Clinical Trial Protocol

Clinical Trial Protocol Number	EMR 200095-005
Title	A Multicenter, Single Arm, Phase Ib/II Study to Evaluate Efficacy, Safety, and PK of MSC2156119J as Monotherapy in Subjects with MET+ Advanced Hepatocellular Carcinoma with Child Pugh Class A Liver Function Who Have Failed Sorafenib Treatment Short Title: c-Met Second-Line HCC
Trial Phase	Ib/II
IND Number	CCI
EudraCT Number	2013-002053-30
Coordinating Investigator	PPD
Sponsor	Merck KGaA Darmstadt, Germany and US only: EMD Serono Research & Development Institute, Inc., Billerica, MA, USA Medical Responsible: PPD EMD Serono Research & Development Institute, Inc., 45 A Middlesex Turnpike, Billerica, MA 01821, USA Telephone: PPD
Clinical Trial Protocol Version	13 June 2016/Version 6.0
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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AFP	Alpha-Fetoprotein
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area Under the Curve from Time Zero to Infinity
AUC_{0-t}	Area Under the Curve from Time Zero to Time t
AUC_{0-tau}	Area Under the Curve within 1 Dosing Interval
BCRP	Breast Cancer Resistance Protein
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CL	Total Body Clearance of Drug
CL/F	Apparent Clearance
C_{av}	Average Plasma Concentration
C_{max}	Maximum Concentration
C_{min}	Minimum Plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation (%)
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EU	European Union
FACT-HP	Functional Assessment of Cancer Therapy-Hepatobiliary
FDA	Food and Drug Administration

FDG	Fluoro-D-Glucose
FHSI-8	Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8
FIM	First-in-Man
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
Hb	Hemoglobin
HBeAg	Hepatitis B e Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
Hct	Hematocrit
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
λz	Area Under the Curve Terminal Phase Rate Constant
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NYHA	New York Heart Association
OCT1	Organic Cation Transporter 1

OS	Overall Survival Time
Pd	Pharmacodynamic
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival Time
P-gp	P-Glycoprotein
CCI	[redacted]
PK	Pharmacokinetic
PS	Performance Status
PT	Prothrombin Time
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
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
TACE	Transcatheter Arterial Chemoembolization
t_{max}	Time to Maximum Concentration
TTP	Time to Progression
TTSP	Time to Symptomatic Progression
CCI	[redacted]
ULN	Upper Limit of Normal
US	United States
V_{ss}/F	Apparent Volume of Distribution at Steady State
V_z/F	Apparent Volume of Distribution Associated to the Terminal Phase
WBC	White Blood Cells

1 Synopsis

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Coordinating Investigator	PPD
Sponsor	Merck KGaA Darmstadt, Germany and US only: EMD Serono Research & Development Institute, Inc., Billerica, MA, USA
Trial centers/countries	*Phase Ib*: At least 15 sites in European countries and the United States *Phase II*: At least 30 sites in European countries and the United States
Planned trial period **(first enrollment-last subject out)**	June 2014 to March 2016
Trial Registry	ClinicalTrials.gov, NCT02115373
Objectives	**Primary objective** *Phase Ib* • Determine the recommended Phase II dose (RP2D) of MSC2156119J administered orally once daily over a 21-day cycle in subjects with advanced hepatocellular

carcinoma (HCC) pretreated with sorafenib and Child Pugh class A liver function. The target RP2D is 500 mg.

Phase II

- Evaluate efficacy of MSC2156119J in subjects with MET+ advanced HCC pretreated with sorafenib and Child Pugh class A liver function.

Secondary objectives

Phase Ib

- Characterize the single and multiple dose pharmacokinetics (PK) of MSC2156119J.
- Assess antitumor activity and biochemical response of MSC2156119J.
- Evaluate safety and tolerability of MSC2156119J.

Phase II

- Evaluate the safety and tolerability of MSC2156119J.
- Evaluate antitumor activity and biochemical response of MSC2156119J.

Exploratory objectives

CCI

	• CCI [redacted]
Methodology	*Phase Ib* Phase Ib is a multicenter, single-arm, nonrandomized, dose escalation trial in subjects with advanced HCC pretreated with sorafenib and with Child Pugh class A liver function using a classical "3+3" design with a dose escalation and a dose confirmation phase. *Phase II* Phase II is a multicenter, single arm, nonrandomized study of the efficacy, safety, and CCI [redacted] of MSC2156119J in subjects with MET+ advanced HCC pretreated with sorafenib and with Child Pugh class A liver function. Subjects will be given MSC2156119J at the RP2D confirmed in Phase Ib. Subjects in both parts of the trial will receive MSC2156119J until the determination of progressive disease [PD; as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1], intolerable toxicity, death, or withdrawal from the trial.
Planned number of subjects	*Phase Ib:* Up to 18 subjects in 2 dose cohorts *Phase II:* 48 subjects
Schedule of visits and assessments	Informed consent will be obtained prior to performing any trial assessment that is not a part of the subject's regular medical care. The schedule of visits and assessments are outlined as follows and are the same for Phase Ib and Phase II except where indicated: **Screening Period:** *Phase Ib*

	For Phase Ib, all procedures will be performed within 28 days before the day of first dosing. The following assessments and examinations will be performed: Demographic data; height; medical history; smoking status and alcohol use; tumor biopsy excluding fine needle aspiration and cytology samples (a pretreatment biopsy taken within 28 days before the day of first dosing is mandatory; if the tumor block is not available, it is recommended to obtain ≥ 15 formalin fixed sections. An additional biopsy [frozen, excluding fine needle aspiration and cytology samples] for Pd/PK analysis is optional but highly recommended to be taken pretreatment and on-treatment [on any day from Cycle 1 Day 15 up through Cycle 3 Day 1]); viral serology; complete tumor assessment using RECIST Version 1.1 and secondarily using modified RECIST (mRECIST) for HCC including computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis to evaluate disease in these locations and CT/MRI of the head for subjects suspected to have central nervous system (CNS) metastases; physical examination including body weight; Eastern Cooperative Oncology Group (ECOG) performance status (PS); vital signs; electrocardiography (ECG); blood samples to assess hematology, chemistry, and coagulation; urinalysis; serum pregnancy test (if applicable); serum alpha-fetoprotein (AFP); assessment of adverse events (AEs), recording of concomitant medications/procedures. *Phase II* For Phase II, a pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples) will be performed and analyzed for MET+ status by immunohistochemistry (IHC) before any other screening procedures are performed. The pretreatment biopsy will be obtained within 28 days before the day of first dosing. If the tumor block is not available, it is recommended to obtain ≥ 15 formalin fixed sections. Subjects with MET+ tumor biopsy tissue will undergo the following additional screening procedures (all must be completed within 28 days before the day of first dosing): Demographic data; height; medical history; smoking

	status and alcohol use; viral serology; complete tumor assessment using RECIST Version 1.1 and secondarily using mRECIST for HCC including CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations and CT/MRI of the head for subjects suspected to have CNS metastases; physical examination including body weight; ECOG PS; vital signs; ECG; blood samples to assess hematology, chemistry, and coagulation; urinalysis; serum pregnancy test (if applicable); serum AFP; assessment of AEs, recording of concomitant medications/procedures; Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8); Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-HP). **Treatment Period: Cycle 1 to End of Treatment** **Cycle 1 Day 1** The following will be performed: optional tumor biopsy excluding fine needle aspiration and cytology samples (frozen; for Pd/PK; may be taken either at screening or pretreatment on Cycle 1 Day 1; Phase Ib only); tumor assessment by ^{18}F-fluoro-D-glucose (FDG) positron emission tomography (PET) CT scan (predose); blood samples for CCI and Pd (predose only); CCI ; ECG (predose and at 4, 10, and 24 hours postdose for Phase Ib; predose and at 4 hours postdose for Phase II; to be performed immediately before CCI sampling at times when both procedures are performed); PK blood samples (predose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose for Phase Ib; CCI assessment of AEs; recording of concomitant medications/procedures; FHSI-8 (Phase II only); FACT-HP (Phase II only). The following assessments will be performed if the last assessments of these parameters were performed > 7 days prior to this visit: viral load of hepatitis B virus (HBV; for subjects with hepatitis B at screening only); viral load of hepatitis C virus (HCV; for subjects with hepatitis C at screening only); physical examination including body weight; ECOG PS; vital signs; blood samples (to assess hematology, chemistry, and coagulation); urinalysis; serum AFP; urine pregnancy test (if applicable).

	Cycle 1 Day 2 and Cycle 1 Day 8 The following will be performed: physical examination including body weight; vital signs; blood samples (to assess hematology, chemistry, and coagulation); assessment of AEs; recording of concomitant medications/procedures. **Cycle 1 Day 15** The following will be performed: physical examination including body weight; ECG (predose and at 4, 10, and 24 hours postdose for Phase Ib; predose and at 4 hours postdose for Phase II; to be performed immediately before CCI sampling at times when both procedures are performed); CCI ; Phase Ib only); blood samples (to assess hematology, chemistry, and coagulation); assessment of AEs; recording of concomitant medications/procedures; optional tumor biopsy (excluding fine needle aspiration and cytology samples) for confirmation of target inhibition and analysis of CCI for subjects (frozen; may be taken on any day from Cycle 1 Day 15 up through Cycle 3 Day 1 during Phase I only; only for subjects who had the optional frozen biopsy during screening); blood sample for evaluation of CCI (predose). **Cycle 2 Day 1** The following will be performed: physical examination including body weight; ECOG PS; vital signs; ECG (predose only); CCI blood samples (to assess hematology, chemistry, and coagulation); urinalysis; serum AFP; assessment of AEs; recording of concomitant medications/procedures; FHSI-8 and FACT-HP (Phase II only); urine pregnancy test (if applicable). **Cycle 2 Day 8** The following will be performed: physical examination including body weight; vital signs; blood samples (to assess hematology, chemistry, and coagulation); assessment of AEs; recording of concomitant

	medications/procedures; FHSI-8 and FACT-HP (Phase II only). **Cycle 2 Day 15** The following will be performed: physical examination including body weight; blood samples (to assess hematology, chemistry, and coagulation); assessment of AEs; recording of concomitant medications/procedures; blood sample for evaluation of CCI [redacted] (predose); FHSI-8 and FACT-HP (Phase II only). **Cycle ≥ 3 Day 1** The frequency of visits will be every 3 weeks up through Cycle 8. From Cycle 9 onward, the frequency of visits will be every 6 weeks, and after Cycle 13, the frequency of visits will be every 12 weeks. The following will be performed: physical examination including body weight; ECOG PS; vital signs; ECG (predose only); blood samples (to assess hematology, chemistry, and coagulation); urinalysis; serum AFP; assessment of AEs; recording of concomitant medications/procedures; FHSI-8 and FACT-HP (Phase II only) at each visit; complete tumor assessment using RECIST Version 1.1, and secondarily using mRECIST for HCC, on Day 1 of Cycles 3, 5, 7, 9, 11, 13, and every 4 cycles thereafter until disease progression or study drug discontinuation; tumor assessment by ^{18}F-FDG PET CT scan (Cycle 3 Day 1 only); urine pregnancy test (if applicable). **End of Treatment Visit:** This visit will be performed on the last day of treatment, whether at the end of a cycle or not, and is defined as the day on which it is determined that the subject will no longer receive trial treatment. The following will be performed: physical examination including body weight; ECOG PS; vital signs; ECG; blood samples (to assess hematology, chemistry, and coagulation); urinalysis; urine pregnancy test (if applicable); serum AFP; blood samples for CCI [redacted] and Pd; assessment of AEs; recording of concomitant medications/procedures; complete tumor assessment using RECIST Version 1.1, and secondarily using mRECIST for HCC (if last assessment was performed ≥ 6 weeks ago); optional tumor biopsy excluding fine needle aspiration and

	cytology samples (biopsies may be taken on the last day of treatment or as soon as possible until up to 7 days after the last day of treatment and prior to the start of subsequent anticancer treatment); FHSI-8 and FACT-HP (Phase II only). **Post-treatment Follow-up Visit:** This visit will be performed 30 ± 3 days after the last treatment for subjects who discontinue trial treatment permanently, including subjects who have completed an End of Treatment Visit. If another anticancer therapy will be started before the end of this period (30 days), the Post-treatment Follow-up Visit should be conducted prior to start of this therapy. The following will be performed: physical examination including body weight; ECOG PS; vital signs; ECG; blood samples (to assess hematology, chemistry, and coagulation); serum pregnancy test (if applicable); urinalysis; assessment of AEs; recording of concomitant medications/procedures; FHSI-8 and FACT-HP (Phase II only). A Trial Procedure Termination electronic Case Report Form (eCRF) will be completed for all subjects when no further trial evaluations are expected (with the exception of potential survival follow-up). The following will be recorded: the date of discontinuation from trial procedures, the primary reason for discontinuation from trial procedures, and whether the subject agrees to be followed for survival. **Follow-up of Subjects Who Discontinue Treatment for Reasons Other than Disease Progression** Subjects who discontinue trial treatment for reasons other than disease progression, withdrawal of consent, loss to follow-up, or death will continue to have tumor assessments according to the same schedule as subjects who remain on the trial treatment. These assessments will continue until disease progression, withdrawal of consent, starting a new anticancer therapy, loss to follow-up, or death, at which time the Trial Procedure Termination eCRF will be completed. **Survival Follow-up**

