Clinical Trial Protocol

Clinical Trial Protocol Number	EMR200095-004
Title	A Multicenter, Randomized, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy Versus Sorafenib in Asian Subjects with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function Short Title: Efficacy, Safety, and PK of MSC2156119J in Asian Subjects with HCC
Phase	Ib/II
Coordinating Investigator	PPD
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany **Medical Responsible:** PPD EMD Serono, Inc. 45A Middlesex Turnpike Billerica MA 01821 United States of America Tel: PPD Fax: PPD
Clinical Trial Protocol Version	19 May 2017/Version 4.0, Amendment No. 4.0
Replaces Version	24 June 2016/Version 3.0

[redacted]

Signature Page

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

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Coordinating Investigator

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

_____ _____

Signature Date of Signature

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Principal Investigator Signature

Trial Title	A Multicenter, Randomized, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy Versus Sorafenib in Asian Subjects with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function
Clinical Trial Protocol Version/Date	19 May 2017/Version 4.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.

I understand that some Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

_____ _____

Signature | Date of Signature

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List of Abbreviations

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
AESI	Adverse events of special interest
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
AUC_{0-t}	Area under the curve from time zero to time t
AUC_{0-tau}	Area under the curve within 1 dosing interval
$AUC_{0-\infty}$	Area under the curve from time zero to infinity following last administration
AUC_{extra}	Area under the curve extrapolated from C_{last}/λ_z
BCLC	Barcelona Clinic Liver Cancer
BCRP	Breast cancer resistance protein
BUN	Blood urea nitrogen
C_{av}	Average plasma concentration within 1 dosing interval
c-Met	Mesenchymal-epithelial transition factor
CI	Confidence interval
CL	Total body clearance of drug
C_{last}	Calculated plasma concentration at the last sampling time point at which the measured plasma concentration is at or above the lower limit of quantification
CL/f	Apparent clearance
C_{max}	Maximum concentration
C_{min}	Observed minimum plasma concentration
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organization
CT	Computed tomography

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation (%)
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR-TKI	Epidermal growth factor receptor-tyrosine kinase inhibitor
FACT-HP	Functional assessment of cancer therapy-hepatobiliary
FDA	Food and Drug Administration
FDG-PET	Fludeoxyglucose positron emission tomography
FIM	First-in-man
FHSI-8	FACT Hepatobiliary Symptom Index 8
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GGT	Gamma-glutamyl transpeptidase
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibodies
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemical/immunohistochemistry
IMP	Investigational medicinal product

Abbreviation	Definition
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-treat
IVRS	Interactive voice response system
λz	Area under the curve terminal phase rate constant
LLQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
mITT	Modified intent-to-treat
MOP	Manual of Operations
mRECIST	Modified RECIST
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association
OCT1	Organic cation transporter 1
OR	Overall response
OS	Overall survival
PCR	Polymerase chain reaction
Pd	Pharmacodynamic
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
CCI	[redacted]
PK	Pharmacokinetic
PoC	Proof of concept
PP	Per protocol
PR	Partial response
PRO	Patient reported outcomes
PS	Performance Status

Abbreviation	Definition
PT	Prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SEM	Standard error of the mean
SMC	Safety monitoring committee
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
t_{max}	Time to maximum concentration
TTP	Time to progression
TTSP	Time to symptomatic progression
ULN	Upper limit of normal
V_{ss}/f	Apparent volume of distribution at steady state
V_z	Volume of distribution associated to the terminal phase
$V_{z/f}$	Apparent volume of distribution associated to the terminal phase

1 Synopsis

Trial title	A Multicenter, Randomized, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy Versus Sorafenib in Asian Subjects with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function Short Title: Efficacy, Safety, and PK of MSC2156119J in Asian Subjects with HCC
Trial number	EMR200095-004
Sponsor	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Phase	Ib/II
Trial under IND	☐ yes ☒ no
FDA "covered trial"	☒ yes ☐ no
Trial centers/countries	Phase Ib: Selected sites in mainland China, South Korea, and Taiwan. Phase II: Approximately 45 to 55 sites in mainland China, South Korea, Taiwan, and other Asian countries
Planned trial period (first enrollment-last subject out)	September 2013 to March 2018
Trial objectives	**Primary Objectives** **Phase Ib** • To confirm the recommended Phase II dose (RP2D) of MSC2156119J administered orally once daily at a 21-day cycle in subjects with advanced hepatocellular carcinoma (HCC) and Child-Pugh class A liver function. The target RP2D in HCC subjects is the RP2D as determined in the global first-in-man (FIM) trial, i.e., 500 mg once daily **Phase II** • To evaluate efficacy as measured by time to progression (TTP) of MSC2156119J as monotherapy in the first-line treatment compared with sorafenib in subjects with

	MET+ advanced HCC and Child-Pugh class A liver function **Secondary objectives** **Phase Ib** • To characterize the single and multiple dose pharmacokinetics (PK), preliminary antitumor activity, and biochemical response of MSC2156119J in Asian subjects with HCC and Child-Pugh class A liver function **Phase II** • To evaluate the safety and tolerability of MSC2156119J versus sorafenib • To evaluate antitumor activity of MSC2156119J versus sorafenib Exploratory objectives will be assessed in Phase Ib and Phase II for subjects with available baseline and on-treatment biopsies and/or blood samples, and/or available patient reported outcome (PRO) data. CCI [redacted]
Trial design and plan	Phase Ib will be an open label, single arm trial at selected sites in mainland China, South Korea, and Taiwan. The classical "3+3" design will be applied for sites in South Korea and Taiwan, with a dose escalation phase and a dose confirmation phase. In addition and separate from the "3+3" trial cohorts, up to 3 subjects will be enrolled in a separate cohort at selected sites in mainland China. Phase II will be a randomized, open label, active controlled trial to evaluate the efficacy, safety, and PK of MSC2156119J as first-line treatment versus sorafenib in subjects with MET+, Barcelona Clinic Liver Cancer (BCLC) Stage B or C, systemic treatment naive advanced HCC and Child-Pugh class A liver function. Phase II is planned to be conducted at 45 to 55 sites in mainland China, South Korea, Taiwan, and other Asian countries. Subjects will receive either MSC2156119J once daily (at

	the RP2D determined from Phase Ib) or 400 mg sorafenib twice daily until disease progression, intolerable toxicity or consent withdrawal from the trial.
Planned number of subjects	**Phase Ib:** Up to 21 subjects, including up to 18 subjects from South Korea and Taiwan following a "3+3" dose escalation method and up to an additional 3 subjects from the mainland China sites. **Phase II:** Approximately 140 subjects were planned to be randomized on a 1:1 basis to receive MSC2156119J or sorafenib. The sponsor subsequently decided to stop prescreening/enrollment after 40 TTP events (assessed by an IRC) or on 15 August 2017, whichever occurs first.
Schedule of visits and assessments	**Screening period** The subject must sign a main informed consent form (ICF) before any trial procedures are performed. In Phase II, subjects must also sign the prescreening and clinical screening ICF. In Phase II, subjects will undergo a Molecular Prescreening period and a Clinical Screening period. MET status will be confirmed during Molecular Prescreening. Clinical Screening must be completed within 14 days prior to the initiation of study treatment, and will include laboratory parameters (including serum pregnancy test if applicable), medical history, concomitant medication/procedure, and tumor imaging to check subject eligibility. **Treatment Period** MSC2156119J (Phase Ib and Phase II) will be administered once daily over a 21-day cycle and sorafenib (Phase II) will be administered twice daily over a 21-day cycle, which may repeat until disease progression (as determined by the investigator), intolerable toxicity, or withdrawal from the trial. For Phase Ib, scheduled visits during the treatment period will occur on Days 1, 2, 8, and 15 of Cycle 1; Days 1, 8, and 15 of Cycle 2; and Day 1 of Cycles ≥ 3. For Phase II, scheduled visits during the treatment period will occur on Days 1, 8, and 15 of Cycle 1; Days 1 and 8 of Cycle 2; and Day 1 of Cycles ≥ 3.

	At each scheduled visit during the treatment period, physical examination/weight, vital signs (except as noted below), hematology, coagulation, chemistry, adverse events (AEs), and concomitant medication/procedure assessments will be performed. Subjects with a known history or evidence of viral hepatitis infection at baseline will be monitored throughout the treatment period. Additional assessments will be performed as described below. **Cycle 1, Day 1** On Cycle 1, Day 1 of Phase Ib, the following assessments/treatment administrations will occur: dispensing of study drug; 12-lead electrocardiogram (ECG); serial PK blood samples; pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples; optional, will be collected after subjects have signed a separate ICF); CCI [redacted] The following assessments will be performed only if screening/last assessments were performed > 7 days prior to Day 1: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS); urinalysis; and serum alpha-fetoprotein (AFP). Assessments for Cycle 1, Day 1 of Phase II include all assessments in Phase Ib with the following changes: randomization by interactive voice response system; CCI [redacted] FACT Hepatobiliary Symptom Index 8 (FHSI-8); and PRO (Functional assessment of cancer therapy-hepatobiliary [FACT-HP]). **Cycle 1, Day 15** On Cycle 1, Day 15 of Phase Ib, the following assessments/treatment administrations will occur: tumor biopsy (excluding fine needle aspiration and cytology samples; optional, will be collected after subjects have signed a separate ICF); 12-lead ECG; and serial PK blood samples.

	Assessments for Cycle 1, Day 15 of Phase II include all assessments in Phase Ib except for PK blood samples, postdose 12-lead ECG, and vital signs. **Cycle 2, Day 1** Assessments for Cycle 2, Day 1 of Phase Ib include all assessments from Cycle 1, Day 1 as defined above, with the following changes: 12-lead ECG at predose only; no tumor biopsy; and no PK and CCI blood samples. Assessments for Cycle 2, Day 1 of Phase II include all assessments from Cycle 1, Day 1, with the following exceptions: no randomization by interactive voice response system; no tumor biopsy; and no CCI blood sample. CCI [redacted] **Cycle 2, Day 15** Assessments for Cycle 2, Day 15 of Phase Ib will be the same as the assessments for Cycle 1, Day 15, except for tumor biopsy, vital signs, 12-lead ECG, and PK blood samples. **Cycles ≥ 3, Day 1** Assessments for Cycles ≥ 3, Day 1 of Phase Ib include all assessments from Cycle 1, Day 1, except a tumor biopsy will not be taken, and PK and CCI blood samples will not be drawn. The second on-treatment blood sample for analysis of CCI [redacted], scheduled for Cycle 3, Day 1, can be drawn between Cycle 2, Day 15 and Cycle 4, Day 1 (mandatory, Cycle 3 only). In addition, a complete tumor assessment of all lesions by radiographic or other modality (using response evaluation criteria in solid tumors [RECIST v 1.1]) identified at the screening visit will be performed predose on, or up to 5 days prior to, Day 1 of Cycles 3, 5, 7, 9, 11, 13, and every 4 cycles

	thereafter until disease progression or trial medication discontinuation. Assessments for Cycles ≥ 3, Day 1 of Phase II include all Cycles ≥3, Day 1 assessments in Phase Ib. In addition, viral load of hepatitis B virus (HBV) will be performed every 3 cycles for subjects with a known history of chronic HBV infection or HBV at baseline, hepatitis C virus (HCV) ribonucleic acid (RNA) using polymerase chain reaction (PCR) will be performed every 3 cycles for subjects with a known history of chronic HCV infection or measurable HCV RNA at baseline, FHSI-8 will be assessed, FACT-HP will be assessed on Cycle 5, Day 1. CCI [redacted] **End of Treatment Visit** At the subject's discontinuation of the trial medication (due to disease progression [as assessed by the Investigator], intolerable toxicity, or withdrawal), the following evaluations, which include safety/tumor assessment, will be performed: tumor biopsy (excluding fine needle aspiration and cytology samples; optional, will be collected after subjects sign a separate ICF); physical examination/weight; ECOG PS; AEs; concomitant medication/procedure; vital signs; 12-lead ECG; hematology; coagulation; chemistry; urinalysis; monitoring of subjects with a known history or evidence of viral hepatitis infection at baseline; complete tumor assessment of all lesions by radiographic or other modality if previous assessment is more than 6 weeks old (using RECIST v 1.1); and serum AFP. Assessments for the end of treatment visit in Phase II include all assessments in Phase Ib. In addition, FHSI-8 and PRO (FACT-HP) will be assessed and blood samples for CCI [redacted] will be performed. Note: end of treatment ECG and laboratory assessments (hematology, coagulation, chemistry, urinalysis, and hepatitis markers) are not required for subjects with previous ECG and laboratory assessments, respectively, within 7 days of the end of treatment visit.

	Post-Treatment Follow-Up Visit Study drug post-treatment follow-up visit will be performed within 30 ± 3 days after the last dose for subjects who discontinue the trial medication, even if the subject starts a new antineoplastic therapy. The following assessments will be performed: AEs; concomitant medication/procedure; physical examination/weight; ECOG PS; vital signs; 12-lead ECG; hematology; coagulation; chemistry; and urinalysis. Assessments for the post-treatment follow-up visit in Phase II include all assessments in Phase Ib. In addition, FHSI-8 will be assessed. Subjects who are discontinued from the trial due to unacceptable toxicity should perform the tumor assessment at 6-week intervals until Cycle 13 and 12-week intervals (4 cycles) after Cycle 13 until disease progression, starting a new therapy, or death. **Survival Follow-up Assessments** Survival data (subject survival and anticancer therapies) in Phase Ib and Phase II will be collected every 3 months (± 2 weeks) after the last dose of study drug. Subjects will be contacted by telephone. **Assessments After the Enrollment Stop Date (15 August 2017)** Subjects who sign the ICF prior to 15 August 2017 and undergo prescreening/screening after the enrollment stop date may still be randomized in the trial. Subjects receiving study treatment may continue treatment after discussion with their Investigator. Subjects who decide to continue treatment will continue on their originally randomized treatment, at their most recent dose according to the protocol. Safety monitoring and data collection will continue without modification through to the end of the trial.

Diagnosis and main inclusion and exclusion criteria	**Inclusion Criteria** For inclusion in the trial, all of the following inclusion criteria must be fulfilled: • Histologically or cytologically confirmed HCC • Subjects with either intermediate HCC of BCLC Stage B, who are not eligible for surgical and/or local-regional therapies or who have progressive disease (PD) after surgical and/or local-regional therapies (note: the local-regional therapy must not contain sorafenib), or advanced HCC of BCLC Stage C • Subjects who have disease progression or are intolerant to the prior standard treatment for advanced HCC (Phase Ib Korean subjects only) • A tumor biopsy (excluding fine needle aspiration and cytology samples) is required for determining MET status (a fresh pretreatment tumor biopsy is recommended but archived tumor sample is acceptable) • MET+ status (Phase II only), as determined by the central laboratory (Phase Ib retrospectively, Phase II for subject selection) is defined as mesenchymal-epithelial transition factor (c-Met) protein overexpression (e.g., moderate [2+] or strong [3+] staining intensity for c-Met using immunohistochemistry [IHC] in the majority [≥ 50%] of tumor cells) • Child-Pugh class A with no encephalopathy according to the screening assessment • Asian male or female, 18 years of age or older • Measurable disease in accordance with RECIST v 1.1. The target lesion that has received previous local therapy should not be considered as measurable unless clear progression has been documented since the therapy (Phase II only) • ECOG PS of 0 or 1 • Eligible for treatment with sorafenib, as assessed by investigators according to the Package Insert and clinical judgment (Phase II only)

	• Signed and dated informed consent indicating that the subject has been informed of all the pertinent aspects of the trial prior to enrollment • Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other trial procedures • Life expectancy judged by the investigator of at least 3 months **Exclusion Criteria** Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria: • Prior systemic anticancer treatment for advanced HCC, including targeted therapy (e.g., sorafenib), chemotherapy, or any other investigational agent (Phase II only) • Prior treatment with any agent targeting the hepatocyte growth factor (HGF)/c-Met pathway • Prior local-regional therapy within 4 weeks prior to Day 1 of trial treatment (e.g., major surgery, radiation therapy [with the exception of palliative bone-directed radiotherapy and radiotherapy administered to superficial lesions], hepatic arterial embolization, transcatheter arterial chemoembolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) NOTE: palliative bone-directed radiotherapy should be within a limited field of radiation and for palliation only; it should be a short course, according to local institutional recommendations, and should be completed at least 7 days prior to the first administration of trial treatment • Prior history of liver transplant • Laboratory abnormalities defined as follows: o Hematological test abnormalities of either hemoglobin ≤ 8.5 g/dL (without transfusion or growth factor support in the preceding 14 days), neutrophils $< 1.5 \times 10^9$/L, or platelets $< 60 \times 10^9$/L (without transfusion

	or growth factor support in the preceding 7 days) ○ Liver dysfunction defined by total bilirubin > 3 mg/dL, or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) ○ Renal impairment as evidenced by serum creatinine ≥ 1.5 × ULN or calculated creatinine clearance (CrCl) < 60 mL/min by Cockcroft-Gault formula (24-hour CrCl might be requested by the investigator for confirmation, if calculated CrCl is < 60 mL/min. In such case, subjects with 24-hour CrCl < 60 mL/min should be excluded) ○ International normalized ratio (INR) > 2.3 (in accordance with the guidance that has been modified for Child-Pugh classification) ○ Albumin < 28 g/L (without transfusion in the preceding 14 days) • Past or current history of neoplasm other than HCC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years • Known central nervous system (CNS) or brain metastasis that is either symptomatic or untreated • Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the tested products • Clinically significant gastrointestinal bleeding within 4 weeks prior to Day 1 of trial treatment • Impaired cardiac function, evidenced by any of the following conditions: (1) left ventricular ejection fraction < 45% on recent echocardiography; (2) serious arrhythmia; (3) unstable angina pectoris; (4) congestive heart failure New York Heart Association III and IV; (5) myocardial infarction within the last 12 months prior to Day 1 of trial treatment; or (6) pericardial effusion

	• Hypertension uncontrolled by standard therapies (not stabilized to ≤ 150/90 mmHg) • Subject with a family history of long QT syndrome, or who takes any agent that is known to prolong QT/QTc interval, or with a marked prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval > 450 msec) • Known human immunodeficiency virus (HIV) infection • Subjects who have acute pancreatitis and/or chronic pancreatitis, with elevated lipase and/or amylase, clinical symptoms, and/or imaging studies that are indicative of the diagnosis (Mainland Chinese subjects only) • Known or suspected drug hypersensitivity to any ingredients of sorafenib (Phase II only) and MSC2156119J • Female subjects who are pregnant or lactating, or males and females of reproductive potential not willing or not able to employ a highly effective method of birth control/contraception to prevent pregnancy from 2 weeks before receiving study drug until 3 months after receiving the last dose of study drug. A highly effective method of contraception is defined as having a low failure rate (< 1% per year) when used consistently and correctly • Concurrent treatment with a non-permitted drug • Substance abuse, other acute or chronic medical or psychiatric condition, or laboratory abnormalities that may increase the risk associated with trial participation in the opinion of the investigator • Participation in another interventional clinical trial within the 28 days prior to Day 1 of trial treatment or within a time period that is less than the cycle length for the investigational treatment (whichever is shorter), or if the subject has any AE caused by the investigational treatment that has not recovered to Grade 1 or less. • Previous anticancer treatment-related toxicities not recovered to baseline or Grade 0-1 (except alopecia)

	• Subjects with any concurrent medical condition or disease that will potentially compromise the conduct of the study at the discretion of the investigators • Clinically significant third space fluid accumulation (despite the use of diuretics), e.g., moderate to large ascites requiring tapping or pleural effusion that either requires tapping or results in shortness of breath • Complete occlusion of the major portal vein or vena cava due to HCC. (The major portal vein is defined as the part of portal vein between the union of the splenic and superior mesenteric veins and the first bifurcation into the left and right vein)
Investigational Medicinal Product: dose/mode of administration/dosing schedule	**Investigational medicinal product** MSC2156119J, 3-(1-{3-[5-(1-Methyl-piperidin-4-ylmethoxy)-pyrimidin-2-yl]-benzyl}-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzonitrile) mono-HCl, monohydrate, is supplied as 25 mg and 100 mg film-coated tablets. **Dose/mode of administration/dosing schedule** **Phase Ib**: For each dose cohort, a fixed dose and administration will be applied. The assigned dose of MSC2156119J will be administered daily, using 25 mg and/or 100 mg film-coated tablets. For "3+3" dose escalation cohorts, the first dose level will be 300 mg once daily, which is 1 level lower than the target dose of RP2D (500 mg, once daily) from the FIM trial. The second dose level will be 500 mg once daily. Subjects will take their assigned doses of MSC2156119J orally, in the morning approximately at the same time, immediately after breakfast, with a full glass of water (approximately 200 mL), every day of each 21-day treatment cycle. Subjects will be instructed to swallow the tablets whole and to avoid biting or breaking the tablets, or attempting to dissolve the tablets in water before taking them. On days when PK samples are to be drawn, subjects should be instructed to attend the clinic in a fasted state, with no breakfast and prior to taking the MSC2156119J

	dose. After a predose PK blood sample is drawn, the assigned dose of MSC2156119J should be taken following breakfast. No further food should be consumed until 2 hours after the dose (water is allowed). **Phase II**: The dose of MSC2156119J will be the RP2D determined in Phase Ib. Subjects who are randomized to MSC2156119J will take their assigned dose orally once daily, approximately at the same time in the morning, immediately after breakfast with a full glass of water (approximately 200 mL), every day of each 21-day treatment cycle. CCI [redacted]
Reference therapy: dose/mode of administration/dosing schedule	Subjects who are randomized to sorafenib will take two 200 mg tablets in the morning and two 200 mg tablets in the evening (800 mg total daily dose), on an empty stomach 1 hour before or 2 hours after ingestion of food with a full glass of water (approximately 200 mL), every day of each 21-day treatment cycle. Subjects should be instructed to take sorafenib at approximately the same times each day.
Planned treatment duration per subject	The minimum duration of treatment for each subject is 1 full 21-day cycle of treatment. Subjects may repeat the treatment cycle without limitation as long as no unacceptable toxicity or no disease progression is documented.
Primary endpoints	**Phase Ib:** • Incidence of subjects experiencing at least 1 dose limiting toxicity (DLT) within the first treatment cycle (i.e., 21 days after the first dose) • Incidence and type of other AEs

	Phase II: • TTP based on tumor assessment by an IRC. TTP is defined as the time (in months) from randomization to date of the observation of radiological PD assessed by an IRC Tumor assessment endpoints are following RECIST v 1.1.
Secondary endpoints	**Phase Ib and Phase II:** • Progression-free survival (PFS) based on tumor assessment by the IRC. PFS time is defined as the time (in months) from randomization to either first observation of disease progression or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment. • PFS based on tumor assessment by the investigator. PFS time is defined as the time (in months) from randomization to either first observation of radiologically confirmed PD by the investigator or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment. • Overall survival (OS) time. OS time is defined as the time (in months) from randomization to the date of death. • TTP assessed by investigator. TTP is defined as the time (in months) from randomization to date of the observation of radiological PD assessed by the investigator. • Time-to-symptomatic progression (TTSP). TTSP is defined as the time (in months) from the date of randomization to the date of deterioration of symptoms assessed by FHSI-8, defined as the total score increase by at least 4 points compared with the baseline value, or deterioration to ECOG PS of 4. • Objective response (OR) based on tumor assessment by the IRC. OR is defined as complete response (CR) or partial response (PR) as the best overall response according to radiological assessments as adjudicated

	by the IRC from randomization to first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1. • OR based on tumor assessment by the investigator. OR is defined as CR or PR as the best overall response according to radiological assessments as adjudicated by the investigator from randomization to first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1. • Disease control based on tumor assessment by the IRC. Disease control is defined as CR, PR, or stable disease (SD) as the best overall response according to radiological assessments as adjudicated by the IRC from the date of randomization to the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization. • Disease control based on tumor assessment by the investigator. Disease control is defined as CR, PR, or SD as the best overall response according to radiological assessments as adjudicated by the investigator from the date of randomization to the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization. • Drug exposure. • Incidence and type of AEs (all grades as per the National Cancer Institute's [NCI]-Common Terminology Criteria for Adverse Events [CTCAE] version 4.0): all treatment emergent adverse events (TEAEs), related TEAEs, treatment emergent serious adverse events (SAEs), related treatment emergent SAEs, TEAEs of NCI-CTCAE (version 4.0) with Grade ≥ 3, related TEAEs Grade ≥ 3, and TEAEs leading to temporary/permanent treatment discontinuation. • Incidence and reasons for deaths, including deaths within 33 days after the last dose of study drug.

