Janssen Research & Development *

Clinical Protocol

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

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Protocol 61186372HCC2001; Phase 2
Version: Amendment 2

JNJ-61186372 (amivantamab)

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	21-February-2023
Amendment 1	23-September-2022
Original Protocol	6-May-2022

Amendment 2 (21 February 2023)

Overall Rationale for the Amendment: The overall reason for this amendment is to clarify the Inclusion Criteria 4 based on health authority's feedback.

The changes made to the clinical protocol 61186372HCC2001 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendment is listed in Section 10.14 Appendix 14: Protocol Amendment History.

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

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 2 Introduction	Add (MET **also known as cMET**) in abbreviation brackets for tyrosine protein kinase mesenchymal epithelial transition.	Editions were made in abbreviation for accuracy and documents consistency.
10.1 Appendix 1 Abbreviations	Modify definition of MET in abbreviation list: MET: ~~tyrosine protein kinase~~ mesenchymal epithelial transition	
1.3 Schedule of Activities (SoA)	Add a suggestion sentence in footnote "d": **Biopsy collection at late time of screening is suggested whenever possible.**	Editions were made for the ethical consideration and more clinical feasible procedure.
3 Objectives and Endpoints	Update to BICR language: Objective response rate (ORR) as determined by investigator, according to the Response Criteria in Solid Tumors (RECIST) v1.1. Confirmation of investigator-assessed ORR **may** ~~will~~ be performed through Blinded Independent Central Review (BICR).	Editions were made due to the BICR review changed to collect and hold review.
8.1 Efficacy Assessments	Update to BICR language: Response **may** ~~will~~ also be assessed by blinded independent central review (BICR) for central confirmation.	
4.1.1 Screening Period	Deletion of below sentence: "~~Informed consent does not expire if the screening evaluations are not performed within the 28-day Screening Period, although evaluations performed outside the screening window will need to be repeated.~~" Add sentence: "**Informed consent does not expire if the screening related procedures are not performed within the 28-day Screening Period, although evaluations performed outside the screening window will need to be**	Edition was made to align with the SoA and other section of the protocol.

Section Number and Name	Description of Change	Brief Rationale
	repeated, the exception to this will be fresh biopsy sample as long as there is no systemic treatment between the first and any subsequent re-screening."	
5.1 Inclusion Criteria	Changes were made in inclusion criteria 4: ~~Participant must be refractory, intolerant to or refused at least 1 prior line of systemic therapy. Prior therapies may include multi-targeted kinase inhibitor (MKI) and/or immunotherapy (eg, PD 1/L1-containing therapy).~~ **Participants should have progressed on standard of care (SoC) therapy with immunotherapy (eg, PD-1/L1-containing therapy) and a multi-targeted kinase inhibitor (MKI). Participation is allowed after progression with just one of these therapies, if the participant is intolerant of, or declining treatment with, the other SoC therapy (PD-1/L1-containing therapy or MKI).** a. Prior adjuvant or neoadjuvant therapy will be considered as 1 prior line of systemic therapy for the purpose of meeting the eligibility criteria **if participant experienced** progression within 24 weeks **of such therapy**. b. The intolerance or declining of further therapy should be documented in medical record, and discussed with the sponsor medical team. Note: A line of therapy is defined as a treatment regimen with subsequent disease progression	Editions were made in key inclusion criteria based on China health authority's recommendation on eligible participants.
5.1 Inclusion Criteria	Changes were made in inclusion criteria 8: "and HBV viral load must be less than 2000 IU/mL prior to **the** first dose of study ~~drug~~**treatment**"	Editions were made for clarification and content consistency
5.1 Inclusion Criteria	Changes were made in pregnancy test in inclusion criteria 12: A female participant of childbearing potential must have a negative ~~highly sensitive~~ serum (β-human chorionic gonadotropin [β-hCG]) pregnancy test at screening and within 72 hours of the first dose of study treatment **and must agree to further serum or urine pregnancy tests during the study**.	Editions were made for content consistency with SoA.
5.1 Inclusion Criteria	Changes were made in inclusion criteria 13: "Note: If a female participant becomes of childbearing potential after start of the study the **female participant**~~woman~~ must comply with point (b.)."	Keep the language consistent with the program template.
5.2 Exclusion Criteria	Change was made in exclusion criteria 3: and asymptomatic for at least 2 weeks and who are off or receiving low dose corticosteroid treatment ~~(~~**[**≤10 mg prednisone or equivalent**]**~~)~~ for at least 2 weeks ~~prior to study treatment~~**prior to the first dose of study treatment**)	Editions were made for clarification and content consistency

Section Number and Name	Description of Change	Brief Rationale
	Text in bold was added in exclusion criteria 5: Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 3 months **prior to the first dose of study treatment**.	
8.2.4 Clinical Safety Laboratory Assessments	Add sentence: "**In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required and may be done locally when an immediate clinical decision needs to be made.**"	Editions were made to provide the option on the local lab test in the urgent safety monitoring and immediate clinical decision.
9.3 Populations for Analysis Sets	Deletion of Safety population and the description of Safety population.	The population set for Safety analysis was the same with population of All treated analysis set. Deletion was made to avoid redundancy.
9.4.5 Safety Analyses	Modification was made on sentence: All safety analyses will be made on the ~~Safety~~ **All treated** Population.	
10.2 Appendix 2	Add "urea" in Protocol-Required Safety Laboratory Assessments: "Blood urea nitrogen (BUN) **or urea**"	Optional collection for urea value was added.
10.12 Appendix 12	The source "Guidance for Industry" reference was added for the calculation of eGFR. Add new references: **Levey (2006, 2007), Mosteller (1987)**	Addition of new references.
10.13 Appendix 13	Child-Pugh Classification scoring table: Prothrombin time prolongation (sec) with observed finding of 1.0-~~3.0~~**<4.0** scored for 1 point. Use "Absent", "Slight" and "Moderate" to describe the observed findings of parameter "Ascites".	Corrections in Child-Pugh Classification scoring table and update the table based on NCCN guideline 2022 version 4.
10.13 Appendix 13 11 References	Deletion of 2 references: ~~Child 1964; Pugh 1973~~ Add new reference: **NCCN 2022**	
Throughout the protocol	Minor editorial, editions for consistency, grammatical, or formatting were made.	Other revisions including minor editorial, grammatical, formatting, or consistency changes were made throughout.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Amivantamab (also known as RYBREVANT® or JNJ-61186372) is a low fucose, fully human immunoglobulin G1 (IgG1)-based bispecific antibody directed against the epidermal growth factor receptor (EGFR) and tyrosine protein kinase mesenchymal epithelial transition (MET, also known as cMET) receptors. Amivantamab is approved in several countries, including the USA and EU, for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Amivantamab shows preclinical activity against NSCLC tumors with overexpressed wild type EGFR and activation of the MET pathway. Overexpression of EGFR and MET have been found in hepatocellular carcinoma (HCC), and the overexpression often associates with poor prognosis. By inhibiting EGFR and MET signaling, either by blocking ligand-induced activation and/or inducing receptor degradation, amivantamab may disrupt these signaling pathways and prevent tumor growth and progression. In addition, the presence of high levels of EGFR and MET on the surface of tumor cells allows for targeting of these cells for destruction by immune effector cells, through antibody-dependent cellular cytotoxicity (ADCC) and antibody dependent cellular trogocytosis (ADCT).

Therefore, this open-label, multicenter Phase 2 study will assess the safety and anti-tumor activity of amivantamab as a monotherapy in participants with HCC.

OBJECTIVES

The primary objective of this study is to characterize the preliminary antitumor activity, by objective response rate (ORR), of amivantamab at the recommended Phase 2 dose (RP2D) in participants with previously systemically treated HCC. Key secondary objective is to further characterize efficacy as well as safety in this population.

Hypothesis

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

OVERALL 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 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 efficacy after 30 response-evaluable participants, and a final analysis after 60 response-evaluable participants. The expansion Part 3 of

the study may be opened based on the outcome of Part 2. 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.

NUMBER OF PARTICIPANTS

A target of approximately 60 participants (at least 30 participants with first line Immuno-Oncology [IO] combination treatment) will be enrolled in this study in Part 1 and 2; an additional 40 participants may be included in Part 3.

TREATMENT GROUPS AND DURATION

Amivantamab as an intravenous (IV) infusion in 28-day cycles:

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

Cycles 2+: Days 1 and 15 of each cycle: 1,050 mg (if body weight is <80 kg) or 1,400 mg (if body weight is ≥80 kg)

Dose and administration schedule may be adjusted based on safety evaluation team (SET) recommendations during the study.

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

EFFICACY EVALUATIONS

Response criteria in solid tumors (RECIST) v1.1 criteria will be used to assess participant response to treatment. Disease assessments will occur every 6 weeks (±1 week) for the first 12 months, then every 12 weeks (±1 week) until disease progression. If a participant achieves partial response (PR) or complete response (CR), confirmation of response may occur at least 4 weeks from the initial response.

PHARMACOKINETIC/IMMUNOGENICITY EVALUATIONS

Blood samples will be collected from all participants for the measurement of serum amivantamab for PK analyses. Sample collection and testing will comply with local regulations.

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

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Tumor tissue samples and blood samples will undergo central analysis to investigate levels of MET, EGFR, relevant MET/EGFR ligands, and other biomarkers relevant to target biology or HCC. The baseline level of these biomarkers and their changes upon treatment will be correlated

with response to amivantamab treatment. The relationship of etiology (eg, Hepatitis B [HepB], Hepatitis C [HepC]) with clinical response will also be analyzed. Blood samples will also be collected from all participants to analyze pharmacodynamics (PD) markers. Sample collection and testing will comply with local regulations.

SAFETY EVALUATIONS

The safety of amivantamab will be assessed by physical examinations, vital signs, safety laboratory assessments, monitoring of adverse events (AEs), and concomitant medication usage. Adverse events that occur from the date of signing the informed consent form (ICF) through 30 days following the last dose of study treatment will be recorded.

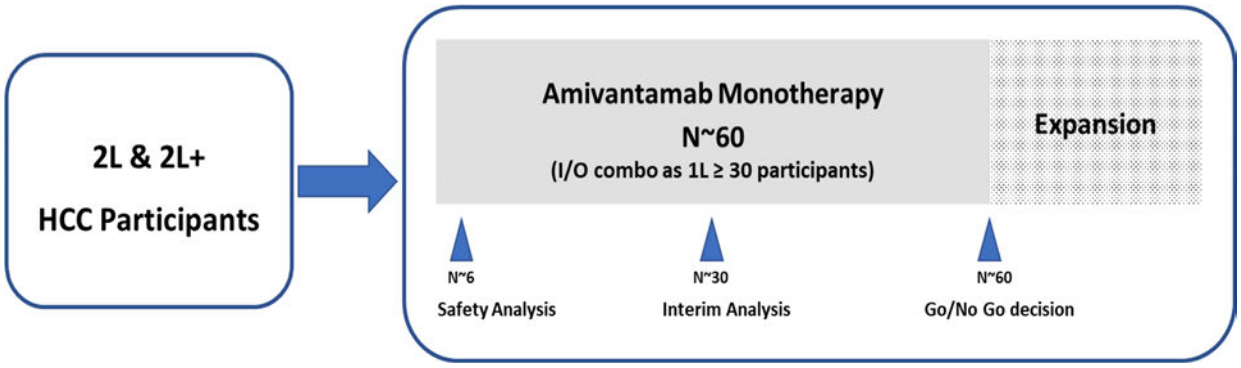
STATISTICAL METHODS

Sample Size

The null hypothesis is that the ORR of amivantamab monotherapy in advanced HCC patients is less than 10%. Assuming the ORR is 20%, approximately 60 participants will be enrolled to have over 85% probability to observe the ORR greater than 15%. With this rule 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. Details will be provided in the Statistical Analysis Plan.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	Scree-ning	Treatment (28 days/cycle)									EOT	FU	Notes
Study Period		Cycle 1					Cycle 2		Cycle 3+		30D After Last Dose	Q12W	
Day	-28 to -1	1	2	8	15	22	1	15	1	15			
Visit Window (Days)		-	-	±1	±1	±1	±1	±1	±3	±3	+7	±14	
STUDY PROCEDURES Perform assessments during in-clinic dosing days prior to administration of study treatment unless otherwise stated. Starting with Cycle 2 Day 1: if dose delay occurs, sampling schedule (except disease assessments) should be delayed accordingly to ensure sampling relative to amivantamab dose administration. In follow-up phase, collect data until the end of study unless the participant has died, is lost to follow-up, or has withdrawn consent.													
SCREENING ASSESSMENTS													
Informed consent	X												
Inclusion/exclusion criteria	X												Confirm all criteria are met before enrollment.
Demography	X												Age, gender, ethnicity and race
Disease characteristics	X												
Smoking status, alcohol use	X												
Medical history	X												Includes past medical diagnoses, and current medical conditions with toxicity grade (including current cancer-related symptoms).
Child-Pugh score	X												Within 7 days before C1D1 at screening.
12-Lead ECG	X	As clinically indicated											
ECOG performance status	X	As clinically indicated											Any decline in ECOG: report as an AE.
Local laboratory Assessments													
Pregnancy test (serum or urine)	X	As clinically indicated, according to local regulation requirements, or following the local practice of the center											Female of child-bearing potential only. Required at Screening and within 72 hours before the first dose of study treatment.
Hematology, chemistry, coagulation, liver and kidney function[a]	X	X		X	X	X	X	X	X	X	X		
Anti-HIV	X												
Urinalysis	X	X		X	X	X	X	X	X	X			Perform urine microscopy if urinalysis abnormal.
Central laboratory Assessments													
HBV serology	X												
Anti-HDV	X												If:

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	Scree-ning	Treatment (28 days/cycle)									EOT	FU	Notes
Study Period		Cycle 1					Cycle 2		Cycle 3+		30D After Last Dose	Q12W	
Day	-28 to -1	1	2	8	15	22	1	15	1	15			
Visit Window (Days)		-	-	±1	±1	±1	±1	±1	±3	±3	+7	±14	
Quantitative HBsAg and HBV viral load	X	X					X		X		X		1. HBsAg+ 2. HBsAg-, HBsAb- and HBcAb+ Perform the quantitative HBsAg and HBV viral load test every 3 cycles starting from Cycle 5 (Day 1 of Cycles 5,8,11, etc) and EOT visit.
Anti-HCV	X												
HCV viral load	X	X					X		X		X		If anti-HCV positive, the respective viral load test will be performed every 3 cycles starting from the Cycle 5 (day 1 of Cycles 5,8,11, etc) and EOT visit.
AFP	X	X			X		X	X	X		X		Day 1 of every cycle starting from Cycle 3.
STUDY TREATMENT ADMINISTRATION													
Amivantamab dosing[b]		X	X	X	X	X	X	X	X	X			
Concomitant medications	X												
SAFETY ASSESSMENTS													
Adverse events	Continuous from time full screening ICF is signed through 30 days after last dose of study treatment (or >30 days, if considered related to study treatment)												
Vital signs	X	X	X	X	X	X	X	X	X	X	X		Heart rate, BP, respiratory rate, temperature, and O_2 saturation <30 min before amivantamab infusion, 30 min intervals (±5 min) during each amivantamab infusion, and at end of infusion (+5 min).
Physical examination	X	X					X		X		X		Screening will include height, weight, general appearance. On Day 1 of each cycle, directed physical examination.
EFFICACY ASSESSMENTS													
CT/MRI tumor imaging[c]	X	6 weeks (+1 week) (ie, no earlier than Day 42) for first assessment, then every 6 weeks (±1 week) for first 12 months, then every 12 weeks (±1 week) relative to first dose											
Brain imaging[c]	X	Every 12 weeks ±1 week if baseline brain metastasis present; as clinically indicated if not at baseline											
Survival and subsequent anticancer therapies												X	May be collected via phone. Collect type of therapy, treatment start date and stop date.

