Janssen Research & Development

Statistical Analysis Plan

A Phase 2, Open-Label Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Amivantamab Monotherapy in Participants with Previously Treated Advanced Hepatocellular Carcinoma

Protocol 61186372HCC2001; Phase 2

JNJ-61186372HCC2001 (Amivantamab**)**

Status: Approved
Date: 8 September 2023
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-RIM-1133716, 2.0

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

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
Original SAP		Not Applicable	Initial release

1. INTRODUCTION

This is an open-label, multicenter Phase 2 study of amivantamab monotherapy in participants with previously treated advanced hepatocellular carcinoma (HCC).

The purpose of the statistical analysis plan (SAP) is to lay out key elements including definitions and statistical methods for the planned analyses for the primary, secondary, exploratory, safety, and other endpoints in HCC2001 as supportive data to evaluate the anti-tumor activity of amivantamab as a monotherapy in previously treated advanced HCC participants and further characterize the safety, tolerability, and preliminary anti-tumor activity of amivantamab.

1.1. Objectives and Endpoints

Following Objectives and endpoints are defined as per protocol amendment 1 (23 September, 2022).

Objectives	Endpoints
Primary	
• To characterize the preliminary antitumor activity of amivantamab at the recommended dose in participants with previously systemically treated HCC	Objective response rate (ORR) as determined by investigator, according to the Response Criteria in Solid Tumors (RECIST) v1.1. Confirmation of investigator-assessed ORR will be performed through Blinded Independent Central Review (BICR)
Secondary	
• To assess additional measures of clinical benefit with amivantamab	• Duration of response (DoR) • Disease control rate (DCR) • Progression-free survival (PFS) • Overall survival (OS)
• To characterize the safety and tolerability of amivantamab in participants with advanced HCC	Incidence of adverse events defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Criteria version 5.0, lab abnormalities and vital signs in participants treated with amivantamab as a monotherapy
• To assess the pharmacokinetics (PK) and immunogenicity of amivantamab following single and 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}), $AUC_{(t1-t2)}$, AUC_{tau}, serum concentration immediately prior the next study treatment administration (C_{trough}), and accumulation ratio (R); incidence of antidrug antibodies
Exploratory	
• To further explore the clinical benefit achieved with amivantamab treatment through alternative response criteria	ORR, as determined by Investigator Review, according to modified RECIST
• Explore tissue biomarkers (including but not limited to EGFR, MET expression) and blood biomarkers predictive of clinical response and resistance to amivantamab	

Objectives	Endpoints
• Explore the relationship between serum PK, pharmacodynamic (PD) markers and clinical outcome • Explore the relationship of etiology (eg, HepB, HepC) and clinical response • Explore primary and acquired resistance to amivantamab treatment	

1.2. Study Design

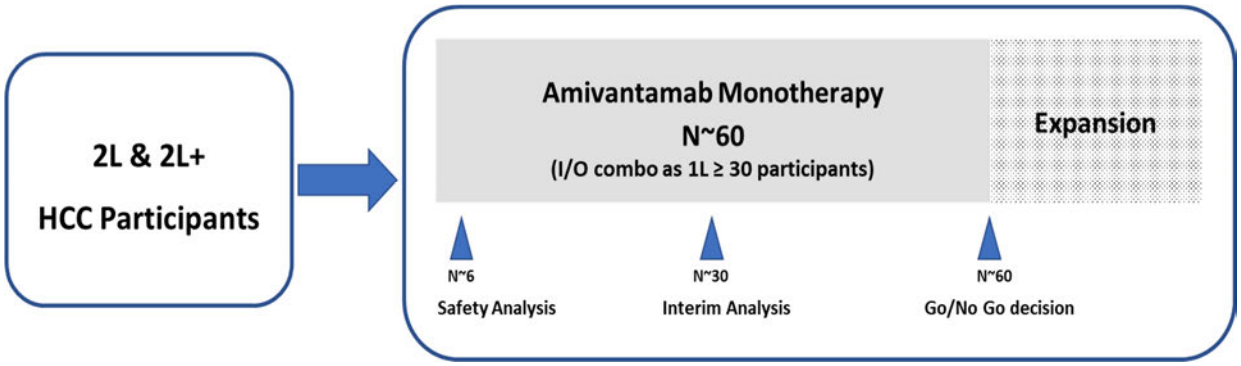
This is an open-label, single arm, multicenter, Phase 2 interventional study of amivantamab as monotherapy in participants with previously treated advanced HCC.