	• Safety laboratory tests graded by NCI-CTCAE (version 4.0). • Vital signs; 12-lead ECG changes; physical examinations, including change in body weight; and ECOG PS.
Pharmacokinetics	**Phase Ib:** PK endpoint (for MSC2156119J only): area under the curve from time zero to time t (AUC_{0-t}), area under the plasma concentration versus time curve within 1 dosing interval (AUC_{0-tau}), maximum concentration (C_{max}), average plasma concentration within 1 dosing interval (C_{av}), observed minimum plasma concentration (C_{min}), time to maximum concentration (t_{max}), area under the curve from time zero to infinity following last administration ($AUC_{0-\infty}$), apparent clearance (CL/f), apparent volume distribution associated to the terminal phase (V_z/f), apparent volume of distribution at steady state (V_{ss}/f), area under the curve terminal phase rate constant (λ_z), and half-life ($t_{1/2}$) when appropriate.
Exploratory endpoints	**Phase Ib** CCI [redacted] **Phase II** • PRO assessments of MSC2156119J compared with sorafenib will be assessed using the FACT-HP questionnaire CCI [redacted]

	CCI [redacted]
Statistical methods (includes sample size calculation)	Statistical analyses of Phase Ib will be carried out in a descriptive manner, whereas Phase II has a confirmatory component when analyzing TTP. Data of Phase Ib will be analyzed after completion of the dose confirmation phase. Primary statistical analyses will be performed using electronic case report form (eCRF) data obtained until a clinical cut-off date in Phase II, which is determined by the date after the required number of events for the primary endpoint has been reported in the primary analysis population, i.e., 40 TTP events for the modified intent-to-treat (mITT) population in Phase II or on 15 August 2017, whichever occurs first. The final statistical analyses for the Phase II study will be performed at approximately 6 months after the last subject is first dosed. Determination of MET status is planned at Molecular Prescreening (Phase Ib retrospectively, Phase II for subject selection); rescoring will be performed as a quality control measure. The mITT population excludes subjects who were randomized but for whom, retrospectively, a c-Met status 1+ or 'not assessable' was detected. All data required for the calculation of time-to-event will be taken from eCRF, but randomization strata will be taken as specified in interactive voice/web response service. The DLT population will be used for analysis of Phase Ib. Statistical analyses in Phase Ib will be carried out in a descriptive manner. The mITT population will be primarily used in the analysis of baseline characteristics and efficacy. Analyses on the mITT population will consider subjects' allocation to treatment groups as randomized.

Selected efficacy analyses will be repeated for the intent-to-treat population, the Per Protocol (PP) population and for subgroups. In case that the PP population includes more than 90% of the mITT population, additional efficacy analyses on the PP population will be omitted.

The safety population will be considered for safety analyses. These analyses will consider subjects as treated.

Unless otherwise indicated, all analyses will be presented separately for the 2 treatment groups.

All statistical tests comparing treatment arms will be performed two-sided using a significance level of $\alpha = 10\%$, unless otherwise specified. If confidence intervals (CIs) are to be calculated, they will be two-sided with a confidence probability of 90%, unless otherwise specified.

Sample size

Phase Ib:

For Phase Ib, the total number of subjects to be enrolled in this trial is up to 21. Of these subjects, up to 18 will be enrolled based on the "3+3" dose escalation method with 2 dose cohorts: 3 to 6 subjects in the first dose cohort and 3 to 12 subjects in the second dose cohort (if dose de-escalation does not occur). In addition, separate from the "3+3" dose escalation cohorts, up to 3 subjects will be enrolled in the mainland China sites. The final sample size will depend on the number of subjects who experience DLTs observed at each dose level, the number of dose levels explored, the safety data, and the decision from the Safety Monitoring Committee (SMC) meeting.

Phase II

For Phase II, the initial sample size planning required 100 TTP events (assessed by an IRC) to ensure 80% power with a two-sided significance level of 10% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio (HR) of 0.6. Assuming a median TTP in Asian subjects for the sorafenib arm of 2.8 months, an HR of 0.6

	represents a 1.87 month increase, resulting in a median TTP of 4.67 months for the MSC2156119J arm. A total number of 140 subjects with MET+ HCC were planned to be randomized on a 1:1 basis to receive MSC2156119J or sorafenib. Prescreening/enrollment will be stopped following 40 TTP events (assessed by an IRC) or on 15 August 2017, whichever occurs first. It is expected that approximately 90 subjects will be randomized by 15 August 2017. The sponsor's decision to stop enrollment is due to business-related considerations not related to any safety issues.

2 Sponsor, Investigators, and Trial Administrative Structure

2.1 Sponsor

Merck KGaA will be the sponsor of this Asian clinical trial of mesenchymal-epithelial transcription factor (c-Met) inhibitor MSC2156119J (International Nonproprietary Name: tepotinib). The address of the sponsor is shown below:

Merck KGaA

Frankfurter Strasse 250

64293 Darmstadt, Germany

2.2 Trial Administrative Structure

A detailed administrative structure is in the trial Manual of Operations (MOP).

2.2.1 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will perform periodic reviews to evaluate the safety of the subjects who follow "3+3" dose escalation method in Phase Ib. Details of the safety monitoring process will be specified in a dedicated SMC charter.

SMC mandatory members will be identified before trial initiation and will include principal investigator(s) or coordinating investigator, the medical responsible, pharmacokineticist, and a safety representative from the sponsor. Ad hoc members will be consulted as needed and may include, but are not restricted to, the biostatistician or the treating investigator in the case of particular safety findings.

Responsibilities of the SMC will include:

- Review of all adverse events (AEs) and potential dose-limiting toxicities (DLTs), laboratory data, vital signs, and electrocardiogram (ECG) data, with determination of how to handle dose escalation and de-escalation and maximum tolerated dose (MTD)/Recommended Phase II dose (RP2D) based on their findings.

- The decision to escalate or de-escalate the investigational medicinal product (IMP), MSC2156119J, to a new dose level based on the criteria defined in this protocol for each dose regimen.

- Cohort review meetings to be held after Cycle 1 is completed by a number of subjects in a given cohort to discuss outcomes, dose escalation, and determination of the MTD/RP2D. The SMC will be responsible for reviewing a full set of safety and available pharmacokinetic (PK) data to make any determinations.

- Ad hoc SMC meetings to address any potential safety concerns.

- The decision of whether or not to continue with the MTD/RP2D determined during the dose escalation based on ongoing outcomes and findings.

SMC will only be responsible for evaluating the safety profile of the subjects who follow the "3+3" dose escalation method in Phase Ib. SMC will not be responsible for safety evaluation of the subjects in the Chinese (Mainland) subject cohort of Phase Ib. Sponsor experts including, but not limited to, medical responsible, safety responsible and pharmacokineticist, and the coordinating investigator will review the safety profile of the subjects in the Chinese (Mainland) subject cohort, if 3 evaluable subjects are enrolled in this cohort. See details in Section 5.1.

2.2.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will perform periodic reviews to evaluate the safety and efficacy of the subjects participating in Phase II. Details and periodicity of the safety monitoring process will be specified in a dedicated IDMC charter.

2.2.3 Independent Review Committee

An Independent Review Committee (IRC) will conduct a blinded review of the images of all subjects using the same criteria based on a separate charter outlining details of the review process. In addition, images will be evaluated by the IRC in accordance with modified Response Evaluation Criteria in Solid Tumors (mRECIST) (1).

3 Background Information

3.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the sixth most common cause of cancer and accounts for more than 626,000 new cases per year worldwide (2). Asia carries nearly 78% of the burden of HCC, with 55% of new cases occurring in mainland China (3, 4).

Many systemic therapies have been investigated for use in subjects with HCC; however, only sorafenib is approved for use in Asian countries, North America, and Europe (5). Sorafenib is not widely used in Asia largely due to affordability and unsatisfactory efficacy (6). Although cost sharing programs in some countries were successful in expanding usage, lack of long term coverage renders this practice unsustainable. In addition, emerging evidence suggests that sorafenib may be less tolerated by Asian cancer subjects compared with those of other ethnicities undergoing treatment in other regions. Hand-foot skin reaction appears to be more frequent in Asians, particularly lower-grade reactions. As a result, dose reduction or reduced starting doses of sorafenib is common in Asia (7, 8). Even with sorafenib, the overall prognosis of these subjects remains very poor, with a median time to progression (TTP) of 2.8 months and a median overall survival (OS) of 6.5 months (8). Therefore, effective systemic treatment of advanced stage HCC remains a high unmet medical need.

3.2 c-Met

The c-Met receptor tyrosine kinase is a cell surface receptor capable of mediating pleiotropic effects, including cell migration, survival, and proliferation. Its ligand is the hepatocyte growth factor (HGF), also known as scatter factor (9). Hepatocyte growth factor binding to the c-Met receptor leads to receptor dimerization and autophosphorylation, resulting in the activation of intracellular signaling cascades, such as the rat sarcoma/extracellular signal-regulated kinase and the phosphoinositide 3-kinase/protein kinase B pathway (10). Under physiological conditions, c-Met regulates invasive growth and morphogenesis in multiple embryonic tissues, such as muscles, nervous system, bones, and vascular system, and is essential for mammalian development. In postnatal life, c-Met signaling has been implicated in wound healing and regeneration of damaged organs, in particular the liver (11).

c-Met and HGF have been implicated in carcinogenesis and metastatic tumor progression because of their ability to enhance angiogenesis, cancer cell proliferation, migration, and invasion, as well as to confer resistance to apoptosis (9, 12). Activating c-Met point mutations and amplification, as well as c-Met/HGF coexpression, have been observed in a number of human tumors including breast, lung, and gastric carcinomas, glioma, multiple myeloma, and certain sarcomas. Hepatocyte growth factor is a critical molecule for hepatocyte regeneration after injury. It is secreted by stellate cells and binds to the c-Met receptor. Aberrant activity of c-Met has been described in human cancers as a result of c-Met amplification, germline or somatic mutations, transcriptional up-regulation, or HGF-dependent autocrine loops (13, 14, 15). Dysregulation of c-Met and HGF are common in HCC, although the exact role of this pathway in the pathogenesis of HCC is not established. Pharmacological interference with the HGF/c-Met axis is considered with increasing interest as a promising strategy to inhibit primary tumor growth and metastasis.

3.3 MSC2156119J

MSC2156119J is a potent, highly selective c-Met inhibitor with a favorable PK profile in humans allowing once daily dosing. It inhibits growth and induces regressions of HGF-dependent and HGF-independent susceptible tumor models and is currently under investigation in an ongoing first-in-man (FIM) trial. Refer to the latest Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and Guidance for the investigator.

3.3.1 Nonclinical Evaluation

Nonclinical studies indicate that MSC2156119J is a highly selective adenosine triphosphate (ATP)-competitive c-Met inhibitor, which effectively inhibits c-Met signaling in tumors. MSC2156119J exhibited marked inhibitory activity on the growth of mouse tumors and of human tumor xenografts and frequently led to complete regressions of established tumors. This antitumor effect was observed in 2 types of clinically relevant models: 1) tumor cells in which c-Met activation was ligand independent, i.e., tumors harboring c-Met amplification or activating mutation; 2) tumors in which c-Met and HGF were co-expressed, thereby creating an autocrine positive feedback loop.

Results of the nonclinical safety pharmacological studies conducted in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use-Guideline 7A/7B suggest a favorable nonclinical safety profile of the development compound.

On the basis of presently available results of the animal in vivo and in vitro studies, there are no reservations from a toxicological point of view against studying MSC2156119J in cancer subjects.

3.3.2 Clinical Experience

A single-center, non-randomized, open label, dose-escalation, FIM trial (EMR200095-001) to explore the safety, tolerability, PK/pharmacodynamics (Pd), and clinical activity of MSC2156119J administered under 2 treatment regimens was initiated in December 2009. Eligible subjects have advanced solid tumors that were either refractory after standard therapy or unsuitable for available therapies. An additional regimen, Regimen 3, was added on 04 April 2012.

The FIM trial started with 2 dosing schedules, each over a 21-day cycle:

- Regimen 1: 14 days on, 7 days off (starting dose: 30 mg once daily)
- Regimen 2: 3 times per week (i.e., Days 1, 3, and 5; starting dose: 30 mg once daily)

The trial was amended in 2012 to introduce a third regimen:

- Regimen 3: continuous dosing over the entire 21-day cycle (starting dose 300 mg once daily)

Regimen 3, which was introduced in 04 April 2012, is to further improve target inhibition by ensuring a constant exposure to the compound. Upon introduction of Regimen 3, Regimen 1 was discontinued and dose escalation continues with Regimen 2 and Regimen 3.

The FIM trial followed a sequential dose escalation "3+3" design. The criteria for dose escalation were based on the occurrence of DLTs and Grade 2 clinically relevant AEs. At the MTD/RP2D, an expansion cohort of 12 subjects carrying c-Met alterations (e.g., protein overexpression or gene mutation/amplification) was to be conducted to consolidate the safety profile, antitumor activity, and PK/Pd profile at the MTD/RP2D level.

The last subject-last visit in the FIM trial took place on 08 October 2015 and the Clinical Trial Report has been finalized.

CCI [redacted]

[redacted]

- CCI [redacted]

[redacted]

[redacted]

[redacted]

Further details, including data from the completed and ongoing trials, are available in the current IB.

3.3.2.1 Clinical Experience in Asian Population

Trial EMR200095-006 is a Phase Ib/II randomized, open-label trial to compare MSC2156119J plus gefitinib versus chemotherapy (pemetrexed + cisplatin) as second-line treatment in subjects with MET+, locally advanced or metastatic non-small cell lung cancer harboring epidermal growth factor receptor (EGFR) mutation and having acquired resistance to prior EGFR-tyrosine kinase inhibitor (EGFR-TKI) therapy.

CCI [redacted]

Preliminary data on the clinical activity of MSC2156119J in combination with gefitinib in this trial are outlined in Section 3.3.2 and indicate antitumor activity in subjects who have received prior EGFR-TKI therapy. Data also suggest that there may be an increased likelihood of response to therapy with increased levels of tumor c-Met expression (16).

CCI [redacted]

Further details are available in the current IB.

Although exposure in Asian subjects is limited, the safety data available to date continues to justify the use of MSC2156119J daily in Asian subjects in the clinical trial setting.

3.4 Rationale for the Current Trial

The pathogenesis and progression of HCC are mediated by a number of molecular defects and deregulated pathways. Among those, deregulation of c-Met and HGF are common in HCC. The presence of a c-Met induced expression signature derived from primary HCC and from liver metastases from extra hepatic tumors showed a significant correlation between increased vascular invasions and decreased mean survival times. Furthermore, recent results from a randomized second line Phase II trial in HCC showed that subjects with c-Met overexpressing tumors had a worse prognosis compared to the overall population, indicating that c-Met overexpression may be a poor prognostic factor in this disease (17).

Based on the results from preclinical studies, tumors in which c-Met and HGF were co-expressed create an autocrine positive feedback loop, thereby resulting in tumor cell proliferation and tumor growth. In SHARP study subgroup analysis by biomarkers, 491 and 305 subjects had usable plasma samples at baseline and at 12 weeks respectively. Subjects with low baseline HGF tended to derive greater benefit from sorafenib (OS: 12.4 months in sorafenib arm versus 9.8 months in placebo arm, hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.53-0.90) than those with high HGF concentration (OS: 6.3 months in sorafenib arm versus 5.3 months in placebo arm, HR: 1.10, 95% CI: 0.72-1.67) (18). Therefore, there is a high unmet medical need for subjects with advanced HCC harboring c-Met dysregulation (17).

At present, proof of concept (PoC) has been established for c-Met inhibition in a spectrum of solid tumors through a number of Phase II trials with a variety of c-Met inhibitors (e.g., rilotumumab in gastric cancer, onartuzumab in non-small cell lung cancer). Furthermore, subjects with c-Met alterations appeared more likely to derive benefit than subjects who do not overexpress c-Met. Specifically for HCC, several non-selective c-Met inhibitors have entered into Phase II trials. Cabozantinib, a c-Met/vascular endothelial cell growth factor receptor 2 inhibitor, demonstrated anti-HCC activity in a second-line Phase II trial. Notably, in subjects with MET Dx(+) tumors (defined as c-Met overexpression by immunohistochemistry [IHC]), improvement in both TTP and OS were more pronounced, suggesting that c-Met inhibition holds promise in treating HCC, especially in subjects with MET+ tumors.

This Phase Ib/II randomized, active controlled trial with a safety run-in period is designed to confirm the RP2D, efficacy and safety of MSC2156119J as monotherapy versus sorafenib in MET+ Asian (non-Japanese) subjects with HCC and Child-Pugh class A liver function. The trial is focused on subjects with Child-Pugh class A liver function because it helps control confounding issues of liver failure or death due to underlying chronic liver disease or cirrhosis, hence, treatment effect can be better assessed.

The rationale that MSC2156119J as monotherapy is to be compared with sorafenib in the first-line treatment for advanced HCC with MET+ is as follows:

- Inhibition of HGF/c-Met signaling has been explored as a therapeutic strategy for advanced HCC and subjects with MET Dx(+) had a worse prognosis and derived more benefit from the therapeutic strategy by c-Met inhibition;

- MSC2156119J is more selective and more potent than other c-Met inhibiting agents, which are already tested in HCC Phase II trials (refer to the latest IB);

- In-house studies indicated that primary liver explants with high levels of HGF/c-Met that are derived from treatment naïve Chinese HCC subjects were sensitive towards c-Met inhibition by monotherapy with MSC2156119J, which resulted in higher antitumor activity compared to sorafenib alone. In contrast, tumors characterized by moderate or low levels of HGF/c-Met were not sensitive to MSC2156119J (refer to the latest IB).

Geographical differences in terms of HCC disease and treatment practice are well documented (6). In clinical trials of sorafenib for advanced HCC, different efficacy outcomes were observed in Asian and other subjects. While the relative improvement in median OS was similar (HR for OS of 0.68 [95% CI: 0.50-0.93] and 0.69 [95% CI: 0.55-0.87] in Asian and other subjects, respectively) the absolute improvement in terms of median OS was 6.5 and 10.7 months in sorafenib arm in Asian subjects and other subjects, respectively (7, 8).

Possible reasons for these outcomes include variation in genetic and/or epigenetic aberrations between different viral etiologies and the propensity for Asian physicians to use local-regional therapy more aggressively and in later stages, resulting in enrollment of a more advanced subject population to trials of systemic therapy. In addition, sorafenib, the only globally approved agent with established OS benefit in advanced HCC, seems to have a slightly different safety profile in Asian subjects. Therefore, a Phase II trial in first-line MET+ HCC subjects in Asia is justifiable.

The proposed focused first-line Phase II trial in cancer subjects of non-Japanese Asian ethnicities will provide the global PoC for MSC2156119J in MET+ HCC; a separate trial in Japanese subjects with solid tumors is ongoing (EMR200095-003). In addition, a complementary development program in Caucasian subjects with HCC will be conducted in parallel to generate supportive data regarding the dose, antitumor activity, safety, and tolerability of MSC2156119J. A positive PoC trial together with the data from the trial in Caucasian subjects with HCC will provide the basis for a subsequent global Phase III trial in first-line HCC subjects with MET+ tumors versus sorafenib.

3.5 Risk-Benefit Evaluation

A safety run-in phase in HCC subjects with Child-Pugh class A liver function is included to confirm the appropriate dose and to better understand the PK and safety profile in subjects with mild impaired liver function who were excluded from the ongoing FIM trial. This approach is in line with recommendations by HCC experts (19).

Hepatocellular carcinoma generally develops from chronic liver diseases, mostly cirrhosis. Liver dysfunction and associated conditions may alter PK and tolerability (19). It is reasonable to set the initial dose level below the RP2D derived from subjects with normal liver function to preserve a margin for potential increased exposure. However, exposure of cancer subjects to subtherapeutic dose levels also should be avoided.

Overall, in the ongoing and completed trials, MSC2156119J was well tolerated (refer to the current IB). Asymptomatic pancreatic enzyme elevations are an identified risk from clinical studies, and

hepatobiliary toxicity and drug-drug interaction with P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic cation transporter 1 (OCT1) mediated transport drugs are potential risks from nonclinical studies.

Given the unmet medical need and limited treatment options in this indication, as outlined in Section 3.1, the overall benefit-risk evaluation remains positive.

A RP2D of 500 mg once daily has been determined. This RP2D is defined as a biologically active dose, based on PK/Pd modeling and supported by data on target inhibition from paired tumor biopsies, rather than as a safety defined MTD. Therefore, a Phase Ib safety run-in phase titrating from only 1 dose level below the RP2D of MSC2156119J (i.e., 300 mg prior to the randomized phase) is justified.

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (ICH Topic E6, GCP) and all applicable regulatory requirements.

4 Trial Objectives

4.1 Primary Objectives

The primary objectives are:

- Phase Ib: To confirm the RP2D of MSC2156119J administered orally once daily at a 21-day cycle in subjects with advanced HCC and Child-Pugh class A liver function. The target RP2D in HCC subjects is the RP2D as determined in the global FIM trial, i.e., 500 mg once daily

- Phase II: To evaluate efficacy as measured by TTP of MSC2156119J as monotherapy in the first-line treatment compared with sorafenib in subjects with MET+ advanced HCC and Child-Pugh class A liver function

4.2 Secondary Objectives

The secondary objectives are:

- Phase Ib: To characterize the single and multiple dose PK, preliminary antitumor activity, and biochemical response of MSC2156119J in Asian subjects with HCC and Child-Pugh class A liver function

- Phase II: To evaluate the safety and tolerability of MSC2156119J versus sorafenib

  To evaluate antitumor activity of MSC2156119J versus sorafenib

4.3 Exploratory Objectives

The exploratory objectives are:

- CCI [redacted]
- Phase II: To evaluate patient reported outcomes (PROs) of MSC2156119J compared with sorafenib. PROs will be assessed using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-HP) questionnaire.

CCI [redacted]

5 Investigational Plan

5.1 Overall Trial Design and Plan

Design

Phase Ib will be an open label, single arm trial at selected sites in mainland China, South Korea, and Taiwan.