Table 1: Schedule of Activities for Study Procedures/Assessments

Phase	Scree-ning	Treatment (28 days/cycle)									EOT	FU	Notes
Study Period		Cycle 1					Cycle 2		Cycle 3+		30D After Last Dose	Q12W	
Day	-28 to -1	1	2	8	15	22	1	15	1	15			
Visit Window (Days)		-	-	±1	±1	±1	±1	±1	±3	±3	+7	±14	
PHARMACOKINETICS AND IMMUNOGENICITY													
PK and immunogenicity blood sampling		Refer to separate Table 2 and Table 3											
PHARMACODYNAMICS AND BIOMARKERS													
Tumor biopsy[d]	X										X		
PD blood samples (soluble EGFR and MET)		Refer to separate Table 2 and Table 3											
Blood sample for exploratory biomarker[e]		X									X		

Abbreviations: AE=adverse event; AFP= alpha fetoprotein; BP=blood pressure; C#D#=Cycle # Day #; CR=complete response; CT=computerized tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; h=hour; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; min=minutes; MRI=magnetic resonance imaging; PR=partial response; Q12W=every 12 weeks; RECIST=response criteria in solid tumors.

Footnotes:

a. Tests may be performed up to 72 hours predose. If performed within 72 hours of the first dose, the assessment does not have to be repeated at Cycle 1 Day 1. Results must be reviewed by the Investigator prior to each study treatment administration. Clinically significant abnormalities should be reported as AEs. Additional testing as needed, per local guidelines and practice for the purposes of chemotherapy dosing, with clinically significant abnormalities reported as adverse events.

b. A missed dose is defined as failure to administer study drug within 3 days of the scheduled dosing date in Cycle 1, or failure to administer study drug within 7 days of the scheduled dosing date in Cycle 2 and beyond. If a dose is missed, as defined above, it will not be made up. Administration may resume at the next planned dosing date. If the first dose in Cycle 2 is delayed, then the dates of all subsequent doses must be maintained as originally scheduled based on Cycle 1 Day 1. If the first dose in Cycle 2 (ie, the fifth dose) is missed, then the Cycle 2 Day 1 PK, PD, immunogenicity, and biomarker samples should replace the sampling scheme for the next dose. All other assessments should be performed relative to actual study drug administration, not on the originally scheduled administration day.

c. At minimum, chest, abdomen and pelvis must be assessed. Brain imaging required only if participant is suspected to have brain metastasis by the investigator. Screening imaging may not have to be repeated if the imaging data is available as part of the routine care performed within 28 days of Cycle 1 Day 1 even prior to signing the ICF if it satisfies the study criteria. If a participant achieves PR or CR, confirmation of response may occur at least 4 weeks from the initial response, per RECIST v.1.1.

d. Wherever possible, non-target lesions should be biopsied rather than target lesions. Biopsy of a target lesion is allowed for the pre-treatment sample, but baseline disease assessment must occur a minimum of 1 week after the biopsy procedure. Biopsy collection at late time of screening is suggested whenever possible. Tumor tissue biopsy acquired at screening is preferred. If not available, the most recent tumor tissue sample is acceptable. Biopsy at EOT is optional. Biopsy of a target lesion is also allowed for EOT sample if the participant has confirmed radiographic disease progression. Sample collection and testing will comply with local regulations.

e. For baseline, it is acceptable blood sample collection occurs at full screening stage. Blood sample at EOT is optional; it should be taken within 30 days of disease progression and must be before the next anticancer therapy. Sample collection and testing will comply with local regulations.

Table 2: Sample Collection Times for Pharmacokinetics, Pharmacodynamics, and Immunogenicity for Amivantamab in 12 Participants

Cycle[a]	Collection Window	1					2		3		4		5 and beyond[b]	End of Treatment Visit	Post-treatment Follow-up
Cycle Day		1	2	8	15	22	1[c]	15	1	15	1	15	1	30 Days After Last Dose	Q12W
Visit window (days)		--	--	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	+7	
Pharmacokinetic Samples[d,e,f]														X	X[g]
Before infusion	(-2 hr)	X	X	X	X	X	X	X	X	X	X	X	X		
EOI	(+10 min)	X	X	X	X	X	X	X	X	X	X	X	X		
EOI+2 hours	(±15 min)		X				X				X				
EOI+6 hours	(±30 min)		X				X				X				
EOI+24 hours	(±60 min)		X				X				X				
EOI+72 hours	(±2 hr)		X				X				X				
EOI+168 hours	(±4 hr)						X				X				
EOI+240 hours	(±4 hr)						X				X				
Immunogenicity Samples[d,e,f]			X (further details below)											X	X[g]
Before infusion	(-2 hr)	X					X		X		X		X		
Pharmacodynamic Samples[d,e,f]															
Before infusion	(-2 hr)	X	X	X	X	X	X		X		X				

Abbreviations: EOI=end of infusion; hr=hours; min=minutes; PK=pharmacokinetic.

a. If a participant undergoes intra-participant dose escalation or de-escalation, sample collection should continue according to the original schedule.
b. The same sampling scheme for PK and immunogenicity samples should be followed on Cycle 7, 10 and 13 then every 12 cycles thereafter.
c. If the Cycle 2 Day 1 dose is missed, the assessments specified in this table for this dose should be applied whenever the next dose is given.
d. At any dose after Cycle 2 Day 1: If a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule should be delayed accordingly to ensure sampling relative to dose administration.
e. All samples collected after the initiation of each amivantamab infusion should be taken from the arm contralateral to the arm in which study treatment is administered, or via a central line if not utilized for study treatment administration. Samples collected prior to the initiation of the amivantamab infusion can be drawn from either arm or central line.
f. Separate blood draws are not required when multiple sample types will be collected at the same time point. Blood volume requirements for each time point and serum aliquot specifications are provided in the Laboratory Manual.
g. PK and immunogenicity samples in post-treatment follow-up: If a participant has an in-person visit, every effort should be made to collect PK and immunogenicity samples at the first post-treatment follow-up visit only (no subsequent visits).

Table 3: Sample Collection Times for Pharmacokinetics, Pharmacodynamics, and Immunogenicity for Amivantamab in the Rest Participants of the Study

Cycle[a]	Collection Window	1					2		3		4		5 and beyond[b]	End of Treatment Visit	Post-treatment Follow-up
Cycle Day		1	2	8	15	22	1[c]	15	1	15	1	15	1	30 Days After Last Dose	Q12W
Visit window (days)		--	--	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	+7	
Pharmacokinetic Samples [d,e,f]			X (further details below)											X	X[g]
Before infusion	(-2 hr)	X	X	X	X	X	X	X	X	X	X	X	X		
EOI	(+10 min)	X	X	X	X	X	X	X	X	X	X	X	X		
Pharmacodynamic Samples [d,e,f]		X (further details below)													
Before infusion	(-2 hr)	X					X				X				
Immunogenicity Samples [d,e,f]			X (further details below)											X	X[g]
Before infusion	(-2 hr)	X					X				X		X[b]		

Abbreviations: EOI=end of infusion; hr=hours; min=minutes; PK=pharmacokinetic.

a. If a participant undergoes intra-participant dose escalation or de-escalation, sample collection should continue according to the original schedule.
b. The same sampling scheme for PK and immunogenicity samples should be followed on Cycle 7, 10 and 13 then every 12 cycle thereafter.
c. If the Cycle 2 Day 1 dose is missed, the assessments specified in this table for this dose should be applied whenever the next dose is given.
d. At any dose after Cycle 2 Day 1: If a dose interruption or missed dose leads to a cycle delay or a dose delay, the sampling schedule should be delayed accordingly to ensure sampling relative to dose administration.
e. All samples collected after the initiation of each amivantamab infusion should be taken from the arm contralateral to the arm in which study treatment is administered, or via a central line if not utilized for study treatment administration. Samples collected prior to the initiation of the amivantamab infusion can be drawn from either arm or central line. Sample collection and testing will comply with local regulations.
f. Separate blood draws are not required when multiple sample types will be collected at the same time point. Blood volume requirements for each time point and serum aliquot specifications are provided in the Laboratory Manual.
g. PK, PD, and immunogenicity samples in post-treatment follow-up: If a participant has an in-person visit, every effort should be made to collect PK and immunogenicity samples at the first post-treatment follow-up visit only (no subsequent visits).

2. INTRODUCTION

Amivantamab, also known as JNJ-61186372, is a low fucose, fully human immunoglobulin G1 (IgG1)-based bispecific antibody directed against the epidermal growth factor receptor (EGFR) and tyrosine protein kinase mesenchymal epithelial transition (MET, also known as cMET) receptors. Unlike EGFR tyrosine kinase inhibitors (TKIs), which bind to the intracellular portion of the EGFR, amivantamab targets the extracellular domain of both EGFR and MET. By inhibiting EGFR and MET signaling, either by blocking ligand-induced activation and/or inducing receptor degradation, amivantamab may disrupt these signaling pathways and prevent tumor growth and progression. In addition, the presence of high levels of EGFR and MET on the surface of tumor cells allows for targeting of these cells for destruction by immune effector cells, through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular trogocytosis (ADCT). Amivantamab shows pre-clinical activity against NSCLC tumors with overexpressed wild type EGFR and activation of the MET pathway (Moores 2016). Both EGFR and MET have been found to be overexpressed in hepatocellular carcinoma (HCC), and the overexpression often associates with poor prognosis.

This is an open-label, multicenter Phase 2 study of amivantamab monotherapy in participants with previously treated advanced HCC. Given the antitumor activity observed in NSCLC, this study will evaluate the safety and confirm the recommended Phase 2 dose (RP2D) of amivantamab and investigate the preliminary anti-tumor activity of amivantamab as a monotherapy in HCC.

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

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

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

2.1. Background

2.1.1. The Epidemiology of HCC

Liver cancer is the 7th most common malignancy and the 3rd leading cause of cancer-related death worldwide, with over 906,000 new primary liver cancer cases resulting in 830,000 deaths globally in 2020 (Sung 2021; Globocan 2020). The major etiologies of liver cancer include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol consumption, steatosis, aflatoxin exposure (Sherman 2005; Thomas 2005). Primary liver cancer includes HCC (comprising 75%-85% of cases) and intrahepatic cholangiocarcinoma (10%-15%), as well as other rare types (Sung 2021).

2.1.2. HCC Current Treatment Options and Outcome

Patients with HCC are often diagnosed at an advanced stage with distance metastases or with disease that is not amenable to surgery or local treatment. Patients have a poor prognosis, with a 5-year overall survival (OS) rate of 10–18% (Zeng 2018; Siegel 2018). In China, liver cancer is the 4th most common cancer and 2nd leading cause of cancer death with over 410,000 new primary liver cancer cases resulting in 391,000 deaths in 2020 (Zheng 2019; Globocan 2020). China accounts for 45.3% and 47.1% of global new primary liver cancer cases, and liver cancer-related deaths, respectively (Globocan 2020). Chronic HBV infection is the most frequent cause (84%) of HCC in China (Chinese chronic hepatitis B guideline 2019), while in the Western countries chronic HCV, alcoholic cirrhosis and non-alcoholic steatohepatitis (NASH) are the main causes (Medavaram 2018).

Systemic therapies are recommended for HCC patients who have advanced disease (BCLC [Barcelona clinic liver cancer] stage C) or intermediate-stage disease (BCLC stage B) and progressed despite transarterial therapies (Villanueva 2019). Sorafenib was approved in 2007 as first-line targeted therapy for advanced HCC based on the success of SHARP and Asia-Pacific trial, ushering in the era of systemic treatment (Huang 2020; Llovet 2008; Cheng 2009). With low rates of objective tumor responses (2%), however, the clinical benefit of sorafenib remains modest and the investigation of additional novel therapeutics that can target the complex molecular pathogenesis of HCC is continued. As first-line treatment, lenvatinib was non-inferior to sorafenib in OS (13.6 months vs 12.3 months; hazard ratio [HR] was 0.92) and objective response rate (ORR) (18.8% vs 6.5%) (Kudo 2018), and has surpassed the use of sorafenib as a front-line therapy in the current treatment of HCC in China. Newly approved atezolizumab plus bevacizumab in first-line treatment shows better OS (19.2 months), PFS (6.8 months) and ORR (30%) than sorafenib (Finn 2020) and has become another frequently utilized front-line option.

The treatment landscape of HCC in second-line setting has been evolving since 2017, with regorafenib, nivolumab, pembrolizumab, cabozantinib, and ramucirumab being approved for patients progressed on or after sorafenib (Bruix 2017; Zhu 2018; Abou 2018; Zhu 2019; Meyer 2018). In China, regorafenib, apatinib, and local anti- programmed cell death 1 (PD-1) antibodies (camrelizumab and tislelizumab) monotherapy are approved for advanced HCC in the second-line setting. Collectively, the approved second-line monotherapies show modest objective response rates (4-17%) and OS benefits (8.5-15.1 months) (Bruix 2017; Zhu 2018; Abou 2018; Zhu 2019; Meyer 2018). Recently United States (US) Food and Drug administration (FDA) conditionally approved nivolumab plus ipilimumab with its encouraging 32% ORR data in advanced HCC patients previously treated with sorafenib (Yau 2020; Saung 2021). However, it is only approved in US and associated with considerable toxicity, with any grade treatment-related adverse events and Grade 3-4 treatment-related adverse events (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks) of 94% and 76%, respectively (Yau 2020; Saung 2021).

Despite the encouraging recent progress with multi-targeted TKIs and immune-based therapies for advanced HCC, several challenges remain. The most important one is the limited efficacy of current treatment options as described above (Bruix 2017; Zhu 2018; Abou 2018; Zhu 2019; Meyer 2018). Another is drug-related adverse events, which often lead to dose reduction,

interruption or discontinuation (Niu 2021). The third challenge is drug resistance, which remains a major cause of the failure of targeted therapy (Niu 2021). The underlying mechanisms include the intrinsic HCC heterogeneity and clonal evolution, and the lack of reliable biomarkers to identify HCC patients most likely to benefit from targeted and immune therapies (Niu 2021; Rizzo 2021). Considering the high malignancy and heterogeneity of HCC and scarce effective treatment options, there is a great unmet need to develop novel drugs for advanced HCC (Yau 2020; Qin 2020).

2.1.3. EGFR and MET Signaling Pathways in HCC

Overexpression and genetic alterations of EGFR and MET have been closely linked to tumorigenesis, aggressive progression, and poor prognosis in multiple cancer types, supporting their importance as therapeutic targets for cancer therapy (Birchmeier 2003; Hynes 2005; Yano 2003). Indeed, agents targeting EGFR (including anti-EGFR antibodies and EGFR TKIs) have revolutionized the treatments for patients with colorectal cancer, non-small cell lung cancer (NSCLC), and head and neck cancer (Hsu 2018; Li 2020; Taberna 2019). Similarly, the recent approval of MET inhibitors in NSCLC with MET Exon14 skipping alteration further expanded the treatment options for biomarker selected patients (Mathieu 2021). Although these 2 pathways are not currently targeted in the context of HCC, it is reported that approximately 63.2-66.0% and 25.4-38.8% of patients with HCC have tumors characterized by overexpression of EGFR and MET, respectively (Huang 2019; Buckley 2008). The overexpression of MET often associates with poor prognosis in HCC (Lee 2013; Kondo 2013). Unlike in NSCLC, where the genetic alterations and gene amplification of EGFR and MET drives pathway activation, the activation of EGFR and MET pathways are frequently driven by the canonical ligand-receptor binding in HCC. Indeed, aberrantly high levels of MET ligand, hepatocyte growth factor (HGF), have been implicated in promoting HCC progression and metastasis (Junbo 1999; Yang 2022). Given the importance of EGFR and MET pathways in HCC, many clinical trials have examined the activities of EGFR or MET targeting agents, although results have been disappointing so far. For example, erlotinib, an EGFR TKI, combined with bevacizumab did not achieve encouraging outcome in sorafenib-refractory HCC population (irrespective of EGFR status) (Niu 2017; Philip 2012). Similarly, studies evaluating the efficacy of tivantinib (a selective oral MET inhibitor, Daiichi Sankyo) failed to show clinical benefit in MET-high advanced HCC in a 2nd line Phase 3 study (Rimassa 2018).