The 61186372HCC2001 study will aim to enroll a participant population that is geographically reflective of the overall incidence/prevalence of this disease.

A target of approximately 60 participants (at least 30 participants with first-line Immuno-Oncology [IO] combination treatment) will be enrolled in this study. The study will commence with Part 1, comprised of 6 participants and data review after at least 1 complete cycle of amivantamab therapy, for confirmation of dose and safety. For the main Part 2 of the study, two analyses are planned: an interim analysis for review of efficacy after 30 response-evaluable participants, and a final analysis after 60 response-evaluable participants. The expansion Part 3 of the study, with approximately 40 participants, may be opened based on the outcomes of the Part 2 final analysis. A retrospective analysis will be conducted to understand the correlation of biomarker(s), including the expression level of receptor, ligand(s) in the EGFR pathway and/or MET pathway, or other biomarkers, with responsive population.

The SET will be commissioned for this study. Participants' safety will be monitored throughout the study by the SET established by the Sponsor.

Figure 1: Schematic Overview of the Study



2. STATISTICAL HYPOTHESES

The hypothesis is that amivantamab monotherapy will lead to an ORR higher than 10% (ie, H_0: ORR≤10%) in participants with advanced HCC.

3. SAMPLE SIZE DETERMINATION

Assuming the ORR is 20% for the entire population, approximately 60 participants with advanced HCC will be enrolled to have over 85% probability to observe the ORR greater than 15%. Additional participants (ie, approximately 40) may be enrolled in an expansion phase to test the ORR of amivantamab against the null hypothesis with alpha=0.05 (two-sided) if supported by emerging data.

Anti-tumor activity within biomarker defined subpopulations will be investigated to identify the most responsive patient population who may benefit from amivantamab. With the prevalence of 50% of the entire population having 25% ORR, it is expected to have approximately 90% power to observe the posterior probability (ORR >15%) ≥50% in this population. On the other hand, if the biomarker defined population has undesirable ORR (ie, 10%), there is less than 20% probability to observe the posterior probability (ORR >15%) ≥50%. More examples are given in the Table .

Table 1: Probability to Detect Signal in Sub-Population Under Different Scenarios

Prevalence of effective population	**ORR for effective population**	**Power to observe posterior probability (ORR > 15%) ≥ 50% in effective population**
25%	10%	18% (type I error)
	20%	60%
	25%	76%
	30%	87%
50%	10%	18% (type I error)
	20%	74%
	25%	90%
	30%	97%

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Population	**Description**
Safety Evaluation	Participants who are enrolled during the safety evaluation
All treated	All participants who receive at least 1 dose of study treatment
Response evaluable	All participants satisfy the following criteria: • Received at least 1 dose of study treatment • At least 1 post-baseline efficacy disease assessments, or discontinued treatment for any reason, or had disease progression/death prior to the first postbaseline disease assessment
Pharmacokinetics	All participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline measurement

Immunogenicity	All participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline measurement
Biomarker	All participants who receive at least 1 dose of study treatment and have at least 1 biomarker measurement

The safety evaluation analysis set will be used to evaluate the safety data for the first SET meeting, which will include the first 6 subjects who have completed at least 1 completed cycle of amivantamab treatment. The supportive analyses for the first SET meeting are specified in the SET Charter. All treated analysis set will be used to summarize the study population and characteristics and the safety data, unless otherwise specified.

5. STATISTICAL ANALYSES

5.1. 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.

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 at the time of the signing informed consent form (ICF) and end at the start of the first administration of study treatment. The ICF must be signed before the first study-related activity is conducted. Screening procedures must be completed within 28 days before the first dose of study treatment.