The classical "3+3" design will be applied for sites in South Korea and Taiwan, with a dose escalation phase and a dose confirmation phase. In addition and separate from the "3+3" trial cohorts, up to 3 subjects will be enrolled in a separate cohort at selected sites in mainland China.

Phase II will be a randomized, open label, active controlled trial to evaluate the efficacy, safety, and PK of MSC2156119J as first-line treatment versus sorafenib in subjects with MET+, Barcelona Clinic Liver Cancer (BCLC) Stage B or C, systemic treatment naive advanced HCC and Child-Pugh class A liver function. Phase II is planned to be conducted at 45 to 55 sites in mainland China, South Korea, Taiwan, and other Asian countries.

Phase Ib

"3+3" Dose Escalation Cohorts

Phase Ib follows the classical "3+3" design, with a dose escalation phase and a dose confirmation phase. The criteria for dose escalation are based on the occurrence of DLTs and safety data; the definition of DLTs is provided in Section 6.2.2.

A SMC composed of sponsor representatives (trial physician, drug safety responsible, PK expert) and the principal investigator(s) will be responsible for making the decision of dose escalation, dose de-escalation, or expansion of enrollment at the same dose level. The decision will be made after all subjects in the preceding cohort have completed the first cycle of treatment and all safety data from Cycle 1 of the cohort under evaluation, as well as potential DLTs have been fully evaluated.

The first dose level will be 1 dose level lower than the target RP2D, which is 300 mg once daily. The second dose level and target RP2D is 500 mg once daily, which was determined as the RP2D in the FIM trial.

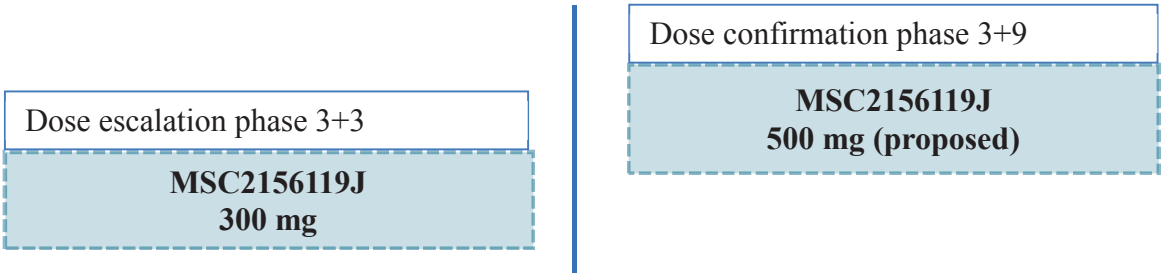
After the initial 3 subjects have completed Cycle 1 at the first dose level (300 mg) and have been fully followed up for potential DLTs, a SMC meeting will be held to evaluate the safety of MSC2156119J and to determine next step (see Figure 1). Depending on the safety observed, the next step will be enrollment of additional 3 subjects at 300 mg or enrollment of 3 subjects at 500 mg (i.e., dose escalation to the target RP2D). A SMC meeting will be held after extension of the first dose level to 6 subjects or/and after the initial 3 subjects at the second dose level are observed.

Once 3 subjects have completed 1 cycle at the second dose level (500 mg), and depending on the safety observed, the next step will be enrollment of an additional 9 subjects at 500 mg to confirm the RP2D, enrollment of an additional 3 subjects at 500 mg for further assessment, or dose de-escalation to a dose level less than 500 mg. In addition, recruitment will be stopped and an ad hoc SMC meeting will be convened if ≥ 33% of subjects experience a DLT. The criteria for dose escalation, de-escalation, or expansion of enrollment at the same dose are described in Section 6.2.1.

At the target RP2D, the safety and PK profile will be assessed in a total of 12 subjects to confirm the RP2D in Asian subjects with advanced HCC.

The sponsor may decide to assess doses higher than the target RP2D (i.e., doses > 500 mg once daily), doses lower than the first dose level (i.e., doses < 300 mg once daily), or doses between 300 mg and 500 mg once daily based on the newly updated information and available safety and PK data in order to determine the appropriate biologically active dose that will be used in Phase II. A new RP2D, which may be higher or lower than target RP2D (i.e. 500 mg once daily), may be recommended by SMC. In this case, up to 12 subjects may be required to confirm the new RP2D, and the "3+3" method will be followed.

Figure 1: Phase Ib Design ("3+3" Dose Escalation Cohorts)



Up to 18 subjects in 2 dose cohorts will be enrolled in Phase Ib following the "3+3" dose-escalation method (up to 6 subjects enrolled in the first dose cohort and up to 12 subjects enrolled in the second dose cohort). The final sample size depends on the number of subjects who experience DLTs, the safety and PK data at each dose level, and the decision from the SMC based on DLTs and other safety data.

Chinese (Mainland) Subject Cohort

Up to an additional 3 subjects will be enrolled in the mainland China sites separately. The subject(s) will be tested at 300 mg once daily. The aim of this cohort is to provide initial and preliminary data of the safety and PK of MSC2156119J in mainland Chinese subjects. The safety data from the mainland Chinese subject(s) will not be used for DLT evaluation and/or RP2D/MTD determination.

The first subject will be followed up for at least 21 days for safety assessment purpose. If the participating investigator and the coordinating investigator see no potential safety concerns from the first subject, the participating investigator and the coordinating investigator may recommend to close enrollment of this mainland Chinese subject cohort and inform the sponsor accordingly.

All subjects in this cohort will be evaluated with the same criteria as the other subjects in this Phase Ib trial. Subjects who are not fully evaluable for safety will be replaced (see Section 5.5.2). If the first subject in this cohort experiences an event listed in Section 6.2.2 of the protocol and if this event is classified as related to MSC2156119J, then additional 2 evaluable subjects at the same dose level may be recruited for further safety evaluation. The participating investigator and the coordinating investigator are required to provide a justified reason to the sponsor for expansion of the cohort or discuss with the sponsor for a final decision.

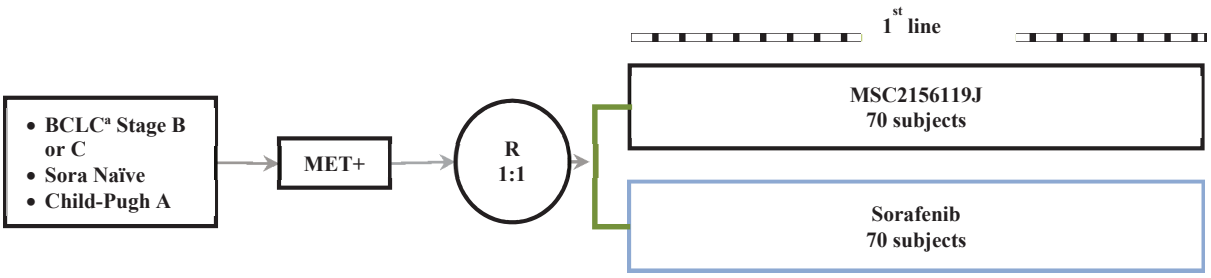
The safety evaluation should be based on a full safety and available PK data review of 21 days after the first dose has been administered. After a follow-up of at least 21 days for the last subject, the sponsor experts and the coordinating investigator will assess the safety profile of all enrolled subjects.

Phase II

Subjects will receive either MSC2156119J once daily (at the RP2D determined from Phase Ib) or 400 mg sorafenib twice daily until disease progression (as determined by the investigator),

intolerable toxicity, or consent withdrawal from the trial (see Figure 2). The dose-modification guideline in this trial for MSC2156119J is described in Section 6.2.5. Dose modification for sorafenib is at the discretion of the investigators based on the clinical circumstance, taking references to the Package Insert. Approximately 140 subjects with MET+ HCC were planned to be randomized on a 1:1 basis to receive MSC2156119J or sorafenib. The assessment for safety profile will be performed by the IDMC in Phase II, as described in Section 8.6.

Figure 2: Phase II Randomization Scheme



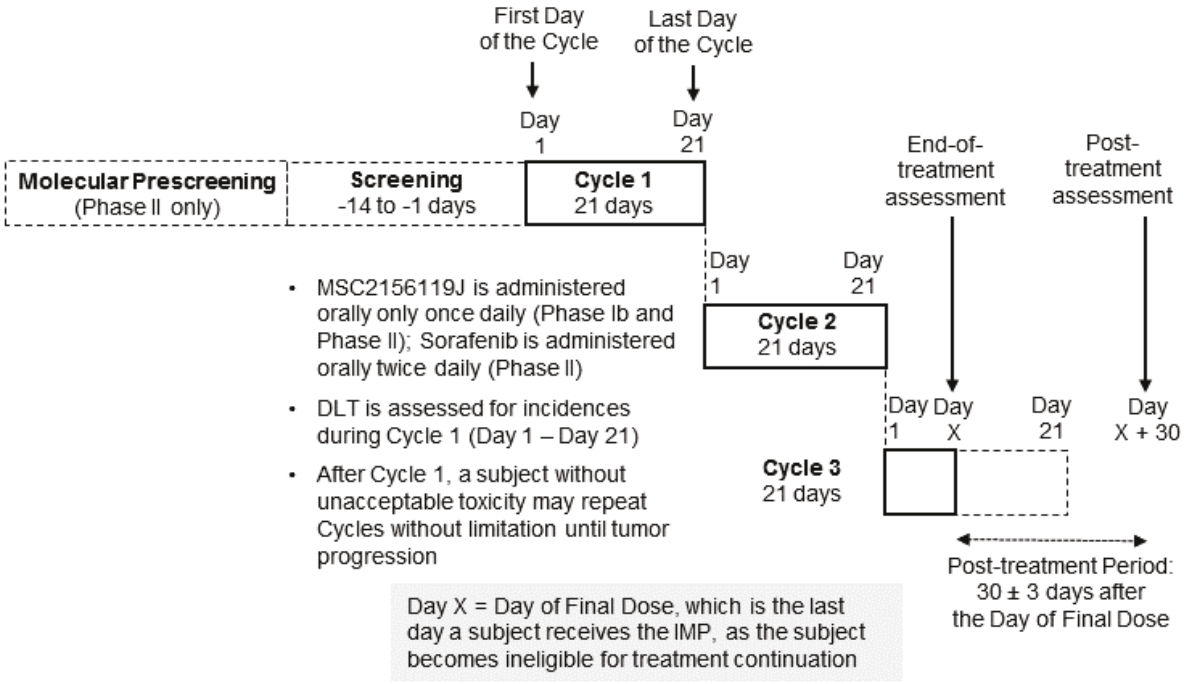
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; R, randomized; Sora, sorafenib.
NOTE: Approximately 70 subjects will be randomized in each arm.
a. Subjects who are not eligible for surgical and/or local-regional therapies or who have progressive disease after surgical and/or local-regional therapies only.

Treatment Duration

MSC2156119J (Phase Ib and Phase II) will be administered once daily over a 21-day cycle and sorafenib (Phase II) will be administered twice daily over a 21-day cycle. The minimum duration of treatment for each subject is 1 full cycle of treatment, i.e., 21 days, unless the subject discontinues treatment prematurely. Subjects who withdraw from Phase Ib may be replaced, as described in Section 5.5.2. Subjects who withdraw from Phase II will not be replaced. Subjects who do not show signs of disease progression and who tolerate the treatment during the Cycle 1 are allowed to repeat the treatment cycle without limitation, as long as no unacceptable toxicity or no disease progression is documented. The treatment with MSC2156119J or comparator must end when the subject experiences disease progression or unacceptable toxicity (see Figure 3).

Treatment duration is summarized in Figure 3.

Figure 3: Treatment Duration



Abbreviations: DLT, dose-limiting toxicity; IMP, investigational medicinal product.
NOTE: IMP (i.e., MSC2156119J) is administered once daily (Phase Ib and Phase II); sorafenib is administered twice daily (Phase II).

5.2 Discussion of Trial Design

This trial was designed based on the safety, tolerability, and PK data observed in the FIM trial in subjects with solid tumors (see Section 3.5).

In the completed FIM trial, MSC2156119J has a favorable safety profile. A RP2D of 500 mg once daily has been determined, based on PK/Pd modeling and supported by data on target inhibition from paired tumor biopsies, rather than as an MTD based on safety signals; there were no DLTs at the RP2D. Therefore, a Phase Ib safety run-in phase titrating from only 1 dose level below the RP2D (300 mg) prior to the randomized phase is justified.

The stepwise dose escalation scheme allows the safety and tolerability of each dose level to be evaluated before subjects are exposed to a higher dose level. The starting dose of 300 mg MSC2156119J once daily corresponds to 1 dose level lower than the RP2D of 500 mg once daily in the FIM trial. Doses exceeding 500 mg once daily will be explored only if there is a reasonable concern that the dose of 500 mg might not be biologically active in Asian subjects and the safety and/or PK data do not preclude further dose escalation.

Rationale for treatment regimen

Continuous once daily administration of MSC2156119J for 21 consecutive days was determined, after consideration of nonclinical data and the FIM trial, as the most appropriate treatment regimen for this trial.

The definition of the RP2D (i.e., 500 mg) was based on the following criteria and considerations (see the latest IB):

1. Based on the results from a nonclinical PK/Pd and tumor growth model, the analysis of target inhibition phospho-c-Met in on-treatment subject biopsies, and from a population PK model, the 500 mg once daily dose achieves target inhibition ≥ 95% and results in sufficiently high steady state (trough) exposure levels in ≥ 90% of subjects to induce activity in tumors with varying degrees of sensitivity to c-Met inhibition. Further support for this recommendation can be found in the latest IB.

2. The SMC evaluated results from an expanded cohort of 14 subjects that were treated with 500 mg MSC2156119J once daily administered over a 21-day cycle. No DLTs were observed in the 12 evaluable subjects. Of the 2 subjects who were not evaluable, 1 subject was replaced due to the AE of Grade 2 bacteremia (assessed by the investigator as not related to MSC2156119J) and the other subject was replaced due to disease progression.

3. The 500 mg once daily dose is, therefore, considered to be safe and in the biologically active range and will be used as the target dose level (i.e., RP2D) in subsequent clinical trials with MSC2156119J.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

5.3.1 Inclusion Criteria

For inclusion in the trial, all of the following inclusion criteria must be fulfilled:

1. Histologically or cytologically confirmed HCC

2. Subjects with either intermediate HCC of BCLC Stage B, who are not eligible for surgical and/or local-regional therapies or who have progressive disease (PD) after surgical and/or local-regional therapies, or with advanced HCC of BCLC Stage C. See Appendix K

   NOTE: local-regional therapy MUST NOT contain sorafenib

3. Subjects who have disease progression or are intolerant to the prior standard treatment for advanced HCC (Phase Ib Korean subjects only)

4. A tumor biopsy (excluding fine needle aspiration and cytology samples) is required for determining MET status (a fresh pretreatment tumor biopsy is recommended but archived tumor sample is acceptable).

5. MET+ status (Phase II only), as determined by the central laboratory (Phase Ib retrospectively, Phase II for subject selection) is defined as c-Met protein overexpression (e.g., moderate [2+] or strong [3+] staining intensity for c-Met using IHC in the majority [≥ 50%] of tumor cells) (see

6 Appendices

6. Appendix A)

   NOTE: the main purpose of the Phase Ib trial is to determine the RP2D, safety, and PK profile of MSC2156119J in HCC subjects, therefore, MET+ status is not an eligibility criterion for Phase Ib

7. Child-Pugh class A (see Appendix B) with no encephalopathy according to the screening assessment

8. Asian male or female, 18 years of age or older

9. Measurable disease in accordance with Response Evaluation Criteria in Solid Tumors (RECIST v 1.1). The target lesion that has received previous local therapy should not be considered as measurable unless clear progression has been documented since the therapy (Phase II only) (see Section 8.3 and Appendix C)

10. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (see Appendix D)

11. Eligible for treatment with sorafenib, as assessed by investigators according to the Package Insert and clinical judgment (Phase II only)

12. Signed and dated informed consent indicating that the subject has been informed of all the pertinent aspects of the trial prior to enrollment

13. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other trial procedures

14. Life expectancy judged by the investigator of at least 3 months

6.1.1 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Prior systemic anticancer treatment for advanced HCC, including targeted therapy (e.g., sorafenib), chemotherapy, or any other investigational agent (Phase II only)

2. Prior treatment with any agent targeting the HGF/c-Met pathway

3. Prior local-regional therapy within 4 weeks prior to Day 1 of trial treatment (e.g., major surgery, radiation therapy [with the exception of palliative bone-directed radiotherapy and radiotherapy administered to superficial lesions], hepatic arterial embolization, transcatheter arterial chemoembolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation)

NOTE: palliative bone-directed radiotherapy should be within a limited field of radiation and for palliation only; it should be a short course, according to local institutional recommendations, and should be completed at least 7 days prior to the first administration of trial treatment

4. Prior history of liver transplant

5. Laboratory index at baseline:

   - Hemoglobin ≤ 8.5 g/dL (without transfusion or growth factor support in the preceding 14 days)
   - Neutrophils < 1.5 x 10^9/L
   - Platelets < 60 x 10^9/L (without transfusion or growth factor support in the preceding 7 days)
   - Total bilirubin > 3 mg/dL
   - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN)
   - Renal impairment as evidenced by serum creatinine ≥ 1.5 x ULN, or calculated creatinine clearance (CrCl) < 60 mL/min by Cockroft-Gault formula (24-hour CrCl might be requested by the investigator for confirmation, if calculated CrCl is < 60 mL/min. In such case, subjects with 24-hour CrCl < 60 mL/min should be excluded)

     $$\text{CrCl (mL/min)} = \frac{[140 - \text{age (year)} \times \text{weight (kg)}]}{72 \times \text{serum creatinine (mg/dL)}} \quad \{\times 0.85 \text{ for female subjects}\}$$

   - International normalized ratio (INR) > 2.3 (in accordance with the guidance that has been modified for Child-Pugh classification; see Appendix B)
   - (*Criterion has been deleted by amendment*)
   - Albumin < 28 g/L (without transfusion in the preceding 14 days)

6. Past or current history of neoplasm other than HCC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years

7. Known central nervous system (CNS) or brain metastasis that is either symptomatic or untreated

8. Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the tested products

9. Clinically significant gastrointestinal bleeding within 4 weeks prior to Day 1 of trial treatment

10. (*Criterion has been deleted by amendment*)

11. Impaired cardiac function:

    - Left ventricular ejection fraction < 45% on recent echocardiography (Note: a screening left ventricular ejection fraction assessment without history of congestive heart failure is not required unless clinically indicated.)
    - Serious arrhythmia
    - Unstable angina pectoris
    - Congestive heart failure New York Heart Association (NYHA) III and IV (see Appendix E)
    - Myocardial infarction within the last 12 months prior to Day 1 of trial treatment
    - Pericardial effusion

12. Hypertension uncontrolled by standard therapies (not stabilized to ≤ 150/90 mmHg)

13. Subject with a family history of long QT syndrome, or who takes any agent that is known to prolong QT/QTc interval, or with a marked prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval > 450 msec)

14. Known human immunodeficiency virus (HIV) infection

15. Subjects who have acute pancreatitis and/or chronic pancreatitis, with elevated lipase and/or amylase, clinical symptoms, and/or imaging studies that are indicative of the diagnosis (Mainland Chinese subjects only).

16. Known or suspected drug hypersensitivity to any ingredients of sorafenib (Phase II only) and MSC2156119J

17. Female subjects who are pregnant or lactating, or males and females of reproductive potential not willing or not able to employ a highly effective method of birth control/contraception to prevent pregnancy from 2 weeks before receiving study drug until 3 months after receiving the last dose of study drug. A highly effective method of contraception is defined as having a low failure rate (< 1% per year) when used consistently and correctly.

18. Concurrent treatment with a non-permitted drug

19. Substance abuse, other acute or chronic medical or psychiatric condition, or laboratory abnormalities that may increase the risk associated with trial participation in the opinion of the investigator

20. Participation in another interventional clinical trial within the 28 days prior to Day 1 of trial treatment or within a time period that is less than the cycle length for the investigational treatment (whichever is shorter), or if the subject has any AE caused by the investigational treatment that has not recovered to Grade 1 or less

21. Previous anticancer treatment-related toxicities not recovered to baseline or Grade 0-1 (except alopecia)

22. Subjects with any concurrent medical condition or disease that will potentially compromise the conduct of the study at the discretion of the investigators

23. Clinically significant third space fluid accumulation (despite the use of diuretics), e.g., moderate to large ascites requiring tapping or pleural effusion that either requires tapping or results in shortness of breath

24. Complete occlusion of the major portal vein or vena cava due to HCC. (The major portal vein is defined as the part of portal vein between the union of the splenic and superior mesenteric veins and the first bifurcation into the left and right vein)

6.2 Criteria for Randomization/Initiation of Treatment with the Investigational Medicinal Product

The inclusion and exclusion criteria will be checked during Molecular Prescreening (confirmation of cMET status in Phase II only) and Clinical Screening. Eligible subjects will be enrolled prior to the initiation of MSC2156119J or sorafenib treatment and after verification that the subject fulfils all inclusion criteria without meeting any of the exclusion criteria.

6.3 Criteria for Subject Withdrawal

6.3.1 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving a reason. A subject must be discontinued in the event of withdrawal of consent.

If a subject fails to attend scheduled trial assessments, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, every effort should be made to complete the investigations scheduled for the last visit, focusing on the most relevant assessments. In any case, the appropriate electronic case report form (eCRF) section must be completed.

In case of withdrawal from the trial, it must be clearly stated if the subject is also withdrawing their consent from the post-treatment follow-up and survival assessments, which include the

collection of data on tumor assessment (if without documented PD), safety, survival and subsequent anticancer therapy.

6.3.2 Replacement of Discontinued Subjects

Subjects withdrawn in Phase Ib may be replaced if they are not fully evaluable for the assessment of the primary endpoints. "Not fully evaluable" is defined as:

- Subjects who discontinue the trial prematurely during Cycle 1 for reasons other than a DLT. Such reasons could include, for example, withdrawal of consent, not meeting the eligibility criteria, noncompliance with follow up, early disease progression, or unrelated AEs.

- Subjects who do not receive at least 80% (i.e., 17 treatment days) of planned cumulative doses of MSC2156119J during Cycle 1, for reasons other than AEs related to MSC2156119J or DLTs.

Subjects withdrawn in Phase II will not be replaced.

6.3.3 Withdrawal from Trial Therapy

The subject must be withdrawn from the IMP or sorafenib in the event of any of the following:

- Therapeutic failure (i.e., oncologic emergency due to serious tumor progression or serious side effect) requiring urgent additional therapy
- AEs if:
    - discontinuation of trial medication is desired or considered necessary by the investigator and/or the subject
    - dose delay time is more than 21 consecutive days at the lowest dose, as defined in Section 7.2.5
- Pregnancy
- Use of a non-permitted concomitant drug, as defined in Section 7.5.2, where the predefined consequence is withdrawal of the trial therapy
- Noncompliance with administration of the trial therapy, as defined in Section 7.2.5;
- Documented progression of the disease
- Initiation of any other anticancer treatment (including radiotherapy, surgery, or hormonal therapy)

If subjects withdraw without documented disease progression, e.g., due to clinical deterioration or AEs, every effort should be made to document objective progression even after discontinuation of treatment.