One possible reason for prior failures in clinical benefit is the redundant signaling pathways that may confer primary or required resistance to the therapeutic intervention against a single receptor target (Zhang Y 2018). It is well known that the EGFR and MET pathways have many overlapping downstream signaling modules, which collectively are pro-tumorigenic and pro-progression (Yamaguchi 2014; Zhang YZ 2018). Co-overexpression of EGFR and MET has been reported in 24.5% of HCC patients (Dong 2019), which has been confirmed by in-house data. Thus, the suppression of EGFR or MET pathway alone may not be sufficient to block the oncogenic signaling and elicit clinical benefit in HCC. In NSCLC, it is well known that MET pathway activation mediates treatment resistance with EGFR inhibitors. Similarly, activation of MET pathway is also found to mediate resistance to Cetuximab in colorectal cancer (CRC) and head and neck squamous cell carcinoma (HNSCC) (Novoplansky 2019). Conversely, EGFR amplification

is recently found as a resistance mechanism in NSCLC treated by MET TKI (Recondo 2020). Importantly, combination of EGFR and MET inhibitors has demonstrated clinical benefit in biomarker selected subpopulation analysis in NSCLC clinical trials (Wu 2020; Scagliotti 2020).

2.1.4. Amivantamab and EGFR / MET Signaling Pathway

Amivantamab, also known as RYBREVANT® or JNJ-61186372, is a low fucose, fully human IgG1-based bispecific antibody directed against the EGFR and MET receptors, that shows preclinical activity against tumors with overexpressed wild type EGFR and activation of the MET pathway. Unlike EGFR TKIs, which bind to the intracellular portion of the EGFR, amivantamab targets the extracellular domain of both EGFR and MET. Preclinical data suggest it has at least 3 potential mechanisms of action, including 1) inhibition of ligand-dependent signaling, 2) downregulation of EGFR and MET expression levels, and 3) initiation of ADCC. It is hypothesized that by targeting the extracellular domain of EGFR and MET, amivantamab can inhibit receptors that display primary resistance to EGFR TKIs (Exon 20 insertion) or have acquired either EGFR resistance mutations (T790M or C797S) or secondary activation of the MET pathway (MET amplification).

Based on early activity observed within the EGFR exon 20 insertion population, amivantamab was awarded Breakthrough Therapy Designation by FDA and China Center for Drug Evaluation (CDE) for the treatment of patients with EGFR exon 20 insertion NSCLC, after progression on prior platinum-based chemotherapy. On 21 May 2021, the US FDA granted amivantamab accelerated approval for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. Amivantamab is currently approved in multiple countries and marketed under the name RYBREVANT®.

2.1.5. Amivantamab in Preclinical HCC PDX models

CCI

Figure 2: CCI

2.2. Study Rationale

HCC has been known to highly express EGFR and MET and the expression of these proteins correlate with poor prognosis. Although many agents targeting EGFR and MET are parts of standard of care for many tumor types, no anti-EGFR therapy and MET inhibitors have been approved in HCC. One potential mechanism behind the lack of clinical activities is the redundancy of receptor tyrosine kinases (RTKs), including EGFR and MET, in upregulating downstream oncogenic signaling (Saraon 2021). Thus, inhibiting EGFR or MET alone may not be sufficient in eliciting clinical activity. In addition, the lack of consensus and reliable biomarker strategies to select participants may also contribute to the failure of many clinical studies. As a bispecific antibody capable of engaging the extracellular domains of both EGFR and MET receptors, amivantamab has a unique mechanism of action that suggests it has the potential to control EGFR overexpressing and/or MET-overexpressing tumors in HCC patients. In addition to the known

Fc-independent EGFR and MET signal inhibition, multiple Fc-dependent mechanisms (including ADCC, macrophage- and monocyte-mediated ADCT) have been implicated in the robust anti-tumor effect of amivantamab (Moores 2016; Grugan 2017; Vijayaraghavan 2020). The complex immune microenvironment in HCC has provided opportunities for immunotherapies. The Fc-driven mechanisms of amivantamab may mobilize immune cells in the microenvironment to contribute to clinical benefit.

Amivantamab inhibits EGFR and MET signaling functions by blocking ligand-induced activation and inducing receptor degradation; disruption of these signaling pathways prevents tumor growth and progression. In addition, due to reduced fucosylation, amivantamab has enhanced capability to engage immune effector cells. The presence of EGFR and MET on the surface of tumor cells allows amivantamab to bind them and to target these cells for destruction by natural killer (NK) cells and macrophages, through ADCC and trogocytosis mechanisms, respectively. Based on nonclinical data, amivantamab may employ multiple mechanisms to inhibit tumors with aberrant EGFR and MET signaling.

Furthermore, preliminary biomarker evaluation has suggested amivantamab to be more active in patients with tumors that have higher expression of EGFR and MET in osimertinib-relapsed EGFR mutated NSCLC disease (Bauml 2021).

This study aims to evaluate the clinical activity of amivantamab as a monotherapy in HCC participants with previously treated advanced HCC.

Amivantamab Intravenous Dose Rationale

Amivantamab will be administered at the recommended dose (approved for treatment of NSCLC with EGFR Exon 20 ins) of 1,050 mg for participants with a baseline body weight (BW) <80 kg and 1,400 mg for participants with a baseline BW ≥80 kg. This dose was based on the totality of exposure, safety, and efficacy data from the ongoing Phase 1 Study 61186372EDI1001 (EDI1001 study). Amivantamab for intravenous administration was generally well tolerated at doses up to 1,750 mg, with no dose limiting toxicity (DLT) reported during the initial dose escalation and no maximum tolerated dose identified in NSCLC participants. The recommended dose achieved a complete soluble target saturation throughout dosing for EGFR and MET in the NSCLC participants. Amivantamab is administered by intravenous (IV) infusion in 28-day cycles, once weekly in Cycle 1 (with a split dose on Days 1 and 2), and then every 2 weeks in subsequent cycles.

Over a thousand patients with NSCLC, characterized by diverse EGFR and MET alterations, have received amivantamab at the recommended dose, as either a monotherapy or in combination with lazertinib, a third generation EGFR TKI, with a safety profile that is consistent with on-target activity against EGFR and MET. Toxicities have been manageable, with the majority of treatment-emergent adverse events (TEAEs) Grade 1 to 2 in severity. Furthermore, amivantamab at doses up to 1,750 mg in a Q2W regimen as a monotherapy, and up to 2,100 mg in combination with carboplatin and pemetrexed in lung cancer patients, has been demonstrated to be safe and tolerable, achieving similar exposures as the approved Q2W dose (Nagasaka 2021).

In currently ongoing studies, amivantamab at the recommended dose has been administered to participants with gastric and esophageal cancer, providing preliminary evidence for a manageable safety profile in patients with digestive system malignancies.

2.3. Benefit-Risk Assessment

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

2.3.1. Risks for Study Participation

The safety and tolerability of amivantamab monotherapy has been demonstrated in the Phase 1 Study 61186372EDI1001 in NSCLC patients. Amivantamab was generally well tolerated with a safety profile consistent with on-target anti-EGFR and MET activity, paronychia, rash, dermatitis acneiform, fatigue and stomatitis (anti-EGFR effects), as well as hypoalbuminemia and peripheral edema (anti-MET effects) were observed. However, given that the available clinical data are limited to NSCLC participants, unforeseen safety risks including alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) increased associated with the study treatments are possible considering the synergistic effect in HCC participants. This study protocol includes the following elements to mitigate risks for study participants:

- The SET, in conjunction with the coordinating investigator, will review the safety and conduct of study periodically. (The initial review of safety will occur after the first 6 participants have enrolled and have completed at least 1 complete cycle of amivantamab therapy).
- Eligibility criteria have been established to minimize risk, with regards to known safety profile of amivantamab. Participants will also be monitored closely for safety throughout the study (refer to Safety Assessments), per the scheduled assessments outlined in the SoA (Table 1).
- Dose modification guidance is provided to manage toxicities that occur during the study (refer to Section 6.5 and Section 5.5, including specific guidance for infusion-related reactions [IRRs], rash, interstitial lung disease [ILD], liver test abnormalities, or paronychia).

2.3.2. Benefits for Study Participation

Although many agents targeting EGFR have been approved and are part of standard of care for many tumor types, no anti-EGFR or anti-MET therapy has been approved in HCC. Amivantamab has demonstrated significant activity as monotherapy for the treatment of NSCLC, receiving Breakthrough Therapy Designation by the US FDA and China CDE, based on an objective response rate (ORR) of 41% in participants with EGFR Exon 20ins disease, after prior treatment with platinum-based chemotherapy. Consistent with the unique mechanism of action of amivantamab, activity was observed in participants with diverse EGFR mutations, as well as in participants with amplification of MET and overexpressed EGFR.

It is anticipated that using this targeted therapeutic approach with amivantamab as a single agent in refractory HCC participants may provide benefit to these participants.

2.3.3. Benefit-Risk Assessment for Study Participation

Considering the measures taken to minimize risk to participants of this study (refer to Section 2.3.1), the potential risks of amivantamab are justified by the anticipated benefits that may be afforded to advanced HCC participants with very limited treatment options (refer to Section 2.3.2). More detailed information about the known and expected benefits and risks of amivantamab may be found in the IB and Addenda for amivantamab.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To 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 may 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 • 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	

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

HYPOTHESIS

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

4. STUDY DESIGN

4.1. Overall 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. Refer to Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for details.

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

4.1.1. Screening Period

The Screening Period starts at the time of the signing informed consent form (ICF) and ends 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.

To be eligible for participation, all participants must have been previously diagnosed with histologically or cytologically confirmed unresectable or metastatic HCC. All participants must have progressed on or after the most recent therapy.

During the screening period, participants will be evaluated for study eligibility, as described in the Schedule of Activities (SoA). Informed consent does not expire if the screening related procedures are not performed within the 28-day Screening Period, although evaluations performed outside the screening window will need to be repeated, the exception to this will be fresh biopsy sample as long as there is no systemic treatment between the first and any subsequent re-screening. Pre-

treatment biopsy samples will be collected for all participants. Tumor biopsy acquired at screening is preferred. If not available, the most recent tumor sample is acceptable. Wherever possible, non-target lesions should be biopsied rather than target lesions. Biopsy of a target lesion is allowed for the pre-treatment sample, but baseline disease assessment must occur a minimum of 1 week after the biopsy procedure. Other types of examinations, eg, bone scintigraphy, may also be conducted at Screening, per the Investigator's clinical judgment and local standard of care. Imaging vendor acquisition guidelines regarding imaging techniques should be followed. Brain MRI (or brain CT scan with contrast if MRI is contraindicated) will also be performed at Screening. If imaging data that satisfy the imaging criteria is available as part of the routine care and performed within 28 days of C1D1, even if prior to signing the ICF, then screening imaging does not have to be repeated.

Participants who fail to meet the inclusion and/or meet the exclusion criteria may be rescreened if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Participants who are determined to be eligible for the study due to changes in their condition after initially failing screening must sign a new ICF. The data obtained closest to the first study treatment administration will be used to determine eligibility.

4.1.2. Treatment Period

The Treatment Phase will begin on 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 Schedule of Activities (SoA). The latest measurements taken before administration of the first study treatment will be defined as baseline values. 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 (Section 7.1).

At each study visit during the treatment phase, participants will undergo safety evaluations, including physical examinations and assessment of AEs, vital signs, concomitant medication usage, and clinical laboratory parameters. Participants will also have blood samples drawn for assessment of PK, PD and immunogenicity parameters and for biomarker evaluations at selected visits.

Safety will be assessed as described in Section 8.2. Any new concomitant medications or changes to concomitant medications will be recorded. Adverse event information will be graded using the NCI-CTCAE, Version 5.0.

Throughout the Treatment Period, the investigator will assess participant response to therapy using RECIST v1.1. Efficacy evaluations are described in Section 8.1.

For participants who discontinue treatment prior to disease progression (reasons such as an adverse event), radiological assessments should be performed according to the Schedule of Activities (SoA) until the earlier of disease progression or initiation of new anti-cancer therapy.

4.1.3. Follow-up Period

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.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

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

Clinical pharmacology assessment

Due to lack of PK, PD and immunogenicity (antibodies to amivantamab, also termed ADA) data in HCC patients and in order to better characterize the PK profiles, PK/PD and ADA for this population, serum samples will be collected and analyzed for amivantamab concentrations, and estimation of basic PK parameters from this concentration-time data will be performed and reported. ADA will be evaluated for impact on PK. Pharmacokinetic profiles and parameters will be assessed relative to clinical safety, PD (soluble EGFR and soluble MET), efficacy, as available, as well as to the efficacious concentrations observed in preclinical studies.

Biomarker Collection

Pre-treatment tumor samples will be assessed at central labs for EGFR and MET expression at protein levels; for HGF and selected EGFR ligands expression at mRNA levels. Post-treatment tumor samples, if collected, will also be assessed for these biomarkers to evaluate the changes from baseline that may indicate target modulation, and track response to treatment.

Blood samples will be collected at before and after treatment in the study to evaluate circulating factors relevant to target and disease biology (eg, MET and EGFR ligands, AFP) and their correlation with treatment response.

Additional biomarkers (eg, DNA, RNA, and protein) relevant to target biology or HCC may also be assessed in blood and tissue samples collected during the study to correlate with response, and to better understand the mechanisms of response or resistance to amivantamab treatment.

Tumor tissue and blood sample collection and analysis in China will be performed only after Human Genetic Resources Administration Office (HGRAO) approval is obtained.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

Thorough scientific evaluation of any treatment before marketing authorization is an ethical and regulatory requirement. As the benefits and risks of amivantamab as a monotherapy in this study population are not fully known, this study will evaluate safety and clinical activity. Participants will be closely monitored throughout the study, as discussed throughout this protocol, for both safety and clinical benefit. The SET will review evolving safety data from this study, as well as efficacy data as appropriate. Based on the observed activity of amivantamab in NSCLC participants, preclinical data of amivantamab in the HCC PDX model, there is adequate justification to initiate this study.

As with all clinical studies, there are risks associated with venipuncture and multiple blood sample collection. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the pharmacology of the study treatment. This minimizes the number of venipunctures and the total volume of blood collected from each participant during the study. The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the Chinese Red Cross blood donation and American Red Cross (Chinese Red Cross Society; American Red Cross).

4.3. Justification for Dose

Amivantamab will be dosed at the approved dose (for treatment of NSCLC with EGFR Exon 20ins) of 1,050 mg for participants with a baseline body weight (BW) <80 kg and 1,400 mg for participants with a baseline BW ≥80 kg. This dose was based on the totality of exposure, safety, and efficacy data from the ongoing Phase 1 Study 61186372EDI1001 (EDI1001 study).

Amivantamab for intravenous administration was generally well tolerated at doses up to 1,750 mg, with no DLT reported during the initial dose escalation and no maximum tolerated dose identified in NSCLC participants. The recommended dose achieved a complete soluble target saturation throughout dosing for EGFR and MET in the NSCLC participants.