The treatment phase will begin on Cycle 1 Day 1 (C1D1) with the administration of the study treatment and continue as 28-day cycles until the End of Treatment visit, approximately 30 days after discontinuation of study treatment. The frequency of study site visits and details of the procedures performed are outlined in the **Error! Reference source not found.** in study protocol. 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 as defined in protocol.

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.

Participants who discontinue study treatment for any reason will be followed for survival in the follow-up phase. Survival, subsequent anticancer treatment, and disease status will be assessed every 12 weeks (±14 days) after the last dose of study treatment or disease progression (whichever occurs first), until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first. If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the participant has died,

the date and cause of death will be collected and documented on the electronic case report form (eCRF). Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF.

5.1.2. Study Day / Relative Day

Study day or relative day is defined as:

- Reference date (Day 1) = First dose date of study drug which is Cycle 1 Day 1 (C1D1).
- 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 the study drug.

5.1.3. Baseline Measurements

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.

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 overall:

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

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

A listing of participants will be provided for the following categories:

- Participants who discontinued study treatment
- Participants who terminated study prematurely

5.3. Primary Efficacy Endpoints Analysis

5.3.1. Objective Response Rate (ORR)

5.3.1.1. Definition

The primary efficacy measure is ORR. ORR is defined as the proportion of participants who achieve either partial response (PR) or complete response (CR), as defined by investigator assessment using RECIST v1.1. Confirmation of investigator-assessed ORR may be performed through BICR.

Data obtained up until progression or last evaluable disease assessment in the absence of progression will be included in the assessment of ORR. However, any CR or PR, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation. Participants who do not have a tumor response assessment for any reason will be considered as non-responders and will be included in the denominator when calculating the response rate.

5.3.1.2. Estimand

The primary estimand for ORR is defined by the following components:

- Population: participants with advanced HCC
- Variable: objective response
- Study treatment: amivantamab monotherapy
- Intercurrent event: subsequent anticancer therapy. The while-on-treatment policy will be used: response after this intercurrent event will not be included
- Summary: ORR

5.3.1.3. Analysis Methods

ORR will be calculated for response evaluable as well as for the all treated population separately. The observed ORR and its exact 95% confidence interval (CI) will be calculated.

5.4. Secondary Efficacy Endpoint(s) Analysis

5.4.1. Duration of Response (DoR)

5.4.1.1. 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 DoR will be censored at the same date with PFS. Participants who started a subsequent anticancer therapy in the absence of progression will be censored at the last disease assessment before the start of subsequent therapy.

5.4.1.2. Analysis Methods

DoR will be analyzed using the response evaluable population.

A Kaplan-Meier plot and median DoR with 95% CI (calculated from the Kaplan-Meier estimate) will be presented. Confirmation of investigator-assessed DoR may be performed through BICR.

5.4.2. Disease Control Rate (DCR)

5.4.2.1. Definition

Disease control rate (DCR) is defined as the percentage of participants achieving complete or partial response, as well as durable stable disease (defined as a duration of at least 11 weeks) as defined by RECIST v1.1.

5.4.2.2. Analysis Methods

The DCR and its exact 95% confidence interval (CI) will be calculated using response evaluable and all treated population.

5.4.3. Progression Free Survival (PFS)

5.4.3.1. Definition

The PFS is defined as the time from the date the first dose until the date of objective disease progression or death by any cause, whichever comes first, based on investigator review according to 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 disease assessment.

Key censoring rules for PFS are summarized below.

Key Censoring rules for PFS

Situation	Date of Censoring
No evaluable baseline or post-baseline disease assessment	Censored at the date of first dose of study treatment
Lost to follow up or withdraw from study	Censored at the date of last evaluable disease assessment
No documented disease progression or death	Censored at the date of last evaluable disease assessment
Started a subsequent anti-cancer therapy in absence of progression	Censored at the date of last evaluable disease assessment before the start of the subsequent therapy

PFS is calculated in months as follows:

$$PFS = \frac{(date\ of\ PD, death\ or\ censoring - date\ of\ first\ dose\ of\ study\ treatment + 1)}{(\frac{365.25}{12})}$$

5.4.3.2. Analysis Methods

PFS will be analyzed using response evaluable and all treated population separately.