	Information about subject survival and anticancer therapies will be collected every 3 months ± 2 weeks after End of Treatment until death, withdrawal of consent, or the end of the trial (defined as 12 months after the last subject's first dose of MSC2156119J), whichever comes first. When survival follow-up is discontinued, the Survival Follow-up Termination eCRF will be completed.
Diagnosis and main inclusion and exclusion criteria	**Inclusion Criteria** For inclusion in the trial, all of the following inclusion criteria must be fulfilled: 1. Histologically confirmed HCC; 2. Child Pugh Class A liver function score; 3. MET+ status, as determined by the central laboratory (in Phase II prospectively for subject selection), defined as MET protein overexpression [moderate (2+) or strong (3+) staining intensity for MET on IHC in the majority (≥ 50%) of tumor cells]. 4. Availability of a pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples) taken after the subject has discontinued sorafenib and within 28 days before the day of first dosing with MSC2156119J. From the pretreatment biopsy either a formalin-fixed (formalin fixation is mandatory) paraffin-embedded block with tumor tissue (preferred) or at least 15 unstained slides must be sent to the central laboratory prior to enrollment. An associated pathology report must also be sent with the sample; 5. Male or female, 18 years of age or older; 6. Measurable disease in accordance with RECIST Version 1.1; 7. ECOG PS 0-1 (inclusive); 8. Previously treated with sorafenib for ≥ 4 weeks and discontinued sorafenib treatment at least 14 days prior to Day 1 due to either intolerance or radiographic progression; 9. Signed and dated informed consent indicating that the subject (or legally acceptable representative if

	applicable by local laws) has been informed of all the pertinent aspects of the trial prior to enrollment; 10. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other trial procedures; and 11. Life expectancy of at least 3 months as judged by the investigator. **Exclusion Criteria** Subjects are not eligible if they fulfill any of the following criteria: 1. Prior systemic anticancer treatment for advanced HCC (except for sorafenib as described in the inclusion criteria); 2. Prior treatment with any agent targeting the HGF/c-Met pathway; 3. Local-regional therapy within 4 weeks before Day 1 (for example, surgery, radiation therapy, hepatic arterial embolization, transcatheter arterial chemoembolization [TACE], chemoembolization, radiofrequency ablation, percutaneous ethanol injection, cryoablation); 4. Laboratory index at baseline: o Hemoglobin ≤ 8.5 g/dl; o Neutrophils < 1.5 x 10^9/L; o Platelets < 60 x 10^9/L; o Total bilirubin > 3 mg/dl; o Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN); o Serum creatinine ≥ 1.5 x ULN; o Calculated creatinine clearance < 60 ml/min according to the Cockcroft-Gault formula; o International normalized ratio (INR) > 2.3; 5. 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;

	6. Known CNS or brain metastasis that is either symptomatic or untreated; 7. Medical history of difficulty swallowing, malabsorption or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the tested products; 8. Clinically significant gastrointestinal bleeding within 4 weeks before trial entry; 9. Peripheral neuropathy Grade ≥ 2 (Common Terminology Criteria for Adverse Events [CTCAE] v 4.0); 10. Impaired cardiac function evidenced by any of the following conditions: o Left ventricular ejection fraction (LVEF) < 45% defined by echocardiograph (screening assessment is not required for subjects without a history of congestive heart failure unless clinically indicated); o Serious arrhythmia; o Unstable angina pectoris; o Myocardial infarction within the last 12 months prior to trial entry, or pericardial effusion; o Subjects with a QTc-prolongation > 470 msec, risk factors for Torsades de Pointes (Heart Insufficiency NYHA II-IV, Hypokalemia, Family Long-QT-Syndrome) should be excluded from the study. 11. Uncontrolled hypertension by standard medication (not stabilized to 150/90 mmHg or below); 12. Known human immunodeficiency virus (HIV) infection; 13. Known or suspected drug hypersensitivity to any ingredients of MSC2156119J; 14. Female subjects who are not of childbearing potential due to being postmenopausal (2 years without menses) or surgical sterilisation (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception.

	All other female subjects are considered to have childbearing potential. These female subjects, as well as childbearing female partners of male subjects, are to use highly effective methods of contraception – defined as one that results in a failure rate of less than 1% per year when used consistently and correctly - throughout the study (from screening until 3 months after last dose of trial medication). Examples are combined oral contraceptives, intrauterine devices, implantable or injectable hormonal contraceptives together with a barrier method. In addition, male subjects should use adequate contraception throughout the study (e.g. condom and spermicidal jelly). Female subjects must have a negative pregnancy test (β-HCG test in serum) prior to enrollment; 15. Concurrent treatment with non-permitted drug per principal investigator and the Merck Serono medical monitor; 16. Substance abuse, other acute or chronic medical or psychiatric condition or laboratory abnormalities that might increase the risk associated with trial participation at the discretion of investigators; 17. Prior treatment with MSC2156119J or other c-Met inhibitors; 18. Participation in another interventional clinical trial within the 28 days prior to Day 1; 19. Previous anticancer treatment-related toxicities not recovered to Grade 0-1 or baseline (except alopecia, peripheral neuropathy, and elevated liver enzymes); 20. History of liver transplant; 21. Active or uncontrolled infections except chronic HBV, chronic HCV, or both; 22. Subjects with any concurrent medical condition or disease that will potentially compromise the conduct of the trial at the discretion of the investigators.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule	**Investigational medicinal product** The investigational medicinal product (IMP) consists of film-coated tablets containing 25 mg or 100 mg of the active pharmaceutical ingredient of MSC2156119J. **Dose/mode of administration/dosing schedule** *Phase Ib*: 300 mg once daily during dose escalation, and the RP2D during dose confirmation (target RP2D is 500 mg once daily). *Phase II*: the RP2D, as determined in Phase Ib of this trial. Throughout the trial, subjects will take their assigned doses of MSC2156119J orally, in the morning and immediately after breakfast, with a full glass of water (approximately 200 mL).
Reference therapy: dose/mode of administration/dosing schedule	None
Planned treatment duration per subject	Subjects will be administered MSC2156119J until the date of first radiological evidence of disease progression (as assessed by RECIST Version 1.1), intolerable toxicity, death, or withdrawal from treatment.
Primary endpoint	*Phase Ib:* Incidence of dose limiting toxicities (DLTs) in Cycle 1 *Phase II:* Progression-free survival (PFS) status at 12 weeks
Secondary endpoints	*Phase Ib* • PK parameters [area under the curve (AUC) parameters including $AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}\infty}$, maximum plasma concentration (C_{max}), time of maximum plasma concentration (t_{max}), minimum plasma concentration (C_{min}), average plasma concentration (C_{av}), apparent clearance (CL/F), apparent volume of distribution associated with the terminal phase (V_z/F), apparent volume of distribution at steady state (V_{ss}/F), area under the curve terminal

	phase rate constant (λz), and half-life time ($t_{1/2}$) when appropriate] • Efficacy parameters [time to progression (TTP), disease control, objective tumor response, PFS time, overall survival time (OS), and biological response as measured by AFP] • Safety parameters (drug exposure; incidence and type of treatment-emergent AEs; incidence and reasons for deaths, including deaths within 33 days after the last dose of MSC2156119J; vital signs; ECG changes; hematology, chemistry, and urinalysis parameters; physical examination including change in body weight; and ECOG PS) *Phase II* • Efficacy parameters (PFS, objective tumor response, disease control, TTP, OS, time to symptomatic progression [TTSP; defined as time from first study drug administration to deterioration of symptoms as assessed by FHSI-8, or by deterioration to ECOG PS 4, or death], and biological response as measured by AFP) • Safety parameters (drug exposure; incidence and type of treatment-emergent AEs; incidence and reasons for deaths, including deaths within 33 days after the last dose of MSC2156119J; vital signs; ECG changes; hematology, chemistry, and urinalysis parameters; physical examination including change in body weight; and ECOG PS)
Pharmacokinetics endpoints	*Phase Ib*: • As described in the secondary endpoints CCI [redacted]
Exploratory endpoints	CCI [redacted]

	• CCI [redacted] 
Statistical methods (includes sample size calculation)	**Sample size calculation** *Phase Ib*: The sample size was not based on any statistical assumptions; rather, it follows the "3+3 rule," a well-established current methodology in the design of dose-finding trials in oncology. *Phase II*: Under the assumption of no treatment effect, the rate of MET+ subjects without progression at 12 weeks was assumed to be ~15% based on historical data. It is expected that MSC2156119J treatment will lead to 30% MET+ subjects without progression at 12 weeks. The null hypothesis of no treatment effect will be tested using a one-stage design based on the exact binomial distribution. To achieve a power of 80% and keeping a type I error rate of 5% (one-sided), this design requires 48 subjects to be treated in Phase II. **Statistical analyses** Analyses for the dose confirmation will be performed on the DLT analysis set, consisting of subjects who have completed Cycle 1 and received at least 80% of planned cumulative doses or have stopped treatment due to a DLT. Other safety analyses and efficacy analyses will be performed on the intent-to-treat (ITT) population/Safety

	population, which is defined as all subjects who have been administered at least one dose of study drug. *Phase Ib* The number and proportion of subjects experiencing a DLT will be used as the primary measure to confirm the RP2D. Information regarding safety and PK data beyond Cycle 1 will also be taken into consideration to confirm the RP2D. The analyses of secondary time-to-event endpoints will follow standard methodology, separately for each dose level. Rates (response rates, disease control rates) will be summarized along with 2-sided, 90% confidence intervals, separately for each dose level. *Phase II* As a primary analysis, the proportion of subjects who are progression-free at 12 weeks will be estimated, including a 90% confidence interval. The numerator of the estimated rate is the number of subjects in the respective analysis population whose tumor assessment at 12 weeks or later indicates stable disease (SD) or better and the denominator is the number of all subjects in the respective analysis population. The null hypothesis of no treatment effect of MSC2156119J ($P \leq 0.15$) will be tested keeping a one-sided type-I error of 5%. If ≥ 12 out of 48 subjects are without progression at 12 weeks, the null hypothesis will be rejected and the trial will have met its primary endpoint. The analyses of secondary time-to-event endpoints will follow standard methodology employing Kaplan-Meier estimates. Response rates and disease control rates will be summarized along with 2-sided, 90% confidence intervals.

2 Sponsor, Investigators, and Trial Administrative Structure

Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany is the sponsor of this clinical trial with the c-Met inhibitor MSC2156119J. In the United States, EMD Serono Research & Development Institute, Inc., 45A Middlesex Turnpike, Billerica, MA 01821 is the sponsor.

The trial will be conducted in at least 15 sites in Europe and the United States for Phase Ib and at least 30 sites in Europe and the United States for Phase II. In the United States, the trial will be conducted in up to 5 sites (at least 1 site) for Phase Ib and approximately 5 sites for Phase II.

The coordinating investigator will be PPD

The contract research organization (CRO) responsible for the conduct of the trial (including trial management, monitoring, biostatistics, and data management) will be PPD with its principal offices located at PPD . In the PPD , the CRO will be PPD .

Analysis of pharmacokinetic (PK) samples will be performed by PPD PPD .

MET+ status will be determined by a central laboratory.

Merck KGaA will supply and release MSC2156119J. Packaging and distribution of clinical supplies will be performed by Clinical Trial Supply at Merck KGaA or by a designated service company.

The sponsor's auditors will perform quality audits.