6.4 Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of MSC2156119J, e.g., due to
  - Evidence of inefficacy

    (Note: evidence of inefficacy may arise from this trial or from other trials).
  - Safety findings that preclude further continuation of the trial

    (Note: unfavorable safety findings may arise from clinical or nonclinical examinations, e.g., toxicology).
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Poor enrollment making completion of the trial within an acceptable time frame unlikely
- Discontinuation of development of MSC2156119J

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

6.5 Definition of End of Trial

The end of the trial was defined as when 80% of the subjects either die or drop-out of the trial. Subjects who are on active treatment with MSC2156119J (or sorafenib) at the time of end of the trial will be offered further treatment with MSC2156119J (or sorafenib if reimbursement is not available in participating countries) and assessments as appropriate in case a potential benefit from further treatment is seen. However, under certain circumstances, subjects may be given the opportunity to participate in a rollover trial or the sponsor may terminate the trial early.

The sponsor will stop prescreening/enrollment following 40 TTP events (assessed by an IRC) or on 15 August 2017, whichever occurs first. Subjects who sign the Informed Consent Form (ICF) prior to 15 August 2017 and undergo prescreening/screening after the enrollment stop date may still be randomized in the trial. Subjects who are currently receiving treatment may continue treatment after discussion with their Investigator. If the subject decides to continue treatment, they will continue on their originally randomized treatment, at their most recent dose according to the protocol. Safety monitoring and data collection will continue without modification through to the end of the trial.

7 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to the investigational drug undergoing trial, i.e., MSC2156119J (International Nonproprietary Name: tepotinib).

7.1 Description of Investigational Medicinal Product

MSC2156119J, 3-(1-{3-[5-(1-Methyl-piperidin-4-ylmethoxy)-pyrimidin-2-yl]-benzyl}-6-oxo-1,6-dihydro-pyridazin-3-yl)-benzonitrile) mono-HCl, monohydrate, is supplied as 25 mg and 100 mg film-coated tablets.

CCI [redacted]. All excipients used are of compendial grade. Supplier's certificates show that there is no transmissible spongiform encephalopathy risk.

7.2 Dosage and Administration

Phase Ib

For each dose cohort, a fixed dose and administration will be applied. The assigned dose of MSC2156119J will be administered daily, with 25 mg and/or 100 mg film-coated tablets.

For "3+3" dose escalation cohorts, the first dose level will be 300 mg once daily, which is 1 level lower than the target dose of RP2D (500 mg, once daily) from the FIM trial. The second dose level will be 500 mg once daily.

Subjects will take their assigned doses of MSC2156119J orally, in the morning approximately at the same time, immediately after breakfast, with a full glass of water (approximately 200 mL), every day of each 21-day treatment cycle.

Subjects will be instructed to swallow the tablets whole and to avoid biting or breaking the tablets, or attempting to dissolve the tablets in water before taking them.

On days when PK samples are to be drawn, subjects should be instructed to attend the clinic in a fasted state, with no breakfast prior to taking the MSC2156119J dose. After a predose PK blood sample is drawn, the assigned dose of MSC2156119J should be taken following breakfast. No further food should be consumed until 2 hours after the dose (water is allowed).

Phase II

The dose of MSC2156119J will be the RP2D determined in Phase Ib.

Subjects who are randomized to MSC2156119J will take their assigned dose orally once daily, approximately at the same time in the morning, immediately after breakfast with a full glass of water (approximately 200 mL), every day of each 21-day treatment cycle.

Subjects who are randomized to sorafenib will take two 200 mg tablets in the morning and two 200 mg tablets in the evening (800 mg total daily dose), taken on an empty stomach 1 hour before or 2 hours after ingestion of food with a full glass of water (approximately 200 mL), every

day of each 21-day treatment cycle. Subjects should be instructed to take sorafenib at approximately the same times each day.

On days when PK samples are to be drawn, subjects should be instructed to attend the clinic in a fasted state, with no breakfast and prior to taking the MSC2156119J dose. After a predose PK blood sample is drawn, the assigned dose of MSC2156119J should be taken following breakfast. No further food should be consumed until 2 hours after the dose (water is allowed).

7.2.1 Dose Escalation Assessment Process

The trial will adopt the sequential "3+3" dose escalation design. Two sequential dose cohorts of escalated dose levels (300 mg and 500 mg) with 3 subjects in each cohort will be conducted.

If ≥ 33% of subjects experience a DLT in the second dose cohort (500 mg), the next step will depend on the decision of the SMC based on the rules described below.

After 3 subjects at a given dose level have completed Cycle 1 (21 days), new enrollment to this trial will be paused and a full safety data set (all AEs, laboratory data, ECG data, and vital signs) and available PK data will be submitted to the SMC, which evaluates the data and confirms the DLT incidence. The details of this process will be described in the SMC Charter.

Decisions on dose escalation are based on the occurrence of DLT and the safety and PK data (see Section 7.2.2) during the Cycle 1 (21 days) and the decision criteria are as follows:

For the first dose cohort (300 mg):

- If no subject experiences a DLT during Cycle 1 (21 days), dose escalation will proceed to the higher dose cohort (500 mg)
- If 1 subject out of the first 3 experiences a DLT during Cycle 1 (21 days), 3 additional subjects will be enrolled at the same dose (300 mg)
    - If none of the additional 3 subjects experiences a DLT; dose escalation will proceed to the higher dose cohort (500 mg)
    - If 1 or more of the additional subjects experience a DLT, no additional subjects will be enrolled and the trial will be discontinued, unless there is evidence to support for further exploration of the potentially biologically active doses lower than 300 mg under the decision from the sponsor
- If 2 or more subjects out of the first 3 experience DLT during Cycle 1 (21 days), no additional subjects will be enrolled and the trial will be discontinued, unless there is evidence to support for further exploration as specified above

If the SMC sees a potential safety concern from the AEs data other than DLT at the first dose cohort, 3 additional subjects may be enrolled at the same dose level under the decision from the SMC meeting.

For the second dose cohort (500 mg):

- If no subject out of the first 3 experience DLT during Cycle 1 (21 days), 9 additional subjects will be enrolled at the same dose cohort (500 mg)
- If 1 subject out of first 3 experience DLT during Cycle 1 (21 days), 3 additional subjects will be enrolled at the same dose cohort (500 mg)
    - If none of the additional 3 subjects experiences a DLT; 6 additional subjects will be enrolled at the same dose cohort (500 mg) to have a total of 12 subjects
    - If 1 or more of the additional 3 subjects experience a DLT, no additional subjects will be enrolled at this dose level, the next step will depend on the decision of the SMC
- If 2 or more subjects out of the first 3 experience DLT during Cycle 1 (21 days), the next step will depend on the decision of the SMC

7.2.2 Definition of DLT

The period of DLT observation is during Cycle 1 (21 days) for each subject.

Using the National Cancer Institute's (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, DLT is defined as any of the following toxicities at any dose level and judged to be related to the trial treatment by the investigator and/or the sponsor:

- Grade 4 neutropenia for more than 7 days
- Grade ≥ 3 febrile neutropenia for more than 1 day
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with non-traumatic bleeding
- Grade ≥ 3 uncontrolled nausea/vomiting and/or diarrhea despite adequate and optimal treatment
- Grade ≥ 3 any non-hematological AE, except the aforementioned gastrointestinal events and alopecia; however, a DLT is defined specifically for the following cases:
    - Grade ≥ 3 liver AE requiring a recovery period of more than 7 days to the baseline or to Grade 1 (or less) (This criterion is not limited to the liver function tests. Other liver AE e.g., jaundice or hepatic encephalopathy suggestive of liver failure should be also considered.)
    - Grade ≥3 lipase and/or amylase elevation with confirmation of pancreatitis, either based on clinical or radiological signs will be considered as DLT. An isolated lipase and/or amylase elevation of ≥ Grade 3 without clinical or radiological evidence of pancreatitis will not be classified as DLT. (For related topics, see below "Asymptomatic Pancreatic Enzyme Elevation")

AEs assessed by the investigators to be exclusively related to the subject's underlying disease or medical condition/concomitant treatment are not considered as DLT.

Asymptomatic Pancreatic Enzyme Elevation

If an asymptomatic lipase/amylase elevation of Grade ≥ 3 occurs during Cycle 1, the subject will undergo clinical evaluation for the presence of signs and symptoms typical of acute pancreatitis and for other risk factors for pancreatitis. In addition, a computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of the abdomen will be performed to assess the pancreas. The sponsor (or delegate) will be notified of the outcome of the CT/MRI. Dosing with MSC2156119J will continue during the evaluation period unless the clinical evaluation indicates pancreatitis. However, the continuation of MSC2156119J for the subject will be individually discussed with the sponsor (or delegate) on a subject by subject basis.

All cases of asymptomatic pancreatic enzyme elevations of Grade ≥ 3 will be reported as Adverse Event of Special Interest (AESI) (see Section 8.4.1.1) to the sponsor (or delegate) in an expedited fashion.

If there are no clinical or radiological signs indicative of pancreatitis, dosing with MSC2156119J will continue and the pancreatic enzyme elevation occurring during Cycle 1 will not be classified as DLT.

Asymptomatic lipase/amylase elevations may occur during or beyond Cycle 1, and 3 different scenarios are forecasted:

- Persistent asymptomatic lipase/amylase elevation at the same grade of Grade ≥ 3
- Recurrent asymptomatic elevation of Grade ≥ 3, after an initial Grade ≥ 3 elevation with subsequent resolution
- Asymptomatic lipase/amylase elevation of Grade ≥ 3 with persistent elevation at the same grade, followed by subsequent further increase in grade

In all cases, the subject will undergo clinical evaluation for the presence of signs and symptoms typical of acute pancreatitis and for other risk factors for pancreatitis. A gastrointestinal consult should be requested and additional investigations (e.g., repeated abdominal CT scan) should be considered, as appropriate. The case will be discussed with the sponsor (or delegate). Treatment with MSC2156119J may be continued during the evaluation period, at the discretion of the treating physician and depending on the circumstances of the individual case.

If there is no clinical or radiological evidence of pancreatitis, treatment with MSC2156119J should be continued, particularly if there may be a potential benefit from treatment for the individual subject. Evaluation of potential clinical benefit will be based on evidence from the literature, preclinical models and/or current experience with MSC2156119J in the subject or other subjects with this tumor type. Otherwise, treatment with MSC2156119J should be discontinued.

7.2.3 MTD/RP2D Definition Process

For determination of the MTD/RP2D of MSC2156119J in Asian subjects, relevant data for the primary endpoint will be presented to the SMC.

MTD

In the "3+3" dose escalation method, the MTD is defined as the next lower dose than the dose at which a DLT occurs in > 1 out of 3 or ≥ 2 out of 6 subjects. This trial will also apply this method. For molecularly targeted oncology drugs in oncology, it may not always be possible or necessary to determine an MTD.

RP2D

The FIM trial specified that the SMC could recommend an RP2D if it was not possible or necessary to reach an MTD in a given regimen on the basis of the review of the cumulative safety, PK, Pd, and clinical data. The definition of an RP2D is then based on the following criteria and considerations:

(A) Preclinical PK/Pd model

Establishment of a nonclinical PK/Pd model that will link plasma concentrations, target inhibition and antitumor activity in c-Met dependent xenograft models, and that will determine expectations for an active dose range in human.

(B) Review of human PK data

Review of human PK data to determine at what dose level the active dose range will be reached in ≥ 90% of subjects.

7.2.4 Criteria for Additional Treatment Cycles

Subjects will repeat the 21-day treatment cycle after completion of Cycle 1 if the disease is not progressing.

To qualify for continued treatment beyond Cycle 1, all of the following criteria must be fulfilled:

- A subject does not show evidence of disease progression
- A subject and the investigator consider it is in the subject's best interest to continue treatment
- A subject does not meet any of the criteria for withdrawal in Section 6.3.

Once the treatment with MSC2156119J beyond Cycle 1 is initiated, the subject can repeat the 21-day treatment cycle without limitation, as long as all the criteria above remain fulfilled.

7.2.5 Dose Adjustment and Missed Dose

Missed doses of trial treatment will not be made up unless the subject is seen to vomit the entire tablet immediately after administration of the study drug. An administration time delay ≤ 12 hours compared to the scheduled administration time is permitted; however, if the time delay is > 12 hours, study drug should not be administered on the current day. In Phase Ib and Phase II, subjects who miss more than 21 consecutive days of trial treatments for non-medical reasons are considered non-compliant and should be withdrawn from trial treatments (see Section 6.3.3).

As for dose adjustment, subjects will remain on their starting dose of MSC2156119J throughout the trial with the exception of dose modification due to tolerability (applicable for Phase Ib and Phase II).

Subjects who miss more than ~20% of doses planned during Cycle 1 (i.e., 4 days) for reasons other than adverse drug reactions or DLTs will not be fully evaluable for the assessment of the primary endpoints of Phase Ib; these subjects will be replaced for assessment of DLT. The overall safety assessment will be performed based on the full data set from all subjects who take at least 1 dose of MSC2156119J.

Subjects are permitted to undergo dose modification to ensure MSC2156119J is well tolerated at the scheduled dose levels. For the Phase II study, a one-level dose schedule will be applied for dose modification, i.e., to the next dose level lower than the RP2D. If a subject still does not tolerate the permitted lower dose, the subject will be withdrawn from the study. Assuming that the RP2D is 500 mg daily, the lower dose strength to adjust to in case of toxicity is 300 mg. The maximum permitted continuous dosing delay time is 21 days.

AEs assessed by the investigators to be exclusively related to the subject's underlying disease or medical condition/concomitant treatment are not applied for the guideline of dose modification.

The following dose modification guideline for MSC2156119J is recommended. However the investigators could otherwise modify the dosage based on clinical circumstances on a case by case basis. Under such circumstance, the investigators should notify the sponsor case by case and provide the reason to the sponsor.

Under the following circumstances, the dose should be interrupted temporarily until AEs recover to Grade 1 (or less) or baseline. Subjects can be rechallenged at the next lower dose level; the dose should be stopped as soon as the investigator becomes aware of the following AEs:

- Grade 4 neutropenia for more than 7 days
- Grade ≥ 3 febrile neutropenia for more than 1 day
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
- Grade ≥ 3 uncontrolled nausea/vomiting and/or diarrhea despite adequate and optimal treatment for more than 3 days
- Grade ≥ 3 non-hematological AE, except the aforementioned gastrointestinal events and alopecia; however, the following cases are specifically defined:
    - Grade ≥ 3 liver AE requiring a recovery period of more than 7 days to the baseline or to Grade 1 (or less)
    - Grade ≥ 3 lipase and/or amylase elevation with confirmation of pancreatitis (for related topics, see below "Asymptomatic Pancreatic Enzyme Elevation")
- Recurrence of Grade ≥ 2 AEs after rechallenging at the same dose level despite adequate and optimal treatment

Under the following circumstances, the dosing could be continued with adequate and optimal supportive treatment:

- Grade 1 AE
- Grade 2 AE that could be tolerated well
- Asymptomatic lipase and/or amylase elevation, i.e., without confirmation of pancreatitis

In the event of a subject experiencing Hepatitis B virus (HBV) or Hepatitis C virus (HCV) reactivation (see Section 7.5.3.1), the following dose modification guidelines should be followed:

- HBV reactivation:
    - Provide antiviral treatment and/or adjust current antiviral treatment
    - Interrupt MSC2156119J until HBV DNA resolves to ≤ baseline levels
        - If resolution takes longer than 21 days, discontinue MSC2156119J
        - If resolution is within 21 days, MSC2156119J can be resumed at a minus 1 dose level
- HCV reactivation: Discontinue MSC2156119J

For the other circumstances not outlined aforementioned, the dose could be interrupted temporarily (for a maximum of 21 days) until recovery to Grade 1 (or less) or baseline and the same dose could be restarted after recovery. The dose should be stopped as soon as the investigator becomes aware of the AE.

The investigators should modify the dose of sorafenib based on the clinical circumstance, taking references to the description in the Package Insert. The Package Insert will be provided as a separate document. The permitted maximum time for continuous dose interruption of sorafenib is also 21 days.

7.2.6 Intrasubject Dose Escalation

Intrasubject dose escalation is not allowed in this trial and each subject will stay on the assigned dose level (except for dose modification due to tolerability) throughout his/her treatment period unless there is a considerable reason to allow intrasubject dose escalation. Any intrasubject dose escalation must be agreed by the sponsor.

7.3 Assignment to Treatment Groups

Subject allocation

Phase Ib is a single arm trial to be conducted at selected sites in mainland China, South Korea, and Taiwan. Subjects will be assigned sequentially to the available dose cohort.

Phase II is a randomized trial to be conducted at 45 to 55 sites in mainland China, South Korea, Taiwan, and other Asian countries. Randomization will be performed centrally by using an interactive voice response system (IVRS).

Subject Number

Subject numbers will be composed of 16 digits:

- The first 9 digits will represent the trial number
- The next 3 digits will represent the site number
- The last 4 numbers will be the sequential order in which subjects are enrolled into the trial by signing the main ICF (beginning with 0001)

Subject numbers will not be reassigned to other subjects or reused in this trial. If a subject is replaced, the replacement will be enrolled with a unique subject number.

7.4 Other Drugs to be used in the Trial

In addition to the treatment with MSC2156119J, commercially available sorafenib is also to be administered to the subjects during the course of the Phase II. Sorafenib will be supplied as red, round film coated tablet, containing 200 mg sorafenib (as the tosylate) and the following excipients: iron oxide red, titanium dioxide, sodium laurylsulfate, magnesium stearate, hypromellose, cellulose microcrystalline, macrogol, and crosscarmellose sodium; however, the actual appearance and composition of the product may depend on the respective marketed product sourced for the participating countries.

7.5 Concomitant Medications and Therapies

7.5.1 Permitted Medicines

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary for the subjects' welfare and will not interfere with the trial medication may be given at the investigator's discretion.

The investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of the main informed consent, in the appropriate section of the eCRF.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration and indication of each drug.

The following are permitted:

- Oral antivirals for chronic hepatitis are permitted before and during the study. The prescription of these agents for subjects with chronic hepatitis during the study is recommended based on the clinical guidelines

- Ongoing interferon therapy for hepatitis started before screening is permitted

- Concomitant medications that have a narrow therapeutic window and are known to be transported by P-gp (e.g., rivaroxaban, apixaban, ranolazine, talinolol, digoxin), BCRP (e.g., rosuvastatin), or OCT1 are permitted, but should be used with caution (refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/default.htm for examples of in vitro, in vivo, and clinical substrates for P-gp and BCRP)

- Concomitant medications that are known to inhibit P-gp (e.g., itraconazole, telaprevir, clarithromycin, ketoconazole, and conivaptan) are permitted but should be used with caution (refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/default.htm for examples of clinical inhibitors for P-gp and BCRP)

- Supportive treatment, e.g., bisphosphonates, agents for improving appetite, if initiated prior to Day 1 of trial treatment, it is allowed to continue. Change in dose/schedule on study is discouraged. Initiation of biphosphates with prophylactic purpose during study treatment should be avoided.

7.5.2 Non-Permitted Medicines

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

The following are not permitted during the trial:

- Drug(s) for which the package insert/Summary of Product Characteristics includes a contraindication for P-gp (e.g., dabigatran, aliskiren, colchicine), BCRP, and/or OCT1 inhibiting drugs must not be combined with MSC2156119J (refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/default.htm for examples of clinical inhibitors for CYP3A-mediated metabolisms)

- Drug(s) that are known to induce P-gp and thereby may decrease the efficacy of MSC2156119J (e.g., avasimibe, carbamazepine, phenytoin, rifampin, St John's Wort) (refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/default.htm for examples of clinical inhibitors for CYP3A-mediated metabolisms)

- Initiation of new interferon therapy

- Traditional Chinese Medicine with an approved anticancer indication

- Any other cancer therapy, including chemotherapy or local regional treatments, with any investigational product other than the MSC2156119J and sorafenib, as defined in this protocol

- Prophylactic granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor
- Experimental or systemic anticancer therapy, except for localized radiotherapy for pain control provided the localized radiotherapy does not compromise tumor assessments of target lesions

Use of non-permitted medicines for any reason must result in withdrawal of the subject from this trial.

7.5.3 Other Trial Considerations

7.5.3.1 Guidelines for Subjects with Hepatitis B or Hepatitis C

Subjects with concurrent hepatitis B or hepatitis C infection are permitted to participate in the trial, provided they meet the eligibility criteria. The safeguards outlined below should be followed in order to ensure that subjects with concurrent hepatitis infection receive appropriate monitoring and care. See also Section 8.4.3.5.

In order to document baseline virology status, all subjects will undergo the following testing at baseline (see Section 8.1.2):

- Hepatitis B virus serology (2 mL serum sample) i.e., hepatitis B surface antigen (HBsAg), hepatitis B core antibodies, hepatitis B surface antibodies (HBsAb), hepatitis B e antigen (HBeAg) and hepatitis B e antibodies
- Hepatitis B virus DNA (2 mL plasma sample)
- Hepatitis C virus RNA using polymerase chain reaction (HCV RNA-PCR) (2 mL plasma sample).

Instructions on sample collection and processing will be provided in the laboratory manual.

Thereafter, HBV DNA, HBV serology, and HCV RNA-PCR will be monitored according to the subject's baseline status and previous HBV/HCV history every 3 cycles during the trial and at the end of treatment visit, as shown in Table 1. See also Section 8.1.3.5.

Table 1: Monitoring of Subjects According to Baseline Virology Status

Subject Status at Baseline	Parameters to be Monitored
Known HBV history (despite negative HBV DNA at Baseline)	HBV DNA and serology
Positive HBV DNA	HBV DNA and serology
Positive HBV serology[a]	HBV DNA and serology
Known HCV history (despite negative HCV RNA at Baseline)	HCV RNA-PCR
Positive HCV RNA	HCV RNA-PCR

Abbreviations: DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; PCR, polymerase chain reaction; RNA, ribonucleic acid.
a. Except for positive hepatitis B surface antibodies after vaccination.

If necessary, appropriate antiviral treatment should be provided to subjects prior to the first dose of trial treatment and/or during trial treatment (refer to local guidelines and to: American Association for the Study of Liver Diseases [AASLD] Guidelines for Treatment of Hepatitis B, 2015 and Hepatitis C Guidance: AASLD-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Adults Infected With Hepatitis C Virus, 2015).

Hepatitis B Virus and Hepatitis C Virus Reactivation

Hepatitis B virus and HCV reactivation are defined, according to the subject's baseline virology status, as shown in Table 2.

Table 2: Hepatitis B Virus and Hepatitis C Virus Reactivation

Subject Status at Baseline	Definition of Reactivation
Positive HBV DNA	1 log increase in HBV DNA
Known history of chronic HBV infection; negative HBV DNA	HBV DNA become measurable
Known history of chronic HCV infection; negative HCV RNA	HCV RNA become measurable

Abbreviations: DNA, deoxyribonucleic acid; HBV, hepatitis B virus; HCV, hepatitis C virus; RNA, ribonucleic acid.

In the event of a subject experiencing HBV or HCV reactivation according to the definition in Table 2, the following dose modification guidelines should be followed:

- HBV reactivation
    - Provide antiviral treatment and/or adjust current antiviral treatment
    - Interrupt MSC2156119J until HBV DNA resolves to ≤ baseline levels
        - If resolution takes longer than 21 days, discontinue MSC2156119J
        - If resolution is within 21 days, MSC2156119J can be resumed at a minus 1 dose level
- HCV reactivation: Discontinue MSC2156119J

In addition, HBV or HCV reactivation should be reported as a Grade 3 AE (CTCAE version 4.0 Infection and Infestation/Hepatitis Viral) unless the investigator considers it is life-threatening, in which case a Grade 4 event should be reported (see Section 8.4.1).

