficacy. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints could identify responsive (or resistant) subgroups. Any PD or other biomarker measures will be listed, tabulated, and plotted, as appropriate.

Serum soluble-free EGFR and MET concentrations versus time by treatment cohort will be summarized using plots.

Assessment of additional genes or biomarkers (DNA, RNA, or protein) relevant to gastric, esophageal or other cancers or the mechanism of action of study interventions, may also be performed in blood samples collected during study to better understand mechanisms of response or resistance to study interventions.

Alterations in blood may be evaluated for correlation with response to study interventions, tumor burden, and disease progression as data warrant.

Plasma mutation data derived from ctDNA and tumor tissue NGS analyses collected from this study will be used to perform mutational analysis and assess the relationship of individual mutations, and classes of mutations, to efficacy endpoints. IHC analyses (may include H score) on tissue specimens collected from this study will be used to assess the relationship of exploratory endpoints to efficacy endpoints. Additional exploratory endpoints may be explored from serum samples collected from this study and may be used to understand the relationship of these endpoints to efficacy endpoints. Results of these analyses will be presented in a separate report.

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.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between PK and PD measures may be evaluated by PK/PD modeling. Participants may be grouped by dose schedule or clinical response. Results of PD and exploratory biomarker analyses will be presented in separate reports.

5.7.5. Health Economics

Not Applicable

5.7.6. Definition of Subgroups

The following pre-specified subgroup analyses are to be performed for the selected efficacy and/or safety endpoints. Additional subgroup analyses may be planned if deemed necessary.

Definition of Subgroups

Subgroup	Variant	Definition
IHC[c]	1	0+, 1+, 2+, 3+
	2	≥0+, ≥1+, ≥2+, ≥3+
EGFR[c]	1	0+, 1+, 2+, 3+
	2	0+/1+, ≥2+
cMET[c]	1	0+, 1+, 2+, 3+
	2	0+/1+, ≥2+

Subgroup	Variant	Definition
Combination of EGFR and cMET[c]		0+/0+, 1+/0+, 2+/0+, 3+/0+, 0+/1+, 1+/1+, 2+/1+, 3+/1+, 0+/2+, 1+/2+, 2+/2+, 3+/2+, 0+/3+, 1+/3+, 2+/3+, 3+/3+
HER2 status		Negative, Positive
Age Group		<65 years, ≥65 years; <75 years, ≥75 years
Sex		Male, Female
Race		Asian, Non-Asian
Weight		<80 kg, ≥80 kg
ECOG performance status score		0, 1
Diagnosis subtype		Adenocarcinoma, Squamous Cell Carcinoma, Other
Number of location of metastasis at screening[c]		1-2, ≥3
Number of prior lines of systemic therapy[c]	1[a]	2, 3, ≥4
	2[b]	1, 2, ≥3
Prior immuno-check inhibitor use [c]		Yes, No
Prior taxane use[c]		Yes, No
Prior irinotecan use[a, c]		Yes, No
Prior trifluridine/tipiracil use[a, c]		Yes, No
Prior ramucirumab use		Yes, No
Prior anti HER2 therapy use		Yes, No

[a]Only for gastric cancer
[b]Only for esophageal cancer
[c]Only for efficacy endpoints

5.8. Interim Analyses

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%. The posterior probability will be calculated the method in Section 5.3.3.

5.8.1. 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 participating principal investigators, 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.

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.

At the end of Phase 2a part, CTMT will review the results and determine which subpopulations 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.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
CI	confidence interval
C_{max}	maximum serum concentration
cMet	tyrosine-protein kinase mesenchymal-epithelial transition
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTMT	clinical trial management team
C_{trough}	plasma/serum concentration immediately prior the next study treatment administration
CV	coefficient of variation
DCR	disease control rate
DoR	duration of response
EC	esophageal cancer
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
EOT	end-of-treatment
GC	gastric cancer
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IQ	interquartile
IRB	Institutional Review Board
IRC	independent review committee
IRR	infusion-related-reaction
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
RECIST	Response Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
T_{max}	time to reach the maximum serum concentration
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by IHC and overall. In addition, the distribution of participants by country and site ID will be presented unless otherwise noted.

Table below presents a list of the demographic variables that will be summarized by IHC group and overall for the All Treated Population.

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (<65 years, ≥65 years; <75 years, ≥75 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, unknown, undifferentiated)	
Weight (<80 kg, ≥80 kg)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Race (Asian, non-Asian)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)	
Baseline ECOG performance status (0, 1)	
Prior fluoropyrimidine agent use (Yes, No)	
Prior platinum agent use (Yes, No)	
Prior immunocheck inhibitor use (Yes, No)	
Prior taxane use (Yes, No)	
Prior irinotecan use (Yes, No)[b]	
Prior trifluridine/tipiracil use (Yes, No)[b]	
Prior ramucirumab use (Yes, No)	
Prior anti HER2 therapy use (Yes, No)	
Prior Cancer-Related Surgery / Procedure(Yes, No)	
Prior Chemoradiation Therapy (Yes, No)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'
[b]Only for gastric cancer

The following table presents a list of the baseline characteristics variables that will be summarized by IHC group and overall for the All Treated Population.