A safety monitoring committee (SMC) will be established for the purpose of assessing adverse events (AEs) during the trial. The committee will evaluate progress of the trial, assess safety and other relevant information for the trial, and will make decisions on dose escalations and de-escalations (Phase Ib), continuation, or discontinuation of the trial. SMC mandatory members will be identified before trial initiation and will include the 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.

For tumor assessments, for quality control purposes, the sponsor would like to reserve the possibility to conduct a confirmatory measurement by an independent external read. For Phase II, all data needed for confirmatory measurements will be collected and held by PPD to ensure availability of data for this purpose.

Details of all structures and associated procedures will be defined in a separate manual of operations (MOP).

3 Background Information

3.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) accounts for more than 626,000 new cases per year worldwide. The incidence of HCC is increasing in the United States (US) and Europe, and it is the third highest cause of cancer-related death globally. In the Western countries, the disease is diagnosed in 30 to 40% of all subjects at early stages and is amenable to potentially curative treatments, such as surgical therapies and loco-regional procedures. However, disease that is diagnosed at an advanced stage or with progression after loco-regional therapy has a dismal prognosis. A multitude of systemic therapies has been investigated for use in HCC and only sorafenib is approved for advanced HCC. However, the overall prognosis of HCC subjects on sorafenib remains very poor, with median time to progression (TTP) of 5.5 months and median overall survival (OS) of 10.7 months (1). Therefore, effective systemic treatment of advanced stage HCC remains a high unmet medical need.

3.2 c-Met and HCC

Emerging data provide evidence that the pathogenesis and progression of HCC are mediated by a number of molecular defects and deregulated pathways. Among those, deregulation of c-Met and hepatocyte growth factor (HGF) are common in HCC. The presence of a c-Met induced expression signature derived from primary HCC and from liver metastases showed a significant correlation between increased vascular invasions and decreased mean survival times. Recent results from a randomized Phase II trial in second-line HCC showed that subjects with MET overexpressing tumors had a worse prognosis compared to the overall population, indicating that MET overexpression may be a poor prognostic factor in this disease (2). In addition, proof of concept 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, such as rilutomumab in gastric cancer and onartuzumab (MetMAb) in non-small cell lung cancer (NSCLC). In all these trials, subjects with c-Met alterations appeared more likely to benefit. For HCC, several non-selective c-Met inhibitors have entered into Phase II trials. Cabozantinib, a c-Met / vascular endothelial growth factor receptor (VEGFR)2 inhibitor, demonstrated anti-HCC activity in a second-line Phase II trial; ARQ 197, a non-selective c-Met inhibitor, demonstrated encouraging results as well in subjects with sorafenib failure in a Phase II study. Notably in this trial, subjects with MET Dx(+) tumors [defined as 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.

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 clinical trials.

Refer to the Investigator's Brochure (IB) for further information about the nonclinical and clinical programs and Guidance for the Investigator.

3.4 Rationale for Trial

This Phase Ib/II trial is proposed as a single arm trial with a safety run-in period to confirm the recommended Phase II dose (RP2D) of MSC2156119J as well as the efficacy and safety of MSC2156119J in HCC subjects with Child Pugh class A liver function score who have been pretreated with sorafenib.

A Phase Ib 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 safety and PK profile in subjects with impaired liver function, who were excluded from the Phase I First-in-Man (FIM) trial in subjects with advanced solid tumors. The starting dose will be lower than the RP2D of 500 mg QD and will be adjusted during the trial depending on the emerging data from the Phase Ib escalation part. This approach is in line with the recommendation from a panel of HCC experts (1).

The trial is designed to capture the potential benefits of MSC2156119J in subjects with well-preserved liver function (Child Pugh class A) because it helps control confounding issues of liver failure or death due to underlying chronic liver disease or cirrhosis, so that treatment effect can be better assessed.

This trial will be conducted in Europe and the United States. The first subject was enrolled in Europe in June 2014.

The rationale to evaluate MSC2156119J as monotherapy in the second-line treatment for advanced HCC subjects with MET+ tumors who have been pretreated with sorafenib is as follows:

- Sorafenib has been more widely used in advanced HCC in US and Europe than in developing regions. A first-line Phase II trial in HCC subjects in Asia vs. sorafenib is planned and will be conducted in parallel to this second-line treatment in Europe and the United States. Evaluating MSC2156119J as a second-line therapy in subjects who have progression after sorafenib treatment will add information on the safety and efficacy of MSC2156119J in subjects from Europe and the United States, who may respond differently to treatment from Asians due to possible differences in tolerability and metabolism.
- Historical data on survival with best supportive care after sorafenib failure or intolerance has been consistent according to the results from the ARQ 197 Phase II trial and Brivanib Phase III trial (1). The Phase III ARQ 197 second-line HCC trial is ongoing and will be finished at the end of 2015. With all the published trial reports, a single-arm Phase II trial can give sufficient information for the decision making on the subsequent trials.
- Inhibition of HGF/c-Met signaling has been explored as a therapeutic strategy for advanced HCC with proof of concept established with c-Met inhibitors as mentioned above. That is, subjects with MET Dx(+) had a worse prognosis and derived more benefit from the therapeutic strategy by c-Met inhibition.
- In-house studies indicated that primary liver cancer explants with high levels of HGF/c-Met are sensitive towards c-Met inhibition by monotherapy with MSC2156119J (refer to the MSC2156119J IB). Tumors with an intrinsically strong c-Met activation

showed high responsiveness to MSC2156119J. In contrast, tumors characterized by moderate or low levels of HGF/c-Met were not sensitive to MSC2156119J.

- The trial will also explore the PK of MSC2156119J in subjects with mild liver impairment.

3.4.1 Strategic Context of Trial

This is a development program in subjects with advanced HCC who have been pretreated with sorafenib which will be conducted in parallel to an Asia focused first-line Phase II HCC trial. This trial will generate supportive data regarding the dose, antitumor activity, safety and tolerability and PK of MSC2156119J in subjects with advanced HCC. A positive Asia focused proof-of-concept trial along with the data from this trial will provide the basis for a subsequent global Phase III trial in first-line subjects with MET+ HCC vs. sorafenib. In addition, results from the single arm trial in second-line HCC subjects may provide the basis for a development program in second-line HCC.

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 (1).

HCC generally develops from chronic liver diseases, mostly cirrhosis. Liver dysfunction and associated conditions may alter PK and tolerability (1). 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 trials, MSC2156119J was well tolerated (refer to the current IB). The important identified risk thus far with the application of MSC2156119J is an asymptomatic elevation of lipases and/or amylases. Potential risks associated with study drug application from preclinical studies are 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.

The biopsies performed in this trial are standard medical practice with manageable risks.

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/pharmacodynamic (Pd) modeling and supported by data on target inhibition from paired tumor biopsies, rather than as a safety defined maximum tolerated dose (MTD). Therefore, a Phase Ib safety run-in phase titrating from only 1 dose level below the RP2D of MSC2156119J (i.e., 300 mg) is justified.

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the pre-clinical and clinical data available to date, the conduct of the trial is considered justifiable using the dose(s) and dosage regimen(s) of the investigational medicinal product (IMP) as specified in this clinical trial protocol. An SMC will assess the ongoing safety information of this trial, as applicable. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship and would render continuation of the trial unjustifiable.

3.6 Conduct of the Trial

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (International Conference on Harmonisation [ICH] Topic E6, GCP) and the applicable regulatory requirements.

4 Trial Objectives

4.1 Primary Objectives

The primary objectives for this Phase Ib/Phase II trial are to:

- Phase Ib: Determine the RP2D of MSC2156119J administered orally once daily over a 21-day cycle in subjects with advanced HCC pretreated with sorafenib and Child Pugh class A liver function. The target RP2D is 500 mg.
- Phase II: Evaluate efficacy of MSC2156119J in subjects with MET+ advanced HCC pretreated with sorafenib and Child Pugh class A liver function.

4.2 Secondary Objectives

The secondary objectives for this Phase Ib/Phase II trial are to:

- Phase Ib: Characterize the single and multiple dose PK of MSC2156119J.

  Assess antitumor activity and biochemical response of MSC2156119J.

  Evaluate safety and tolerability of MSC2156119J.
- Phase II: Evaluate the safety and tolerability of MSC2156119J.

  Evaluate antitumor activity and biochemical response of MSC2156119J.

4.3 Exploratory Objectives

CCI [redacted]

5 Investigational Plan

5.1 Overall Trial Design and Plan

5.1.1 Design

Phase Ib is a multicenter, single arm, nonrandomized, dose escalation trial.

Phase II part is a multicenter, single arm, nonrandomized trial of the efficacy, safety, and PK of MSC2156119J in subjects with MET+ advanced HCC with Child Pugh class A liver function who have been pretreated with sorafenib.

5.1.2 Dose Escalation/Dose Selection

Phase Ib

Phase Ib follows the classical "3+3" design with a dose escalation and a dose confirmation phase. The criteria for dose escalation and dose confirmation will be based on the occurrence of dose limiting toxicities (DLTs) and other safety data; the definition of a DLT is provided in Section 6.2.2.

An SMC 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 at the last dose level, as well as all safety data from any cycles at all previous dose levels, 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 (EMR 200095-001).

After the initial 3 subjects have completed Cycle 1 at the first dose level (300 mg) and have been fully followed up for safety, an SMC meeting will be held to evaluate the safety of MSC2156119J

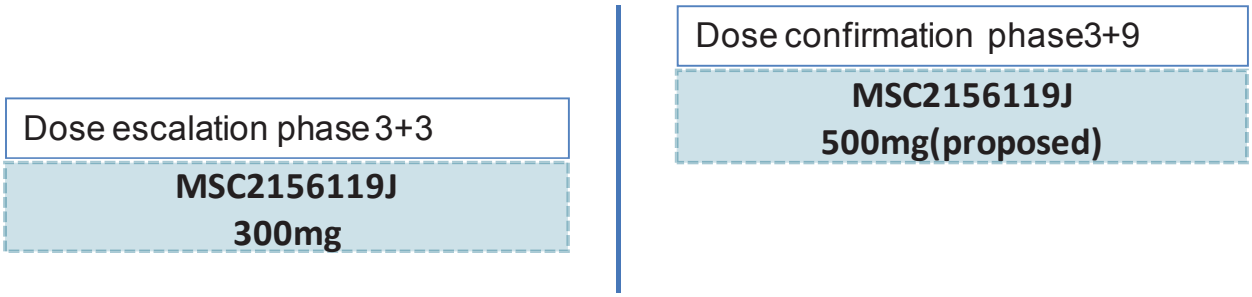
and to determine the next step (see Figure 1). Depending on the safety observed, the next step will be enrollment of an additional 3 subjects at 300 mg or enrollment of 3 subjects at 500 mg (i.e., dose escalation to the target RP2D). A further SMC meeting will be held after extension of the first dose 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, enrolling an additional 3 subjects 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 at the same dose level 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 subjects with advanced HCC.

The sponsor may decide to assess doses higher than the target RP2D (i.e., doses greater than 500 mg once daily), doses lower than the first dose level (i.e., doses less than 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.

Figure 1 **Phase Ib Dose Escalation and Dose Selection Plan for MSC2156119J Monotherapy Based on Pharmacokinetic/Pharmacodynamic Modelling**



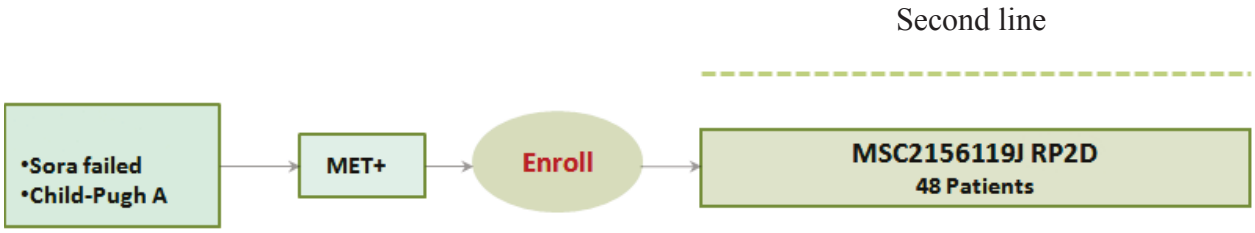
Up to 18 subjects in 2 dose cohorts will be enrolled in Phase Ib following the "3+3" dose-escalation method (up to 6 subjects in the first dose cohort and up to 12 subjects in the second dose cohort). The final sample size depends on the number of subjects who experience DLTs, the safety and PK data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

Phase II

Subjects will receive MSC2156119J once daily (at the RP2D determined from Phase Ib) until the date of first radiological evidence of progressive disease (PD; as assessed by the investigator), intolerable toxicity, death, or withdrawal from the trial. In Phase II, the SMC will review the safety of MSC2156119J after the first 12 subjects have completed Cycle 1, and again after the first 24 subjects have completed Cycle 1.