7.6 Packaging and Labeling

Packaging and labeling will be in accordance with Manufacture of Investigational Medicinal Products (Annex 13, Volume 4), applicable local regulatory requirements, and applicable Good Manufacturing Practice (GMP) Guidelines.

MSC2156119J tablets will be supplied in aluminum-aluminum blisters. A blister sheet contains tablets of 25 mg and/or 100 mg MSC2156119J suitable to support the dose escalation setting of the trial. The blisters will be packed in a suitable carton box which is labeled with (but not limited

to) the following required information: trial number, number of tablets per box, storage condition, the word "for clinical trial use", batch number, and the sponsor's name.

Sorafenib is a marketed product and will be provided by the sponsor.

7.7 Preparation, Handling and Storage

The pharmacy or designee will receive MSC2156119J and sorafenib labeled and packaged according to the local regulatory requirements and the storage requirements. MSC2156119J and sorafenib are formulated as tablets, and are ready for use. The responsible pharmacist will dispense the necessary amount of the MSC2156119J or sorafenib until the next visit to each subject. Detailed guidance will be provided from the sponsor in a manual of operations.

The drug supplies will be recorded in a drug inventory and stored in a locked cabinet, protected from environmental extremes until used in the trial.

CCI [redacted]

7.8 Investigational Medicinal Product Accountability

The storage manager at the trial site who will be assigned by the head of the trial site is responsible for ensuring accountability for the IMP, including reconciliation of drugs and maintenance of drug records.

After the conclusion of the trial contract with the site, the sponsor (or designee) may deliver the IMP to the storage manager at the trial site.

- Upon receipt of IMP, the investigator (or designee) will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the sponsor and returning it to the sponsor. A copy will be retained for the investigator file.
- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided by the sponsor/contract research organization (CRO) and an accurate accounting will be available for verification by the sponsor/CRO monitor at each monitoring visit.
- IMP accountability records will include:
  - Confirmation of IMP delivery to the trial site
  - The inventory at the site of IMP provided by the sponsor and prepared at the site
  - The use of each dose by each subject
  - Disposition of unused IMP
  - Dates, quantities, batch numbers, expiry dates, and (for IMP prepared at the site) formulation, as well as the subjects' trial numbers
- The storage manager should maintain records that adequately document:

- That the subjects were provided the doses specified by the clinical trial protocol/amendment(s)
- That all IMP provided by the sponsor was fully reconciled

Unused IMP must not be discarded or used for any purpose other than the present trial. IMP that has been dispensed to a subject must not be redispensed to a different subject.

The sponsor/CRO monitor (or delegate) will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the trial site.

7.9 Assessment of Investigational Medicinal Product Compliance

Each subject will record on a diary card the number and dosage of IMP taken daily and the time of taking the IMP daily. This diary card will be returned to the investigator site at each visit.

Subjects should be instructed to bring with them to each visit both opened and unopened IMP packages, in order to allow the assessment of compliance with trial treatment. The IMP administration must be recorded in the eCRF, as applicable.

7.10 Method of Blinding

Not applicable; this is an open label trial.

7.11 Emergency Unblinding

Not applicable.

7.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or non-serious) – must be reported to the sponsor's Global Drug Safety department in an expedited manner using the appropriate reporting form (see Section 8.4.1.4).

In case of an overdose that needs to be treated, the investigator should use his/her clinical judgment for the management of the overdose.

7.13 Medical Care of Subjects after the End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice, and depending on the subject's individual medical needs.

8 Trial Procedures and Assessments

Trial periods and assessments apply to both Phase Ib and Phase II, except where noted.

8.1 Schedule of Assessments

A chart of all treatment and assessments is presented in Appendix H (Phase Ib) and Appendix I (Phase II). Details of the assessments performed are provided in their respective sections. Assessments are performed on an outpatient basis. However, hospitalization for at least the first 3 days (Days 1 to 3) of Cycle 1 may be needed. In addition, if clinically indicated, subjects may be hospitalized for assessments at the discretion of the investigator.

The AE reporting period for safety surveillance and a concomitant medication/procedure recording period begins when the subject first signs the main informed consent and continues through the post-treatment period defined in Section 8.1.5.

In the below subsections 8.1.1 to 8.1.6, the assessment schedule other than AEs and concomitant medication/procedure are presented.

8.1.1 Informed Consent

Prior to performing any trial assessments not part of the subject's routine medical care, the investigator will ensure that the subject or the subject's legal representative has provided written informed consents according to the procedure described in Section 10.2.

In Phase II, subjects will have a Molecular Prescreening period during which their MET status will be determined (see Section 8.1.2). A separate prescreening informed consent is required to permit the collection, shipment and testing of archival or fresh tumor samples prior to the planned Clinical Screening activities. Demographic data and disease history may also be collected during Molecular Prescreening (subject to the provision of informed consent).

8.1.2 Screening Period

During screening, the subject must sign the prescreening (Phase II only) and the main ICF before any trial procedures are performed.

Molecular Prescreening (Phase II only)

In Phase II, subjects will have a Molecular Prescreening period prior to Clinical Screening during which (subject to the provision of informed consent) their MET status will be determined in order to confirm their suitability for the trial, and demographic data and disease history will also be collected.

Screening (Phase Ib)/Clinical Screening (Phase II)

The Screening/Clinical Screening period must be completed for all subjects within the 14 days prior to the initiation of study treatment. Screening/Clinical Screening will include evaluation of

laboratory parameters (including serum pregnancy test if applicable), medical history, concomitant medication/procedure, and tumor imaging to check subject eligibility, plus demographic data and disease history if not already collected at Molecular Prescreening (Phase II only). The laboratory analyses for the subject eligibility check during Screening/Clinical Screening will be performed by a local laboratory (although a duplicate sample will also be sent to the central laboratory) (see Section 8.4.3 for full details).

Assessments for the screening period of Phase Ib include:

- Eligibility evaluation (review of inclusion/exclusion criteria)
- Demography (date of birth, gender, race), height
- Medical history
    - Smoking status and alcohol use
- Physical examination/weight
- ECOG PS
- Vital signs (body temperature, respiratory rate, blood pressure, and heart rate)
- 12-lead ECG
- Hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, and platelet count)
- Coagulation (prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio [INR])
- Chemistry (blood nitrogen urea [BUN], creatinine, AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin [including direct fraction if total bilirubin is abnormal], lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, and glucose)
- Urinalysis (dipstick followed by microscopic examination if abnormal results)
- Hepatitis B virus serology: HBsAg, hepatitis B core antibodies, HBsAb, HBeAg and hepatitis B e antibodies
- Hepatitis B virus DNA (viral load)
- HCV RNA-PCR

Note: Hepatitis markers (serology and viral load) for HBV and HCV are part of the baseline assessments and can be collected either during Screening/Clinical Screening or at Cycle 1 Day 1, if not done during Screening/Clinical Screening.

- Serum pregnancy test for female subjects of childbearing potential, including those who have had tubal ligation

- Complete tumor assessment of all lesions by radiographic or other modality (using RECIST v 1.1). Computed tomography or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations. CT/MRI of the head for subjects who are suspected to have CNS metastases

- Serum AFP

Assessments for Phase II include all assessments in Phase Ib plus recording of ethnicity and FACT Hepatobiliary Symptom Index 8 (FHSI-8) (see Appendix F). The pretreatment tumor biopsy (fresh biopsy or archived material) is mandatory for Phase Ib and Phase II.

8.1.3 Treatment Period

MSC2156119J (Phase Ib and Phase II) will be administered once daily over a 21-day cycle and sorafenib (Phase II) will be administered twice daily over a 21-day cycle, which may repeat until disease progression (as determined by the investigator), intolerable toxicity, or withdrawal from the trial.

For Phase Ib, scheduled visits during the treatment period will occur on Days 1, 2, 8, and 15 of Cycle 1; Days 1, 8, and 15 of Cycle 2; and Day 1 of Cycles ≥ 3. Note: the 24-hour postdose PK sample from Day 1 and Day 15 are the predose samples from Day 2 and Day 16, respectively. For Phase II, scheduled visits during the treatment period will occur on Days 1, 8, and 15 of Cycle 1; Days 1 and 8 of Cycle 2; and Day 1 of Cycles ≥ 3.

In Sections 8.1.3.1 to 8.1.3.5, the assessment schedule other than physical examination/weight, vital signs, hematology, coagulation, chemistry, AEs, and concomitant medication/procedure are presented, as these assessments will be performed at each scheduled visit during the treatment period (with the exception of vital signs, as noted below).

In addition, subjects who have a known history of HBV (despite being negative for HBV DNA at baseline), or who are positive for HBV DNA at baseline, or have positive HBV serology will continue to be monitored for HBV DNA and serology every 3 cycles. Similarly, subjects who have a known history of HCV (despite being negative for HCV RNA at baseline) or who are positive for HCV RNA at baseline will continue to be monitored for HCV RNA-PCR throughout the trial. See Section 7.5.3.1.

8.1.3.1 Cycle 1, Day 1

On Cycle 1, Day 1 of Phase Ib, the following assessments/treatment administrations will occur:

- Dispensing of study drug

- Tumor biopsy (excluding fine needle aspiration and cytology samples). Undergoing paired tumor biopsy is not mandatory, but highly recommended for subjects with accessible tumors:

the paired tumor biopsy will be performed before the first treatment (i.e., during screening or on Cycle 1, Day 1 prior to the first dose of trial treatment), and anytime between Cycle 1, Day 15 and the beginning of Cycle 3 (optional, will be collected after subjects have signed a separate ICF)

- Triplet 12-lead ECG recordings with 2-minute intervals (± 1 minute) after at least 5 minutes rest in supine position at predose (within 60 minutes prior to dose) and 4 hours (± 12 minutes) postdose. ECGs should be performed within 10 minutes prior to PK sampling at time points where both assessments are performed

- PK blood samples. Samples will be taken predose (within 60 minutes prior to dose) and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose. Note: the 24-hour postdose sample from Day 1 and Day 15 are the predose samples from Day 2 and Day 16, respectively. Postdose PK samples should be taken within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose sample should be obtained at 4 hours ± 12 minutes

- CCI [redacted]

- CCI [redacted]

The following assessments will be performed only if screening/last assessments were performed > 7 days prior to Day 1:

- ECOG PS

- Urinalysis (dipstick followed by microscopic examination if abnormal results)

- Serum AFP

Assessments for Cycle 1, Day 1 of Phase II include all assessments in Phase Ib with the following changes:

- Randomization by IVRS

- PK blood samples. Samples will be taken predose (within 60 minutes prior to dose) and 4 hours postdose in the MSC2156119J arm. At selected sites, PK sampling will be performed predose (within 60 minutes prior to dose) and at 1.5, 3.5, and 6.5-8 hours postdose. Postdose PK samples should be taken within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose sample should be obtained at 4 hours ± 12 minutes

- FHSI-8

- PRO (FACT-HP) (see Appendix G)

8.1.3.2 Cycle 1, Day 15

On Cycle 1, Day 15 of Phase Ib, the following assessments/treatment administrations will occur:

- Tumor biopsy (excluding fine needle aspiration and cytology samples). Undergoing paired tumor biopsy is not mandatory, but highly recommended for subjects with accessible tumors: the paired tumor biopsy will be performed before treatment at screening or on Cycle 1, Day 1 and anytime between Cycle 1, Day 15 and beginning of Cycle 3 (optional, will be collected after subjects have signed a separate ICF). A predose PK is recommended to be taken on the day of the second biopsy.

- A single 12-lead ECG recording after at least 5 minutes rest in supine position at predose (within 40 minutes prior to dose) and triplet 12-lead ECG recordings with 2-minute intervals (± 1 minute) at 4 hours (± 12 minutes) postdose. ECGs should be performed within 10 minutes prior to PK sampling at time points where both assessments are performed

- PK blood samples (samples will be taken predose [trough value, within 30 minutes prior to dose] and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose). Note: the 24-hour postdose sample from Day 1 and Day 15 are the predose samples from Day 2 and Day 16, respectively. Postdose PK samples should be taken within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose sample should be obtained at 4 hours ± 12 minutes

Assessments for Cycle 1, Day 15 of Phase II include all assessments in Phase Ib except for PK blood samples, 4-hour postdose ECG, and vital signs.

8.1.3.3 Cycle 2, Day 1

Assessments for Cycle 2, Day 1 of Phase Ib include all assessments from Cycle 1, Day 1 as defined in Section 8.1.3.1, with the following changes:

- Single 12-lead ECG recording after at least 5 minutes rest in supine position at predose (within 60 minutes prior to dose) only

- No tumor biopsy

- No PK blood sample

- CCI blood sample

Assessments for Cycle 2, Day 1 of Phase II include all assessments from Cycle 1, Day 1, with the following changes:

- No randomization by IVRS

- No tumor biopsy

- CCI blood sample

- Triplet 12-lead ECG recordings with 2-minute intervals (± 1 minute) after at least 5 minutes rest in supine position at predose (within 40 minutes prior to dose) and 4 hours (± 12 minutes) postdose. ECGs should be performed within 10 minutes prior to PK sampling at time points where both assessments are performed

- PK blood samples. Samples will be taken predose (trough value, within 30 minutes prior to dose) and at 4 hours postdose in the MSC2156119J arm. At selected sites, PK sampling will be performed predose (trough value, within 30 minutes prior to dose) and at 2 and 6-8 hours postdose. Postdose PK samples should be taken within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose sample should be obtained at 4 hours ± 12 minutes

CCI [redacted]

8.1.3.4 Cycle 2, Day 15

Assessments for Cycle 2, Day 15 of Phase Ib will be the same as the assessments for Cycle 1, Day 15, as defined in Section 8.1.3.2, except for tumor biopsy, vital signs, 12-lead ECG, and PK blood samples.

8.1.3.5 Cycles ≥ 3, Day 1

Assessments for Cycles ≥ 3, Day 1 of Phase Ib include all assessments from Cycle 1, Day 1, except a tumor biopsy will not be taken, and CCI [redacted] blood samples will not be drawn. CCI [redacted] In addition, a complete tumor assessment of all lesions by radiographic or other modality (using RECIST v 1.1) identified at the screening visit will be performed predose on, or up to 5 days prior to, Day 1 of Cycles 3, 5, 7, 9, 11, 13, and every 4 cycles thereafter until disease progression, starting a new anti-tumor therapy, or death.

Assessments for Cycles ≥ 3, Day 1 of Phase II include all Cycles ≥ 3, Day 1 assessments in Phase Ib.

In addition, HBV DNA, HBV serology, and HCV RNA-PCR will be monitored every 3 cycles according to the subject's baseline status and previous HBV/HCV history (see Section 7.5.3.1), FHSI-8 will be assessed, FACT-HP will be assessed on Cycle 5, Day 1.

CCI [redacted]

8.1.4 End of Treatment Visit

At the subject's discontinuation of the trial medication (due to disease progression [as assessed by the investigator], intolerable toxicity, or withdrawal), the following evaluations, which include safety/tumor assessment, will be performed:

- Tumor biopsy to be taken at the time of progression on the last day of drug application (excluding fine needle aspiration and cytology samples; optional, will be collected after subjects sign a separate ICF). Whenever possible, the biopsy taken at progression for determination of the MET status should be taken from the progressing lesion, provided that the lesion is accessible and there are no medical or safety reasons precluding a biopsy of the progressing lesion.
- Physical examination/weight
- ECOG PS
- AEs
- Concomitant medication/procedure
- Vital signs (body temperature, respiratory rate, blood pressure, and heart rate)
- 12-lead ECG
- Hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, and platelet count)
- Coagulation (PT, aPTT, and INR)
- Chemistry (BUN, creatinine, AST, ALT, GGT, total bilirubin [including direct fraction if total bilirubin is abnormal], lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, and glucose)
- Urinalysis (dipstick followed by microscopic examination if abnormal results)
- Complete tumor assessment of all lesions by radiographic or other modality if previous assessment is more than 6 weeks old (using RECIST v 1.1)
- Serum AFP
- CCI [redacted]
- HBV DNA and serology (subjects with a known history of HBV, or who are positive for HBV DNA at baseline, or have positive HBV serology only)

- HCV RNA-PCR (subjects with a known history of HCV or who are positive for HCV RNA at baseline only)

Assessments for the end of treatment visit in Phase II include all assessments in Phase Ib. In addition, FHSI-8 and PRO (FACT-HP) will be assessed.

NOTE: end of treatment ECG and laboratory assessments (hematology, coagulation, chemistry, urinalysis, and hepatitis markers) are not required for subjects with previous ECG and laboratory assessments, respectively, within 7 days of the end of treatment visit.

8.1.5 Post-Treatment Follow-Up Visit

Study drug post-treatment follow-up visit will be performed within 30 ± 3 days after the last dose for subjects who discontinue the trial medication, even if the subject starts a new antineoplastic therapy. Subjects who terminated their treatment early will be encouraged to return to the clinic for the post-treatment follow-up visit. If an end of trial visit is not possible, the reason should be clearly documented in the subject's medical record.

The following assessments will be performed:

- AEs
- Concomitant medication/procedure
- Physical examination/weight
- ECOG PS
- Vital signs (body temperature, respiratory rate, blood pressure, and heart rate)
- 12-lead ECG
- Hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, and platelet count)
- Coagulation (PT, aPTT, and INR)
- Chemistry (BUN, creatinine, AST, ALT, GGT, total bilirubin [including direct fraction if total bilirubin is abnormal], lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, and glucose)
- Urinalysis (dipstick followed by microscopic examination if abnormal results)

Assessments for the post-treatment follow-up visit in Phase II include all assessments in Phase Ib. In addition, FHSI-8 will be assessed.

Subjects who are discontinued from the trial without documented progressive disease, for example, due to unacceptable toxicity or clinical deterioration, should perform the tumor assessment at 6-week intervals until Cycle 13 and 12-week intervals (4 cycles) after Cycle 13 until disease progression, starting a new therapy, or death.

8.1.6 Survival Follow-up Assessments

Survival data (subject survival and anticancer therapies) in Phase Ib and Phase II will be collected every 3 months (± 2 weeks) after the last dose of study drug. Subjects will be contacted by telephone.

8.2 Demographic and Other Baseline Characteristics

Prior to the first dosing (Cycle 1, Day 1), all subjects will have screening and baseline examinations to ensure their eligibility for this trial. Before any examination, they will be informed about the trial aims, procedures, and possible risks of MSC2156119J and the investigator will ensure that the subject or the subject's legal representative has provided written informed consent(s), according to the procedure described in Section 10.2.

The following screening and baseline assessments will be performed:

- Demographics

  Demographic data will be collected, including date of birth, race, and gender. Height will also be recorded. Ethnicity will be recorded in Phase II only.

- Medical History

  The medical history will include:

  - The starting and ending dates or duration of the medical condition/disease
  - Concomitant illnesses at screening, including chronic diseases or abnormal conditions
  - Previous relevant illnesses
  - Major relevant surgery not related to the cancerous condition, as well as other relevant prior procedures
  - Smoking status and alcohol use

- Oncology History

  The oncology history will include: date of diagnosis, tumor type, histological type and location, BCLC stage (see Appendix K), staging information at the initial histological diagnosis, previous treatments (surgery, radiotherapy) and outcome, current symptoms, and tumor involvement at the time of screening.

- Medication History of Oncology

  The medication history of oncology will include: the starting and ending dates of previous anticancer therapies, the best response to each treatment (including both prescription and over-the-counter medications) and other relevant tumor-related interventions.

- Other treatment History of Oncology
- Tumor Biopsy

  Tumor biopsy will be performed as described in Section 8.6.1.
- Tumor Assessment

  Tumor imaging assessment will be performed as described in Section 8.3.
- Physical Examination/Weight

  A physical examination will be performed as described in Section 8.4.4.1. Weight will also be recorded.
- Vital Signs

  Vital signs will be recorded as described in Section 8.4.4.2.
- 12-lead ECG

  A standard 12-lead ECG will be performed as described in Section 8.4.4.3.
- Pregnancy Test

  If applicable, a serum pregnancy test for beta-human chorionic gonadotropin will be administered.
- Chest X-ray

  A chest X-ray will be performed per institutional standard.
- ECOG PS

  The ECOG PS is a value between 0 and 5 assigned by a clinician based on observations of the subject's ability to perform common tasks. Thus, 0 signifies normal physical abilities with no evidence of disease. Increasing numbers indicate a reduced ability to perform activities of daily living, where 5 represents death. Subjects should have a score of < 2 to participate in this trial. Details are described in Appendix D.
- Blood Samples for
  - Hematology
  - Biochemistry
  - Coagulation
  - CCI [redacted]

  An overview of laboratory assessments is presented in Section 8.4.3. Preparation of blood samples are described in the MOP. The amount of blood volume for laboratory assessments is shown in Appendix J.
- Urinalysis

  Urinalysis assessments are described in Section 8.4.3.4.
- Concomitant medication/procedures

Concomitant medication/procedures and therapies will be documented as described in Section 7.5.

- AEs

  AEs (since signature of the main informed consent) will be recorded as described in Section 8.4.1.

- Hepatitis markers
- Serum AFP

8.3 Assessment of Efficacy

Tumor Assessment (Tumor Response Assessment)

Tumor assessment will be performed according to RECIST v 1.1 (see Appendix C) locally by the Investigators and centrally by an independent radiologist. The baseline tumor assessment is scheduled to be performed during the Screening period of Phase Ib (see Section 8.1.2) and during the Clinical Screening period of Phase II.

CT or MRI with contrast enhancement is required for tumor assessment. CT scans are required to be with intravenous contrast and to include phases/series of the entire liver, at a minimum, 1) hepatic arterial and 2) portal venous. If a subject has a known history of contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest and a contrast-enhanced MRI (if possible) of the abdomen and pelvis are recommended. Contrast-enhanced MRI of the entire liver should include, at a minimum, 1) hepatic arterial and 2) portal venous.

Imaging studies, including CT or MRI of the chest (MRI is not recommended for chest due to respiratory artifacts), abdomen, and pelvis must be performed at baseline in order to survey metastasis. At baseline, the organs with metastatic disease and target and non-target lesions should be documented. CT/MRI of the head for subjects suggestive of CNS metastasis can be performed at baseline. The bone scan and/or positron emission tomography (PET) scan could be considered for subjects suggestive of bone metastasis at baseline or when suspecting any bone metastasis during the study, however X-ray or CT/MRI scan must be used for tumor assessment at the baseline and at the subsequent visits. The bone scan or PET could not be used for tumor assessment.

At baseline, all subjects should have at least 1 measurable lesion by CT scan or MRI. Any lesion that has been subjected to local-regional or surgical therapy should not be considered as measurable at baseline unless clear progression has been documented since the therapy. Otherwise, previously treated lesions will be considered as non-target lesions.