A Kaplan-Meier plot and median PFS with 95% CI (calculated from the Kaplan-Meier estimate) will be presented. Confirmation of investigator-assessed PFS may be performed through BICR. PFS rates at landmarks (6 months, 9 months and 12 months) with 95% CI will be estimated by Kaplan Meier method.

5.4.4. Overall Survival (OS)

5.4.4.1. Definition

The overall survival (OS) is defined as the time from the date of the first dose until the date of death due to any cause. Participants who are 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.

5.4.4.2. Analysis Methods

OS will be analyzed using response evaluable and all treated population separately.

A Kaplan-Meier plot and median OS with 95% CI (calculated from Kaplan-Meier estimate) will be presented. OS rates at landmarks (6 months, 9 months and 12 months) with 95% CI will be estimated by Kaplan Meier method.

5.5. Exploratory Efficacy Endpoint Analysis

5.5.1. Objective Response Rate by mRECIST (mORR)

5.5.1.1. Definition

The mORR is defined as the proportion of participants who achieve either partial response (PR) or complete response (CR), as defined by investigator assessment using mRECIST.

5.5.1.2. Analysis Methods

mORR will be calculated for response evaluable as well as for the all treated population separately. The observed mORR and its exact 95% confidence interval (CI) will be calculated.

5.6. Safety Analyses

All safety analyses will be based on the all treated population, unless otherwise specified.

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

5.6.1. Extent of Exposure

The number and percentage of participants who receive study treatment will be summarized overall and by visit.

Descriptive statistics for duration of study treatment (N, mean, SD, median, and range (minimum, maximum)) will be summarized. Duration of study treatment are calculated as [(date of last dose of study treatment – date of first dose of study treatment) +1].

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 maximum number of treatment cycles received for each subject will be summarized by frequency and descriptive statistics.

Number of amivantamab treatment interruption during the infusion due to AE will also be summarized.

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

The number (%) of participants with a dose reduction/dose not administrated will be summarized. Reasons for dose reduction/dose not administrated will also be summarized.

The number (%) of participants with cycle delay will be summarized. The reason for cycle delay 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 using 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

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) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. 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, is considered to be treatment

emergent. If the event occurs on the day of the initial administration of study treatment, 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 treatment based on partial onset date or resolution date. All reported treatment-emergent adverse events (TEAEs) 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.

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

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.

Incidence of AE / TEAE

Incidence rate (%) is defined as follows:

$$Incidence\ rate = \frac{Number\ of\ new\ cases\ during\ that\ period}{total\ number\ of\ subjects\ at\ risk\ during\ that\ period} * 100$$

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 drug, with TEAEs of maximum toxicity grade of 1 to 5, Serious TEAEs, TEAEs leading to discontinuation of any study drug, and deaths due to TEAE.

5.6.3.1.1. All TEAEs

- Incidence (%) of TEAE by SOC and PT

5.6.3.1.2. Toxicity Grade 3 or higher TEAEs

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

5.6.3.1.3. Study Related TEAEs

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

- Incidence (%) of TEAEs leading to study drug discontinuation related to treatment/study drug, 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 related to treatment/study drug, by SOC and PT
- Listing of participants with any serious TEAEs

5.6.3.1.5. TEAE leading to Study Drug Interruption/ Dose Reduction

- Incidence (%) of TEAEs leading to study drug/dose reduction will be summarized respectively by SOC and PT. The summaries will be presented for all toxicity grades and for toxicity grade 3 or higher

5.6.3.1.6. TEAE leading to Study Drug Discontinuation:

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

5.6.3.2. Adverse Events of Special Interest

Adverse events of special interest are pneumonitis/interstitial lung disease (ILD), rash, infusion-related-reaction (IRR), liver event and hypoalbuminemia. The MedDRA preferred terms associated with each of these categories are identified in Appendix 6. Additional information will be collected to fully describe 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 related to study drug
- Serious TEAEs by PT
- Serious TEAEs related to study drug
- TEAEs leading to study drug discontinuation by PT
- TEAEs leading to study drug discontinuation related to study drug

- 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 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, duration, and time between onset and the preceding infusion administration in days will be summarized by descriptive statistics (N, mean, standard deviation, median, and range).