A schematic diagram of the enrollment plan for the Phase II part of the trial is displayed in Figure 2.

Figure 2 Phase II Plan for MSC2156119J Monotherapy Based on PK/Pharmacodynamic Modelling



Abbreviations: Sora, sorafenib; RP2D, recommended Phase II dose

A total of 48 subjects will receive MSC2156119J at the RP2D.

Treatment Duration

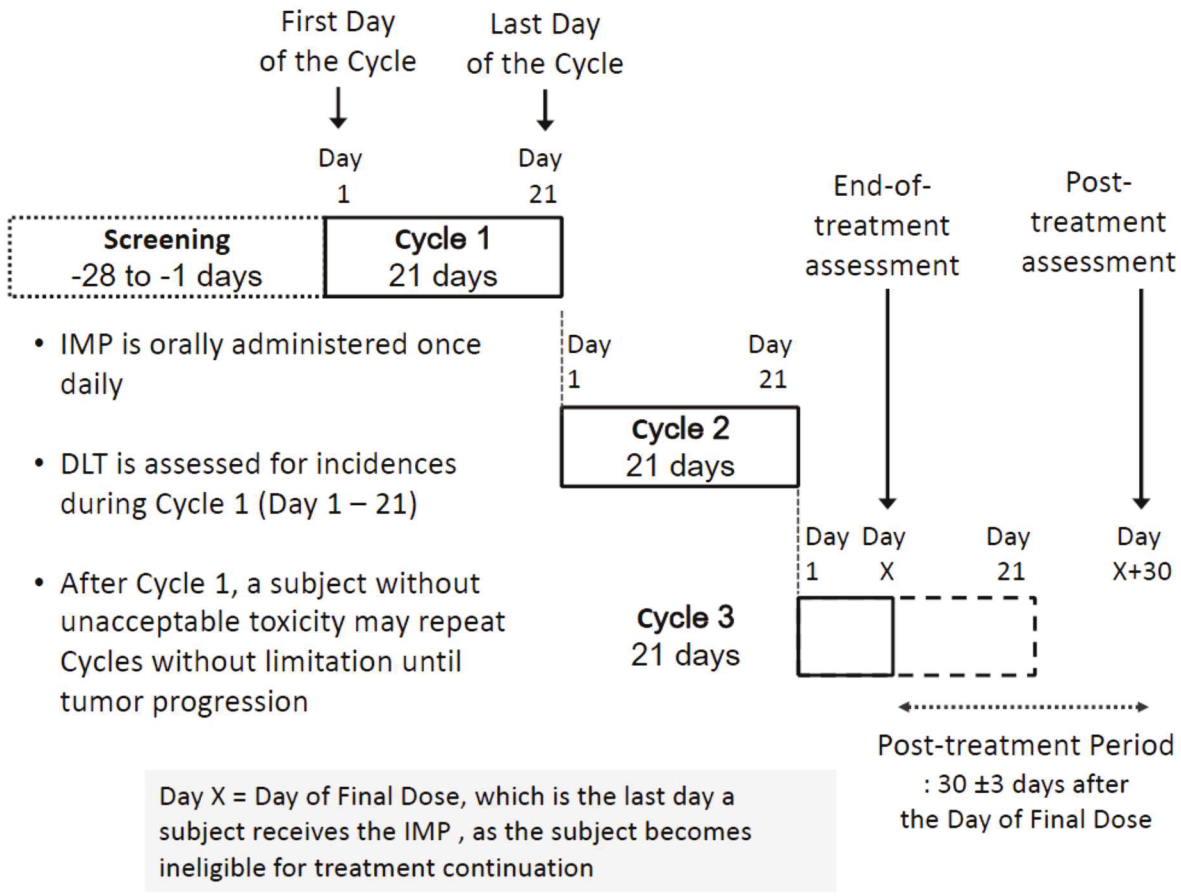
The trial periods and treatment duration are the same for both Phase Ib and Phase II. Each will contain a screening period of up to 28 days prior to trial treatment, to assess subject eligibility.

At the conclusion of screening, eligible subjects will be enrolled into the trial and will then enter a treatment period, during which subjects will be administered MSC2156119J once daily, in 21-day cycles. Subjects will continue taking MSC2156119J until PD [as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1], intolerable toxicity, death, or withdrawal from treatment. Subjects will be evaluated for efficacy, safety, and PK.

Upon discontinuation from MSC2156119J, subjects will have an end-of-treatment evaluation. A Post-treatment Follow-up Visit will also be performed 30 ± 3 days after the last dose.

A schematic of the flow of events for each subject is displayed in Figure 3.

Figure 3 Treatment Duration



Abbreviations: DLT, dose-limiting toxicity; IMP, investigational medicinal product.
Subjects may repeat cycles without limitation until determination of progressive disease or intolerable toxicity, so that the maximum number of cycles received by an individual subject may be > 3.

Survival data will be collected every 3 months after the Post-treatment Follow-up Visit until death or until the end of the trial, whichever comes first.

The planned trial period is from June 2014 (first subject enrolled) to March 2016 (last subject's last visit).

Trial endpoints are described in Section 8.3.

5.1.3 Data Evaluation and Interim Analysis

An SMC will be established for the purpose of assessing safety data (AEs, laboratory changes, vital signs, and electrocardiogram [ECG] deviations) and PK data for the duration of the trial (see Section 6.2.1.1). The SMC will evaluate progress of the trial, assess safety and other relevant information for the trial, and will make decisions on dose escalations and de-escalations, continuation, or discontinuation of the trial.

In addition, administrative interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

5.2 Discussion of Trial Design

The design of this trial is based on the safety, tolerability, and PK data observed in the FIM trial conducted with solid tumor subjects. Data from the FIM trial (EMR 200095-001) have revealed no safety and/or tolerability concerns thus far (refer to the current IB). The SMC proposed a dose of 500 mg administered once daily over a 21-day cycle as the RP2D for MSC2156119J. This RP2D is based on nonclinical PK/Pd modelling, which was supported by data on target inhibition from paired tumor biopsies.

In the current trial, a safety run-in phase will start dose escalation at 300 mg, thereby allowing for an additional safety step before exposing subjects to the full RP2D. Since liver/bile ducts have been identified as the main target organ in toxicology studies in dogs, and since it is expected that the majority of HCC subjects present with a history of chronic liver disease such as viral hepatitis or cirrhosis, careful monitoring of liver enzymes, hepatitis B virus (HBV) and hepatitis C virus (HCV) viral load, bile related parameters and other lab parameters and clinical signs related to viral reactivation, hepatitis flare, liver function degradation will therefore be implemented.

This trial uses standard measurements and assessments of HCC and tumors. The single-arm design is selected based on historical data with best supportive care after sorafenib failure or intolerance, which has been consistent across multiple studies (see Section 3.4). The decision to conduct this trial of MSC2156119J as second-line treatment is due to the relatively widespread use of sorafenib as a first-line treatment in Europe and the US.

5.2.1 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 EMR 200095-001, as the most appropriate treatment regimen for this trial.

The definition of the RP2D of 500 mg was based on the following criteria and considerations (Refer to the IB):

1. Based on the results from a nonclinical PK/Pd and tumor growth model, the analysis of target inhibition phosphorylated mesenchymal-epithelial transition factor gene (phospho-c-Met) in on-treatment subject biopsies, and from a population PK model, the 500 mg once daily dose achieves target inhibition $\geq 90\%$ and results in sufficiently high steady state (trough) exposure levels in $\geq 90\%$ of subjects to induce activity in tumors with varying degrees of sensitivity to mesenchymal-epithelial transition factor (c-Met) inhibition.

2. The SMC for the FIM trial EMR 200095-001 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.

5.2.2 Inclusion of Special Populations

The selection of HCC subjects with well-preserved liver-function (Child Pugh class A) is to help control confounding issues of liver failure or death due to underlying chronic liver disease or cirrhosis, so that treatment effect can be better assessed.

The selection of MET+ subjects in Phase II is based on the intended biological activity of MSC2156119J as a c-Met inhibitor, and the observation that subjects with c-Met alterations appeared more likely to benefit from treatment with c-Met inhibitors than subjects without these alterations.

This trial will be conducted in Europe and the United States. A first-line Phase Ib/II trial in HCC subjects in Asia versus sorafenib will be conducted in parallel. This trial is anticipated to add information on the safety and efficacy of MSC2156119J in subjects from Europe and the United States, who may respond differently to treatment compared with an Asian population due to possible differences in tolerability and metabolism.

5.3 Selection of Trial Population

5.3.1 Inclusion Criteria

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

1. Histologically confirmed HCC;

2. Child Pugh Class A liver function score (Appendix D);

3. MET+ status, as determined by the central laboratory (in Phase II prospectively for subject selection), defined as MET protein overexpression [moderate (2+) or strong (3+) staining intensity for MET on IHC in the majority (≥ 50%) of tumor cells (Appendix C)].

4. Availability of a pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples) taken after the subject has discontinued sorafenib and within 28 days before the day of first dosing with MSC2156119J. From the pretreatment biopsy either a formalin-fixed (formalin fixation is mandatory) paraffin-embedded block with tumor tissue (preferred) or at least 15 unstained slides must be sent to the central laboratory prior to enrollment. An associated pathology report must also be sent with the sample;

5. Male or female, 18 years of age or older;

6. Measurable disease in accordance with RECIST Version 1.1;

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (inclusive);

8. Previously treated with sorafenib for ≥ 4 weeks and discontinued sorafenib treatment at least 14 days prior to Day 1 due to either intolerance or radiographic progression;

9. Signed and dated informed consent indicating that the subject (or legally acceptable representative if applicable by local laws) has been informed of all the pertinent aspects of the trial prior to enrollment;

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

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

5.3.2 Exclusion Criteria

Subjects are not eligible if they fulfill any of the following criteria:

1. Prior systemic anticancer treatment for advanced HCC (except for sorafenib as described in the inclusion criteria);

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

3. Local-regional therapy within 4 weeks before Day 1 (for example, surgery, radiation therapy, hepatic arterial embolization, transcatheter arterial chemoembolization [TACE], chemoembolization, radiofrequency ablation, percutaneous ethanol injection, cryoablation);

4. Laboratory index at baseline:
    - Hemoglobin ≤ 8.5 g/dl;
    - Neutrophils < 1.5 x 10^9/L;
    - Platelets < 60 x 10^9/L;
    - Total bilirubin > 3 mg/dl;
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN);
    - Serum creatinine ≥ 1.5 x ULN;
    - Calculated creatinine clearance < 60 ml/min according to the Cockcroft-Gault formula;
    - International normalized ratio (INR) > 2.3;

5. 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;

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

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

8. Clinically significant gastrointestinal bleeding within 4 weeks before trial entry;

9. Peripheral neuropathy Grade ≥ 2 (Common Terminology Criteria for Adverse Events [CTCAE] v 4.0);

10. Impaired cardiac function evidenced by any of the following conditions:
    - left ventricular ejection fraction (LVEF) < 45% defined by echocardiograph (screening assessment is not required for subjects without a history of congestive heart failure unless clinically indicated);
    - serious arrhythmia;
    - unstable angina pectoris;

- myocardial infarction within the last 12 months prior to trial entry, or pericardial effusion;
- Subjects with a QTc-prolongation > 470 msec, risk factors for Torsades de Pointes (Heart Insufficiency NYHA II-IV (Appendix B), Hypokalemia, Family Long-QT-Syndrome) should be excluded from the study.

11. Uncontrolled hypertension by standard medication (not stabilized to 150/90 mmHg or below);

12. Known human immunodeficiency virus (HIV) infection;

13. Known or suspected drug hypersensitivity to any ingredients of MSC2156119J;

14. Female subjects who are not of childbearing potential due to being postmenopausal (2 years without menses) or surgical sterilisation (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception.

    All other female subjects are considered to have childbearing potential. These female subjects, as well as childbearing female partners of male subjects, are to use highly effective methods of contraception – defined as one that results in a failure rate of less than 1% per year when used consistently and correctly - throughout the study (from screening until 3 months after last dose of trial medication).