Tumor response evaluations will be assessed by CT or MRI and other modalities at the end of every 2 cycles, i.e., every 6 weeks (every 4 cycles after Cycle 13, i.e., every 12 weeks). The scheduled 6-week (or 12-week) interval between tumor response evaluations should be maintained through the trial regardless of any delay or interruption to trial treatment. Tumor response evaluations should include a complete assessment of all target and non-target lesions. In case of

symptoms suggestive of symptomatic progression, subjects should be evaluated by imaging studies thereafter. A CT or MRI must also be performed at the end of treatment (see Appendix I). Evaluation of lesions should be based on images obtained by either CT or MRI. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the trial. If a chest X-ray indicates metastatic disease while the subject is enrolled in this trial, a CT of the chest is required for confirmation. It is recommended that, for a given subject, the tumor assessment is provided by the same physician or radiologist during the study. A change in methodology is defined as a change in contrast use or a change in technique. A change in methodology will result in a "Not Assessable" overall lesion response assessment unless a definitive response assessment can be justified by the current available information.

All measurements should be recorded in metric notation.

Further guidance and recommendations on image acquisition are provided in the Image Acquisition Guidelines.

If subjects discontinue MSC2156119J or sorafenib treatment for a reason other than PD or death, tumor assessment will be performed at the end of treatment visit if it has not been done within the past 6 weeks, and will be repeated every 6 weeks (± 1 week) until radiological progression per RECIST v 1.1, death or start of a new anticancer therapy, whichever occurs first.

Clinical progression, at any time, requires a physical examination and prompt radiological confirmation rather than waiting for the next scheduled imaging assessment. If unscheduled imaging does not meet progressive disease by RECIST v 1.1, the next scheduled imaging assessment should still be performed on time unless the next scheduled imaging assessment is within 14 days following the unscheduled imaging.

8.4 Assessment of Safety

The safety profile of MSC2156119J will be assessed through the recording, reporting, and analyzing of baseline medical conditions, AEs, 12-lead ECG, physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed from the time of the subject's signature of main informed consent throughout the trial. The investigator will report any AEs, whether observed by the investigator or reported by the subject (see Section 8.4.1.2). The reporting period for AEs is described in Section 8.4.1.3.

8.4.1 Adverse Events

8.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The investigator is required to grade the severity/intensity of each AE by referencing the NCI-CTCAE, version 4.0 (publication date: 28 May 2009). This is a descriptive terminology that can be used for AE reporting. A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If a particular AE's severity is not specifically graded by the guidance document, the investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment.

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

According to sponsor convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as a SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to MSC2156119J using the following definitions. Decisive factors for the assessment of causal relationship of an AE to MSC2156119J include, but may not be limited to, temporal relationship between the AE and MSC2156119J, known side effects of MSC2156119J, medical history, concomitant medication/procedure, course of the underlying disease, or trial procedures.

Not related: Not reasonably related to MSC2156119J/sorafenib. AE could not medically (pharmacologically/clinically) be attributed to MSC2156119J/sorafenib under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to MSC2156119J/sorafenib. AE could medically (pharmacologically/clinically) be attributed to MSC2156119J/sorafenib under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g. on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g. anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

  NOTE: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via MSC2156119J is also considered an SAE, as described in Section 8.4.1.4.

Events that Do Not Meet the Definition of a SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as baseline medical conditions, and are NOT to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the subject's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the AE reporting period (as defined in Section 8.4.1.3).

AEs of Special Interest

Subjects might experience asymptomatic elevations in serum pancreatic enzyme (lipase and amylase). Such an enzyme elevation of Grade ≥ 3 is considered an AESI in this trial.

When such AESI is not serious, a specific AESI form should be filled at the site and the sponsor must be notified immediately (within 24 hours). Reporting process of an AESI should follow the same procedure for reporting SAEs (see Section 8.4.1.4).

Should the AESI be serious, a SAE Report Form instead of the AESI form should be filled and the procedure for reporting SAEs (see Section 8.4.1.4) should be followed.

In addition to SAEs, all DLTs will be expeditiously sent by the investigator to the sponsor using the AE section of the eCRF.

8.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and all nonserious AEs of special interest must be additionally documented and reported using the appropriate Report Form as described in Section 8.4.1.4.

It is important that each AE report includes a description of the event, its duration (onset and resolution dates and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of MSC2156119J/sorafenib) and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the sponsor.

8.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of main informed consent) and continues through the trial's post-treatment follow-up visit, as defined in Section 8.1.5, regardless of whether the subject starts a new antineoplastic therapy prior to the post-treatment follow-up visit. If the post-treatment follow-up visit was not performed (e.g., the subject could not come back to the site for a visit), a telephone contact should be completed and documented for AE assessment.

Any SAE assessed as related to trial treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration of trial treatment.

8.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the investigator must immediately (within a maximum 24 hours after becoming aware of the event) inform the sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the investigator following specific completion instructions. In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone. In these cases, a written report must be sent immediately thereafter by fax or e-mail. The same reporting procedures apply for follow up cases.

Names, addresses, telephone and fax numbers for SAE reporting will be included in the trial specific SAE Report Form.

Additional documents may be provided by the investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the sponsor or designee and (as applicable) to allow the sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible monitor, although in exceptional circumstances the Global Drug Safety department may contact the investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a nonserious AESI, the investigator will complete the AESI Report Form and send it to the sponsor/designee within 24 hours after becoming aware of the event. Names, addresses, telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs have to be reported in an expedited manner as SAEs as outlined above.

Dose Limiting Toxicities (Phase Ib)

Each event meeting the criteria of a DLT (see Section 7.2.2) has to be recorded in the eCRF within 24 hours after becoming aware of the event. Serious DLTs have to be reported in an expedited manner as SAEs as outlined above.

8.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particular deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP guidelines, the sponsor/designee will inform the investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the sponsor/designee will inform the investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The investigator should place copies of safety reports in the Investigator Site File. National regulations with regard to safety report notifications to investigators will be taken into account.

When specifically required by regulations and guidelines, the sponsor/designee will provide appropriate Safety reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidances.

8.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the study (see Section 8.4.1.3) and are assessed for final outcome at the post-treatment follow-up visit. All SAEs and AESIs ongoing at

the post-treatment follow-up visit must be monitored and followed up by the investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

8.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the investigator as related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The investigator must notify the sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 8.4.1.4.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The investigator must notify the sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 8.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from the trial immediately. The sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

8.4.3 Laboratory Assessments

Samples will be sent to a central laboratory for analysis, and these values will be entered into the eCRF. However, during Screening/Clinical Screening, the laboratory samples taken for the purposes of confirming subject eligibility should be reported by a local laboratory. The investigator should use the local laboratory results to determine whether the subject meets the eligibility criteria and should enter these data into the relevant eCRF page. A duplicate sample should also be sent to the central laboratory for analysis and reporting.

The investigator may also use local laboratory results for safety evaluations and real time individual dose adjustments. In the event of any discrepancy between the results of the analyses performed by the local and the central laboratories, the investigator will use their discretion to determine any appropriate action with regard to the subject. Any repeat testing must be done by the central laboratory.

It is essential that the sponsor be provided with a list of laboratory normal ranges before shipment of the trial medication. Any change in laboratory normal ranges during the trial will additionally be forwarded to the sponsor. The amount of blood volume for laboratory assessments is shown in Appendix J.

8.4.3.1 Hematology

Hematology assessments for Phase Ib and Phase II are presented in Table 3.

Table 3: Hematology Assessments

Parameter
Hemoglobin
Hematocrit
Red blood cell count
White blood cell count
Differential
Platelet count

8.4.3.2 Biochemistry

Biochemistry assessments for Phase Ib and Phase II are presented in Table 4.

Table 4: Biochemistry Assessments

Parameter
Albumin
Alkaline phosphatase
Alanine aminotransferase
Amylase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Creatinine
Gamma-glutamyl transpeptidase
Glucose
Lipase
Magnesium
Potassium
Sodium
Total bilirubin (direct fraction if total bilirubin is abnormal)
Total protein

8.4.3.3 Coagulation

Coagulation assessments for Phase Ib and Phase II are presented in Table 5.

Table 5: Coagulation Assessments

Parameter
Activated partial thromboplastin time
International normalized ratio
Prothrombin time

8.4.3.4 Urinalysis

Urinalysis assessments (dipstick) for Phase Ib and Phase II are presented in Table 6. The dipstick urinalysis will be followed by microscopic examination if abnormal results.

Table 6: Urinalysis Assessments

Parameter
Blood
Glucose
Ketones
Leukocytes
Nitrites
pH
Proteins

8.4.3.5 Hepatitis Markers

Serological investigations (HBV panel) to be performed at baseline (either during Screening/Clinical Screening or predose on Cycle 1 Day 1) for Phase Ib and Phase II are presented in Table 7. In addition, all subjects will be tested (plasma sample) for HBV DNA and HCV RNA-PCR. Based on the results of these tests, subjects may be given prophylactic or antiviral treatment following the institutional guidelines (see Section 7.5.1).

Table 7: Hepatitis B Virus Serology Panel

Parameter
HBc antibodies
HBs antibodies
HBs antigen
HBe antigen
HBe antibodies

Abbreviations: HBc, Hepatitis B core; HBe, Hepatitis B e; HBs, Hepatitis B surface

Thereafter, subjects with a known history of HBV (despite being negative for HBV DNA at baseline), or who are positive for HBV DNA at baseline, or have positive HBV serology will continue to be monitored every 3 cycles for HBV DNA and serology and at the end of treatment visit. Similarly, subjects with a known history of HCV (despite being negative for HCV RNA at baseline) or who are positive for HCV RNA at baseline will continue to be monitored every 3 cycles for HCV RNA-PCR and at the end of treatment visit. See Section 7.5.3.1.

8.4.4 Vital Signs, Physical Examinations, and Other Assessments

8.4.4.1 Physical Examinations

The physical examination will be identical to a general medical check-up comprising a whole body inspection (general appearance, body height and weight, skin/subcutaneous tissue, head, eyes, ears, nose, throat, neck, thyroid, respiratory, cardiovascular, peripheral vascular, lymphatic, lymph nodes/immunology, abdomen, musculoskeletal, neurological, and psychiatric), palpation,

percussion, and auscultation. Any clinically significant abnormal findings or worsening of conditions previously recorded in the medical history must be documented in the eCRF.

8.4.4.2 Vital Signs

Systolic blood pressure, diastolic blood pressure, respiratory rate, and pulse rate (beats per minute) will be measured in seated position after 5 minutes resting (for individual subjects, measurements at different visits should be taken in the same position). Body temperature will be recorded.

Vital signs should be taken within 30 minutes prior to each 12-lead ECG recording after sitting position of 5 minutes. Where ECGs are recorded in triplicate, vital signs only need to be recorded once prior to the first ECG recording.

8.4.4.3 Electrocardiogram

A single standard 12-lead ECG will be recorded after the subject has rested at least for 5 minutes in a supine position. At least 5 to 7 beats are required for each lead run.

For time points where both ECGs and PK samples are obtained, 12-lead ECGs should be taken in triplicate at 2-minute intervals (± 1 minute), and should be performed within a maximum of 10 minutes prior to PK sampling. Thus, the triplicate ECGs performed prior to collection of the predose trough PK samples must be completed within a maximum of 40 minutes prior to dosing. Postdose ECGs should be recorded within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose ECG should be recorded within ± 12 minutes of the 4-hour time point. In addition, the time of the ECG recordings (relative to dosing) should be recorded.

Results of the 12-lead ECG recordings will be included in the subject's eCRF.

8.5 Pharmacokinetics

Plasma concentrations of MSC2156119J for all subjects will be examined on Cycle 1, Day 1 and Day 15 of Phase Ib (samples will be taken predose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose; Note: the 24-hour postdose sample from Day 1 and Day 15 are the predose samples from Day 2 and Day 16, respectively).

CCI [redacted]

The predose PK sample on Cycle 1 Day 1 may be collected up to 60 minutes predose. Thereafter, predose (trough) samples should be collected within 30 minutes predose.

Postdose PK samples should be collected within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose sample should be collected within ± 12 minutes of the 4-hour time point. In addition, the time of the PK sample (relative to dosing) should be recorded.

For both phases, the concentration of MSC2156119J will be determined by a validated liquid chromatography-tandem mass spectrometry method. The validation of the method will be presented separately.

Details about the sampling and processing procedures, storage, and transportation will be provided in a separate laboratory manual. Schedule of dosing is detailed in Appendix H and Appendix I for Phase Ib and Phase II respectively. Sampling time points are detailed in Appendix J.

8.5.1 Body Fluids

Blood sampling will be taken as specified in the schedule of assessments (see Section 8.1, Appendix H, and Appendix I). Preparation of blood samples is described in the MOP.

Whole blood (2 mL samples) will be collected in ethylenediaminetetraacetic acid-coated tubes and may be kept at ambient temperature until centrifuged to prepare plasma. A laboratory manual will provide detailed instructions on proper centrifugation, and further processing of samples for plasma collection.

The plasma samples for PK must be divided into 2 equal aliquots (A and B). Plasma aliquots A will be assigned for analysis of MSC2156119J for calculation of PK parameters. Plasma aliquots B will be used as back-up samples. CCI [redacted]

During this research trial, blood, urine, and tumor tissue samples will be collected for laboratory testing. These samples will be collected, prepared and shipped at the site according to the laboratory instruction manual for this study. The samples will be shipped via courier to the relevant central laboratory "PPD " located in PPD (for samples from outside of China) and Beijing (for samples from China), where they will either be analyzed or stored until shipment to third party vendors for analysis.

The eCRF will contain provisions for recording the protocol-specified nominal time of each specimen, as well as the actual time and date that the specimen was obtained. Recording of the test results in the eCRF is not required.

8.5.2 Pharmacokinetic Calculations

The following PK parameters will be calculated and summarized from the measured individual plasma concentrations of MSC2156119J using non-compartmental methods based on frequent PK sampling as applied in Phase Ib.

- C_{max}: observed maximum plasma concentration
- C_{min}: observed minimum plasma concentration

- C_{av}: Average plasma concentration within 1 dosing interval
- t_{max}: time to reach maximum plasma concentration
- AUC_{0-t}: area under the plasma concentration versus time curve from time zero to the last sampling time t at which the concentration is at or above the lower limit of quantification (LLQ). AUC_{0-t} will be calculated according to the mixed log-linear trapezoidal rule
- AUC_{0-tau}: area under the plasma concentration versus time curve within 1 dosing interval

Further derived PK parameters will be calculated, when appropriate:

- λ_z: apparent terminal rate constant determined by log-linear regression analysis of the measured plasma concentrations of the terminal log-linear phase
- $t_{1/2}$: apparent terminal half-life, calculated by $\ln 2/\lambda_z$
- $AUC_{0-\infty}$: area under the plasma concentration versus time curve from time zero to infinity. $AUC_{0-\infty}$ will be calculated by combining AUC_{0-t} and AUC_{extra}. AUC_{extra} represents an extrapolated value obtained by C_{last}/λ_z, where C_{last} is the calculated plasma concentration at the last sampling time point at which the measured plasma concentration is at or above the LLQ. If the value of AUC_{extra} provides more than 20% of $AUC_{0-\infty}$, this parameter and all related parameters (e.g., total body clearance of drug [CL] and volume of distribution associated to the terminal phase [V_z]) will be rejected as implausible and not included for further statistical analysis.
- CL/f: apparent body clearance of the drug from plasma, $CL = Dose/AUC_{0-\infty}$
- V_z/f: apparent volume of distribution associated to the terminal phase, calculated by $Dose/(AUC_{0-\infty}*\lambda_z)$
- V_{ss}/f: apparent volume of distribution at steady state, CL·MRT

The PK evaluation shall be carried out under the responsibility of the sponsor.

The PK variables will be analyzed descriptively for each treatment and administration separately. Descriptive statistics include N, arithmetic mean, geometric mean, standard deviation, standard error of the mean (SEM), median, minimum, maximum, and coefficient of variation (CV in %). The drug concentration in plasma at each sampling time will be presented on the original scale for all subjects who participated in the trial. Values below LLQ will be taken as zero for descriptive statistics of concentrations.

Individual plasma concentration-time profiles (linear and semi-logarithmic scale) will be plotted by treatment. Mean plasma concentrations per treatment and administration will be plotted with StD using schedule time points. The weight-normalized PK parameters will be calculated if it would be appropriate.

Formal statistical hypotheses are not set up. All statistical tests will be performed in an explorative way. All analyses will be based on the PK analysis set. Details of the statistical analyses will be described in the Statistical Analysis Plan (SAP).

When appropriate, the determinants of PK variability will be studied using a non-linear mixed effects modeling analysis of the sparse-sampling pharmacokinetic data generated in the Phase II part of this trial, using the software NONMEM. This statistical modeling methodology will allow estimation of interindividual PK variability in the population, to calculate estimates of individual parameters and to assess quantitative relationships between PK parameters and potential influencing factors. Special consideration will be given to age, weight, gender, race, CrCl, total bilirubin, and smoking status. However, other covariates will be considered. In an optimal way the data will be merged with data from other MSC2156119J trials and the analysis may be reported separately as appropriate.

The PK base model for the HCC population will be developed first based on the frequent PK sampling data from Phase Ib. If applicable, the model used will be a one-compartment model. Basic PK parameters (clearance, volume of distribution) for each individual subject will be estimated with the same statistical methodology. The relationships between parameters and covariates will be first explored graphically before inclusion in the statistical model.

The relationship between efficacy measures, safety measures, and PK parameters will be explored using graphical methods, correlation, and modeling techniques. The detailed statistical methods for the PK analyses will be detailed in a specific SAP.

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8.7 Other Assessments

Not planned.

9 Statistics

9.1 Sample Size

For Phase Ib, the total number of subjects to be enrolled in this trial is up to 21. Of these subjects, up to 18 will be enrolled based on the "3+3" dose-escalation method with 2 dose cohorts: 3 to 6 subjects in the first dose cohort and 3 to 12 subjects in the second dose cohort (if dose de-escalation does not occur). In addition, separate from the "3+3" dose escalation cohorts, up to 3 subjects will be enrolled in the mainland China sites. The final sample size will depend on the number of subjects who experience DLTs observed at each dose level, the number of dose levels explored, the safety data, and the decision from the SMC meeting.

For Phase II, the initial sample size planning required 100 TTP events (assessed by an IRC) to ensure 80% power with a two-sided significance level of 10% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio (HR) of 0.6. Assuming a median TTP in Asian subjects for the sorafenib arm of 2.8 months, a HR of 0.6 represents a 1.87 month increase, resulting in a median TTP of 4.67 months for the MSC2156119J arm. With other assumptions:

- Accrual period of 12 months and follow-up period of 6 months,
- Overall drop-out rate of 17.4%.

A total number of 140 subjects with MET+ HCC were planned to be randomized on a 1:1 basis to receive MSC2156119J or sorafenib.

However, due to business-related considerations not related to any safety issues, the sponsor will stop prescreening/enrollment when 40 TTP events are observed (assessed by an IRC) or 15 August 2017, whichever occurs first. It is expected that approximately 90 subjects will be randomized by 15 August 2017.

9.2 Randomization

Randomization will only occur in Phase II. All eligible subjects will be randomized (1:1 basis) to receive MSC2156119J or sorafenib. Randomization will be performed centrally by using an IVRS.

A stratified permuted block randomization procedure will be employed using the following strata:

- BCLC Stage: Stage B versus Stage C

The purpose of stratification is to ensure an even distribution of the 2 treatment arms within the stratum.

9.3 Endpoints

9.3.1 Primary Endpoints

The primary endpoints are:

- Phase Ib: Incidence of subjects experiencing at least 1 DLT within the first treatment cycle (i.e., 21 days after the first dose)

  Incidence and type of other AEs

- Phase II: TTP based on tumor assessment by an IRC. TTP is defined as the time (in months) from randomization to date of the observation of radiological PD assessed by an IRC

Tumor assessment endpoints are following RECIST v 1.1 (see Appendix C).

9.3.2 Secondary Endpoints

The secondary endpoints are:

- PFS based on tumor assessment by the IRC. PFS time is defined as the time (in months) from randomization to either first observation of disease progression or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment.

- PFS based on tumor assessment by the investigator. PFS time is defined as the time (in months) from randomization to either first observation of radiologically confirmed PD by the investigator or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment.

- OS time. OS time is defined as the time (in months) from randomization to the date of death.

- TTP assessed by investigator. TTP is defined as the time (in months) from randomization to date of the observation of radiological PD assessed by the investigator.

- Time-to-symptomatic progression (TTSP). TTSP is defined as the time (in months) from the date of randomization to the date of deterioration of symptoms assessed by FHSI-8, defined as the total score increase by at least 4 points compared with the baseline value, or deterioration to ECOG PS of 4. This is the PRO endpoint.

- Pharmacokinetics (Phase Ib only): $AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, C_{max}, C_{av}, C_{min}, t_{max}, $AUC_{0\text{-}\infty}$, CL/f, V_z/f, V_{ss}/f, λ_z and $t_{1/2}$ when appropriate.

- Objective response (OR) based on tumor assessment by the IRC. OR is defined as complete response (CR) or partial response (PR) as the best overall response according to radiological assessments as adjudicated by the IRC from randomization to first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1 (see Appendix C).

- OR based on tumor assessment by the investigator. OR is defined as CR or PR as the best overall response according to radiological assessments as adjudicated by the investigator from randomization to first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1 (see Appendix C).

- Disease control based on tumor assessment by the IRC. Disease control is defined as CR, PR, or stable disease (SD) as the best overall response according to radiological assessments as adjudicated by the IRC from the date of randomization to the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization.

- Disease control based on tumor assessment by the investigator. Disease control is defined as CR, PR, or SD as the best overall response according to radiological assessments as adjudicated by the investigator from the date of randomization to the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization.

9.3.3 Safety Endpoints

The safety endpoints, not including the DLT primary objective (see Section 9.3.1), are:

- Drug exposure

- Incidence and type of AEs (all grades as per NCI-CTCAE version 4.0): all treatment emergent adverse events (TEAEs), related TEAEs, treatment emergent SAEs, related treatment emergent SAEs, TEAEs of NCI-CTCAE (version 4.0) Grade ≥ 3, related TEAEs Grade ≥ 3, and TEAEs leading to temporary/permanent treatment discontinuation

- Incidence and reasons for deaths, including deaths within 33 days after the last dose of study drug

- Safety laboratory tests graded by NCI-CTCAE (version 4.0)

- Vital signs; 12-lead ECG changes; physical examinations, including change in body weight; and ECOG PS

9.3.4 Further Endpoints of Interest

Further endpoints of interest in this trial are:

- CCI [redacted]

  CCI [redacted]

- Phase II: PRO assessments of MSC2156119J compared with sorafenib will be assessed using the FACT-HP questionnaire

CCI [redacted]

CCI [redacted]

9.4 Analysis Sets

- All Subjects Set:

  The All Subjects Set includes all subjects who have signed the main informed consent (i.e., screening failures plus subjects enrolled).

- DLT Analysis Set (Phase Ib only):

  The DLT Analysis Set includes all subjects who experienced a DLT during Cycle 1, or did not experience a DLT, and completed at least 80% of planned treatment during the DLT observation period (21 days after the first dose administered). Subjects who have been replaced during the Cycle 1 or whom belong to the Chinese (Mainland) subject cohort will be excluded from the DLT Analysis Set (for replacement criteria, see Section 6.3.2).

- Safety Analysis Set:

  The Safety Analysis Set includes all subjects who have received at least 1 dose of MSC2156119J or sorafenib. Subjects who were replaced for evaluation of DLT will still be included in the Safety Analysis Set, if they are treated at least once (i.e., if the above criterion is met).