IRR

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

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

Liver Event

Relative onset day and duration in days of liver event will be summarized by descriptive statistics (N, mean, standard deviation, median, and range).

Hypoalbuminemia

Relative onset day and duration in days of hypoalbuminemia will be summarized by descriptive statistics (N, mean, standard deviation, median, and range).

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 drug. 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

5.6.4.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the all treated population.

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points. Change from baseline 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 study (from treatment start to 30 days after last dose or the End of Treatment visit date or until the start of subsequent anti-cancer therapy, whichever is later) will be provided. The worst toxicity grade during the study will be tabulated.

An eDISH plot of peak ALT/ AST versus peak BILI will be provided along with a listing of subjects who had ALT/ AST values > 3xULN or BILI values > 2xULN.

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

- Peak aminotransaminases (AT, either ALT or AST) of >3xULN (Upper Limit of Normal)
- 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 (post-baseline) 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, Body Mass Index (BMI) from physical examination will be summarized at each scheduled timepoint. Body Mass Index will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation.

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.

5.6.4.3. Electrocardiogram

Electrocardiograms (ECG) will be performed at screening, and then to confirm any clinically significant finding during the study.

The ECG variables include heart rate, PR interval, QRS interval, QT interval, and QT corrected according to Fridericia's formula (QTcF).

A listing of clinically relevant ECG abnormalities will be provided.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Serum and Plasma samples will be collected from participants for PK and immunogenicity assessment of amivantamab as described in SoA in the study protocol.

PK analyses will be performed on the PK analysis set.

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 concentration-time data collected from this study may be combined with 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 analysis set.

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.

Assessment of biomarkers (DNA, RNA, or protein) relevant to hepatocellular carcinoma 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.

Biomarker data derived from IHC, RNAscope analyses on tissue specimens collected from this study will be used to assess the relationship of exploratory endpoints to efficacy endpoints. Both baseline levels and changes of these tissue biomarkers during the study will be analyzed and correlated to treatment response and/or resistance.

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. Results of PD and exploratory biomarker analyses will be presented in separate reports.

5.8. Interim Analyses

Two interim analyses are planned: an early review of safety after the first 6 participants have enrolled and have completed at least 1 complete cycle of amivantamab therapy, and a futility analysis based on ORR will be conducted after 30 participants have been enrolled and are response evaluable. The enrollment may be terminated for futility if less than or equal to 2 responders are

observed. Otherwise, additional participants will be enrolled for a total of approximately 60 participants for the initial analysis, with the potential for expansion to approximately 100 participants.

5.8.1. Safety Evaluation Team (SET)

The Safety Evaluation Team (SET) will be chaired by sponsor's Study Responsible Physician or designee. SET membership will consist at least of the following members:

- Principal investigators (or their designees)
- Clinical leader, Study Responsible Physician, Study Responsible Scientist or designee
- Clinical pharmacologists or their designees
- Medical safety leader or designee
- Statistician
- Biomarker scientist
- Any other sponsor or independent expert that the SET determines to be required

In general, the SET will monitor the safety and the conduct of the study. After review of cumulative study data, the SET may decide on modifications in the study conduct which may include but are not restricted to: (1) study treatment administration schedule, (2) study treatment dosing regimen (including dose escalation, dose de-escalation), (3) recommendations for best-supportive-care measures and AE management, (4) allowing further enrollment or terminate enrollment of a specific subpopulation, (5) opening the expansion cohort 3 or adding a cohort for potential combination regimen, and (6) PK or biomarker sampling times. Based on these potential modifications to regimens, schedules, and best supportive care measures, the SET may recommend re-assessment of a monotherapy dose regimen and the right expansion population.

The timing of SET meeting will be convened based on study design:

1. In the part 1, after 6 participants have completed at least 1 cycle of amivantamab therapy
2. In the part2, an interim analysis for efficacy after 30 response-evaluable participants
3. In the part2, a final analysis after 60 response-evaluable participants
4. If unexpected safety findings are identified or other reason, ad-hoc SET meetings may be called by any member of the SET.