    Examples are combined oral contraceptives, intrauterine devices, implantable or injectable hormonal contraceptives together with a barrier method.

    In addition, male subjects should use adequate contraception throughout the study (e.g. condom and spermicidal jelly).

    Female subjects must have a negative pregnancy test (β-HCG test in serum) prior to enrollment;

15. Concurrent treatment with non-permitted drug per principal investigator and the Merck Serono medical monitor, in accordance with Section 6.5.2 of the protocol;

16. Substance abuse, other acute or chronic medical or psychiatric condition or laboratory abnormalities that might increase the risk associated with trial participation at the discretion of investigators;

17. Prior treatment with MSC2156119J or other c-Met inhibitors;

18. Participation in another interventional clinical trial within the 28 days prior to Day 1;

19. Previous anticancer treatment-related toxicities not recovered to Grade 0-1 or baseline (except alopecia, peripheral neuropathy, and elevated liver enzymes);

20. History of liver transplant;

21. Active or uncontrolled infections except chronic HBV, chronic HCV, or both;

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

5.4 Criteria for Initiation of Treatment with the Investigational Medicinal Product

Subjects will be screened for eligibility during the screening period.

For Phase Ib, eligible subjects will be enrolled into the appropriate dose cohort being enrolled at the time.

For Phase II, eligible subjects will be enrolled at the RP2D (see Section 5.1).

Subjects will then initiate treatment with the IMP (MSC2156119J). There is no randomization in this trial.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons. A subject must be withdrawn in the event the subject withdraws his or her consent.

If the withdrawal is due to AE, the subject will be followed-up until the condition is resolved or is stable and the subject is able to resume care by his/her physician.

If a subject has failed 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 End of Treatment visit, if possible, with focus on the most relevant assessments including all safety assessments (see Section 7.1 “Schedule of Assessments”). In any case, the appropriate electronic Case Report Form (eCRF) section must be completed.

Subjects who are withdrawn for any reason must not re-enter this trial at any time.

5.5.1.1 Replacement of Discontinued Subjects for Phase Ib

During Phase Ib, subjects must 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% (17 days) of planned cumulative doses of MSC2156119J during Cycle 1, for reasons other than AEs related to MSC2156119J or DLTs.

Data from subjects who withdraw due to a DLT will be included in the determination of the RP2D. These subjects will not be replaced.

5.5.1.2 Replacement of Discontinued Subjects for Phase II

Subjects who withdraw for any reason after receiving trial treatment in Phase II will not be replaced.

5.5.2 Withdrawal from MSC2156119J

The subject must be withdrawn in the event of any of the following:

- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the investigator and/or sponsor;
- Therapeutic failure (i.e., oncologic emergency due to serious tumor progression or serious side effect) requiring urgent additional drug;
- QTc >500 msec or change of QTc from Baseline > 60 msec;
- Occurrence of AEs, if discontinuation of trial drug is desired or considered necessary by the investigator and/or the subject;
- Occurrence of pregnancy;
- Use of a non-permitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from MSC2156119J;
- Non-compliance with administration of MSC2156119J;
- Documented progression of the disease;
- Initiation of any other anticancer treatment (including radiotherapy, surgery, hormonal therapy).

If a subject withdraws from MSC2156119J, every effort should be made to document objective progression even after discontinuation of treatment. Subjects who discontinue trial treatment for reasons other than disease progression or withdrawal of consent will continue to have tumor assessments according to the same schedule as subjects who remain on the trial treatment. These assessments will continue until disease progression, withdrawal of consent, starting a new anticancer therapy, or death.

5.6 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 of MSC2156119J;

Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions; or

Other unfavorable safety findings.

(Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, e.g., toxicology.)

- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons;
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely; and
- 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 trial may be terminated or suspended upon request of Health Authorities.

5.7 Definition of End of Trial

The end of the trial will be defined as 12 months after the last subject's first dose of MSC2156119J. Subjects who are on active treatment with MSC2156119J at the time of end of the trial will be offered further treatment with MSC2156119J and assessments will be made as appropriate to determine whether a potential benefit from further treatment is seen.

6 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.

6.1 Description of Investigational Medicinal Product

MSC2156119J, CCI [redacted] 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 encephalophathy risk.

6.2 Dosage and Administration

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

Subjects will take their assigned doses of MSC2156119J orally once daily, in the morning at approximately the same time each day (± 2 hours), immediately after breakfast, with a full glass of water (approximately 200 mL), every day of each 21 day treatment cycle until the determination of PD (as assessed by the investigator according to RECIST Version 1.1), intolerable toxicity, or withdrawal from the trial.

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

On days when PK samples are to be drawn, subjects should be instructed to attend the trial visit in a fasted state, with no breakfast and prior to taking their dose of MSC2156119J. 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).

Dosage – Phase Ib

The first dose level will be 300 mg once daily, which is one dose-level lower than the target dose of RP2D (500 mg, once daily) from the FIM trial (EMR 200095-001). The second dose level is planned to be 500 mg once daily, which has been determined as the RP2D in the FIM trial.

Dosage – Phase II

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

6.2.1 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 is paused and a full safety data set (all AEs, laboratory data, ECG data, and vital signs) and available PK data are 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 DLTs (see Section 6.2.2) and the safety and PK data during Cycle 1 (21 days), and the decision criteria are as follows:

For the first dose cohort (300 mg):

- If no subject out of the first 3 experiences a DLT during Cycle 1 (21 days), dose escalation will proceed to the higher dose cohort (500 mg);
- If 1 subject out of 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 further exploration of potentially biologically active doses lower than 300 mg as decided by the sponsor;

- If 2 or more subjects out of the first 3 experience a DLT during Cycle 1 (21 days), no additional subjects will be enrolled and the trial will be discontinued, unless there is evidence to support further exploration as specified above.

If the SMC sees a potential safety concern from AE data other than a 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 a 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 experiences a 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, and the next step will depend on the decision of the SMC

- If 2 or more subjects out of the first 3 experience a DLT during Cycle 1 (21 days), the dose will be considered too toxic and the SMC will decide whether to step down to a lower dose or discontinue the study. This SMC decision will be made by consideration of the DLTs, other clinically relevant safety data, and emerging PK data.

6.2.1.1 Safety Monitoring Committee

During the trial, all serious AEs (SAEs) and potential DLTs will be sent to the SMC on a continual basis. The constitution of the SMC is described in Section 2.

In Phase Ib, the SMC will be responsible for making the decision of dose escalation (or de-escalation) to a new dose level after all subjects in the preceding cohort have completed Cycle 1 and all events during this cycle have been fully evaluated. In dose confirmation of Phase Ib of the trial, the SMC will meet after the initial 3 subjects have completed Cycle 1, to evaluate the safety of MSC2156119J and PK at the dose level being used for the confirmation phase. Depending on the emerging data, the next step will either be to enroll an additional 9 subjects at the same dose

level to confirm the RP2D, or to de-escalate to a lower dose level. After all 12 subjects have completed Cycle 1, the SMC will decide whether or not to continue with the MTD/RP2D determined during the dose escalation.

In Phase II, the SMC will review the safety of MSC2156119J after the first 12 subjects have completed Cycle 1, and again after the first 24 subjects have completed Cycle 1.

Ad hoc SMC meetings can be performed at any time in case a safety concern should arise.

Further information describing a scope of work and procedures for the SMC will be provided in the SMC Charter, and a separate statistical analysis plan (SAP) for the SMC will be established prior to the start of recruitment.

6.2.2 Definition of DLT

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

Using the National Cancer Institute (NCI)-CTCAE Version 4.0, a 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 nontraumatic bleeding
- Grade ≥ 3 uncontrolled nausea/vomiting and/or diarrhea despite adequate and optimal treatment for more than 3 days
- Grade ≥ 3 any nonhematological 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 AEs such as jaundice or hepatic encephalopathy suggestive of liver failure should also be considered.)

Grade ≥ 3 lipase and/or amylase elevation with confirmation of pancreatitis, either based on clinical or radiological signs will be considered as a DLT. An isolated lipase and/or amylase elevation of ≥ Grade 3 without clinical or radiological evidence of pancreatitis will not be classified as a 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 DLTs.

Asymptomatic Lipase/Amylase 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)/magnetic

resonance imaging (MRI) scan 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 lipase/amylase elevations of Grade ≥ 3 will be reported as AEs of special interest (AESIs; see Section 7.4.1) 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 lipase/amylase elevation occurring during Cycle 1 will not be classified as a 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; and
- 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, nonclinical models and/or current experience with MSC2156119J in the subject or other subjects with this tumor type. Otherwise, treatment with MSC2156119J should be discontinued.

Persistent Grade 3 amylase/lipase elevations without clinical or radiological evidence of pancreatitis can occur before the first scheduled RECIST CT scan for evaluation of objective benefit (i.e. Day 1 of Cycle 3). Subjects are allowed to continue MSC2156119J until treatment discontinuation due to disease progression or the next scheduled RECIST CT scan.

6.2.3 Dose Adjustments and Missed Doses

If a dose is missed during breakfast, subjects will be instructed to take it immediately with food before the end of day.

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 both 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 evaluable for the assessment of the primary endpoints of Phase Ib.

Subjects are permitted to have dose modifications to ensure the MSC2156119J is well tolerated at the scheduled dose levels. A two-level dose schedule is applied for dose modification, i.e., the next 2 lower levels than RP2D. If a subject still does not tolerate the permitted lowest dose, the subject will be withdrawn from the trial. Assuming that the RP2D is 500 mg daily, the next 2 lower dose strengths to adjust to in case of toxicity would be 300 mg and then 200 mg. The maximum permitted dosing delay 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 temporarily discontinued on the first day of occurrence 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 any nonhematological 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
- 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

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 temporarily discontinued on the first day of occurrence of the AE.

Adverse events requiring treatment interruption can occur before the first scheduled RECIST CT scan for evaluation of objective benefit (i.e. Day 1 of Cycle 3). Subjects are allowed to restart treatment after a maximum of 21 days of interruption, provided the AE goes down to ≤Grade 1 or baseline.

- Subjects experiencing Grade 4 pancreatitis will not be rechallenged with MSC2156119J at any dose.

6.2.4 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.

6.3 Assignment to Treatment Groups

Not applicable; all subjects will receive MSC2156119J. Subjects will be enrolled into the appropriate dose cohort and part of the trial being enrolled at the time.

Subject Number

The subject number will consist of a 4-digit site number followed by a 4-digit subject number in ascending order (e.g., Subject 0102-0001 is the first subject at Site 0102). The first 2 digits of the site number indicate the country. For subjects participating in Phase II, 2000 will be added to the subject number (e.g., Subject 0102-2001 is the first subject in Phase II at site 0102).

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.

6.4 Other Drugs to be Used in the Trial

Not applicable.

6.5 Concomitant Medications and Therapies

6.5.1 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/procedures taken by the subject during the trial, from the date of signature of 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 either prior to or during the trial;
- Ongoing interferon therapy for hepatitis started before entering the trial; and
- 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.
- 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.

The investigator may decide not to include a subject in the trial, if the subject cannot withdraw the drugs that have a narrow therapeutic range and that are known to be transported via P-gp; If the investigator decides to enroll a subject who is treated with a drug that is transported via P-gp, BCRP or OCTI and has a narrow therapeutic range, close safety monitoring is advised.

6.5.2 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:

- Initiation of new interferon therapy for hepatitis within 30 days prior to Day 1 or at any time during the trial;
- Any other cancer therapy, including chemotherapy or local regional treatments, or any investigational product other than MSC2156119J as defined in this protocol;
- Prophylactic granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF);

- 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;
- Drug(s) that are known to induce P-gp and thereby may decrease efficacy of MSC2156119J such as drugs known to induce P-gp (e.g., avasimibe, carbamazepine, phenytoin, rifampin, Saint John's wort);
- Subjects who receive a drug that is known to prolong QTc interval and cause respective cardiac side effects (see Appendix L).

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

6.5.3 Other Trial Considerations

If a subject undergoes non-permitted local-regional therapy during the trial (as described in the Exclusion Criteria; see Section 5.3.2), the subject must be withdrawn from the trial.

6.5.4 Special Precautions

MSC2156119J is considered to be an inhibitor of P-gp with an in vitro 50% inhibitory concentration of 0.41 ± 0.04 μM from in vitro study. Therefore, caution should be exercised when administering concomitant medications that have a narrow therapeutic range and are known to be transported by P-gp (see Section 6.5.1).