Amivantamab is administered by IV infusion in 28-day cycles, once weekly in Cycle 1 (with a split dose on Days 1 and 2), and then every 2 weeks in subsequent cycles. Over a thousand patients with NSCLC, characterized by diverse EGFR and MET alterations, have received amivantamab at the recommended dose either as monotherapy or in combination. Amivantamab was generally

well tolerated with a safety profile consistent with on-target anti-EGFR and MET activity: paronychia, rash, dermatitis acneiform, fatigue and stomatitis (anti-EGFR effects), as well as hypoalbuminemia and peripheral edema (anti-MET effects) and IRR were observed. Furthermore, amivantamab at doses up to 1,750 mg in a Q2W regimen as a monotherapy, and up to 2,100 mg in combination with carboplatin and pemetrexed in lung cancer patients, has been demonstrated to be safe and tolerable, achieving similar exposures as the approved Q2W dose (Nagasaka 2021). In addition to NSCLC, amivantamab at the recommended dose has been administered to participants with gastric and esophageal cancer, providing preliminary evidence for a manageable safety profile in patients with gastrointestinal malignancies.

For HCC population, at least comparable antitumor potency in vivo between NSCLC and HCC animal models was observed. For above reasons, it is considered appropriate to administer the RP2D of amivantamab for HCC indication.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement (approximately 12 months after the last participant is enrolled).

For participants who complete treatment and who are eligible for continued access program (post study access or other open-label extension study under a different/separate protocol), the end of study is defined as the end of treatment visit.

Participant Study Completion Definition

A participant will be considered to have completed the study if he or she has died before the end of the study or has not been lost to follow-up or withdrawn consent by the end of the study.

When a participant withdraws consent for follow-up before completing the study, the reason for withdrawal is to be documented in the case report form (CRF) and in the source document. Every effort should be made to clarify to participants the importance of post-treatment follow-up, and that withdrawal of consent to further treatment can still allow for participation in follow-up period of study.

5. STUDY POPULATION

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

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor

representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

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

5.1. Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristic

2. Participant must agree to provide protocol defined clinically feasible tissue samples Refer to Section 8.6 for details.

3. Participant must have histologically or cytologically confirmed diagnosis of HCC (fibrolamellar and mixed hepatocellular / cholangiocarcinoma subtypes are not eligible) based on pathology report, who have BCLC Stage C disease or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach.

4. Criterion modified per Amendment 2.

   4.1. Participants should have progressed on standard of care (SoC) therapy with immunotherapy (eg, PD-1/L1-containing therapy) and a multi-targeted kinase inhibitor (MKI). Participation is allowed after progression with just one of these therapies, if the participant is intolerant of, or declining treatment with, the other SoC therapy (PD-1/L1-containing therapy or MKI).

   a. Prior adjuvant or neoadjuvant therapy will be considered as 1 prior line of systemic therapy for the purpose of meeting the eligibility criteria if participant experienced progression within 24 weeks of such therapy.

   b. The intolerance or declining of further therapy should be documented in medical record, and discussed with the sponsor medical team.

   Note: A line of therapy is defined as a treatment regimen with subsequent disease progression

5. Child-Pugh A classification for liver function assessed within 7 days of first dose of study drug. Refer to Appendix 13 for details of Child-Pugh A classification.

6. Participant must have measurable disease according to RECIST Version 1.1. Selected target lesions must meet 1 of 2 criteria: 1) not previously treated with local therapy or 2) within the field of prior local therapy but with documented subsequent progression as per RECIST v1.1. If only 1 measurable lesion exists and was used for screening biopsy, baseline tumor assessment scans must be performed ≥ 7 days after the biopsy.

7. Participant must have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 within 7 days of first dose of study treatment.

8. Criterion modified per Amendment 2.

   8.1. Participants are eligible to enroll if they have non-viral-HCC or if they have HBV-, or HCV-HCC, defined as follows:

   a. Chronic HBV infection as evidenced by detectable HBV surface antigen or HBV DNA. Participants with chronic HBV infection must be on antiviral therapy [per local standard of care, eg, entecavir (ETV) or tenofovir disoproxil fumarate (TDF)] for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study, and HBV viral load must be less than 2000 IU/mL prior to the first dose of study treatment. Those participants who are anti-HBc (+), and negative for HBsAg, and negative for anti-HBs, and have an HBV viral load under 20 IU/mL do not require HBV anti-viral prophylaxis but need close monitoring.

   b. Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody.

9. Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion, platelet transfusion, growth factors or albumin infusion within 14 days prior to the date of the laboratory test.

   a. Adequate hematologic function:

      - Hemoglobin ≥9 g/dL
      - Absolute neutrophil count ≥1.5× 10^3/μL, without use of granulocyte colony stimulating factor (G-CSF) within 10 days prior to the date of the test
      - Platelets ≥75 × 10^3/μL
      - For participants not receiving therapeutic anticoagulation: international normalized ratio (INR) or activated partial thromboplastin time (aPTT) ≤2 × ULN (upper limits of normal)

b. Adequate hepatic function with serum albumin ≥3.1 g/dL, serum bilirubin ≤2.5 × ULN, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN

c. Have an estimated glomerular filtration rate (eGFR), based on the Modified Diet in Renal Disease (MDRD) 4-variable formula (see Appendix 12), of >50 mL/min

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

a. No detectable viral load (ie, <50 copies/mL) at screening

b. CD4+ count >300 cells/mm^3 at screening

c. No acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of screening

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

Note: HAART that could interfere with study treatment is excluded (consult the sponsor for a review of medications prior to enrollment).

Prior Malignancies

11. May have a prior or concurrent second malignancy (other than the disease under study) which natural history or treatment is unlikely to interfere with any study endpoints of safety or the efficacy of the study treatment(s) (see Appendix 9 on Allowed Recent Second or Prior Malignancies for details).

Sex and Contraceptive/Barrier Requirements

12. Criterion modified per Amendment 2.

12.1. A female participant of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) pregnancy test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.

13. Criterion modified per Amendment 2.

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

a. Not of childbearing potential or

b. Of childbearing potential and practicing at least 1 highly effective method of contraception (details in Appendix 5: Contraceptive and Barrier Guidance) contraception throughout the study and through 6 months after the last dose of study treatment.

Note: If a female participant becomes of childbearing potential after start of the study the female participant must comply with point (b.).

14. A female participant must not be pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 months after the last dose of study treatment.

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

16. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 6 months after receiving the last dose of study treatment.

    If the male participant's partner is a female of childbearing potential, the male participant must use condoms with spermicide and the female partner of the male participant must also be practicing a highly effective method of contraception (see Appendix 5: Contraceptive and Barrier Guidance). A male participant who is vasectomized must still use a condom (with or without spermicide), but the partner is not required to use contraception. His female partner, if of childbearing potential, must also be practicing a highly effective method of contraception.

    If the male participant is vasectomized, he still must wear a condom, but his female partner is not required to use contraception.

17. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 6 months after receiving the last dose of study treatment. Male participants should consider preservation of sperm prior to study treatment as anti-cancer treatments may impair fertility.

18. Participant must agree not to plan to father a child while enrolled in this study or within 6 months after the last dose of study treatment.

Informed Consent

19. Participant must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

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

5.2. Exclusion Criteria

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

Medical Conditions

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

    a. Uncontrolled diabetes

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

    c. Active bleeding diathesis

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

    e. Impaired oxygenation requiring continuous oxygen supplementation.

2. Participants with any of the below due to the underlying HCC

    a. Prior liver transplant

    b. History of hepatic encephalopathy

    c. Portal vein invasion at the main portal branch (Vp4), inferior vena cava, or cardiac involvement of HCC based on imaging.

    d. Any current moderate or severe ascites as measured by physical examination that requires active paracentesis for control.

3. Criterion modified per Amendment 2.

    3.1. Participants have symptomatic brain metastases (exception: the participant with definitively, locally-treated metastases that are clinically stable, and asymptomatic for at least 2 weeks and who are off or receiving low dose corticosteroid treatment [≤10 mg prednisone or equivalent] for at least 2 weeks prior to the first dose of study treatment). If brain metastases are diagnosed on Screening imaging, the participant may be rescreened for eligibility after definitive treatment.

4. History or known presence of leptomeningeal disease.

5. Criterion modified per Amendment 2.

5.1. Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 3 months prior to the first dose of study treatment.

6. Participant has a history of (non-infectious) ILD/pneumonitis/pulmonary fibrosis, or has current ILD/pneumonitis/pulmonary fibrosis, or where suspected ILD/pneumonitis/pulmonary fibrosis cannot be ruled out by imaging at screening.

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

   a. Diagnosis of deep vein thrombosis or pulmonary embolism within 4 weeks prior to the first dose of study treatment or any of the following within 6 months prior to the first dose of study treatment: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated clots, are not exclusionary.
   b. Prolonged corrected QT interval using Fridericia's formula (QTcF) >480 msec or clinically significant cardiac arrhythmia or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate). Note: Participants with cardiac pacemakers who are clinically stable are eligible.
   c. Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg, or Congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III/IV or Hospitalization for CHF (any NYHA class) within 6 months of study enrollment.
   d. Pericarditis/clinically significant pericardial effusion.
   e. Myocarditis.

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

Prior/Concomitant Therapy

9. Participant had prior approved therapy which may include MKI and/or PD-1/L1-containing therapy within 2 weeks or 4 half-lives whichever is longer. For agents with long half-lives, the maximum required time since last dose is 28 days. Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less, (except for alopecia or Grade ≤2 hypothyroidism stable on hormone replacement).

10. Participant had surgery, radiotherapy, and/or locoregional therapy within 4 weeks before the first administration of study treatment. Minor surgery (eg, simple excision, tooth extraction) have occurred within 7 days before C1D1.

11. Participant has received prior EGFR or MET-directed therapies.

12. Participants has received a live or live attenuated vaccine within 3 months before study enrollment. Note: the seasonal influenza vaccine and non-live vaccines against coronavirus disease 2019 (COVID-19) are not exclusionary.

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

    a. An invasive operative procedure (except the treatment for the ascites should be discussed with sponsor's medical monitor) with entry into a body cavity, within 4 weeks or without complete recovery before C1D1. If needed, abdominal biopsy for baseline tumor tissue sample may be done less than 4 weeks prior to C1D1, as long as the participant has adequately recovered from the procedure prior to the first dose of study treatment in the clinical judgement of the investigator.

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

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

Diagnostic Assessments

14. Active co-infection with

    a. Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA. (Participants with a history of HCV infection but who are negative for HCV RNA by polymerase chain reaction [PCR] will be considered non-infected with HCV.)

    b. Hepatitis D infection as evidenced by hepatitis D virus (HDV) antibody in participants with hepatitis B.

Other Exclusions

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

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

3. Agree to use sun protective measures (such as a hat, sunglasses, and protective clothing), limit prolonged exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) from baseline until at least 2 months after the last dose of study treatment. Avoid unnecessary exposure to sunlight. Use broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥30.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

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

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

5.5. Criteria for Temporarily Delaying Administration of Study Treatment

In instances where temporarily study treatment delay is indicated, study treatment with amivantamab may be delayed until recovery of toxicity to a level allowing continuation of therapy. A participant for whom study treatment was delayed should be assessed at least weekly to ensure adequate supportive care is being administered and to assess for improvement of toxicity. For majority of clinically significant toxicities dose delay and dose modifications should occur as per the guidelines described below (Section 6.5). If dose delay is continued for more than 28 days, consult with the medical monitor before restarting study treatment.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

Study treatment administration must be captured in the source documents and the CRF.

Amivantamab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Description of Study treatment

Amivantamab is supplied for this study in a glass vial containing 350 mg/vial with concentration of 50 mg/mL in a 7 mL vial. The IV infusion will be prepared at the site in 250 mL of diluent (Refer to Investigational Product Preparation Instructions [IPPI]).

Dosage Level(s)	Based on the participant's body weight at screening: 1,050 mg (if body weight is <80 kg) or 1,400 mg (if body weight is ≥80 kg)
Dosing Instructions	Amivantamab will be administered intravenously in 28-day cycles as follows: • Cycle 1: Once weekly (with the first dose split over Day 1 [350 mg] and Day 2 [700 mg if body weight is <80 kg or 1,050 mg if body weight is ≥80 kg]) • Cycles 2+: Day 1 and 15 of each cycle
IP Packaging and Labeling	Study treatment will be provided in 7 mL glass vials, with 350 mg/vial

Amivantamab will be administered intravenously using the escalating infusion rate regimen as specified in the IPPI. The product must be infused via a peripheral vein for all Cycle 1 doses; infusion via central line is allowed for subsequent dosing starting with the C2D1 dose.

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

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

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

Dose and administration schedule may be adjusted based on SET recommendations during the study.

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

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study treatment must be stored at controlled temperatures according to the requirements on the label and protected from light prior to use.

Refer to the pharmacy manual/study site investigational product and procedures manual (SIPPM) for additional guidance on study treatment preparation, handling, and storage.

Accountability

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

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Study Treatment Allocation

Procedures for Randomization

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

Blinding

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

6.4. Study Treatment Compliance

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

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

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

6.5. Dose Modification

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

6.5.1. Dose Delay Guidance

In instances where treatment delay is indicated, treatments may be delayed until recovery of toxicity to a level allowing continuation of therapy. A participant for whom treatment was delayed should be assessed at least weekly to ensure adequate supportive care is being administered and to assess for improvement of toxicity.

Participants must meet retreatment criteria for amivantamab (as per Section 6.5.2) in accordance with protocol, prior to redosing with the respective agents.

- Amivantamab: If there is a delay due to toxicity resulting in 2 consecutive missed doses of amivantamab, then participants will discontinue amivantamab infusion unless there is a clear clinical benefit after approval by the sponsor.

6.5.2. Amivantamab Dose Modification

The following guidance should be followed for dose delay and modification of amivantamab based on the toxicity grade of adverse events other than IRRs (Section 6.5.3), rash (Section 6.5.4), pruritus (Section 6.5.5), paronychia (Section 6.5.6), oral mucositis (Section 6.5.7), liver chemistry abnormalities (Section 6.5.8), and pulmonary toxicity (Section 6.5.9). When possible, the Medical Monitor should be notified prior to dose modifications.

Table 4: Guidance for Amivantamab Dose Delay and Modification for Toxicities (Other Than Rash, Infusion-Related Reaction, Liver Toxicity, or Pulmonary Toxicity)

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

a. Per National Cancer Institute - CTCAE version 5.0.
b. For all toxicities, consider supportive care according to protocol or local standards (if no protocol guidance provided), as appropriate.
c. Resolution defined as: Grade ≤1 non-hematologic toxicity or back to baseline.
d. If interruption occurs for more than 1 cycle, contact the Medical Monitor to discuss retreatment.

In case a dose reduction is necessary, the study treatment will be administered as follows: Guidance for stepwise dose modification of amivantamab is outlined below in Table 5.

Table 5: Dose Reduction for Amivantamab

Dosage Level	Amivantamab	
	Participant <80 kg	Participant ≥80 kg
1 (initial dosage)	1,050 mg Q2W	1,400 mg Q2W
2	700 mg Q2W	1,050 mg Q2W
3	350 mg Q2W	700 mg Q2W
4	Withhold	Withhold
Q2W=every 2 weeks (eg, Day 1 and Day 15 of each 28-day cycle).		

Dose re-escalation of amivantamab to planned dose may be considered if the toxicity led to the dose reduction of amivantamab resolves to baseline or below/to Grade 1 after consultation with the Sponsor.

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

6.5.3. IRRs

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

During the amivantamab infusions, participants should be clinically monitored at regular intervals (including an assessment prior to the start of infusion) as specified in the Schedule of Activities (SoA) (Table 1). The monitoring should include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation measurements. Particularly with the initial dose (C1D1 and C1D2), participants should be educated on 1) the likelihood of experiencing an IRR with the initial dose, 2) the symptoms to anticipate (which include chills, dyspnea, chest discomfort, fever, flushing, among others), 3) that they should alert nursing staff if they experience these symptoms, and 4) that the experience of an IRR will not preclude further therapy with amivantamab. Participants must be monitored closely for early signs and symptoms indicative of an acute IRR. Even with mild symptoms, the study treatment infusion should be interrupted immediately, as described in the tables below, to prevent more serious grade IRRs from occurring. Trained clinical personnel should be prepared to intervene in the event of IRRs. Resources necessary for resuscitation (ie, agents such as epinephrine, aerosolized bronchodilator, IV antihistamines, IV corticosteroids; medical equipment such as oxygen, airway management equipment including suction, and a defibrillator) must be readily available.