- Intent-to-treat (ITT) Analysis Set:

  The ITT Analysis Set in the Phase II part of this trial consists of all subjects who were randomized to study treatment. Subjects will be allocated as randomized.

- Modified intent-to-treat (mITT) Analysis Set:

  The mITT Analysis Set in the Phase II part of this trial consists of all subjects with MET+ HCC who were randomized to study treatment. Subjects will be allocated as randomized. Determination of MET status is planned at Molecular Prescreening (Phase Ib retrospectively, Phase II for subject selection); rescoring will be performed as a quality control measure. Subjects with IHC c-Met status 1+ or 'not assessable' on re-scoring will be excluded from the primary analysis.

  The mITT Analysis Set will be used for the primary analysis of tumor activity and efficacy of the compound.

- PP Analysis Set:

  The PP Analysis Set is defined as all mITT subjects who meet the following criteria:

  - Histologically or cytologically confirmed hepatocellular carcinoma
  - Correct treatment allocation according to randomization or dose selection
  - Measurable or evaluable disease at baseline
  - Completed at least 1 cycle of study therapy
  - Received only permitted medications or procedures according to this protocol

- Subgroups of Interest:

  The following subgroups are considered to be of interest to explore the treatment effect of MSC2156119J. Other subgroups may be analyzed as well in an exploratory manner.

  - Age: < 65 years versus ≥ 65 years
  - Gender: male versus female
  - Geographic region: Greater China versus outside of Greater China
  - BCLC stage: Stage B versus Stage C
  - Type of MET+: overexpression versus amplification (including subjects with co-existing amplification and overexpression)
  - Vascular invasion and/or extrahepatic spread: presence versus absence
  - The underlying disease or medical condition related to etiology: HBV versus Other
  - AFP elevation at the baseline: Yes versus No
  - Prior local-regional therapy: Yes versus No
  - Subjects with a change in IHC c-Met status from 2+ or 3+ to either 1+ or 'not assessable', based on a re-assessment planned for quality assurance purposes (subgroup of the ITT Analysis Set)

- PK Analysis Set:

  All subjects who have received at least 1 dose of the MSC2156119J and who have provided at least 1 plasma concentration measurement of MSC2156119J after the first dose.

- CCI [redacted]

9.5 Description of Statistical Analyses

9.5.1 General Considerations

Statistical analyses will be performed by the Merck Serono Global Biostatistics Department and CRO, except for the analysis of PK parameters. The computer program SAS® System (version 9.1 or higher; SAS Institute, Cary, North Carolina, USA) or R (version 2.10.1 or higher) will be used.

Any subject, who received MSC2156119J but is "not fully evaluable," will be clearly identified in the summaries of subject disposition and in listings. The definition of "not fully evaluable" is provided in Section 6.3.2.

Statistical analyses of Phase Ib will be carried out in a descriptive manner, whereas Phase II has a confirmatory component when analyzing TTP.

Data of Phase Ib will be analyzed after a follow-up of at least 21 days for the last subject. Statistical analyses will be performed using eCRF data in general. Primary statistical analysis of endpoints will be performed using eCRF data obtained until a clinical cut-off date in Phase II. The Phase II clinical cut-off date is determined by the date after the required number of events for the primary endpoint has been reported in the primary analysis population, i.e., 40 TTP events for the mITT population (assessed by an IRC) in Phase II, or on 15 August 2017, whichever occurs first. The final statistical analyses for the Phase II study will be performed at approximately 6 months after the last subject is first dosed.

Safety analyses will be performed according to the as-treated principle. Safety data will be descriptively analyzed on the Safety Analysis Set. Adverse events will be coded according to the current Medical Dictionary for Regulatory Affairs (MedDRA) and reported by preferred term and system organ class. The severity of AEs will be graded using NCI-CTC toxicity grades.

The mITT population will be primarily used in the analysis of baseline characteristics and efficacy. Analyses on the mITT population will consider subjects' allocation to treatment groups as randomized.

Selected efficacy analyses will be repeated for the ITT population, the PP population and for subgroups (see Section 9.4). In case that PP population includes more than 90% of the mITT population, additional efficacy analyses on the PP population will be omitted.

In order to provide overall estimates of the treatment effect data will be pooled across centers. The factor center will not be considered in statistical models or for subgroup analyses because of high number of participating centers and the anticipated small number of subjects randomized in each center.

All **statistical tests** comparing treatment arms will be performed two-sided using a significance level of $\alpha = 10\%$, unless otherwise specified. If CIs are to be calculated, they will be two-sided with a confidence probability of 90%, unless otherwise specified.

Continuous variables will be summarized using descriptive statistics, i.e., number of subjects (N), mean, median, standard deviation, 25th and 75th percentiles (Q_1, Q_3), minimum and maximum. Confidence intervals will be presented where appropriate.

Qualitative variables will be summarized by means of counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

In general, the last measurement prior to or on the day of randomization will serve as the baseline measurement.

Details of the statistical analyses will be defined in the SAP.

9.5.1.1 Protocol Violations

All protocol violations, including inclusion/exclusion criteria violations and violations during the trial, will be listed, even if they are believed not to influence any of the results. The SMC meetings will evaluate potential protocol deviations that could affect the MTD/RP2D determination. The definition of protocol deviations will be specified in the SMC's charter or in the SMC's SAP.

9.5.1.2 Missing Data

Unless otherwise specified, missing data will not be imputed. For the derivation of new variables the following rules will apply:

Incomplete AE-related dates will be handled as follows:

- In case the onset date is completely missing or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of study treatment then the onset date will be replaced by the minimum of start of study treatment and AE resolution date.
- In all other cases the missing onset day or onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed.

For imputing missing parts of dates for the efficacy analyses the missing day in a date will be imputed as the 15th of the month, if month and year is documented. This includes also dates of start of follow-up therapy. In all other cases missing or incomplete dates will not be imputed if not indicated otherwise.

In individual subject data listings the documented date as given in the eCRF will be reported (e.g., __May 2013 in case of day missing, but month and year available). No imputed values will be presented in clinical trial report. In all other subject data listings, imputed values will be presented. In those listings imputed date of death, last date known to be alive, start of AE, and relationship of AE to study treatment will be flagged.

9.5.2 Analysis of Primary Endpoints

9.5.2.1 Statistical Analysis of the Dose Escalation Cohort

The DLT Analysis Set will be used for evaluation of the number of subjects experiencing any DLTs at the end of each cohort and for the assessment of the MTD/RP2D.

For final statistical analysis, the number and proportion of subjects in the DLT population who experienced DLT during the Cycle 1 of treatment with MSC2156119J will be presented by dose level. Subject disposition will be reported for each dose level, and subject profiles will be presented.

Listings and graphics of information which is relevant to the primary endpoint will be prepared for the SMC, for the purpose of determination of the MTD/RP2D of MSC2156119J in Asian subjects, according to the content agreed and specified in the SMC's charter.

The MTD/RP2D will be determined as described in Section 7.2.3.

9.5.2.2 Statistical Analysis of Primary Endpoint of Phase II

The primary endpoint of Phase II in this trial is TTP based on tumor assessment by an IRC. TTP is defined as the time (in months) from randomization to date of the observation of radiological PD assessed by an IRC. Death without radiological progression date will be censored. In subjects without a progression date or loss to follow-up at time of analysis, the time between the date of randomization and the date of last tumor assessment will be calculated and used as a censored observation in the analysis. In principle, all tumor assessment should be considered to determine and derive the date of radiological progression.

The primary analysis will test the equality of TTP between treatment groups, based on the mITT population, applying two-sided unstratified log-rank test at a significance level of 10%.

The following null-hypothesis is tested:

$$H_0: \lambda_A(t) = \lambda_B(t) \text{ versus } H_1: \lambda_A(t) = \theta\lambda_B(t), \theta \neq 1,$$

where $\lambda(t)$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in the allocated treatment groups (MSC2156119J and sorafenib).

The HR (including 90% CI) of MSC2156119J compared to sorafenib will be calculated by Cox's proportional hazards model.

Kaplan-Meier survival curves (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics (median survival time, 6-month, 12-month survival rate estimates and estimates for every 6 months thereafter as applicable) including the corresponding two-sided 90% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley, and CIs for the survival function estimates at above defined time points will be derived directly from the Kaplan-Meier estimates. The estimate of the standard error will be computed using Greenwood's formula. Comparisons of survival rates will be performed from a Z-test using estimates and standard errors derived from the Kaplan-Meier method and Greenwood's formula.

TTP will be further explored considering the ITT population, the PP population and pre-defined subgroups (see Section 9.4).

9.5.3 Analysis of Secondary Endpoints

9.5.3.1 Progression-free Survival

Progression-free survival (assessed by the IRC) time is defined as the time (in months) from randomization to either first observation of progression disease or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment. If no progression or death is observed at the time of analysis, or if death without previously documented PD is observed after more than 84 days of last tumor assessment without progression, the PFS time will be censored on the date of last tumor assessment or date of randomization, whatever occurs later. The 84-day time window represents the time between 2 scheduled tumor assessments.

Treatment groups will be compared based on mITT population, applying two-sided unstratified log-rank test at a significance level of 10%.

The same survival analysis methods will be employed as for the primary endpoint, PFS will be further explored considering the ITT population, the PP population and pre-defined subgroups (see Section 9.4).

Progression-free survival based on tumor assessment by the investigator will also be analyzed in the same way as described above.

9.5.3.2 Overall Survival

Overall survival will be measured as the time (in months) between the date of randomization and the date of death. The analysis will be performed on the basis of the ITT principle on the primary analysis population. OS time (in months) is defined as:

(date of death or last date known to be alive – date of randomization + 1) / 30.4375.

For subjects not known to be deceased at time of analysis, the time between date of randomization and date of last contact or date of lost to follow-up will be calculated and used as a censored observation in the analysis. If this date is after the data cut-off, subjects will be censored at the date of data cut-off.

Treatment groups will be compared based on the mITT population, applying two-sided unstratified log-rank test ($\alpha = 10\%$).

OS data will be further explored considering the ITT population, the PP population and predefined subgroups (see Section 9.4).

9.5.3.3 Time-to-symptomatic Progression

Time-to-symptomatic progression is defined as the time (in months) from the date of randomization to the date of deterioration of symptoms assessed by FHSI-8, defined as the total score increase by at least 4 points compared with the baseline value, or deterioration to ECOG PS 4. The analysis will be performed on the basis of the ITT principle on the primary analysis population at time when TTP is statistically analyzed.

Treatment groups will be compared based on the mITT Population, applying two-sided unstratified log-rank test ($\alpha = 10\%$).

9.5.3.4 Antitumor Activity

Objective response and disease control will be evaluated based on the mITT population.

The **objective response rate** is defined as the proportion of subjects having achieved CR or PR as the best overall response according to radiological assessments as adjudicated by the IRC from randomization until the first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1 (see Appendix C).

The **disease control rate** is defined as the proportion of subjects having achieved CR, PR, or SD as the best overall response according to radiological assessments as adjudicated by the IRC from randomization until the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization.

Fisher's exact test will be performed for analysis and will test the following two-sided hypothesis:

$$H_0: \Psi = 1 \text{ versus } H_1: \Psi \neq 1$$

where Ψ defines the odds ratio between treatments.

The OR rate and disease control rate will be presented for each treatment group including the corresponding 90% Newcombe-Wilson CIs.

Duration of response will be presented descriptively.

Objective response rate and disease control rate based on tumor assessment by the investigator will also be analyzed in the same way as described above.

9.5.3.5 Safety and Tolerability

The Safety Analysis Set will be used for summaries of demographic and baseline characteristics, as well as for all summaries of safety data (except for DLT analysis).

Safety analyses will be performed according to as-treated principle. Any treatment emergent AEs will be summarized, i.e., those events that emergent during treatment having been absent pretreatment, or worsen relative to the pretreatment state and with onset dates occurring within the first dosing day of study treatment until 33 days after the last dose of study treatment. No formal statistical comparisons are planned.

The extent of exposure to MSC2156119J and sorafenib will be characterized by time on treatment (weeks), cumulative dose, dose intensity, relative dose intensity (actual cumulative dose/planned dose), number of dose reductions, and number of dose delays.

AEs will be coded according to the MedDRA. Severity of AEs will be graded using NCI-CTCAE (version 4.0) toxicity grade. The incidence and type of AEs, SAEs, study treatment-related AEs and SAEs, AEs of Grade ≥ 3 by NCI-CTCAE, study treatment-related AEs of Grade ≥ 3 by NCI-CTCAE, AEs leading to death, study treatment-related AEs leading to death, and AEs leading to temporary/permanent treatment discontinuation will be summarized in total and for each treatment group according to MedDRA system organ class and MedDRA preferred terms. Adverse event summaries will be prepared for Cycle 1 and the whole treatment period.

All deaths and deaths within 33 days after last dose of study treatment as well as reasons for death will be tabulated.

Laboratory results will be classified according to NCI-CTCAE (version 4.0). The worst on-treatment grades after the first dose of the study treatment will be summarized. Shifts in toxicity grades from treatment start to the highest grade will be displayed. Results for variables that were not part of the NCI-CTCAE will be presented as below, within and above the normal limits of the local laboratory. Only subjects with post-baseline laboratory values will be included in these analyses. The last measurement before study treatment will serve as the baseline measurement. Descriptive summaries of actual (absolute) laboratory values and changes from baseline will be presented.

Changes in body weight from baseline to measurements during the treatment phase will be classified according to the NCI-CTCAE (version 4.0) criteria. The highest change from baseline will summarized.

Clinically significant, abnormal findings from 12-lead ECG during treatment phase will be descriptively presented.

Changes from baseline to worst on-treatment value will be summarized descriptively for the QTc interval (including absolute changes and categorical shifts).

Vital signs (body temperature, heart rate, blood pressure, respiratory rate) recorded at baseline will be descriptively presented.

The baseline results of the physical examination will be presented. Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination during and after treatment will not be provided.

The ECOG PS will be summarized descriptively by visit.

Further details on safety analyses will be specified in the SAP.

Statistical Analyses for the Dose Escalation Decision

Within each dose level and upon completion of Cycle 1 (i.e., the first 21 days) of treatment by the last subject, data from analyses will be presented to the SMC for a decision on dose escalation. These analyses will include safety data from Cycle 1, including listings of AEs graded according to NCI-CTCAE and DLT, listings of laboratory data, vital signs, 12-lead ECG, as well as each subject's demographics, disease history, and treatment compliance in Cycle 1. Additionally, data from all other cycles for subjects dosed in previous dose levels have to be provided for each SMC meeting. Any protocol violation that could affect DLT will be monitored and reported at each SMC. The full data to be presented will be documented in detail in the SMC charter.

Any subject who is replaced with another subject in Cycle 1 will be included in the listings, but the information that the subject is not included in the DLT analysis population will be contained in the listings.

9.5.3.6 Pharmacokinetics

All PK parameters will be determined for each subject as described in Section 8.5.2. PK data of subjects enrolled up to 15 August 2017 will be considered for the analysis. The following analyses will be performed for each dose group of Phase Ib.

For PK, individual serum and mean (± standard deviation) concentration time plots will be provided for each treatment group using a linear and semi-logarithmic scale. Scatter-plots may also be prepared for exploratory purposes.

The plasma concentration data for MSC2156119J will be summarized descriptively per dose cohort and per time point. Descriptive statistics will include number of subjects (N), arithmetic mean, geometric mean, median, standard deviation, minimum and maximum values, and CV in %. Mean plasma concentration-time profiles will be generated on both linear and semi-logarithmic scales using time values as scheduled.

The derived PK parameters will be summarized descriptively per dose cohort. Descriptive statistics will include number of subjects (N), the arithmetic mean, geometric mean, standard deviation, SEM, median, minimum and maximum values, and CV in %.

The potential drug accumulation will be evaluated according to an appropriate manner. Additionally, the PK/Pd relationship may be explored. Pharmacodynamic variables might be chosen based on the trial outcome; efficacy, as well as safety variables, might be considered.

The PK population includes all subjects who have received MSC2156119J and who have had at least 1 blood sample drawn that provide drug concentration data for PK evaluation. CCI [redacted] Further details regarding PK analyses will be provided in the SAP.

CCI [redacted]

CCI [redacted]

[redacted]

9.5.4 Safety Analyses

See Section 9.5.3.5.

9.6 Interim Analysis

An IDMC will be formed from a group of 3 experts and will consist of at least a statistician and 1 oncologist who will not be either participant in the trial or an employee of the sponsor of this study as well as the independent statistician who is not a voting member of the IDMC. An IDMC charter and IDMC Analysis Plan will provide the details about the conduct of the IDMC meeting, frequency, and decision making rules.

The IDMC will be responsible for periodic (as defined by the IDMC charter) evaluations of the clinical trial to ensure continued subject safety as well as the validity and scientific merit of the study.

The designated independent statistician will provide the IDMC with the safety summaries periodically for review. No individuals involved with the direct monitoring of this study will have access to the treatment identities.

In addition to periodic evaluations and a final analysis, a formal primary analysis based on key statistical endpoints will occur after observation of 40 TTP events (assessed by an IRC) in the primary analysis population or 15 August 2017, whichever occurs first.

10 Ethical and Regulatory Aspects

10.1 Responsibilities of the Investigator

The investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the investigator must ensure that only subjects who have given their informed consent(s) are included into the trial.

In 1998, the US Food and Drug Administration (FDA) introduced a regulation (Code of Federal Regulations Title 21 Part 54) entitled "Financial Disclosure by Clinical Investigators". For trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the investigational medicinal product (named "covered trials" by the FDA), the investigator and all sub-investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the sponsor or the sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial.

10.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent(s). The subject's written informed consent(s) to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the investigator before informed consent is obtained (a person designated by the investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) will be provided by the sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the investigator or his/her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the investigator may inform the subject and sign the ICF(s), as above.

Where the information is provided by the investigator, the ICF must be signed and personally dated by the subject and the investigator.

The signed and dated declaration of informed consent(s) will remain at the investigator's site, and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The investigator will explain the changes to the previous version.

Absorption, distribution, metabolism, and elimination CCI will be conducted for subjects who have consented specifically to them. The objectives and description of the CCI and the biopsy should be included in the subject information sheet for CCI, and subjects are to give consent by checking the consent on CCI and tumor biopsy in the ICF for CCI.

10.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after the main informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

After the additional research for CCI is done, all remaining de-identified biological material (CCI) will be kept for a maximum of 12 years. During this time, samples will be stored at the sponsor's biobank or a third party's biobank. It is possible that the samples will be re-analyzed with newer, more exact technologies during that time.

CCI

[redacted]

10.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial; and this may include the possibility of emergency unblinding if needed, in case of blinded trials.

Clinical trial investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial investigator caring for the affected subject. The investigator agrees to provide his or her emergency contact information on the card for this purpose. If the investigator is available when an event occurs, she/he will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard processes established for the investigators.

In cases where the investigator is not available, Merck Serono/EMD Serono provides the appropriate means to contact a sponsor physician. This includes the provision of a 24 hour contact number at a call center, whereby the health care providers will be given access to the appropriate sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

10.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each country participating to the trial. Insurance conditions shall meet local standards, as applicable.

10.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents to the responsible IEC/IRB for its favorable

opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at the sponsor.

The trial must not start at a site before the sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (see Section 11.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

10.7 Health Authorities

The clinical trial protocol and any applicable documentation (e.g., Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

11 Trial Management

11.1 Case Report Form Handling

The investigator or designee will be responsible for entering trial data in the eCRF provided by the designated CRO, PPD. It is the investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The data management department of the designated CRO, PPD, will be responsible for data processing, in accordance with the defined data management procedures, under the supervision of the sponsor. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. Portable document format files of the eCRFs will be provided to the investigators at the completion of the trial.

11.2 Source Data and Subject Files

The investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name
- Date of birth

- Sex
- Height
- Weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification (Trial EMR200095-004)
- Date of subject's inclusion into the trial (i.e., date of giving the main informed consent)
- Subject number in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All AEs observed in the subject
- Date of subject's end of the trial
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if applicable

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives, X-rays, CT or MRI, 12-lead ECG recordings, laboratory value listings, a subject diary for the compliance to IMP administration, etc. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the investigator.

The following information described in the eCRF is regarded as the source data.

- Any investigator's comments
- Subject number

11.3 Investigator Site File and Archiving

The investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for sponsor audit, as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICF(s). If archiving of the Investigator Site File is no longer possible at the site, the investigator must notify the sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the investigator should ensure that no destruction of medical records is performed without the written approval of the sponsor.

11.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996). The site Monitor will perform visits to the trial site at regular intervals.

In line with ICH GCP guidelines, monitoring will include verification of data entered in the eCRF against original subject records. This verification will be performed by direct access to the original subject records, and the sponsor guarantees that subject confidentiality will be respected at all times. Participation in this trial will be taken as agreement to permit direct source data verification.

Representatives of the sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the IMP, and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

11.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see Section 10.2).

11.6 Clinical Trial Report and Publication Policy

11.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the sponsor in consultation with the coordinating investigator.

11.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoints that will include data from all trial sites.

The investigator will inform the sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require presubmission review by the sponsor.

The sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

12 References

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

2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137-2150.

3. International Agency for Cancer Research. GLOBCAN 2002: http://www-dep.iarc.fr (accessed March 18, 2009).

4. Parkin D, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.

5. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.

6. Poon D, Anderson BO, Chen L-T, et al. Management of hepatocellular carcinoma in Asia: Consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009;10:1111-1118.

7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.

8. Cheng AL, 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.

9. Birchmeier C, Birchmeier W, Gherardi E, et al. Met, metastasis, motility and more. Nat Rev Mol Cell Biol 2003;4(12):915-25.

10. Comoglio PM, Giordano S, Trusolino L. Drug development of MET inhibitors: Targeting oncogene addiction and expedience. Nat Rev Drug Discov 2008;7(6):504-516.

11. Gherardi E, Birchmeier W, Birchmeier C, et al. Targeting MET in cancer: rationale and progress. Nat Rev Cancer 2012;12(2):89-103.

12. Liu X, Yao W, Newton RC, et al. Targeting the c-MET signaling pathway for cancer therapy. Expert Opin Investig Drugs 2008;17:997-1011.

13. Benvenuti S, Comoglio PM. The MET receptor tyrosine kinase in invasion and metastasis. J Cell Physiol 2007;213:316-325.

14. Gentile A, Trusolino L, Comoglio PM. The Met tyrosine kinase receptor in development and cancer. Cancer Metastasis Rev 2008;27:85-94.

15. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet 1997;16:68-73.

16. Kim DW, Soo RA, Yang JCH, et al. Antitumor activity of tepotinib plus gefitinib in Asian patients with Met-positive NSCLC. 16th World Congress on Lung Cancer. 2015 September, Abstract No. 763.

17. Rimassa L. Tivantinib (ARQ 197) versus placebo in subjects (Pts) with hepatocellular carcinoma (HCC) who failed one systemic therapy: Results of a randomized controlled phase II trial (RCT). 2012 ASCO Annual Meeting.

18. Llovet JM, Peña CE, Lathia CD, et al. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012;18(8):2290-2300.

19. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698-711.