6.6 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 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 conditions, the word "for clinical trial use", batch number, and the sponsor's name.

6.7 Preparation, Handling and Storage

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

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]. Any deviations from the recommended storage conditions should be immediately reported to the sponsor, and the medication should not be used until authorization has been received from the sponsor.

6.8 MSC2156119J Accountability

The storage manager at the trial site who was assigned by the head of the trial site is responsible for ensuring accountability for MSC2156119J, 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 MSC2156119J to the storage manager at the trial site.

- Upon receipt of MSC2156119J, 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 MSC2156119J will be carefully recorded on the appropriate drug accountability forms provided by the sponsor/CRO and an accurate accounting will be available for verification by the sponsor/CRO monitor at each monitoring visit;
- MSC2156119J accountability records will include:

Confirmation of MSC2156119J delivery to the trial site.

The inventory at the site of MSC2156119J provided by the sponsor and prepared at the site.

The use of each dose by each subject.

Disposition of unused MSC2156119J.

Dates, quantities, batch numbers, expiry dates and (for MSC2156119J prepared at the site) formulation, as well as the subjects' trial numbers.

- The storage manager should maintain records that adequately document that:

Subjects were provided the doses specified by the clinical trial protocol/amendment(s), and

All MSC2156119J provided by the sponsor was fully reconciled.

Unused MSC2156119J must not be discarded or used for any purpose other than the present trial. MSC2156119J that has been dispensed to a subject must not be re-dispensed to a different subject.

The sponsor/CRO monitor will periodically collect the MSC2156119J accountability forms and will check all returns (both unused and used containers) before authorizing their destruction by the trial site.

6.9 Assessment of MSC2156119J Compliance

Each subject will record on a diary card the number and dosage of MSC2156119J taken daily and the time of taking MSC2156119J 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 MSC2156119J packages, in order to allow the assessment of compliance with trial treatment. The MSC2156119J administration must be recorded in the eCRF, as applicable.

6.10 Method of Blinding

Not applicable; this is an open-label trial.

6.11 Emergency Unblinding

Not applicable.

6.12 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 7.4.1.4).

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

6.13 Medical Care of Subjects After 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.

7 Trial Procedures and Assessments

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

7.1 Schedule of Assessments

A chart of all treatment and assessments is presented in Appendix G (Phase Ib) and Appendix H (Phase II).

7.1.1 Informed Consent

Prior to performing any trial assessments not part of the subject's routine medical care, the investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

7.1.2 Screening Period

The subject must sign an informed consent form (ICF) before any trial procedures are performed. Screening procedures must be performed within 28 days before the day of first dosing.

7.1.2.1 Phase Ib

For Phase Ib, all procedures will be performed within 28 days before the day of first dosing. The following assessments and examinations will be performed:

- Tumor biopsy, excluding fine needle aspiration and cytology samples (mandatory; formalin fixation is mandatory; if the tumor block is not available, it is recommended to obtain ≥ 15 formalin fixed sections; a second pretreatment biopsy [second pass, frozen] for analysis of exploratory biomarkers is highly recommended but optional; subjects who will have the second optional biopsy should also have an on-treatment biopsy on any day from Cycle 1 Day 15 through Cycle 3 Day 1 [frozen, paired biopsy])
- Demographic data;
- Height;
- Medical history;
- Smoking status and alcohol use;
- Viral serology;
- Complete tumor assessment using RECIST Version 1.1 and secondarily using modified RECIST (mRECIST) for HCC, including CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations and CT/MRI of the head for subjects suspected to have CNS metastases;
- Physical examination including body weight;
- ECOG PS;

- Vital signs;
- ECG;
- Blood samples to assess hematology, chemistry, and coagulation;
- Urinalysis;
- Serum pregnancy test (if applicable);
- Serum alpha-fetoprotein (AFP);
- AE assessment;
- Recording of concomitant medications/procedures.

7.1.2.2 Phase II

For Phase II, a pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples) will be performed and analyzed for MET+ status by IHC (Appendix C) before any further screening procedures are performed. The pretreatment biopsy will be obtained within 28 days before the day of first dosing. If the tumor block is not available, it is recommended to obtain ≥ 15 formalin fixed sections.

Subjects with MET+ tumor biopsy tissue will undergo the following additional screening procedures (all must be performed within 28 days before the day of first dosing):

- Demographic data;
- Height;
- Medical history;
- Smoking status and alcohol use;
- Viral serology;
- Complete tumor assessment using RECIST Version 1.1 and secondarily using mRECIST for HCC, including CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations and CT/MRI of the head for subjects suspected to have CNS metastases;
- Physical examination including body weight;
- ECOG PS;
- Vital signs;
- ECG;
- Blood samples to assess hematology, chemistry, and coagulation;
- Urinalysis;
- Serum pregnancy test (if applicable);
- Serum AFP;

- AE assessment;
- Recording of concomitant medications/procedures;
- Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8) and Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-HP).

7.1.3 Treatment Period

MSC2156119J will be administered once daily over a 21 day cycle until PD, or intolerable toxicity, death, or withdrawal from treatment.

7.1.3.1 Cycle 1 Day 1

The following assessments and examinations will be performed on this day:

- Optional tumor biopsy, excluding fine needle aspiration and cytology samples (frozen; for Pd/PK; may be taken either at screening or pretreatment on Cycle 1 Day 1; Phase Ib only; subjects who will have the optional biopsy should also have an on-treatment biopsy on any day from Cycle 1 Day 15 through Cycle 3 Day 1 [frozen, paired biopsy]);
- Tumor assessment by ^{18}F-fluoro-D-glucose (FDG) positron emission tomography (PET) CT scan (predose only);
- Blood samples for CCI and Pd (predose only);
- CCI ;
- A urine pregnancy test will be completed in women of childbearing potential before administration of the dose. If the pregnancy test is positive, it must be confirmed with a serum pregnancy test.
- ECG [predose and at 4, 10, and 24 hours postdose for Phase Ib (the 24-hour postdose ECG is to be performed predose on the following day), and predose and at 4 hours postdose for Phase II]. ECGs will be performed immediately before PK sampling at times when both procedures are performed;
- PK blood samples [predose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose for Phase Ib (the 24-hour postdose PK blood sample is to be drawn predose on the following day); CCI];
- AE assessment;
- Recording of concomitant medications/procedures;
- FHSI-8 and FACT-HP (Phase II only).

Additionally, the following assessments will be performed if the last assessments of these parameters were performed > 7 days prior to this visit:

- Viral load of HBV (for subjects with hepatitis B at screening) and viral load of HCV (for subjects with hepatitis C at screening);

- Physical examination including body weight;
- ECOG PS;
- Vital signs; blood samples (to assess hematology, chemistry, and coagulation);
- Urinalysis;
- Serum AFP.

7.1.3.2 Cycle 1 Day 2 and Cycle 1 Day 8

The visit on Cycle 1 Day 8 may be performed within ± 1 day of Cycle 1 Day 8. The following assessments and examinations will be performed on the days of these visits:

- Physical examination including body weight;
- Vital signs;
- Blood samples (to assess hematology, chemistry, and coagulation);
- AE assessment;
- Recording of concomitant medications/procedures.

7.1.3.3 Cycle 1 Day 15

This visit may be performed within ± 2 days of Cycle 1 Day 15. The following assessments and examinations will be performed on this day:

- Physical examination including body weight;
- ECG [predose and at 4, 10, and 24 hours postdose for Phase Ib (the 24-hour postdose ECG is to be performed predose on the following day), and predose and at 4 hours postdose for Phase II]. ECGs will be performed immediately before PK sampling at times when both procedures are performed;
- PK blood samples (predose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose; Phase Ib only; the 24-hour postdose PK blood sample is to be performed predose on the following day);
- Blood samples (to assess hematology, chemistry, and coagulation);
- AE assessment;
- Recording of concomitant medications/procedures;
- Optional tumor biopsy, excluding fine needle aspiration and cytology samples (optional frozen sample for subjects who had the optional frozen pretreatment biopsy; this biopsy may be taken on any day from Cycle 1 Day 15 up through Cycle 3 Day 1; Phase Ib only);
- Blood sample for evaluation of CCI [redacted].

7.1.3.4 Cycle 2 Day 1

This visit may be performed within ± 5 days of Cycle 2 Day 1. Efforts should be made to strictly maintain the schedule defined in the protocol. Cycle 1 Day 1 should be used as a reference to calculate Day 1 of all subsequent cycles even in the case of treatment or visit delays.

The following assessments and examinations will be performed on this day:

- Physical examination including body weight;
- A urine pregnancy test will be completed in women of childbearing potential before administration of the dose. If the pregnancy test is positive, it must be confirmed with a serum pregnancy test.
- ECOG PS;
- Vital signs;
- ECG (predose only);
- CCI [redacted]
- Blood samples (to assess hematology, chemistry, and coagulation);
- Urinalysis;
- Serum AFP;
- AE assessment;
- Recording of concomitant medications/procedures;
- FHSI-8 and FACT-HP (Phase II only).

7.1.3.5 Cycle 2 Day 8

This visit may be performed within ± 5 days of Cycle 2 Day 8. The following assessments and examinations will be performed on this day:

- Physical examination including body weight;
- Vital signs;
- Blood samples (to assess hematology, chemistry, and coagulation);
- AE assessment;
- Recording of concomitant medications/procedures;
- FHSI-8 and FACT-HP (Phase II only).

7.1.3.6 Cycle 2 Day 15

This visit may be performed within ± 5 days of Cycle 2 Day 15. The following assessments and examinations will be performed on this day:

- Physical examination including body weight;
- Blood samples (to assess hematology, chemistry, and coagulation);
- AE assessment;
- Recording of concomitant medications/procedures;
- Blood sample for evaluation of CCI [redacted];
- FHSI-8 and FACT-HP (Phase II only).

7.1.3.7 Cycle 3 Day 1 (and Day 1 of All Subsequent Cycles)

The frequency of visits will be every 3 weeks up through Cycle 8. From Cycle 9 onward, the frequency of visits will be every 6 weeks, and after Cycle 13, the frequency of visits will be every 12 weeks. These visits may occur within ± 5 days of Day 1 of the applicable cycle. Refer to Section 7.1.3.4 for the calculation of Day 1 of each cycle.

The following assessments and examinations will be performed on this day of each cycle for which there is a visit:

- Physical examination including body weight;
- A urine pregnancy test will be completed in women of childbearing potential before administration of the dose. If the pregnancy test is positive, it must be confirmed with a serum pregnancy test.
- ECOG PS;
- Vital signs; ECG (predose only);
- Blood samples (to assess hematology, chemistry, and coagulation);
- Urinalysis;
- Serum AFP;
- Complete tumor assessment using RECIST Version 1.1 and secondarily using mRECIST for HCC (on Day 1 of Cycles 3, 5, 7, 9, 11, 13, and every 4 cycles thereafter until disease progression or study drug discontinuation; can occur within 5 days prior to the start of each of these cycles but must be performed prior to the start of each of these cycles);
- AE assessment;
- Recording of concomitant medications/procedures;
- Tumor assessment by ^{18}F-FDG PET CT scan (Cycle 3 Day 1 only);
- FHSI-8 and FACT-HP (Phase II only).

7.1.4 End of Treatment Visit

This visit should be performed on the last day of treatment, whether at the end of a cycle or not, but may be performed up to 7 days after the last day of treatment and prior to the start of subsequent

anticancer therapy. The last day of treatment is defined as the day on which it is determined that the subject will no longer receive trial treatment (due to PD [as assessed by the investigator], intolerable toxicity, or withdrawal from the trial). The following assessments and examinations will be performed at this visit:

- Optional tumor biopsy, excluding fine needle aspiration and cytology samples (in both phases, samples may be taken on the last day of treatment until up to 7 days after the last day of treatment and prior to the start of subsequent anticancer treatment; in both phases, samples must be formalin fixed);
- Physical examination including body weight;
- ECOG PS;
- Vital signs;
- ECG;
- Blood samples (to assess hematology, chemistry, and coagulation);
- Urinalysis;
- Urine pregnancy test (if applicable);
- Serum AFP;
- Blood sample for CCI [redacted] and Pd;
- Complete tumor assessment using RECIST Version 1.1 and secondarily using mRECIST for HCC (only if last tumor assessment was performed ≥ 6 weeks ago);
- AE assessment;
- Recording of concomitant medications/procedures;
- FHSI-8 and FACT-HP (Phase II only).