Prevention of IRRs

Required prophylaxis for IRRs is described in Section 6.8.1.

Treatment of IRRs

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

Table 6: Management of Infusion-related Reactions

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

eCRF=electronic case report form; IRR=infusion-related reaction; IV=intravenous.
*Per National Cancer Institute - CTCAE Version 5.0

6.5.4. Rash-related Adverse Events

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

Prophylaxis Recommendations

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

- Avoid exposure to sunlight.
- Wear protective clothing (including hat, sunglasses, etc).
- Use broad-spectrum sunscreen with an SPF of ≥30 and reapply as necessary. Ultraviolet A light can penetrate glass; therefore, sunscreen should also be worn indoors and in vehicles if exposed to direct sunlight. Recommended active sunscreen ingredients are zinc oxide and/or titanium dioxide.
- Apply alcohol-free emollient cream or ointments (eg, glycerin, cetomacrogol, or ceramide-based cream) or skin moisturizer on dry areas of the body. These topical agents can be applied on a daily basis starting on Day 1 and more often as needed. Ideal time for application is after bathing. Creams and ointments are preferred over gels, lotions and oils.
- Alcohol-based (eg, gel formulations) topical agents such as steroids, antibiotics, or hand sanitizers can dry the skin and should be avoided.

Reactive Management Recommendations

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

- Consider consultation with a dermatologist, especially if the rash is Grade 3, atypical in appearance or distribution, or does not improve within 2 weeks (for Grade 2 rash).
- Consultation with a dermatologist is required if the rash is Grade 4.
- Initiate a topical corticosteroid (cream or ointment) twice daily
  - Examples to use for face: betamethasone valerate 0.05%, hydrocortisone valerate 0.2%, or desonide 0.05%
  - Examples to use for body: betamethasone valerate 0.1%, triamcinolone acetonide 0.1%
- If not already initiated for prophylaxis, initiate systemic antibiotic (such as doxycycline 100 mg twice daily, minocycline 100 mg twice daily, or cephalexin 500 mg twice daily), or increase the dosing if already administered.
- If an associated skin infection is suspected, obtain bacterial and fungal cultures followed by adjustment of antibiotic or antifungal therapy, based upon culture and susceptibility determination.
- For skin fissures, use of Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream is recommended.

- For xerosis, fragrance-free moisturizing creams or sprays are recommended.
- For desquamation, emollients and mild soap are recommended.
- After the rash is controlled, consider gradually tapering the antibiotic.

A suggested algorithm for stepwise management of rash is provided in Table 7.

Table 7: Suggested Algorithm for Management of Rash

Grade[a]	Management	Dose Adjustment[b,c]
1	• Initiate reactive management as above • Reassess after 2 weeks	• Continue current dose of study treatment
2	• Initiate reactive management as above • Reassess after 2 weeks	• Continue current dose of study treatment
3	• Initiate reactive management as above • Start moderate strength topical corticosteroids[d] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess after 2 weeks • Consider dermatology consultation and manage rash per recommendation	• Temporarily dose delay of study treatment until rash improves to ≤Grade 2 • For guidance on dose delay of study treatment and dose modification, refer to Table 4
4	• Initiate reactive management as above • Start moderate strength topical corticosteroids[d] and systemic antibiotics as above, plus systemic prednisone (0.5 mg/kg) for 7 days • Consider low doses of acitretin or isotretinoin (20-30 mg/day) • Reassess after 2 weeks • Consider dermatology consultation and manage rash per recommendation	• Permanently discontinue JNJ-61186372
Severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN)	• Consult dermatologist and manage rash per recommendation.	• Permanently discontinue JNJ-61186372

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

Scalp Rash

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

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

- Application of a steroid lotion may also be effective (eg, betamethasone valerate 0.1% lotion, mometasone furoate 0.1% lotion, or betamethasone dipropionate 0.05% lotion).
- Initiation of a systemic antibiotic (eg, doxycycline 100 mg twice daily, minocycline 100 mg twice daily) may also be used to treat acute scalp infection.

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

6.5.5. Pruritus

Reactive Management Recommendations

Grade 1 pruritus:

- Apply topical low to moderate strength steroid cream (eg, hydrocortisone 2.5%, desonide 0.05%, or betamethasone valerate 0.05%), topical calcineurin inhibitor (eg, tacrolimus or pimecrolimus), or topical antipruritic containing numbing agent (eg, pramoxine) and menthol.

Grade 2 pruritus:

- Apply topical moderate to high strength steroid cream (eg, betamethasone valerate 0.1%, triamcinolone acetate 0.1%) or topical antipruritic containing numbing agent (eg, pramoxine) and menthol.
- Initiate an oral antipruritic (eg, cetirizine, fexofenadine, rupatadine, bilastine) one dose twice daily. If still pruritic after 2-5 days, may increase to double dose twice daily.

Grade 3 pruritus:

- Initiate an oral antipruritic (as above for Grade 2 pruritus).
- Initiate oral pregabalin or gabapentin.
- Initiate an oral corticosteroid (eg, prednisone 0.5-1.0 mg/kg/day or equivalent for 5 days).

6.5.6. Paronychia

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

Prophylaxis Recommendations

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

Reactive Management Recommendations

Grade 1 paronychia:

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

Grade 2 or 3 paronychia:

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

6.5.7. Oral Mucositis

Mucositis is a well-recognized toxicity associated with anti-EGFR therapeutics, and may be mild/moderate and localized (Grades 1-2) or severe and widespread (≥Grade 3). As a result, there are recommendations that should be followed to prevent or minimize patient discomfort associated with this toxicity. Prophylaxis should occur according to local institutional practice and guidelines, and should include the following:

Prophylaxis Recommendations

- Use good oral hygiene, dentition review and referral to an oral hygienist if necessary.
- Use a soft toothbrush.
- Use mild-flavored toothpastes.
- Use saline-peroxide or salt and soda mouthwashes 3 or 4 times per day.
- Use water soluble lubrication agents like artificial saliva (for xerostomia or dry mouth).
- Avoid spicy, acidic, hard, and hot food and beverages.

Reactive Management Guidelines

- Asymptomatic or mild symptoms: topical steroid (dexamethasone 0.5/mL elixir) and lidocaine 2-5% jelly or solution (swish and spit) 4 times per day.
- Co-trimoxazole lozenges can be used to prevent secondary candida infection.
- In cases of moderate to severe pain:
  - Compounded mouthwash (eg, “magic mouthwash”) including an antifungal, steroid, antihistamine, anesthetic, and/or antacid/mucosal coating agent as per local practice and guidelines.

- Dexamethasone solution 3.3 mg/5 mL swish and spit 4 times per day, and lidocaine jelly 2-5% or solution 4 times per day.

6.5.8. Liver Chemistry Abnormalities

Liver chemistry should be monitored according to the Schedule of Activities (SoA). In addition, if the following modified Hy's Law criteria are observed, study treatment should be held, and the event should be reported as a serious adverse event to the Sponsor within 24 hours:

a) Treatment-emergent ALT or AST >3 x baseline value in combination with total bilirubin >2 x ULN (of which >35% is direct bilirubin)

b) Treatment-emergent ALT or AST >3 x baseline value in combination with clinical jaundice

Treatment with amivantamab should be permanently discontinued and the event should be reported as a serious adverse event to the Sponsor within 24 hrs when

- AST or ALT >10 x ULN for >2 weeks,
- AST or ALT >15 x ULN irrespective of duration,
- Total bilirubin >5 x ULN for those with normal total bilirubin at entry or >8 x ULN for participants with elevated bilirubin at study entry, irrespective of duration.
- ALT/ AST elevated ≥3 x baseline value and total bilirubin elevated ≥2 x ULN or with clinical jaundice, if no other alternative explanation is identified after completing work-up
- Regardless of laboratory values, symptom of hepatic decompensation including
  - Encephalopathy
  - Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)
  - New onset of clinical detectable ascites*

Note: *Regarding discontinuation due to ascites, investigators should discuss with sponsor medical monitor.

If isolated ALT or AST increase was observed, liver chemistry should be closely monitored (within 1-3 days and until abnormal values resolve/return to baseline) when

- ALT/AST ≥10 × ULN (The event should be reported as a serious adverse event to the Sponsor within 24 hrs. Initiate workup for competing etiologies)
- ALT/AST ≥5 × ULN (if normal at baseline) or ALT/AST ≥3 × baseline (if abnormal at baseline)

In the event abnormalities of liver function tests require withholding study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. Etiology of the liver chemistry abnormality should be investigated, as described below.

Liver Event Follow-up Requirements

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

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

6.5.9. Suspected Pulmonary Toxicity

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

The following evaluations are recommended in order to exclude alternative etiologies such as lymphangitic carcinomatosis, pulmonary embolism, infection, allergy, and cardiogenic edema:

- Detailed focused history reviewing respiratory status and exercise tolerance.
- Focused physical exam including full assessment of vital signs (with pulse oximetry).

- Unscheduled radiological assessment, including chest X-ray or CT scan (high-resolution CT is preferred).
- Infectious evaluation, including blood and sputum cultures, atypical pneumonia panels, and SARS-CoV-2 testing, if indicated
- Hematology and other laboratory tests, including serum albumin levels
- Referral to pulmonologist for evaluation, including bronchoscopy with biopsy, cell counts, and cultures as feasible
- Evaluation of cardiac function, if indicated

Where other causes of respiratory symptoms have been excluded, a diagnosis of ILD/pneumonitis should be considered, and study treatment permanently discontinued. For participants with symptomatic pneumonitis (Grade 2 or above), treatment with steroids should be initiated per local guidelines, in addition to withholding of study treatment.

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

6.6. Continued Access to Study Treatment After the End of the Study

Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status as noted in the ICF (refer to Informed Consent in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations).

Participants will be instructed that study treatment will not be made available to them after they have completed/discontinued study treatment and that they should return to their primary physician to determine standard of care.

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of amivantamab becomes available during the study or program.

No continued access will be proposed for this study. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine standard of care, if applicable.

6.7. Treatment of Overdose

There are no data on overdose from studies of amivantamab.

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

- Contact the Medical Monitor immediately.

- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study treatment must be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.8. Concomitant Therapy

Prestudy therapies administered up to 28 days before first dose of study treatment must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study treatment to 30 days after the last dose of study treatment. Concomitant therapies should also be recorded beyond 30 days only in conjunction with Grade 3 or Grade 4 AEs considered related to study treatment, until resolution of event or start of subsequent therapy.

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

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

6.8.1. Amivantamab Pre-infusion and Post-infusion Medications

6.8.1.1. Amivantamab Pre-infusion Medications

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

Table 8: Amivantamab Pre-infusion Medications

Medication	Dose	Route of Administration	Recommended Dosing Window Before Infusion	Cycle/Day
Required Pre-infusion Medications[a,b]				
Glucocorticoid	Dexamethasone (10 mg) or Methylprednisolone (40 mg)	IV	45 to 60 minutes	C1D1 C1D2
Antihistamine[d]	Diphenhydramine (25 to 50 mg) or equivalent	IV	15 to 30 minutes	All
		Oral	30 to 60 minutes	
Antipyretic[d]	Paracetamol (acetaminophen 650 to 1,000 mg) or equivalent	IV	15 to 30 minutes	All
		Oral	30 to 60 minutes	

Table 8: Amivantamab Pre-infusion Medications

Medication	Dose	Route of Administration	Recommended Dosing Window Before Infusion	Cycle/Day
Optional Pre-infusion Medications[a]				
Glucocorticoid[c,d]	Dexamethasone (10 mg)	IV	45 to 60 minutes	C1D8 and beyond
	Methylprednisolone (40 mg)	Oral	60 to 90 minutes	
H_2 antagonist	Ranitidine (50 mg) or equivalent	IV	15 to 30 minutes	Any
Antiemetic[d]	Ondansetron (16 mg) or equivalent	IV	15 to 30 minutes	Any
	Ondansetron (8 mg) or equivalent	Oral	15 to 30 minutes	

C=Cycle; D=Day X; IV=intravenous.
a. If a medication noted in this table is not locally available, a similar medication and dose may be substituted and administered per local guidelines.
b. Participants for whom required medications are contraindicated should explore alternative medications with their study physician. If alternative medications are not suitable for the intent above, participants are not required to take the corresponding medication.
c. Beginning with C1D8, optional predose steroids may be administered if clinically indicated for participants who experienced an infusion-related reaction on C1D1 or C1D2.
d. Either IV or oral route is selected for antihistamine, antipyretic, glucocorticoid and antiemetic medications.

6.8.1.2. Amivantamab Post-infusion Medications

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

Table 9: Amivantamab Post-infusion Medications

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

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

6.8.2. Prohibited or Restricted Medications and Therapies

Prohibited Medications and Therapies

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

- Any non-study systemic anticancer therapy approved or experimental therapy (other than study treatments) for the treatment of HCC is prohibited.
- Surgery, radiotherapy, and/or locoregional therapy (eg: radiofrequency ablation [RFA], percutaneous ethanol [PEI] or acetic acid injection [PAI], cryoablation, high-intensity focused ultrasound [HIFU], transarterial chemoembolization [TACE], transarterial embolization [TAI], etc.) to target lesions prior to disease progression.
- Use of live or live attenuated vaccines is prohibited until at least 90 days after the last dose of study treatment. For additional guidance, refer to Guidance on Study Conduct During COVID-19.

Restricted Medications and Therapies

The following concomitant medications and therapies are restricted until the End of Treatment visit and should be avoided, when possible, or used with caution.

- Due to the potential for hypomagnesemia associated with EGFR inhibitors, concomitant medications that may decrease serum magnesium should be avoided if possible.

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

6.8.3. Permitted Medications and Therapies

- Supportive care (eg, antibiotics, analgesics, transfusions, diet, osteoclast inhibitors) and concomitant medications may be administered according to the standard of care at the site, and at the treating physician's discretion, as clinically indicated.
- Localized therapy of short duration for palliative purposes may be permitted, but only after consultation with the Medical Monitor. Study treatment interruption is not required but is allowed as per investigator discretion.
- Women using hormonal contraceptives as a means of birth control must continue to use the same hormonal contraceptives throughout the study and through 6 months after the last dose of study treatment.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

A participant's study treatment must be discontinued if:

- The participant withdraws consent to receive study treatment

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study treatment
- The participant becomes pregnant (refer to Section 10.5, Appendix 5: Contraceptive and Barrier Guidance).
- Noncompliance with study drug administration or procedure requirements.
- Documented radiographic (RECIST, Version 1.1) disease progression, unless treatment beyond disease progression has been approved by the Medical Monitor.

  Exception: Continuation of study treatment after disease progression may be allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believes the participant is deriving clinical benefit. If the participant is treated beyond documented disease progression, disease assessments will continue according to the Section 1.3 Schedule of Activities (SoA), and the investigator and sponsor medical monitor must review clinical benefit after each disease assessment.
- General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the judgment of the investigator.

If a participant discontinues study treatment for any reason before the end of the treatment period, then the end of treatment assessments must be obtained and scheduled assessments off study treatment should be continued. Study treatment assigned to the participant who discontinued study treatment may not be assigned to another participant. Additional participants will not be entered.

7.1.1. Liver Chemistry Stopping Criteria

Stopping of study treatment for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments and Study treatment Rechallenge Guidelines or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

Study treatment should be withheld for any liver chemistry abnormality of ≥Grade 3 severity based on CTCAE 5.0 (refer to Table 4). In addition, if the following modified Hy's Law criteria are observed, study treatment should be held, and the event should be reported as a serious adverse event to the Sponsor within 24 hours:

a) Treatment-emergent ALT or AST >3 x baseline value in combination with total bilirubin >2 x ULN (of which >35% is direct bilirubin)

b) Treatment-emergent ALT or AST >3 x baseline value in combination with clinical jaundice

Treatment with amivantamab should be permanently discontinued when:

- AST or ALT >10 x ULN for >2 weeks.
- AST or ALT >15 x ULN irrespective of duration.