Gastric Cancer	**Continuous Variables**	**Summary Type**
	Time since initial gastric cancer diagnosis (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
	Number of prior lines of systemic therapy	
	Number of location of metastasis at screening	
	Categorical Variables	
	GC initial diagnosis (gastric cancer, gastroesophageal junction cancer)	Frequency distribution with the number and percentage of participants in each category.
	GC subtype at initial diagnosis (adenocarcinoma, squamous cell carcinoma, other)	
	Histology grade at initial diagnosis (well differentiated, moderately differentiated, poorly differentiated, other)	
	Lauren classification (intestinal, diffuse, mixed, unclassified)	
	Location of metastasis at screening (bone, liver, brain, lymph node, adrenal gland, lung, peritoneum, other)	
	Number of prior lines of systemic therapy (2, 3, ≥4)	
	Number of location of metastasis at screening (1-2, ≥3)	
	HER2 status (Positive, Negative)	
	Result by IHC (Central) (0, 1+, 2+, 3+, unknown)	
	Result by EGFR (Central) (0, 1+, 2+, 3+, unknown)	
	Result by cMET (Central) (0, 1+, 2+, 3+, unknown)	
	Result by combination of EGFR and cMET (Central)	
Esophageal Cancer	**Continuous Variables**	
	Time since initial esophageal cancer diagnosis (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
	Number of prior lines of systemic therapy	
	Number of location of metastasis at screening	
	Categorical Variables	
	EC subtype at initial diagnosis (adenocarcinoma, squamous cell carcinoma, other)	Frequency distribution with the number and percentage of participants in each category.
	Histology grade at initial diagnosis (well differentiated, moderately differentiated, poorly differentiated, other)	
	Location of metastasis at screening (bone, liver, brain, lymph node, adrenal gland, lung, peritoneum, other)	
	Number of prior lines of systemic therapy taken (1, 2, ≥3)	
	Number of location of metastasis at screening (1-2, ≥3)	
	Result by IHC (Central) (0, 1+, 2+, 3+, unknown)	
	Result by EGFR (Central) (0, 1+, 2+, 3+, unknown)	
	Result by cMET (Central) (0, 1+, 2+, 3+, unknown)	
	Result by combination of EGFR and cMET (Central)	

6.3. Appendix 3 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock in each phase and the participants with major protocol deviations will be summarized by category in the All Treated Population.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Any major protocol deviation due to COVID
- Other

A listing of all major protocol deviations including participant ID, type of deviation, and reason will be provided.

6.4. Appendix 4 Prior and Concomitant Medications

Prior and Concomitant medications collected in the CRF page will be coded using the World Health Organization Drug Dictionary (WHO-DD) and summarized by IHC and overall for the All Treated Population.

Prior medications will be summarized by ATC level/preferred terms and treatment. The number and percentage of participants who received prior systemic therapy will be summarized.

Summaries of concomitant medications will be presented by ATC level/preferred terms. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

The incidence (%) of pre-infusion and post-infusion medication will be presented by ATC level/preferred terms.

6.5. Appendix 5 Medical History

Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term by IHC and overall for the All Treated Population.

6.6. Appendix 6 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE of Special Interest Category	Preferred Term
Infusion Related Reaction	INFUSION RELATED REACTION
Rash	ACNE ACNE CONGLOBATA ACNE CYSTIC ACNE FULMINANS ACNE PUSTULAR ACNE VARIOLIFORMIS ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS DERMATITIS DERMATITIS ACNEIFORM DERMATITIS EXFOLIATIVE DERMATITIS INFECTED DRUG ERUPTION EPIDERMOLYSIS ERYTHEMA ERYTHEMA MULTIFORME EXFOLIATIVE RASH FOLLICULITIS HERPES GESTATIONIS IMPETIGO HERPETIFORMIS MACULE MUCOCUTANEOUS RASH NODULAR RASH PALMAR ERYTHEMA PAPULE PERINEAL RASH PRIDE SYNDROME PUSTULE RASH RASH ERYTHEMATOUS RASH FOLLICULAR RASH MACULAR RASH MACULO-PAPULAR RASH MACULOVESICULAR RASH MORBILLIFORM RASH PAPULAR RASH PRURITIC RASH PUSTULAR RASH VESICULAR SJS-TEN OVERLAP SKIN EXFOLIATION SKIN LESION STEVENS-JOHNSON SYNDROME TOXIC EPIDERMAL NECROLYSIS TOXIC SKIN ERUPTION
Interstitial Lung Disease	ACUTE INTERSTITIAL PNEUMONITIS INTERSTITIAL LUNG DISEASE PNEUMONITIS

6.7. Appendix 7 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale, but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Haptoglobin decreased	<LLN	-	-	-	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, eg, grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN with signs or symptoms; *>5.0 x ULN and asymptomatic*	>5.0 x ULN and with signs or symptoms	"Asymptomatic" ranges are not taken into consideration for grading, ie, worst case grading is applied.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN *with signs or symptoms;* *>5.0 x ULN and asymptomatic*	>5.0 x ULN *and with signs or symptoms*	"Asymptomatic" ranges are not taken into consideration for grading, ie, worst case grading is applied.
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Acidosis	pH <normal, but >=7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; *symptomatic*	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, ie, worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms* Sodium <130-120 mmol/L	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; urinary protein 1000 - <3500 mg/day **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol	**Adult:** 4+ proteinuria; urinary protein >=3.5 g/24 hrs; urinary protein >=3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine collection take precedence over dipstick. Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol). Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18].

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

7. REFERENCES

Jenkins M, et al. An adaptive seamless phase II/III design for oncology trials with subpopulation selection using correlated survival endpoints. Pharmaceutical statistics. 2011;10(4):347-356.