7.1.5 Post-treatment Follow-up Visit

This visit will be performed 30 ± 3 days after the last treatment for subjects who discontinue trial treatment permanently, including subjects who have completed an End of Treatment Visit. If another anticancer therapy will be started before the end of this period (30 days), the Post-treatment Follow-up Visit should be conducted prior to start of this therapy. Subjects who terminated their treatment early, for whatever reason, will be encouraged to return to the clinic for the Post-treatment Follow-up Visit. If the subject is unable to return for the Post-treatment Follow-up Visit, the reason should be clearly documented in the subject's medical record.

The following assessments and examinations will be performed on this day:

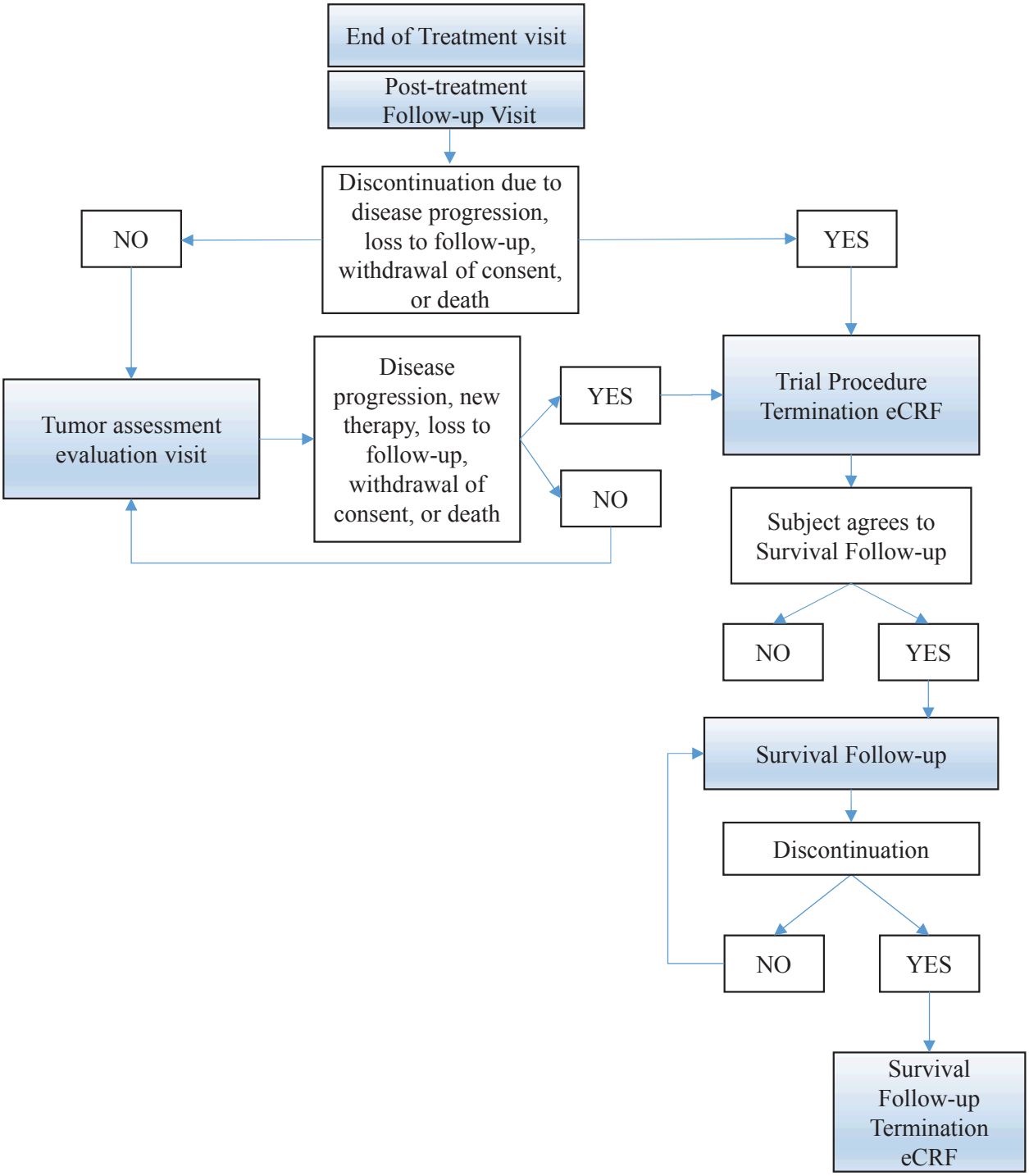
- Physical examination including body weight;
- ECOG PS;
- Vital signs;

- ECG;
- Blood samples (to assess hematology, chemistry, and coagulation);
- Serum pregnancy test (if applicable);
- Urinalysis;
- AE assessment;
- Recording of concomitant medications/procedures;
- FHSI-8 and FACT-HP (Phase II only).

For operational purposes, a Trial Procedure Termination eCRF will be completed for all subjects when no further trial evaluations are expected (with the exception of potential survival follow-up). The following will be recorded in the eCRF: the date of discontinuation from trial procedures, the primary reason for discontinuation from trial procedures, and whether the subject agrees to be followed for survival.

Refer to Figure 4 for a schematic depicting when the Trial Procedure Termination eCRF will be completed. The Trial Procedure Termination eCRF will be completed at the Post-treatment Follow-up Visit for subjects who terminated their treatment due to disease progression, withdrawal of consent, loss to follow-up, or death. Subjects who discontinued trial treatment for all other reasons will continue to have tumor assessments according to the same schedule as subjects who remained on trial treatment. These assessments will continue until disease progression, withdrawal of consent, starting a new anticancer therapy, loss to follow-up, or death, at which time the Trial Procedure Termination eCRF will be completed.

Figure 4 Schematic of Trial After Discontinuation of Treatment



eCRF=electronic Case Report Form.

7.1.6 Survival Follow-up

Information about subject survival and anticancer therapies will be collected every 3 months (± 2 weeks) after End of Treatment until death, withdrawal of consent, or the end of the trial, whichever comes first. This information will be documented by the trial site personnel in the subject's source documents.

After discontinuation of survival follow-up, a Survival Follow-up Termination eCRF will be completed. The investigator must determine the primary reason for a subject's premature discontinuation from the trial and record this information on the Survival Follow-up Termination eCRF. For subjects who are lost to follow-up, the investigator should show due diligence by documenting in the source documents steps taken to contact the subject.

7.2 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, according to the procedure described in Section 9.2.

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.

- Medical History

  The medical history will include:

  The starting and ending dates or duration of the medical incidences.

  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, tumor, lymph nodes, metastasis (TNM) classification, staging information at the initial histological diagnosis, previous treatments (surgery, radiotherapy, and systemic therapies), 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.

- Tumor Biopsy

  Tumor biopsy will be performed as described in Section 7.6.1. Tumor tissue will be analyzed (at a central laboratory) for c-Met in both Phase Ib and Phase II; results must be obtained prior to any further screening of subjects in Phase II because MET+ status is an inclusion criterion for subjects enrolling into Phase II (see Section 5.3.1). It is not necessary to obtain the c-Met status of subjects in Phase Ib prior to subject enrollment.

- Physical Examination

  A physical examination will be performed as described in Section 7.4.4.1.

- ECOG Status

  Subjects' ECOG status will be assessed and scored as described in Appendix A.

- Vital Signs

  Vital signs will be recorded as described in Section 7.4.4.3.

- ECG

  A standard 12-lead ECG will be performed as outlined in Section 7.4.4.4.

- Blood Samples for Hematology and Coagulation

  Blood samples for analysis of hematology and coagulation parameters will be collected as described in Section 7.4.3.1.

- Blood Samples for Chemistry

  Blood samples for analysis of chemistry parameters will be collected as described in Section 7.4.3.2.

- Urinalysis

  Urine samples for analysis of safety parameters will be collected as described in Section 7.4.3.3.

- HBV Panel and Anti-HCV Antibodies

  A blood sample will be taken to test for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-hepatitis B core antigen (anti-HBc), and anti-HCV.

- Viral Load of HBV/HCV

  A blood sample will be taken to assess the viral load of HBV in subjects with hepatitis B at screening, and of HCV in subjects with hepatitis C at screening.

- Pregnancy Test

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

- Tumor Assessment

  Tumor imaging assessment by RECIST Version 1.1 and secondarily using mRECIST for HCC will be performed as described in Section 7.3.

- Serum AFP

  A blood sample will be taken to assess the level of serum AFP.

- Concomitant Medications/Procedures

  Concomitant medications and therapies will be documented as described in Section 6.5.

- AEs

  All AEs reported after signing of the ICF will be recorded as described in Section 7.4.1.

- FHSI-8 and FACT-HP (Phase II only)

The FHSI-8 and FACT-HP questionnaires will be administered as described in Section 7.3.3.

7.3 Assessment of Efficacy

7.3.1 Tumor Evaluations

Tumor assessment will be performed according to RECIST Version 1.1 as summarized in Appendix J (3) and secondarily according to mRECIST for HCC as summarized in Appendix K (4). The baseline tumor assessment is scheduled to be performed during the screening period (see Section 7.1.2). CT or MRI with contrast enhancement is recommended for tumor assessment. Imaging studies, including CT or MRI of the chest, 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 should be performed at baseline. 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.

All tumor responses (partial response and/or complete response [CR]) should be assessed every time with the same methods (CT or MRI) used at the first evaluation of the response.

Tumor evaluations will be done by the investigator. For quality control purposes, the sponsor would like to reserve the possibility to conduct a confirmatory measurement by an independent external read, but the evaluations done by the investigator will be used for the primary evaluations of efficacy endpoints as described in Section 8.3. For Phase II, all data needed for confirmatory measurements will be collected and held by a central facility to ensure availability of the data for an independent external read.

Exploratory tumor assessments will also be performed by ^{18}F-FDG PET CT scan according to the schedule described in Appendix G (Phase Ib) or Appendix H (Phase II).

All measurements should be recorded in metric notation.

7.3.2 Serum AFP

Serum AFP will be determined from blood samples taken according to the schedule described in Appendix G (Phase Ib) or Appendix H (Phase II). Procedures for handling these blood samples will be described in a separate laboratory manual.

7.3.3 FHSI-8 and FACT-HP

The FHSI-8 questionnaire will be administered in Phase II according to the schedule described in Appendix E, and the FACT-HP questionnaire will be administered in Phase II according to the schedule described in Appendix F.

7.3.4 ECOG Performance Status

ECOG PS will be assessed as described in Appendix A.

7.3.5 Survival Follow-up

Subjects will be followed to collect information about survival and anticancer treatments according to the schedule described in Appendix G (Phase Ib) or Appendix H (Phase II).

7.4 Assessment of Safety

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

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. The investigator will report any AEs, whether observed by the investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 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 or disabling
- Grade 5 or Death

If death occurs, the primary cause of death (or event leading to death) should be recorded and reported as an 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 (e.g., sudden death, unexplained death), the death per se might be reported as an SAE.

According to sponsor's 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.

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, course of the underlying disease, and trial procedures.

Not related: Not reasonably related to MSC2156119J. The AE could not medically (pharmacologically/clinically) be attributed to MSC2156119J. A reasonable alternative explanation must be available.

Related: Reasonably related to MSC2156119J. The AE could medically (pharmacologically/clinically) be attributed to MSC2156119J.

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 7.4.1.4.

Events that Do Not Meet the Definition of an 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 which 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

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms should not be reported as AEs.

However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs and reported as SAEs if they meet criteria for seriousness.

AEs of Special Interest (AESIs)

Subjects might experience asymptomatic elevations in serum pancreatic enzyme (lipase and amylase). Such enzyme elevations of Grade ≥ 3 will be considered to be AESIs 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 7.4.1.4).

Should the AESI be serious, an SAE form, instead of the AESI form, should be filled and the procedure for reporting SAEs (see Section 7.4.1.4) should be followed. In addition to SAEs, all nonserious DLTs will be promptly reported by the investigator using the AE section of the eCRF.

7.4.1.2 Methods of Recording and Assessing Adverse Events

The subject will be queried on changes in his/her condition during each trial visit. Any unfavorable changes in the subject's condition during the reporting period of the trial 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 AEs, all SAEs, and all AESIs must be additionally documented and reported using an SAE Report Form or an AESI Report Form as described in Section 7.4.1.4.