- Total bilirubin >5 x ULN for those with normal total bilirubin at entry or >8 x ULN for participants with elevated bilirubin at study entry, irrespective of duration.

- ALT/ AST elevated ≥3 x baseline value and total bilirubin elevated ≥2 x ULN or with clinical jaundice, if no other alternative explanation is identified after completing work-up.

- Regardless of laboratory values, symptom of hepatic decompensation including:

    - Encephalopathy

    - Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

    - New onset of clinical detectable ascites*

Note: *Regarding discontinuation due to ascites, investigators should discuss with sponsor medical monitor.

In the event abnormalities of liver function tests require withholding study treatment, liver chemistry should be repeated within 1-3 days and until abnormal values resolve/return to baseline. Etiology of the liver chemistry abnormality should be investigated.

7.1.2. Rechallenge Criteria

Resumption of study drug administration may be considered if the following criteria are met unless the criteria for permanent discontinuation are reached.

- A reversible underlying cause not associated with study treatments (eg, alcohol or concomitant medication) is clearly identified and agreed upon in consultation with sponsor's medical monitor.
- Liver chemistry abnormalities have resolved, or values have returned to baseline.

Note: Any rechallenge case, a discussion should occur with the Sponsor before restarting amivantamab.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent

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

Withdrawal of Consent

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

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of screening, efficacy, PK, immunogenicity, PD, biomarker, benefit-risk, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG, vital signs, blood draw. Urine and blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and/or the CRF.

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

The total blood volume to be collected from each participant depends upon the duration of participation and the required blood volume for local laboratory assessments. The total blood volume collected for each participant at screening, end of treatment and follow-up period will be approximately 43.5 mL, 36 mL, and 8.5 mL, respectively.

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

Sample Collection and Handling

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

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

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Sample collection and testing will comply with local regulations.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for amivantamab
- Clinical Protocol
- IPPI and SIPPM
- Laboratory manual and kits
- eCRF completion guidelines
- NCI-CTCAE Version 5.0
- RECIST guidelines Version 1.1 & Modified RECIST
- eDC Manual
- Sample ICF

- Wallet cards
- Study treatment (amivantamab will be supplied centrally)
- Ancillary supplies (as needed)

8.1. Efficacy Assessments

Disease assessments will be performed as described in the SoA regardless of any dose modifications. More frequent radiologic assessments are allowed if clinically indicated.

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

The baseline disease assessments should be performed as close as possible to the start of treatment, but no more than 28 days prior to the first dose. Subsequent assessments should be performed at 6 weeks (+1 week) after initiation of study treatment administration, then every 6 weeks (±1 week) for the first 12 months and then every 12 weeks (±1 week) until objective radiographic disease progression. If a participant achieves partial response (PR) or complete response (CR), confirmation of response may occur at 4 weeks from the initial response, per RECIST v.1.1. Timing for each disease assessment is relative to the first dose of study treatment administration, regardless of dose modifications, and will continue until disease progression. If an assessment is performed outside of the scheduled visit and the participant has not progressed, every attempt should be made to perform the subsequent assessment at their scheduled visit timepoint. Any other site at which new disease is suspected should also be imaged.

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

documented in the source documents. Every effort should be made to document radiographic progression even after discontinuation of treatment for symptomatic deterioration, but prior to subsequent therapy, if possible. For participants who discontinue study treatment due to toxicity or a reason other than objective progressive disease, tumor assessments should be continued per schedule until radiographic progressive disease is documented.

Brain MRI scan of participants (CT scan with contrast may also be used to determine the presence of brain lesions if MRI is contraindicated) will also be performed at screening if the participant has a history of brain metastasis or suspected brain metastasis at screening. Brain scan is not required with every subsequent disease assessment, unless clinically indicated, according to local guidelines and practices. Participants with a history of brain metastasis at Screening will be monitored every 12 weeks (±1 week).

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

A lesion that will be biopsied during Screening should only be assessed as a target lesion if a post-biopsy imaging is performed ≥7 days and confirms that it still meets target lesion criteria per RECIST v1.1.

8.2. Safety Assessments

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

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

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

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

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

8.2.1. Physical Examinations

Screening physical examination will include, at a minimum, height, weight, general appearance, and an examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. On Day 1 of each cycle, directed

physical examination of involved organs and other body systems will be performed as indicated, with clinically significant abnormalities reported as adverse events.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure and O_2 saturation will be assessed.

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

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

8.2.3. Electrocardiograms

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

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

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.2 Appendix 2: Clinical Laboratory Tests. In the event of additional safety monitoring, unscheduled laboratory assessments may be performed as required and may be done locally when an immediate clinical decision needs to be made. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. At the start of each new cycle, the investigator must confirm that participants meet treatment criteria.

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

8.2.5. Pregnancy Testing

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

8.2.6. ECOG Performance Status

ECOG performance status score will be evaluated during the screening phase to determine the eligibility. Decline in ECOG PS score (refer to Appendix 11: Eastern Cooperative Oncology Group [ECOG] Performance Status) should be reported as an AE.

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

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

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

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

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

All Adverse Events

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

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

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

Unsolicited Adverse Events

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

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

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

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

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

8.3.5. Pregnancy

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

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, and any postnatal sequelae in the infant will be required.

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

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Expected progression of disease should not be considered or reported as an AE (or SAE).

However, if determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease, the treatment-invoked progression (ie, the treatment involved signs/symptoms of such progression) should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 4, Section 10.4.1 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Death that is attributed by the Investigator explicitly to progression of disease should not be considered nor reported as an AE (or SAE).

However, if determined by the investigator to be more likely related to the study treatment than being expected from the underlying disease, the treatment-invoked death should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Section 10.4.1).

Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form). Signs or symptoms of disease progression that are of clinical significance, such as, but not limited to, spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure should be documented on the appropriate eCRF forms (eg, the Clinical Progression form).

8.3.7. Adverse Events of Special Interest

Adverse events of special interest for this study include pneumonitis/ILD, rash, IRR, liver event and hypoalbuminemia. Additional information may be collected to more fully describe these events. Confirmed cases of pneumonitis/ILD (regardless of grade) and liver events meeting the threshold in Section 6.5.8 should be reported as serious adverse events (see Section 8.3.1). All Grade 3 or 4 IRRs and hypoalbuminemia should be reported within 24 hours to the Medical Monitor. Events of rash should follow standard reporting guidelines.

8.4. Pharmacokinetics

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

8.4.1. Evaluations

Blood samples will be collected from all participants for the measurement of serum amivantamab for PK analyses. Sample collection and testing will comply with local regulations. Population PK modeling may be performed to assess the potential effect of intrinsic factors on the PK of amivantamab and reported separately. Serum samples will be screened for antibodies binding to amivantamab and the number of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of amivantamab. Table 2

Serum samples will be collected from all participants for PK and immunogenicity assessments of amivantamab at the time points outlined in Table 2 (Intense PK Sampling Schedule, 12 participants) and Table 3 (Sparse PK Sampling Schedule, rest participants).

The exact dates and times of blood sampling must be recorded on the laboratory requisition form. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under specified, controlled conditions for the temperatures indicated in the Laboratory Manual. Blood collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

8.4.2. Analytical Procedures

Pharmacokinetics

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

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Pharmacokinetic analysis of serum concentration data for amivantamab will be performed. Serum amivantamab concentrations and PK parameters will be listed and summarized by the sampling interval. In addition, a population pharmacokinetic-based modeling approach may also be applied for PK analysis to assess the potential effect of intrinsic and extrinsic factors on the PK of amivantamab.

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.5. Pharmacogenomics

Pharmacogenomics are not evaluated in this study.

8.6. Biomarkers/Pharmacodynamics

Analyses are planned to explore biomarkers in tumor tissue and blood samples that may predict sensitivity or resistance to treatment and may indicate the mechanisms of action or mechanism of resistance to amivantamab treatment. Correlation of baseline biomarker levels, or changes in biomarker levels upon treatment, with response or time-to-event endpoints could identify responsive (or resistant) subgroups. The relationship of etiology (eg, HepB, HepC) with clinical response will also be analyzed.

Pre-treatment tumor tissue samples will undergo central analysis to investigate levels of MET, EGFR, and relevant MET/EGFR ligands. Tumor biopsy acquired at screening is preferred. If not available, the most recent tumor sample is acceptable. Post-treatment tumor samples, if collected, may also be evaluated for these biomarkers. The changes will be analyzed to indicate target modulation, and track response to amivantamab. Samples may be collected from primary (preferred) or metastatic tumor sites (acceptable), preferably from non-target lesions that are actively growing. Biopsy of a target lesion is allowed for the pre-treatment sample, but baseline disease assessment must occur a minimum of 1 week after the biopsy procedure. The sponsor's medical monitor must give approval prior to the biopsy of a target lesion at baseline. During the study, biopsy of a target lesion is not allowed unless disease progression has occurred.

Blood samples will be collected at timepoints specified in the Schedule of Activities (SoA) for analysis of circulating biomarkers (eg, relevant EGFR and MET ligands, AFP) in samples taken prior to and after exposure to study treatment. The baseline level of these biomarkers and their changes upon treatment will be correlated with response to amivantamab treatment.

Additional biomarkers (DNA, RNA, and/or protein) relevant to target biology and HCC may also be assessed in blood and tissue samples collected during the study to help identify sensitive (or resistant) population subgroups, to evaluate the drug and clinical response relationship, to better understand the mechanisms of response or resistance to amivantamab.

Blood samples will be collected from all participants at selected time points (Table 2 and Table 3) to analyze PD markers (eg, soluble EGFR and MET) to evaluate whether the soluble target saturation was achieved throughout the dosing.

Sample collection, testing and analysis will comply with local regulations.

Decision on Analysis

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

Additional Collections

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

Additional blood and tumor tissue samples collection and analysis in China should be performed after the approval of HGRAO.

8.7. Immunogenicity Assessments

Antibodies to amivantamab will be evaluated in serum samples collected from all participants according to the Table 2 and Table 3. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to amivantamab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to amivantamab and/or further characterize the immunogenicity of amivantamab. Immunogenicity assessment may also be performed on any PK sample. Sample collection and testing will comply with local regulations.

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

Analytical Procedures

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

8.8. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

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

9.2. 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%. With this rule, 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. Details will be provided in the SAP.

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 10.

Table 10: 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%

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

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

9.4. Statistical Analyses

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

9.4.1. General Considerations

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

9.4.2. Primary Endpoint(s)

9.4.2.1. ORR

The primary efficacy measure is ORR. ORR is defined as the proportion of participants who achieve either PR or CR, determined by investigator assessment using RECIST Version 1.1.

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

- Population: Participants with advanced HCC
- Variable: overall response
- Study drug: 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

The observed ORR and its 95% CI will be calculated.

9.4.3. Secondary Endpoint(s)

9.4.3.1. DoR

The 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. A Kaplan-Meier plot and the median DoR with its 95% CI will be presented.

9.4.3.2. DCR

The DCR is defined as the proportion of participants achieving complete or partial response or stable disease of at least 11 weeks as defined by RECIST Version 1.1. Observed DCR and its two-sided exact 95% CI will be presented.

9.4.3.3. PFS

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. PFS will be analyzed using the same methodology applied to the analysis for DoR.

9.4.3.4. OS

The 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. OS will be analyzed using the same methodology applied to the analysis for DoR. In addition, the 6-month and 12-month OS rate along with their 95% CI will also be calculated from the Kaplan-Meier estimate.

9.4.4. Exploratory Endpoint(s)

Objective Response Rate by mRECIST (mORR)

The mORR is defined as the proportion of participants who achieve either PR or CR, determined by investigator assessment using mRECIST. The observed mORR and its 95% CI will be calculated.

9.4.5. Safety Analyses

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

Adverse Events

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

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

Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables.

Clinical Laboratory Tests

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

Vital Signs

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

9.4.6. Other Analyses

9.4.6.1. Pharmacokinetic Analyses

The PK analyses will use the PK population. Serum amivantamab concentrations will be summarized in tables of mean, SD, median, and range over time, as appropriate.

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

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

Descriptive statistics will be used to summarize amivantamab serum concentrations at each sampling timepoint and PK parameters of amivantamab, including but not limited to C_{max}, T_{max}, $AUC_{(t1\text{-}t2)}$ (eg, $AUC_{Day\ 1\text{-}8}$, $AUC_{Day\ 29\text{-}36}$), AUC_{tau}, C_{trough}, and R. Additional serum PK parameters could be determined as appropriate.

Mean or median serum amivantamab concentration versus time profiles will be plotted, and individual serum concentration-time profiles may also be plotted.

Population PK modeling of serum concentration-time data may be performed using nonlinear mixed-effects modeling if appropriate. The exposure-response relationship between amivantamab exposure and key efficacy and safety parameters may be explored if the data allow. Details will be provided in an analysis plan and detailed results may be reported separately from the Clinical Study Report.

9.4.6.2. Pharmacodynamic/Biomarkers Analyses

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

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

Additional biomarkers (DNA, RNA, and/or protein) relevant to target biology and HCC may also be assessed in blood and tissue samples collected during the study to help identify sensitive (or resistant) population subgroups, to evaluate the drug and clinical response relationship, to better understand the mechanisms of response or resistance to amivantamab.

9.4.6.3. Immunogenicity Analyses

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

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

9.5. Interim Analysis

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. Specific details will be provided in the SET Charter and interim analysis plan. 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.

The SAP will describe the planned interim analyses in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCT	antibody-dependent cellular trogocytosis
AE	adverse event
AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the curve
BCLC	Barcelona clinic liver cancer
β-hCG	β-human chorionic gonadotropin
BICR	Blinded Independent Central Review
BP	blood pressure
BW	body weight
C#D#	Cycle # Day #
CDE	Center for Drug Evaluation
CHF	congestive heart failure
C_{max}	maximum serum concentration
CI	confidence interval
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRO	Contract Research Organization
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
CTM	Clinical Trial Manager
C_{trough}	serum concentration immediately prior the next study treatment administration
DBL	database lock
DCR	disease control rate
DLT	dose limiting toxicity
DoR	duration of response
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
ETV	entecavir
FDA	Food and Drug administration
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GFR	Glomerular Filtration Rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
h/hrs	hour
HA	Health Authority
HAART	highly active antiretroviral therapy
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
Hep B	Hepatitis B
Hep C	Hepatitis C
HGF	hepatocyte growth factor
HGRAO	Human Genetic Resources Administration Office
HIFU	high-intensity focused ultrasound
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMS	isotope dilution mass spectrometry
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IgM	immunoglobulin M
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	Investigational New Drug
INR	international normalized ratio
IO	Immuno-Oncology
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
LD	longest diameter
LDH	lactic acid dehydrogenase
LFT	liver function test
LTMs	Local Trial Managers
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition
min	minutes
MKI	multi-targeted kinase inhibitor
MRI	magnetic resonance imaging
NASH	non-alcoholic steatohepatitis
NK	natural killer
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAI	acetic acid injection
PEI	percutaneous ethanol
PET	positron emission therapy
PCC	protocol clarification communication
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PD-1	programmed cell death 1
PDX	patient-derived xenograft
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)

PQC	Product Quality Complaint
PR	partial response
PT	prothrombin time
Q12W	every 12 weeks
R	accumulation ratio
RECIST	response criteria in solid tumors
RFA	radiofrequency ablation
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SET	safety evaluation team
SIPPM	Site Investigational Product and Procedures Manual
SoA	Schedule of Activities
SoC	standard of care
SPF	skin protection factor
TACE	transarterial chemoembolization
TAI	transarterial embolization
TBL	total bilirubin
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse events
TEN	toxic epidermal necrolysis
TGI	tumor growth inhibition
TKI	tyrosine kinase inhibitors
T_{max}	time to reach the maximum serum concentration
ULN	upper limit of normal
US	United States
V_{ss}	steady state volume of distribution
WBC	white blood cell

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the local and central laboratory (if the local lab is not able to be performed the relevant tests, the tests can be performed at the central lab):

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**	
Hematology	• Hemoglobin • Platelet count	• Absolute neutrophil count and white blood cell (WBC) count
Coagulation	• Prothrombin time (PT) or International normalized ratio (INR)	• Activated partial thromboplastin time (APTT)
Clinical Chemistry	• Magnesium • Sodium • Calcium • Potassium • Blood Glucose	• Cholesterol • Triglycerides • Gamma-glutamyl transferase (GGT) • Lactic acid dehydrogenase (LDH) • Uric acid
Liver& Kidney function	• LFTs (ALT, AST, total and indirect bilirubin, alkaline phosphatase) • Albumin	• Blood urea nitrogen (BUN) or urea • Creatinine[a] • Potassium
Urinalysis	Dipstick • Specific gravity • pH • Glucose • Protein • Blood • Ketones • Bilirubin • Nitrite • Leukocyte esterase	If dipstick is abnormal and clinically important then urine microscopy • Red blood cells • White blood cells • Epithelial cells • Crystals • Casts • Bacteria
Serology	• Anti-HIV antibody • Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e-antigen (HBeAg), hepatitis B e-antibody (HbeAb) and hepatitis B core antibody (HBcAb) (participants tested positive for HBsAg or HBcAb, or both are also required to have HBV DNA quantification and HBsAg quantification) • Anti-hepatitis C virus (HCV) antibody (participants tested positive for HCV antibody are also required to have HCV RNA quantification.) • Hepatitis D (HDV) antibody	
Tumor marker	Alpha-fetoprotein (AFP)	

a. estimated Glomerular Filtration Rate (eGFR), calculated using the MDRD formular, will be recorded in the eCRF.