13 Appendices

Appendix A: Scoring System for Met Immunohistochemistry

Diagnostic	Clinical Score	Scoring Criteria
Positive	3+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with strong intensity
	2+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with moderate intensity
Negative	1+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with weak intensity but < 50% tumor cells with moderate or high intensity
	0	Samples with no staining, or with < 50% tumor cells with membrane and/or cytoplasmic staining (could be combination of any staining intensities)

Appendix B: Child-Pugh System

The text below was obtained from the University of Washington Medical Center's Criteria for Child-Pugh classification, which cites the following references:

Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg 1997;3(6):628-637.

Pugh RNH, Murray-Lyon IN, Dawson DL, Pietroni MC, and Williams R. Transection of the esophagus for bleeding esophageal varices. Brit J Surgery 1973;60:646-645.

Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.

Child-Pugh classification is defined as Grade A (mild; 5 to 6 points), Grade B (moderate; 7 to 9 points), or Grade C (severe; 10 to 15 points). The clinical and biochemical measurements to determine Child-Pugh classification are presented in Table 8.

Table 8: Clinical and Biochemical Measurements for Child-Pugh Classification

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	2	3
Hepatic encephalopathy (grade)[a]	0[b]	1[c] or 2[d]	3[e] or 4[f]
Ascites	Absent	Mild	Moderate
Total bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time (sec prolonged) or Prothrombin time INR[g]	< 4 or < 1.7	4 to 6 or 1.7 to 2.3	> 6 or > 2.3

Abbreviations: INR, international normalized ratio.

[a] Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.

[b] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.

[c] Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.

[d] Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.

[e] Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

[f] Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

[g] Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg 1997;3(6):628-637.

Appendix C: Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

Definitions

Response and progression will be evaluated in this trial using the international criteria proposed by the RECIST Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered

as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article cited above, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the trial, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between partial response (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse event (AE) of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

RESPONSE CRITERIA

Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on trial. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Electronic case report forms or other data collection methods may therefore be designed to have target nodal lesions

recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on trial, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

When the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the

size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease. This circumstance arises in some Phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the subject who has visceral disease at baseline and while on trial has a brain CT or MRI ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fludeoxyglucose positron emission tomography (FDG-PET) response assessments need additional trial, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best OR is the best response recorded from the start of the trial treatment until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment assessments are to be considered in determination of best OR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best OR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best OR'.

The best OR is determined once all the data for the subject is known. Best response determination in trials where confirmation of complete or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best OR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR*	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
	Non-PD		
Not all evaluated		No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.
See text for more details.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of 'zero' on the CRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials, it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping trial therapy.

Conditions that define 'early progression, early death and inevaluability' are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. The use of FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (Phase II or III) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the trial protocol.

Duration of Overall Response

The duration of OR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on trial).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on trial (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of subjects achieving SD for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these

limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix D: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Appendix E: New York Heart Association (NYHA) Criteria

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such subjects are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although subjects are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix F: FACT Hepatobiliary Symptom Index 8

The sponsor will provide training for relevant personnel (e.g., key investigators, clinical research associates) in the administration of the questionnaires so that subjects fill in the questionnaires as completely and accurately as possible. It is important that the significance and relevance of the data are explained carefully to participating subjects so that they are motivated to comply with data collection. The measures are self-reported and the subject must complete the questionnaires in private and should not be given help from relatives or clinic staff; help in interpreting the questions is not allowed. All subjects are required to take part in all PRO assessments. If feasible, ePRO software may be used for direct data entry by the subject.

Below is a list of statements that other people with your illness have said are important. **Please circle or mark 1 number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
CNS7	I have pain in my back	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
Hep2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep8	I have discomfort or pain in my stomach area	0	1	2	3	4

Appendix G: Functional Assessment of Cancer Therapy – Hepatobiliary

The sponsor will provide training for relevant personnel (e.g., key investigators, clinical research associates) in the administration of the questionnaires so that subjects fill in the questionnaires as completely and accurately as possible. It is important that the significance and relevance of the data are explained carefully to participating subjects so that they are motivated to comply with data collection. The measures are self-reported and the subject must complete the questionnaires in private and should not be given help from relatives or clinic staff; help in interpreting the questions is not allowed. All subjects are required to take part in all PRO assessments. If feasible, ePRO software may be used for direct data entry by the subject.

Below is a list of statements that other people with your illness have said are important**. Please circle or mark 1 number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

Please circle or mark 1 number per line to indicate your response as it applies to the past 7 days.

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark 1 number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark 1 number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4

Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

Appendix H: Phase Ib Schedule of Dosing and Assessments

	Screening	Cycle 1 Day				Cycle 2 Day[a]			Cycle ≥ 3 Day	EoT Visit[b]	Post-Treatment F/U Visit[c]	Survival F/U[d]
DAY	**-14 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**			
MSC2156119J		QD										
Written informed consent	X											
Dispensing of study drug		X				X			X			
Demography, height	X											
Medical history	X											
Smoking status and alcohol use	X											
Tumor biopsy		X[e]			X[e]					X[f]		
Physical examination/weight	X	X[g]	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X[g]				X			X	X	X	
Vital signs[h]	X	X	X	X	X	X	X		X	X	X	
ECG[i]	X	X[j]			X[j]	X[k]			X[k]	X[l]	X	
Hematology and coagulation[m]	X	X[g]	X	X	X	X	X	X	X	X[l]	X	
Chemistry[n]	X	X[g]	X	X	X	X	X	X	X	X[l]	X	
Urinalysis[o]	X	X[g]				X			X	X[l]	X	
HBV viral serology panel[p]	X[q]								X[r]	X[l,r]		
HBV DNA (viral load)[r]	X[q]								X[r]	X[l,r]		
HCV RNA-PCR (viral load)[s]	X[q]								X[s]	X[l,s]		
Serum pregnancy test (if applicable)[t]	X											
Tumor assessment (RECIST v 1.1)[u]	X								X[v]	X[w]		
Serum AFP	X	X[g]				X			X	X		
PK blood samples		X[x]			X[x]							

	Screening	Cycle 1 Day				Cycle 2 Day[a]			Cycle ≥ 3 Day	EoT Visit[b]	Post-Treatment F/U Visit[c]	Survival F/U[d]
DAY	**-14 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**			
CCI [redacted] CCI												
Subject survival and anticancer therapies												X
Adverse events assessment	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication/procedure	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; F/U, follow-up; GGT, gamma-glutamyl transpeptidase; HBc, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC; hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; RECIST, response evaluation criteria in solid tumors; MRI, magnetic resonance imaging; CCI [redacted]; PK, pharmacokinetic; PT, prothrombin time; RNA, ribonucleic acid.

a All visits and assessments from Cycle 2 onwards may be performed +/- 5 days to accommodate unforeseen delays, holidays, or vacations.

b End of treatment visit, performed on the last day of treatment, whether at the end of a cycle or not. The last day of treatment is defined as the day on which it is determined that the subject will no longer receive the study drug.

c Post-treatment follow-up visit, performed within 30 ± 3 days after the last treatment for all subjects who discontinue trial treatment permanently, including subjects who have completed an end of treatment visit.

d Survival data will be collected every 3 months after end of treatment until death or the end of the trial.

e Undergoing paired tumor biopsy is not mandatory but highly recommended for subjects with accessible tumors: the paired tumor biopsy will be performed before the first trial treatment (i.e., during Screening or on Cycle 1, Day 1, prior to the first dose of trial treatment) and anytime between Cycle 1, Day 15, and the beginning of Cycle 3 (optional, will be collected after subjects have signed a separate Informed Consent Form). A predose PK is recommended to be taken on the day of the second biopsy.

f Optional tumor biopsy, to be taken at the time of progression on the day of the last treatment.

g Only if last assessments were performed > 7 days prior to Cycle 1, Day 1.

h Heart rate, diastolic and systolic blood pressure in a seated position of 5 minutes. On days when ECGs are taken, vital signs should be taken within 30 minutes prior to the ECG recording. Where ECGs are performed in triplicate, vital signs only need to be recorded once prior to the first ECG.

i All ECGs to be taken as single 12-lead resting ECGs, except at time points where PK samples are also obtained, in which case triplicate ECGs should be obtained at 2-minute intervals (± 1 minute). Vital signs (heart rate, systolic, and diastolic blood pressure, in a seated position) should be taken within 30 minutes prior to each ECG recording after sitting for 5 minutes.

j ECGs are recorded after at least 5 minutes rest in supine position at predose (within 60 minutes prior to dosing on Cycle 1 Day 1 and within 40 minutes prior to dosing on Cycle 1 Day 15) and at 4 hours (± 12 minutes) postdose. ECG recordings should be performed within 10 minutes before PK sampling time-points on days where both assessments are performed.

k Predose only.

l Not required for subjects with a previous assessment within 7 days of the EoT visit.

m Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count, and coagulation (PT, aPTT, and INR). For the subject eligibility check at screening, these samples must be reported by a local laboratory.

n BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin is abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium, and glucose. For the subject eligibility check at screening, these samples must be reported by a local laboratory.

o Urinalysis: dipstick followed by microscopic examination if abnormal results.

p HBV serology panel: HBc antibodies, HBs antibodies, HBs antigen, HBe antigen, HBe antibodies.

q The purpose of these samples is to establish baseline values. Alternatively, samples may be taken predosing on Day 1 of Cycle 1.

r HBV DNA will be evaluated in all subjects at baseline. Thereafter, HBV DNA and serology will be monitored every 3 cycles and at EoT for all subjects with known HBV history, or who were positive for HBV DNA at baseline, or are positive for HBV serology. See Section 7.5.3.1.

s HCV RNA-PCR will be evaluated in all subjects at baseline. Thereafter, HCV RNA-PCR will be monitored every 3 cycles and at EoT for all subjects with known HCV history or who were positive for HCV RNA-PCR at baseline. See Section 7.5.3.1.

t Only for women of childbearing potential, including those who have had a tubal ligation.

u Complete tumor assessment of all lesions by radiographic or other modality (using RECIST v 1.1). CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations. CT/MRI of the head at baseline for subjects who are suspected to have CNS metastases. Tumor assessments to be performed at baseline and after every 2 cycles (6 weeks) (i.e., before start of next odd-numbered cycle) until Cycle 13 and after every 4 cycles (12 weeks) after Cycle 13. The scheduled 6-week (or 12-week) interval between tumor response evaluations should be maintained through the trial regardless of any delay or interruption to trial treatment. Subjects who are discontinued from the trial due to unacceptable toxicity should perform the tumor assessment at 6 week intervals until Cycle 13 and 12 week interval (4 cycles) after Cycle 13 until disease progression, starting a new therapy, or death. Clinical progression, at any time, requires a physical examination and prompt radiological confirmation rather than waiting for the next scheduled imaging assessment. If unscheduled imaging does not meet progressive disease by RECIST v1.1, the next scheduled imaging assessment should still be performed on time unless the next scheduled imaging assessment is within 14 days following the unscheduled imaging. See Section 8.3.

v To be performed predose on, or within 5 days prior to, Day 1 of Cycles 3, 5, 7, 9, 11, 13, i.e., at 6-week intervals, and every 4 cycles thereafter, i.e., at 12-week intervals, until disease progression, starting a new anti-tumor therapy, or death. The scheduled 6-week (or 12-week) interval between tumor response assessments should be maintained through the trial regardless of any delay or interruption to trial treatment.

w If a subject discontinues trial treatment for a reason other than disease progression or death, tumor assessment will be performed at EoT if it has not been done within the past 6 weeks, and will be repeated every 6 weeks (± 1 week) until radiological progression per RECIST v 1.1, death or start of new anticancer therapy, whichever occurs first.

x Samples will be taken predose, and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose. Note: The 24-hour postdose samples from Day 1 and Day 15 are the predose samples from Day 2 and Day 16, respectively. The predose sample on Cycle 1 Day 1 should be taken within 60 minutes prior to dose. The predose sample on Cycle 1 Day 15 (trough value) should be taken within 30 minutes predose. Postdose PK samples should be taken within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose sample should be obtained at 4 hours ± 12 minutes.

CCI [redacted]

CCI [redacted]

Appendix I: Phase II Schedule of Dosing and Assessments

	Screening		Cycle 1 Day			Cycle 2 Day[a]		Cycle ≥ 3 Day	EoT Visit[b]	Post-Treatment F/U Visit[c]	Survival F/U[d]
	Molecular Prescreening	Clinical Screening									
DAY		**≤ -14 to 0**	**1**	**8**	**15**	**1**	**8**	**1**			
MSC2156119J			QD								
Sorafenib			BID								
Written informed consent (Prescreening)[e]	X										
Written informed consent (main study)[e]		X									
Eligibility		X[e]									
Randomization by IVRS			X								
Dispensing of study drug			X			X		X			
Demography, height[e]		X									
Medical history[e]		X									
Smoking status and alcohol use		X									
Tumor biopsy			X[f]		X[f]				X[g]		
MET status determination[e]	X										
Physical examination/weight[h]		X	X[i]	X	X	X	X	X	X	X	
ECOG PS[h]		X	X[i]			X		X	X	X	
Vital signs[h,j]		X	X	X		X	X	X	X	X	
ECG[h,k]		X	X[l]		X[m]	X[l]		X[m]	X[n]	X	
Hematology and coagulation[h,o]		X	X[i]	X	X	X	X	X	X[n]	X	
Chemistry[h,p]		X	X[i]	X	X	X	X	X	X[n]	X	
Urinalysis[h,q]		X	X[i]			X		X	X[n]	X	
HBV viral serology panel[h,r]		X[s]						X[t]	X[n,t]		

	Screening		Cycle 1 Day			Cycle 2 Day[a]		Cycle ≥ 3 Day	EoT Visit[b]	Post-Treatment F/U Visit[c]	Survival F/U[d]
	Molecular Prescreening	Clinical Screening									
DAY		≤ -14 to 0	1	8	15	1	8	1			
HBV DNA (viral load)[h,t]		X[s]						X[t]	X[n,t]		
HCV RNA-PCR (viral load)[h,u]		X[s]						X[u]	X[n,u]		
Serum pregnancy test (if applicable)[h,v]		X									
Tumor assessment (RECIST v 1.1)[w]		X						X[x]	X[y]		
Serum AFP		X	X[i]			X		X	X		
CCI											
CCI											
CCI											
Subject survival and anticancer therapies											X
Adverse events assessment		X	X	X	X	X	X	X	X	X	
Concomitant medication/procedure		X	X	X	X	X	X	X	X	X	
FHSI-8		X	X			X		X	X	X	
PRO (FACT-HP)			X			X		X[dd]	X[dd]		

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, end of treatment; CCI ; FHSI-8, FACT Hepatobiliary Symptom Index 8; F/U, follow-up; GGT, gamma-glutamyl transpeptidase; HBc, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC; hepatocellular carcinoma; HCV, hepatitis C virus; ICF, Informed Consent Form; INR, international normalized ratio; IVRS; interactive voice response system; RECIST, response evaluation criteria in solid tumors; MRI, magnetic resonance imaging; CCI ; CCI ; PRO, subject reported outcomes; PT, prothrombin time; RNA, ribonucleic acid.

a All visits and assessments from Cycle 2 onwards may be performed +/- 5 days to accommodate unforeseen delays, holidays, or vacations.

b End of treatment visit, performed on the last day of treatment, whether at the end of a cycle or not. The last day of treatment is defined as the day on which it is determined that the subject will no longer receive the study drug.

c Post-treatment follow-up visit, performed within 30 ± 3 days after the last treatment for all subjects who discontinue trial treatment permanently, including subjects who have completed an end of treatment visit.

d Survival data will be collected every 3 months after end of treatment until death or the end of the trial.

e MET status will be confirmed during Molecular Prescreening after the subject has signed the prescreening ICF. Demographic data and disease history will also be collected during Molecular Prescreening once the subject has signed the main ICF. Clinical Screening will include laboratory parameters, medical history and all other assessments needed to confirm subject eligibility, plus demographic data and disease history if not already collected. Clinical Screening assessments must be completed within 14 days prior to the initiation of study treatment. MET status rescoring will be performed as a quality control measure; subjects with a MET status of 1+ or 'not assessable' on rescoring will be excluded from the modified intent-to-treat population.

f Undergoing paired tumor biopsy is not mandatory, but highly recommended for subjects with accessible tumors: the paired tumor biopsy will be performed before the first treatment (i.e., during screening or on Cycle 1, Day 1, prior to the first dose of trial treatment) and anytime between Cycle 1, Day 15 and the beginning of Cycle 3 (optional, will be collected after subjects have signed a separate ICF).

g Optional tumor biopsy, to be taken at the time of progression on the day of the last treatment.

CCI [redacted]

i. Only if screening/last assessments were performed > 7 days prior to Cycle 1, Day 1.

j Heart rate, diastolic and systolic blood pressure in a seated position of 5 minutes. On days when ECGs are taken, vital signs should be taken within 30 minutes prior to the ECG recording. Where ECGs are performed in triplicate, vital signs only need to be recorded once prior to the first ECG.

k All ECGs to be taken as single 12-lead resting ECGs, except at time points where PK samples are also obtained, in which case triplicate ECGs should be obtained at 2-minute intervals (± 1 minute). Vital signs (heart rate, systolic, and diastolic blood pressure, in a seated position) should be taken within 30 minutes prior to each ECG recording after sitting for 5 minutes.

l ECGs are recorded after at least 5 minutes rest in supine position at predose (within 60 minutes prior to dosing on Cycle 1 Day 1 and within 40 minutes prior to dosing on Cycle 2 Day 1) (MSC2156119J and sorafenib arms) and at 4 hours (± 12 minutes) postdose (MSC2156119J arm only). ECG recordings should be performed within 10 minutes before PK sampling time-points on days where both assessments are performed.

m Predose only.

n Not required for subjects with a previous assessment within 7 days of the EoT visit.

o Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count, and coagulation (PT, aPTT, and INR). For the subject eligibility check at Clinical Screening, these samples must be reported by a local laboratory.

p BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, sodium, potassium, calcium, magnesium and glucose. For the subject eligibility check at Clinical Screening, these samples must be reported by a local laboratory.

q Urinalysis: dipstick followed by microscopic examination if abnormal results.

r HBV serology panel: HBc antibodies, HBs antibodies, HBs antigen, HBe antigen, HBe antibodies.

s The purpose of these samples is to establish baseline values. They may be taken during Clinical Screening or predose on Day 1 of Cycle 1.

t HBV DNA will be evaluated in all subjects at baseline. Thereafter, HBV DNA and serology will be monitored every 3 cycles and at EoT for all subjects with known HBV history, or who were positive for HBV DNA at baseline, or are positive for HBV serology. See Section 7.5.3.1.

u HCV RNA-PCR will be evaluated in all subjects at baseline. Thereafter, HCV RNA-PCR will be monitored every 3 cycles and at EoT for all subjects with known HCV history or who were positive for HCV RNA-PCR at baseline. See Section 7.5.3.1.

v Only for women of childbearing potential, including those who have had a tubal ligation.

w Complete tumor assessment of all lesions by radiographic or other modality (using RECIST v 1.1). CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations. CT/MRI of the head at baseline for subjects who is suspected to have CNS metastases. Tumor assessments to be performed at baseline and after every 2 cycles (6 weeks) (i.e., before start of next odd-numbered cycle) until Cycle 13 and after every 4 cycles (12 weeks) after Cycle 13. The scheduled 6-week (or 12-week) interval between tumor response evaluations should be maintained through the trial regardless of any delay or interruption to trial treatment. Subjects who are discontinued from the trial due to unacceptable toxicity should perform the tumor assessment at 6-week intervals until Cycle 13 and 12-week interval (4 cycles) after Cycle 13 until disease progression, starting a new therapy, or death. Clinical progression, at any time, requires a physical examination and prompt radiological confirmation rather than waiting for the next scheduled imaging assessment. If unscheduled imaging does not meet progressive disease by RECIST v1.1, the next scheduled imaging assessment should still be performed on time unless the next scheduled imaging assessment is within 14 days following the unscheduled imaging. See Section 8.3.

x To be performed predose on, or within 5 days prior to, Day 1 of Cycles 3, 5, 7, 9, 11, 13, i.e., at 6-week intervals, and every 4 cycles thereafter, i.e., at 12-week intervals, until disease progression, starting a new anti-tumor therapy, or death. The scheduled 6-week (or 12 week) interval between tumor response assessments should be maintained through the trial regardless of any delay or interruption to trial treatment.

y If a subject discontinues trial treatment for a reason other than disease progression or death, tumor assessment will be performed at EoT if it has not been done within the past 6 weeks, and will be repeated every 6 weeks (± 1 week) until radiological progression per RECIST v 1.1, death or start of new anticancer therapy, whichever occurs first.

CCI [redacted]

CCI [redacted]

dd On Cycle 5, Day 1 and the end of treatment visit (only if the subject discontinued before Cycle 5, Day 1).

Appendix J: Blood Sampling Schedule and Blood Volumes for PK, CCI , and CCI

Phase Ib

Cycle	Day	Time points H = hours after dosing	PK 2 mL	CCI
Cycle 1	Day 1	Predosing	X	
		H 0.25	X	
		H 0.5	X	
		H 1	X	
		H 2	X	
		H 4	X	
		H 8	X	
		H 10	X	
		H 24[b]	X	
	Day 15	Predosing	X	
		H 0.25	X	
		H 0.5	X	
		H 1	X	
		H 2	X	
		H 4	X	
		H 8	X	
		H 10	X	
		H 24[c]	X	
Cycle 2	Day 1	Predosing	-	
Cycle 3	Day 1	Predosing	-	
	EoT		-	

Abbreviation: EoT, end of treatment; H, hour; Pd, pharmacodynamic; CCI ; PK, pharmacokinetic.
[a] Optional. Will be collected after subjects have signed a separate Informed Consent Form.
[b] The 24-hour postdose sample is the predose samples from Day 2.
[c] The 24-hour postdose sample is the predose samples from Day 16.
The predose PK sample on Cycle 1 Day 1 should be taken within 60 minutes prior to dose. The predose PK sample on Cycle 1 Day 15 (trough value) should be taken within 30 minutes prior to dose. Postdose PK samples should be taken within ± 5% of the scheduled assessment time, e.g., the 4-hour postdose sample should be obtained at 4 hours ± 12 minutes.
All other predosing samples should be taken within 60 minutes before each treatment administration.
An anticipated total blood sample volume of approximately 122 mL will be taken in Phase Ib.

Document No. CCI
Object No. CCI

Appendix K: Barcelona Clinic Liver Cancer Staging Classification

The BCLC staging classification is used to stage HCC at baseline according to the number and size of tumors, and the subject's ECOG performance status and hepatic function (using the Child-Pugh score) (Table 9).

Table 9: Barcelona Clinical Liver Cancer Staging Classification

Barcelona Clinic Liver Cancer Staging Classification[a]			
Stage	**ECOG PS**	**Tumor characteristics**	**Hepatic Function**
A1	0	Solitary < 5 cm	No portal hypertension; normal bilirubin
A2	0	Solitary < 5 cm	Portal hypertension; normal bilirubin
A3	0	Solitary < 5 cm	Portal hypertension; abnormal bilirubin
A4	0	Multifocal ≤ 3 and < 3 cm	Child Pugh A-B
B	0	Multifocal > 3 or ≥ 3 cm	Child Pugh A-B
C	1-2	Vascular invasion or extrahepatic spread	Child Pugh A-B
D	3-4	Any	Child Pugh C

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

a Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329-38.