The SET will monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study. Data and reports to be reviewed for SET meeing are specified in the SET Charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
BICR	Blinded independent central review
BILI	Bilirubin
BMI	body mass index
BSA	body surface area
DCR	Disease control Rate
CI	confidence interval
CR	Complete response
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of Response
DPS	Data Presentation Specifications
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Objective response rate
OS	Overall survival
PD	pharmacodynamic(s)
PFS	Progression free survival
PI	principal investigator
PK	pharmacokinetic(s)
PR	Partial response
QT	Uncorrected QT interval
QTc	Corrected QT
QTcF	Corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SoA	Schedule of Activities
ULN	Upper limit of normal
TEAE	treatment-emergent adverse event
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. In addition, the distribution of participants by site ID will be presented.

Table below presents a list of the demographic variables that will be summarized for all treated population.

Demographic Variables

Continuous Variables	**Summary Methods**
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 (<55, ≥ 55; <65 years, ≥65 years; <75years, ≥75years)	Frequency distribution with the number and percentage of participants in each category.
Weight (<80 Kg, ≥80 Kg)	
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
History of Alcohol use (Yes, No)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

The following table presents a list of the baseline disease characteristics variables that will be summarized for all treated population.

Baseline Disease Characteristics Variables

Continuous Variables	**Summary Methods**
Time from initial diagnosis to first dose (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Categorical Variables	
Baseline ECOG performance status score (0,1)	Frequency distribution with the number and percentage of participants in each category.
Baseline BCLC stage	
Baseline AFP (<400, ≥400)	
Baseline Child-Pugh score (A5, A6)	
Baseline HBV and/or HCV	
Prior lines of therapy	
First line treated with immunology/oncology [I/O] combination	
Intolerance / PD to prior line of therapy (Yes or No)	
History of vascular invasion (Yes or No)	
History of metastatic disease (Yes or No)	
History of extrahepatic metastasis (Yes or No)	

Type of tumor sample (Fresh or Archival)	

6.3. Definition of Subgroups

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

Subgroup	Definition
Age Group	<55 years, ≥55 years ; <65 years, ≥65 years; <75 years, ≥75 years
Sex	Male, Female
Race	Asian, Non-Asian
Weight	<80 Kg, ≥80 Kg
History of Alcohol use	Yes, No
Baseline ECOG performance status score	0, 1
Baseline BCLC Stage	B, C
Baseline AFP	≥400, <400
Baseline Child-Pugh score	A5, A6
Baseline HBV and/or HCV	Yes, No; HBV, HCV
Prior lines of therapy	1, 2, ≥3
Frist line treated with immunology/oncology [I/O] combination	Yes, No
Intolerance / PD to prior line of therapy	Yes, No
History of vascular invasion	Yes, No
History of Extrahepatic Metastasis	Yes, No
Prior cancer-related surgery or procedure	Surgery, nonsurgical local therapy

6.4. 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 and the participants with major protocol deviations will be summarized by category in 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
- Other

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

6.5. 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 for all treated population. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Prior medications will be summarized by ATC level/preferred terms. 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.

6.6. Appendix 5 Medical History

Medical history collected at Baseline or Screening visit will be summarized by body system class and preferred terms for all treated population.

6.7. Appendix 6 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE Clinical Importance 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

AE Clinical Importance Category	Preferred Term
Liver Event	
Hypoalbuminemia	

6.8. Appendix 7 Laboratory Toxicity Grading

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

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 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.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal;	>1.5 - 3.0 x ULN if baseline was normal;	>3.0 - 10.0 x ULN if baseline was normal;	>10.0 x ULN if baseline was normal;	Ranges defined for "abnormal baseline" are

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
	> 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x baseline if baseline was abnormal	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, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
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.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
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, i.e. 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, i.e. 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.
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.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
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. Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized.
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. Note: For Hypercalcemia or Hypocalcemia in the CTCAE Lab Toxicity grading scale, the reference ranges from serum calcium (ULN /LLN) from the local or central lab are being utilized.
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, i.e. 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.
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 <120 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
			Sodium <130-120 mmol/L		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

1) Park, Joong-Won, et al. "Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study." *Liver International* 35.9 (2015): 2155-2166.