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

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

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

Protocol Clarification Communications

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

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

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

Protocol Amendments

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

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

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

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

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

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

Country/Territory Selection

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

Other Ethical Considerations

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

10.3.2. Financial Disclosure

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

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

10.3.3. Informed Consent Process

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

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

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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

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

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

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

10.3.4. Data Protection

Privacy of Personal Data

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

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures

or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/ territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

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

10.3.5. Long-Term Retention of Samples for Additional Future Research

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

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

10.3.6. Committees Structure

The safety and conduct of the study will be monitored by the SET in conjunction with the coordinating investigators. The SET 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 SET determines it is necessary. In general, SET will monitor the conduct of the study and review study data on an ongoing basis. The SET 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) allowing further enrollment or terminate enrollment of a specific subpopulation to better characterize the specific population (3) opening the expansion cohort (4) PK or biomarker sampling times.

All decisions made by the SET will be documented in a SET decision document. The Independent Ethics Committee/Institutional Review Board (IEC/IRB) will be notified for all SET decisions, if required. The recommendations of the SET may be instituted by the study team, pending protocol amendment, as long as they are consistent with the benefit-risk and fall within the populations already reviewed and approved by HA and local IRBs. All the SET documentation will be maintained in the sponsor's study master file and, as applicable, in the investigator's study files. If unexpected safety findings are identified, ad-hoc SET meetings may be called by any member of the SET, for any issue or concern, and the SET will assess the safety data in a prompt manner. The study will include a screening phase, a treatment phase, and a follow-up phase.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

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

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

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

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

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

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

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

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor may review the CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with

the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

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

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

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

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

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

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

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

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

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

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

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

10.3.11. Monitoring

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

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

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

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

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

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

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

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

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

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

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

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

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

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

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

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. **Note**: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

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

Serious Adverse Event

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

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

Note: Events that do not qualify as an AE cannot be reported as a SAE, even if the conditions for seriousness are met. In particular, this is the case for events due to disease progression leading to death, hospitalization, etc.

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For amivantamab, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

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

Related

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

Not Related

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

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

10.4.3. Severity Criteria

An assessment of severity grade will be made by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 5.0). Any adverse events or serious adverse events not listed in the NCI-CTCAE Version 5.0 should be evaluated for severity/intensity by using the standard grades as follows:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.*

Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.
*	Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**	Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

ADL=activities of daily living
Notes: A semi-colon indicates 'or' within the description of the grade.

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

10.4.4. Special Reporting Situations

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

- Overdose of a sponsor study treatment
- Suspected abuse/misuse of a sponsor study treatment
- Accidental or occupational exposure to a sponsor study treatment
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study treatment from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy
- Liver chemistry abnormalities that meet the SAE reporting criteria defined in Section 7.1.1.

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

10.4.5. Procedures

All Adverse Events

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

AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

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

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

Serious Adverse Events

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

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

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

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

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Information regarding SAEs will be transmitted to the sponsor using the SAE reporting form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

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

Procedures

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

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

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance

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

Definitions

Females of Childbearing Potential (FOCBP)

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

Females Not of Childbearing Potential

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

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

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

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

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

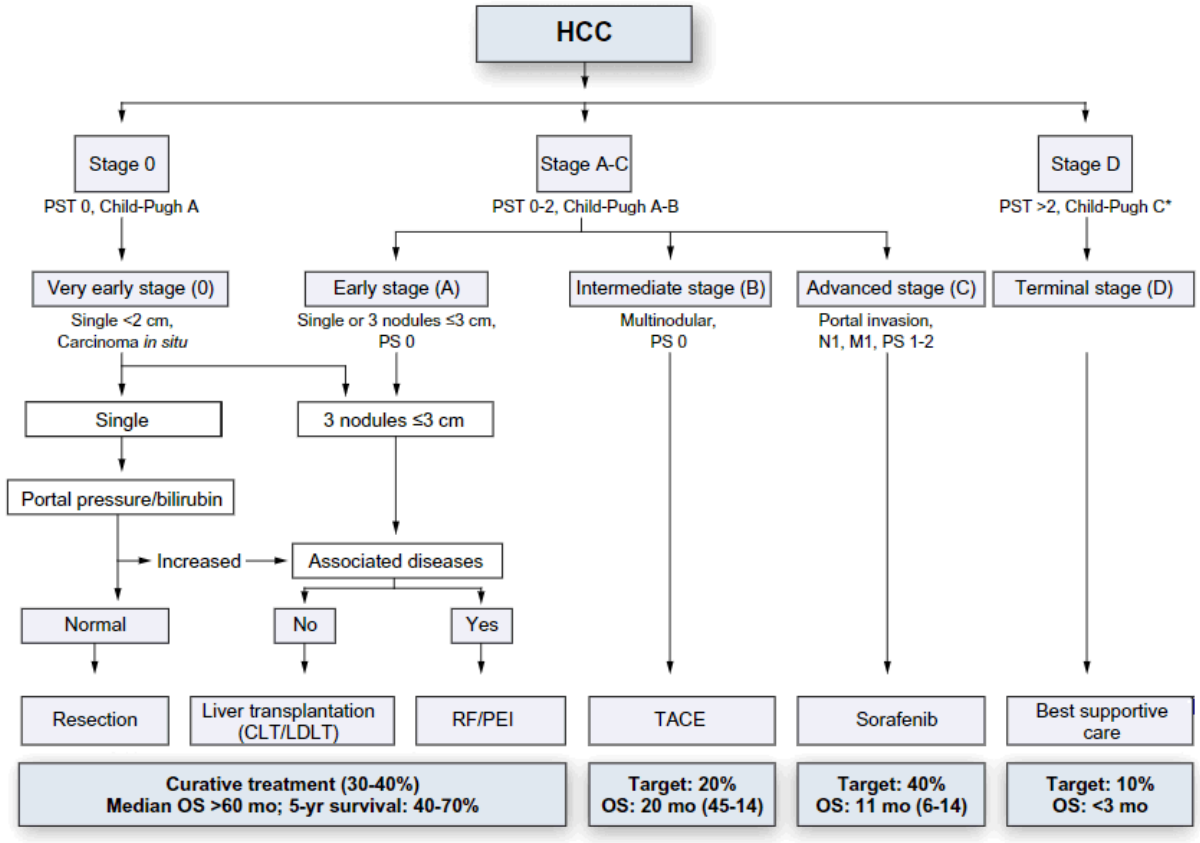
Examples of Contraceptives

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

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

10.6. Appendix 6: BCLC Staging System

BCLC classification: outcome prediction and treatment allocation.



Source: European Association for Study of Liver, 2012

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-up Assessments

10.7.1. Follow-up assessment Algorithm

Treatment-emergent ALT or AST	Treatment-emergent TBL[a]	Liver-related symptoms	Actions
ALT/AST ≥3× BL	Total bilirubin ≥2 x ULN (of which ≥ 35% is direct bilirubin)		Interrupt study drug. Repeat LFT tests within 1-3 days and until abnormal values resolve/return to baseline. The event should be reported as a serious adverse event to the Sponsor within 24. Initiate workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to normal or baseline.
ALT/AST ≥3× BL		Clinical jaundice	Interrupt study drug. Repeat LFT tests within 1-3 days and until abnormal values resolve/return to baseline. The event should be reported as a serious adverse event to the Sponsor within 24. Initiate workup for competing etiologies. Study drug can be restarted only if another etiology is identified, and liver enzymes return to normal or baseline.
ALT/AST ≥5× ULN (if normal at baseline) or ALT/AST ≥3× BL (if abnormal at baseline)	Normal (or no changes in baseline TBL in patients with Gilbert's syndrome or hemolysis)		Repeat LFT tests within 1-3 days and until abnormal values resolve/return to baseline. Interrupt study drug if abnormal values worsened meeting stopping criteria (Section 7.1.1) or follow above or below additional guidance if ALT/AST ≥10 × ULN, or if total bilirubin ≥2 x ULN or jaundice are observed
ALT/AST ≥10 × ULN			Repeat LFT tests within 1-3 days and until abnormal values resolve/return to baseline. The event should be reported as a serious adverse event to the Sponsor within 24 hrs. Initiate workup for competing etiologies. Interrupt study drug if abnormal values meet stopping criteria (Section 7.1.1) or follow above guidance if total bilirubin ≥2 x ULN or jaundice are observed.

Note: If baseline value is > 50% higher than the screening value, it should prompt a discussion with the medical monitor
BL = baseline defined as Day 1 predose test; LFT = liver function test; TBL = total bilirubin.
a. Study treatment should be withheld for any liver chemistry abnormality of ≥Grade 3 severity based on CTCAE 5.0 (Table 4).

10.7.2. Follow-up Assessments

Liver Event Follow-up Requirements

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

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

Note: If the local lab is not able to be performed the relevant tests, the tests can be performed at the central lab.

Rechallenge Criteria

Resumption of study drug administration may be considered if the following criteria are met unless the criteria for permanent discontinuation are reached.

- A reversible underlying cause not associated with study treatments (eg, alcohol or concomitant medication) is clearly identified and agreed upon in consultation with sponsor's medical monitor.

- Liver chemistry abnormalities have resolved, or values have returned to baseline.

Note: Any rechallenge case, a discussion should occur with the Sponsor before restarting amivantamab.

10.8. Appendix 8: New York Heart Association Criteria

The following table presents the NYHA classification of cardiac disease:

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

* Classification of Functional Capacity and Objective Assessment.

Available at: https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure Accessed 13 Dec 2021.

10.9. Appendix 9: Allowed Recent Second or Prior Malignancies

i. Any malignancy that was not progressing nor requiring treatment change in the last 12 months.

ii. Malignancies treated within the last 12 months and considered at very low risk for recurrence:

a) Non-muscle invasive bladder cancer (solitary Ta-PUNLMP or low grade, <3 cm, no CIS).

b) Skin cancer (non-melanoma or melanoma).

c) Non-invasive cervical cancer.

d) Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ, localized breast cancer and receiving antihormonal agents.

e) Localized prostate cancer (M0, N0) with a Gleason Score ≤7a, treated locally only (RP/RT/focal treatment).

iii. Other malignancy that is considered at minimal risk of recurrence.

In the event of any questions, consult with the sponsor's medical monitor prior to enrolling a participant.

10.10. Appendix 10: RECIST 1.1 and mRECIST Quick Reference

	RECIST 1.1
Measurable Tumor Burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥10 mm in longest diameter (LD) and 2X the slice thickness for extranodal lesions. ≥15 mm in short axis for nodal lesions. ≥10 mm in LD for clinical lesions (must be measured using electronic calipers). ≥20 mm in LD for chest X-ray (if clearly defined and surrounded by aerated lung); CT is preferable. Ultrasound (US) cannot be used to measure lesions.
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in short axis. To be measurable, nodal lesions must be ≥15 mm in short axis. Nodal lesions with short axis >10 mm and <15 mm are non- measurable. The sum of the diameters (LD for extranodal target lesions, short axis for nodal lesions) is followed through the course of therapy.
Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emission therapy (PET) or plain films are non-measurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Non-cystic lesions are preferable.
Lesions with Prior Local Treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy.
Too Small To Measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions That Split or Coalesce	If extranodal target lesions fragment, the LDs of the fragmented portions are added to calculate the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of Complete Response (CR)	CR requires the disappearance of all extranodal lesions, the regression of all nodal lesions to <10 mm short axis and the normalization of tumor marker level.
Definition of Progressive Disease (PD)	PD is assessed if the sum of the diameters has increased by ≥20% and ≥5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.
Assessment of New Lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (ie, 'new' bone lesions may be healing or flare of pre- existing lesions). If on is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET:(-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to preexisting lesion on CT that is not progressing; not PD.

Recurrence of Lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall Response	One overall response table integrates target, non-target and new lesions and another table integrates non-target and new lesions for the assessment of subjects without measurable disease.
Confirmation of Response	Confirmation of PR/CR is ONLY required for non-randomized trials where response is the primary endpoint. In these trials, subsequent confirmation of PR with one interim timepoint of SD is acceptable.

Source: Eisenhauer 2009.

Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for HCC Following the AASLD-JNCI Guideline:

RECIST	mRECIST for HCC
CR = Disappearance of all target lesions	CR = Disappearance of any intratumoral arterial enhancement in all target lesions
PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD = Any cases that do not qualify for either partial response or progressive disease	SD = Any cases that do not qualify for either partial response or progressive disease
PD = An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD = An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Overall Response Assessment in mRECIST: Responses for All Possible Combinations of Tumor Responses in Target and Nontarget Lesions with or without the Appearance of New Lesions

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.
Source: Lencioni 2010.

10.11. Appendix 11: Eastern Cooperative Oncology Group Performance Status Score

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

Source: Oken 1982

10.12. Appendix 12: Formulas for Estimating Glomerular Filtration Rate Using Modified Diet in Renal Disease Formula (in mL/min)

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

$$eGFR = 175\ x\ S_{Cr}\ (mg/dL)^{-1.154}\ x\ age\ (years)^{-0.203}\ x\ 1.212_{if\ black}\ x\ 0.742_{if\ female}\ x\ \frac{BSA\ (m^2)}{1.73}$$

Body surface area (BSA) is estimated based on height and weight (Mosteller, NEJM 1987):

$$BSA\ (m^2) = \sqrt{\frac{height\ (cm)\ x\ weight\ (kg)}{3600}}$$

If creatinine levels are given in µmol/L, the equation above can be used after converting the creatinine level to mg/dL:

$$creatinine\ (mg/dL) = \frac{creatinine\ (\mu mol/L)}{88.4}$$

Alternatively, for standardized serum creatinine (S_{Cr}) in **µmol/L**, the eGFR in **mL/min** is:

$$eGFR = 30849\ x\ S_{Cr}\ (\mu mol/L)^{-1.154}\ x\ age\ (years)^{-0.203}\ x\ 1.212_{if\ black}\ x\ 0.742_{if\ female}\ x\ \frac{BSA\ (m^2)}{1.73}$$

NOTES:

- Renal clearance of a drug is proportional to individual GFR (expressed in **mL/min**) and not BSA-standardized GFR (mL/min/1.73m^2).
- The formulas above for the calculation of eGFR are based on MDRD (Levey, Ann Intern Med 2006) but have been adapted to estimate GFR in **mL/min**. (Guidance for Industry)
- Serum creatinine values must be standardized: creatinine assay calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure (this is the case for most assays)

Sources: Levey (2006, 2007), Mosteller (1987) and Guidance for Industry "Pharmacokinetics in patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing" available at: https://www.fda.gov/media/78573/download

10.13. Appendix 13: Child-Pugh Classification

CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) Increasing Abnormality		
	1 Point	**2 Points**	**3 Points**
Encephalopathy (grade)	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time **Seconds over control** **International normalized ratio**	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Bilirubin (mg/dL) • **For primary biliary cirrhosis**	<2 <4	2-3 4-10	>3 >10

Class A=5-6 points; Class B=7-9 points; Class C=10-15 points

Class A:Good operative risk

Class B: Moderate operative risk

Class C: Poor operative risk

References: NCCN 2022

10.14. Appendix 14: Protocol Amendment History

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

Protocol amendment summary for previous amendment is provided below.

Amendment 1 (23 September 2022)

Overall Rationale for the Amendment: The overall reason for this amendment is to add revised rash and TEN toxicity guidelines to align with the current compound level guidelines.

The changes made to the clinical protocol 61186372HCC2001 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Other revisions including minor editorial changes were made in Table 1 and footnotes. Editions were made for Local laboratory Assessments: "Hematology, ~~Chemistry~~chemistry, **coagulation, liver and kidney** function" Footnote d: add sentence "**Biopsy at EOT is optional.**" Footnote e: add sentence "**Sample collection and testing will comply with local regulations.**"	Minor editions were made for content consistency and clarification.
6.5.4 Rash-related Adverse Events	Added text for management of severe bullous, blistering, or exfoliating skin conditions including toxic epidermal necrolysis (TEN).	To provide guidance on management of severe bullous, blistering, or exfoliating skin conditions including TEN.
6.5.4 Rash-related Adverse Events	Changed dose adjustment of Grade 4 Rash to permanent discontinuation of JNJ-61186372.	To change the dose adjustment guidance on Grade 4 Rash.
10.2 Appendix 2 Clinical Laboratory Tests	Editions were made to the first sentence: The following tests will be performed according to the Schedule of Activities by the local **and central** laboratory **(if the local lab is not able to be performed the relevant tests, the tests can be performed at the central lab).**	LabCorp has been set up to perform tests for serology and AFP. Text was added to align with the SOA table descriptions.
10.2 Appendix 2 Clinical Laboratory Tests	Added Hepatitis D (HDV) antibody assessment in the Protocol-Required Safety Laboratory Assessments table.	This test was missing in previous version.
10.2 Appendix 2 Clinical Laboratory Tests	Correction was made to sentence "participants tested positive for HBsA**g**~~b~~ or HBcAb, or both are also required to have HBV DNA quantification and HBsAg quantification" in the Protocol-Required Safety Laboratory Assessments table.	Minor error was noted.
10.4.3 Severity Criteria	Deletion of notes for "outcome fatal" and "Grade 5" adverse events.	To ensure all Grade 5 events are captured.
10.7.2 Follow-up Assessments	Add text: **Note: If the local lab is not able to be performed the relevant tests, the tests can be performed at the central lab.**	LabCorp has been set up to perform follow-up assessments for liver safety. Note was added to provide this option.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall Design Section 10.1 Abbreviations	The abbreviation "I/O" was changed to "IO" for clarification. The definition of "IO" was corrected to "Immuno-Oncology".	To clarify and correct the definition error of an abbreviation.
Throughout the protocol	Minor editorial, grammatical, formatting, or spelling changes were made.	Other revisions including minor editorial, grammatical, formatting, or spelling changes were made throughout.

11. REFERENCES

Abou-Alfa GK (2018), Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018; 379: 54–63.

American Red Cross. http://www.redcrossblood.org/donating-blood/eligibility-requirements. Accessed on 06 December 2021.

Baltschukat S (2019), Engstler BS, Huang A, et al. Capmatinib (INC280) Is Active Against Models of Non-Small Cell Lung Cancer and Other Cancer Types with Defined Mechanisms of MET Activation. Clin Cancer Res. 2019;25(10):3164-3175.

Bauml J (2021), Cho BC, Park K, et al. Amivantamab in combination with lazertinib in the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant non-small cell lung cancer and potential biomarkers for response. 2021 ASCO Annual Meeting. Abstract 9006. Presented June 4, 2021.

Birchmeier C (2003), Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nat Rev Mol Cell Biol. 2003;4(12):915-925.

Bruix J (2017), Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 389:56–66.

Buckley AF (2008), Burgart LJ, Sahai V, Kakar S. Epidermal growth factor receptor expression and gene copy number in conventional hepatocellular carcinoma. Am J Clin Pathol. 2008;129(2):245-251.

Cheng AL (2009), Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10:25–34.

China Red Cross. https://www.redcross.org.cn/html/2019-01/56084.html. Accessed on 06 December 2021.

Chinese Society of Infectious Diseases (2019), Chinese Medical Association; Chinese Society of Hepatology, Chinese Medical Association. Chinese chronic hepatitis B guideline. Chinese J Infect Dis. December 2019;37(12):711-736.

Dong Q (2019), Du Y, Li H, et al. EGFR and c-MET Cooperate to Enhance Resistance to PARP Inhibitors in Hepatocellular Carcinoma. Cancer Res. 2019;79(4):819-829.

Eisenhauer EA (2009), Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

European Association for Study of Liver (2012); European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer. 2012;48(5):599-641.

Finn RS (2020), Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-1905.

Globocan 2020: https://gco.iarc.fr/

Grugan KD (2017), Dorn K, Jarantow SW, et al. Fc-mediated activity of EGFR x c-Met bispecific antibody JNJ-61186372 enhanced killing of lung cancer cells. MAbs. 2017;9(1):114-126.

Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function –Study Design, Data Analysis, and Impact on Dosing. Available at https://www.fda.gov/media/78573/download

Haura EB (2019), et al. Oral presentation at ASCO 2019 Congress, Chicago, USA; abstract 9009.

Haura EB (2020), Hicks JK, Boyle TA. Erdafitinib overcomes FGFR3-TACC3-mediated resistance to Osimertinib. J Thorac Oncol. 2020;15(9):e154-e156.

Hsu WH (2018), Yang JC, Mok TS, Loong HH. Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol. 2018;29(suppl_1):i3-i9.

Huang A (2020), Yang XR, Chung WY, Dennison AR, Zhou J. Targeted therapy for hepatocellular carcinoma. Signal Transduct Target Ther. 2020;5(1):146.

Huang SZ (2019), Wei MN, Huang JR, et al. Targeting TF-AKT/ERK-EGFR Pathway Suppresses the Growth of Hepatocellular Carcinoma. Front Oncol. 2019;9:150.

Hynes NE (2005), Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors [published correction appears in Nat Rev Cancer. 2005 Jul;5(7):580]. Nat Rev Cancer. 2005;5(5):341-354.

Investigator's Brochure: JNJ-61186372 (amivantamab), edition 6. Janssen Research & Development, LLC. (16 Jul 2021).

Junbo H (1999), Li Q, Zaide W, Yunde H. Increased level of serum hepatocyte growth factor/scatter factor in liver cancer is associated with tumor metastasis. In Vivo. 1999;13(2):177-180.

Kondo S (2013), Ojima H, Tsuda H, et al. Clinical impact of c-Met expression and its gene amplification in hepatocellular carcinoma. Int J Clin Oncol. 2013;18(2):207-213.

Kudo M (2018), Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391: 1163–73.

Lee SJ (2013), Lee J, Sohn I, et al. A survey of c-MET expression and amplification in 287 patients with hepatocellular carcinoma. Anticancer Res. 2013;33(11):5179-5186.

Lencioni R (2010), Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60.

Levey AS (2007), Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007;53(4):766-772.

Levey AS (2006), Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-254.

Li QH (2020), Wang YZ, Tu J, et al. Anti-EGFR therapy in metastatic colorectal cancer: mechanisms and potential regimens of drug resistance. Gastroenterol Rep (Oxf). 2020;8(3):179-191.

Llovet JM (2008), Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359:378–90.

Mathieu LN (2021), Larkins E, Akinboro O, et al. FDA Approval Summary: Capmatinib and Tepotinib for the Treatment of Metastatic NSCLC Harboring MET Exon 14 Skipping Mutations or Alterations [published online ahead of print, 2021 Aug 3]. Clin Cancer Res. 2021;10.1158/1078-0432. CCR-21-1566.

Medavaram S (2018), Zhang Y. Emerging therapies in advanced hepatocellular carcinoma. Exp Hematol Oncol 2018; 7:17.

Meyer T (2018), Melero I, Yau T, et al. Hepatic safety and biomarker assessments in sorafenib-experienced patients with advanced hepatocellular carcinoma treated with nivolumab in the CheckMate-040 study. 2018 EASL Annual meeting. J Hepatol 68 (suppl 1): S16.

Moores SL (2016), Chiu ML, Bushey BS, et al. A Novel Bispecific Antibody Targeting EGFR and cMet Is Effective against EGFR Inhibitor-Resistant Lung Tumors. Cancer Res. 2016;76(13):3942-3953.

Mosteller RD (1987). Simplified calculation of body-surface area. N Engl J Med. 1987;317(17):1098.

National Comprehensive Cancer Network (NCCN) (2022). Hepatobiliary Cancer (Version 4.2022). Accessed on 5 January 2023 at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

Nagasaka (2021) et al. Amivantamab in Combination With Chemotherapy in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC). Journal of Thoracic Oncology, Volume 16, Issue 10, Supplement, 2021, Page S1116.

Niu L (2017), Liu L, Yang S, Ren J, Lai PBS, Chen GG. New insights into sorafenib resistance in hepatocellular carcinoma: Responsible mechanisms and promising strategies. Biochim Biophys Acta Rev Cancer. 2017;1868(2):564-570.

Niu M (2021), Yi M, Li N, Wu K, Wu K. Advances of Targeted Therapy for Hepatocellular Carcinoma. Front Oncol. 2021;11:719896.

Nonclinical Study Report E0229-T2035. In Vivo Efficacy and Pharmacodynamics Studies of CNTO-4424, JNJ-55323394 and Sorafenib in the Treatment of HuPrime® Liver Cancer Xenograft Model LI1098 in Female BALB/c Nude Mice. Crown Bioscience Inc. (19 Jan 2022)

Novoplansky O (2019), Fury M, Prasad M, et al. MET activation confers resistance to cetuximab, and prevents HER2 and HER3 upregulation in head and neck cancer. Int J Cancer. 2019;145(3):748-762.

Philip PA (2012), Mahoney MR, Holen KD, et al. Phase 2 study of bevacizumab plus erlotinib in patients with advanced hepatocellular cancer. Cancer. 2012;118(9):2424-2430.

Qin S (2020), Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol. 2020;21(4):571-580.

Recondo G (2020), Bahcall M, Spurr LF, et al. Molecular Mechanisms of Acquired Resistance to MET Tyrosine Kinase Inhibitors in Patients with MET Exon 14-Mutant NSCLC. Clin Cancer Res. 2020;26(11):2615-2625.

Rimassa L (2018), Assenat E, Peck-Radosavljevic M, et al. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. Lancet Oncol. 2018;19(5):682-693.

Rizzo A (2021), Brandi G. Biochemical predictors of response to immune checkpoint inhibitors in unresectable hepatocellular carcinoma. Cancer Treat Res Commun. 2021;27:100328.

Saraon P (2021), Pathmanathan S, Snider J, Lyakisheva A, Wong V, Stagljar I. Receptor tyrosine kinases and cancer: oncogenic mechanisms and therapeutic approaches. Oncogene. 2021;40(24):4079-4093.

Saung MT (2021), Pelosof L, et al. FDA Approval Summary: Nivolumab Plus Ipilimumab for the Treatment of Patients with Hepatocellular Carcinoma Previously Treated with Sorafenib. The Oncologist 2021;26:1–10.

Scagliotti G (2020), Moro-Sibilot D, Kollmeier J, et al. A Randomized-Controlled Phase 2 Study of the MET Antibody Emibetuzumab in Combination with Erlotinib as First-Line Treatment for EGFR Mutation-Positive NSCLC Patients. J Thorac Oncol. 2020;15(1):80-90.

Sherman M (2005). Hepatocellular carcinoma: epidemiology, risk factors, and screening. Semin Liver dis. 2005;25(2):143 154.

Siegel RL (2018), Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68: 7–30.

Sung H (2021), Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.

Taberna M (2019), Oliva M, Mesía R. Cetuximab-Containing Combinations in Locally Advanced and Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. Front Oncol. 2019;9:383.

Thomas MB (2005), Zhu AX. Hepatocellular carcinoma: the need for progress. J Clin Oncol. 2005;23(13):2892 2899.

Takeda T (2021), Tsubaki M, Kato N, et al. Sorafenib treatment of metastatic melanoma with c-Kit aberration reduces tumor growth and promotes survival. Oncol Lett. 2021;22(6):827.

Villanueva A (2019). Hepatocellular Carcinoma. N Engl J Med. 2019;380(15):1450-1462.

Vijayaraghavan S (2020), Lipfert L, Chevalier K, et al. Amivantamab (JNJ-61186372), an Fc Enhanced EGFR/cMet Bispecific Antibody, Induces Receptor Downmodulation and Antitumor Activity by Monocyte/Macrophage Trogocytosis. Mol Cancer Ther. 2020;19(10):2044-2056.

Wu YL (2020), Cheng Y, Zhou J, et al. Tepotinib plus gefitinib in patients with EGFR-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): an open-label, phase 1b/2, multicentre, randomised trial [published correction appears in Lancet Respir Med. 2020 Jul;8(7):e59]. Lancet Respir Med. 2020;8(11):1132-1143.

Yamaguchi H (2014), Chang SS, Hsu JL, Hung MC. Signaling cross-talk in the resistance to HER family receptor targeted therapy. Oncogene. 2014;33(9):1073-1081.

Yang Z (2022), Suda G, Maehara O, et al. Changes in Serum Growth Factors during Lenvatinib Predict the Post Progressive Survival in Patients with Unresectable Hepatocellular Carcinoma. Cancers (Basel). 2022;14(1):232.

Yano S (2003), Kondo K, Yamaguchi M, et al. Distribution and function of EGFR in human tissue and the effect of EGFR tyrosine kinase inhibition. Anticancer Res. 2003;23(5A):3639-3650.

Yau T (2020), Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial [published correction appears in JAMA Oncol. 2021 Jan 1;7(1):140]. JAMA Oncol. 2020;6(11):e204564.

Zeng H (2018), Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health 2018; 6: e555–67.

Zhang Y (2018), Gao X, Zhu Y, et al. The dual blockade of MET and VEGFR2 signaling demonstrates pronounced inhibition on tumor growth and metastasis of hepatocellular carcinoma. J Exp Clin Cancer Res. 2018;37(1):93.

Zhang YZ (2018), Xia M, Jin K, et al. Function of the c-Met receptor tyrosine kinase in carcinogenesis and associated therapeutic opportunities. Mol Cancer. 2018;17(1):45.

Zheng RS (2019), Sun KX, Zhang SW, et al. Zhonghua Zhong Liu Za Zhi. 2019;41(1):19-28.

Zhu AX (2018), Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018; 19: 940–52.

Zhu AX (2019), Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20: 282–96.

INVESTIGATOR AGREEMENT

JNJ-61186372 (amivantamab) Clinical Protocol 61186372HCC2001 Amendment 2

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signatu PPD Date: PPD
(Day Month Year)

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 113

Status: Approved, Date: 21 February 2023