It is important that each AE report include 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) and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented. If an AE constitutes a DLT this has to be documented accordingly.

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

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's Post-treatment Follow-up visit, as described in Section 7.1.5. 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 interview should be performed to document any AEs that occurred in this time period.

Any SAE assessed as related to MSC2156119J must be reported whenever it occurs, irrespective of the time elapsed since the last administration of MSC2156119J.

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

In the event of any new SAE occurring during the reporting period, the investigator must immediately (i.e., 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.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

Names, addresses, and 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, e.g., 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/reporter 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 described for initial reports. This is necessary to permit a prompt assessment of the event by the sponsor/designee and (as applicable) to allow the sponsor/designee 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.

AESIs

In the event of a ***nonserious*** AESI, the investigator has to complete the AESI Report Form and send it to the sponsor/designee immediately, within 24 hours after becoming aware of the event. Names, addresses, and 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.

DLTs

Each event meeting the criteria of a DLT (see Section 6.2.2) 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.

7.4.1.5 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 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 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.

7.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the study (see Section 7.4.1.3) and are assessed for final outcome at the Post-treatment Follow-up visit (30-Day Safety 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 the 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.

7.4.2 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 7.4.1.3 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 7.4.1.4.

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 7.4.1.4, 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 trial medication immediately. The sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Laboratory Assessments

It is essential that the sponsor be provided with a list of laboratory normal ranges before shipment of trial drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the sponsor.

7.4.3.1 Hematology and Coagulation

Hematology assessments, shown in Table 1, will be performed during the course of this trial including screening period (3 mL of blood for blood counts plus 4.5 mL for coagulation tests, for a total of 7.5 mL).

Table 1 Hematology Assessments

Parameter
Hemoglobin (Hb)
Hematocrit (Hct)
Red blood cell (RBC) count
White blood cell (WBC) count
Differential WBC
• Neutrophils
• Eosinophils
• Basophils
• Monocytes
• Lymphocytes
• Other
Platelet count
Prothrombin time (PT)
Activated thromboplastin time (aPTT)
International normalized ratio (INR)

7.4.3.2 Chemistry

Chemistry assessments, shown in Table 2, will be performed during the course of this trial including screening period (5 mL of blood for each sample).

Table 2 Chemistry Assessments

Blood urea nitrogen (BUN)
Creatinine
ALT
AST
Gamma-glutamyl transpeptidase (GGT)
Total bilirubin
Direct fraction of bilirubin (if total bilirubin is abnormal)
Lipase
Amylase
Total protein
Albumin
Alkaline phosphatase
Creatinine clearance
Sodium
Potassium
Calcium
Magnesium
Glucose

7.4.3.3 Urinalysis

The following urinalysis parameters will be evaluated on dipsticks, followed by a microscopic examination in the case of abnormal results:

- Glucose
- Ketones
- Blood
- pH
- Proteins
- Nitrites
- Leukocytes

7.4.3.4 Viral Load of HBV and HCV

The viral load of HBV will be analyzed in subjects with hepatitis B at screening, and the viral load of HCV will be analyzed in subjects with hepatitis C at screening.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Physical Examinations

The physical examination will be identical to a general medical check-up comprising a whole body inspection (general appearance, 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. Body weight will be recorded. Any clinically significant abnormal findings or worsening of conditions previously recorded in the medical history must be documented in the eCRF.

7.4.4.2 ECOG

ECOG PS will be assessed according to the criteria described in Appendix A, at the times described in Appendix G (Phase Ib) and Appendix H (Phase II).

7.4.4.3 Vital Signs

Systolic blood pressure, diastolic blood pressure, and heart rate will be measured after 5 minutes in a supine position. Body temperature will be recorded.

7.4.4.4 Electrocardiogram

Subjects will undergo 12-lead ECGs after the subject has rested immediately after measurement of vital signs (see Section 7.4.4.3). ECGs will be taken in triplicate within 2 minutes at each assessment time point to monitor the heart rhythm and PR, QRS, QT, RR, and QTc intervals (calculated in the eCRF).

7.5 Pharmacokinetics

7.5.1 Body Fluids

Blood samples for PK will be taken according to the schedule provided in Appendix G (Phase Ib) and Appendix H (Phase II).

Details about the sampling and processing procedures, storage and transportation will be provided in a separate laboratory manual.

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.

7.5.2 Pharmacokinetic Calculations

The following PK parameters will be calculated and summarized from the measured individual plasma concentrations of MSC2156119J using noncompartmental 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. 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 lower limit of quantification. 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
- CCI [redacted]

CCI [redacted]

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 the lower limit of quantification will be taken as zero for descriptive statistics of concentrations.

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

Formal statistical hypothesis tests are not planned. Any statistical tests that might be performed will be considered exploratory. All analyses will be based on the PK analysis set. Details of the statistical analyses will be described in the SAP.

CCI [redacted]

The PK base model for the HCC population will be developed first based on the frequent PK sampling data from Phase Ib. If applicable, a one-compartment model will be used. 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 first be explored graphically, before inclusion in the statistical model.

The relationship between efficacy measures and 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.

CCI [redacted]

[redacted]

[redacted]

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7.6.1 Tumor Biopsies

The first tumor biopsy is required during the screening period (pretreatment biopsy). This biopsy must be fixed in neutral buffered formalin (formalin fixation is mandatory). If a tumor block is not available, at least 15 unstained slides of the pretreatment biopsy may be sent to the central laboratory. Undergoing paired tumor biopsy is optional for subjects with accessible tumors during Phase Ib. Paired frozen tumor biopsies may be taken before the treatment period (may be taken at screening or pretreatment on Cycle 1 Day 1) and during the treatment period (may be taken any time between Cycle 1 Day 15 and Cycle 3 Day 1). If a tumor shows progression after initial response to the MSC2156119J, an optional biopsy may be taken on the day of last treatment or ≤ 7 days after the last day of treatment and prior to the start of subsequent anticancer treatment.

For all subjects of Phase Ib and Phase II, the feasibility of a paired biopsy and end of treatment biopsy should be regularly reviewed.

Analysis of c-Met status will be performed at a central laboratory on the pretreatment biopsy after consent has been obtained from the subjects. Tumor biopsies will also be used for analysis of specific markers (see Section 7.6.3).

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.7 Other Assessments

The FHSI-8 questionnaire (Appendix E) and the FACT-HP questionnaire (Appendix F) will be administered according to the schedule presented in Appendix H (Phase II only).

8 Statistics

Details of the statistical analyses will be described in a separate SAP.

8.1 Sample Size

For Phase Ib, the sample size of up to 18 subjects was not based on any statistical assumptions; rather, it follows the "3+3 rule," a well-established current methodology in the design of dose-finding trials in oncology.

For Phase II, the sample size of 48 subjects was determined as follows. Under the assumption of no treatment effect, the rate of MET+ subjects without progression at 12 weeks (the primary endpoint) was assumed to be ~15% based on historical data. It is expected that MSC2156119J treatment will lead to 30% MET+ subjects without progression at 12 weeks. The null hypothesis (that the true rate of subjects without progression at 12 weeks is ≤ 15%) will be tested using a one-stage design based on the exact binomial distribution (5). With a type I error rate of 5% (one-sided) if the true rate of subjects without progression at 12 weeks is ≤ 15%, to reach a power of 80% if the true rate of subjects without progression at 12 weeks is 30%, this design requires 48 subjects to be treated in Phase II.

8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoints for the two parts of the trial are as follows:

- Phase Ib: Incidence of DLTs occurring during Cycle 1. The definition of a DLT for the Phase Ib part of the trial is provided in Section 6.2.2.
- Phase II: Progression-free survival (PFS) status at 12 weeks, defined as 'progression-free' if subject has tumor assessment of CR, partial response, or stable disease (SD) (as assessed by the investigator according to RECIST Version 1.1) 12 weeks after start of treatment or later. In any other case, progression-free status is not regarded as 'progression-free'.

Analyses of these endpoints are described briefly in Section 8.5.2.

8.3.2 Secondary Endpoints

8.3.2.1 Efficacy Endpoints

Secondary endpoints are as follows:

- TTP, measured as the time (in months) from the date of first study drug administration to the date of radiological confirmation of PD performed according to RECIST Version 1.1. In HCC, TTP is recommended as a sensitive endpoint in measuring antitumor activity of molecularly targeted agents in HCC Phase II trials since it is less vulnerable to the potential confounding effect of underlying liver disease than the traditional endpoint PFS. For this reason, TTP will be regarded as the major sensitivity analysis for the primary endpoint of PFS status.

- PFS, defined as the time (in months) from first study drug administration to either first observation of PD (as assessed by RECIST Version 1.1) or occurrence of death due to any cause within 12 weeks of the last tumor assessment, whichever occurs first.
- PFS, defined as the time (in months) from first study drug administration to either first observation of PD (as assessed by mRECIST for HCC) or occurrence of death due to any cause within 12 weeks of the last tumor assessment, whichever occurs first.
- Time-to-symptomatic progression (TTSP) as subject-reported outcome, defined as the time (in months) from first study drug administration to the date of deterioration of symptoms assessed by FHSI-8 (defined as at least a 4-point increase, i.e., higher score, compared with baseline value), or deterioration to ECOG performance score 4, or death (applicable for Phase II only).
- OS time, defined as the time (in months) from first study drug administration to the date of death.
- Objective tumor response: Subjects with best overall tumor assessment of CR or partial response according to RECIST Version 1.1 from first study drug administration until first occurrence of PD.
- Disease control: Subjects with best overall tumor assessment of CR, partial response, or SD according to RECIST Version 1.1 from first study drug administration until first occurrence of PD. SD must be observed at the end of Cycle 2 or later.
- Biological response as measured by serum AFP, defined as a > 20% decrease in AFP level by Cycle 2 compared with baseline.

8.3.2.2 Pharmacokinetic Endpoints: Phase Ib

For Phase Ib, PK endpoints may include AUC parameters (including $AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, and $AUC_{0\text{-}\infty}$), C_{max}, t_{max}, C_{min}, C_{av}, CL/F, V_z/F, V_{ss}/F, λz, and $t_{1/2}$ when appropriate (see Section 7.5.2).

8.3.3 Safety Endpoints

Safety endpoints apart from the DLT objective include the following:

- Drug exposure
- Incidence and type of AEs (all grades as per NCI-CTCAE Version 4.0): all treatment emergent AEs, related treatment emergent AEs, treatment emergent SAEs, related treatment emergent SAEs, treatment emergent AEs of NCI-CTCAE (Version 4.0) with Grade ≥ 3, related treatment emergent ≥ Grade 3, and treatment emergent AEs leading to permanent treatment discontinuation
- Incidence and reasons for deaths, including deaths within 33 days after the last dose of study drug
- 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

Analyses of secondary safety endpoints are described in Section 8.5.4.

8.3.4 Further Endpoints of Interest

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

8.4 Analysis Sets

Analysis sets include the following.

The intent-to-treat (ITT)/safety set includes all subjects who have been administered at least one dose of MSC2156119J.

For Phase Ib only, the DLT analysis set includes all subjects who completed Cycle 1 and who received 80% or more of the planned cumulative dose of MSC2156119J in Cycle 1, and subjects who stopped treatment with MSC2156119J during Cycle 1 because of a DLT. Subjects who have been replaced during the Cycle 1 will be excluded from the DLT analysis set.

The PK population includes all subjects who have received MSC2156119J and who had at least one blood sample drawn that provides drug concentration data for PK evaluation.

The Pd analysis set for each parameter includes all subjects who received at least one dose of MSC2156119J and have baseline and at least one postbaseline plasma or tumor assessment.

The following subgroups are considered to be of interest to explore the treatment effect of MSC2156119J:

- Age: < 65 years versus ≥ 65 years
- Gender: male versus female
- Country
- Baseline ECOG: 0 versus 1
- Vascular invasion and/or extrahepatic spread: presence versus absence

- The underlying disease or medical condition related to etiology: HBV versus other
- AFP elevation at baseline: ≥ 200 IU/mL or < 200 IU/mL
- Prior local-regional therapy: yes versus no

8.5 Description of Statistical Analyses

8.5.1 General Considerations

All analyses will be performed separately by trial phase (Phase Ib or Phase II), if not stated otherwise.

Analyses for the dose finding process will be performed on the DLT analysis set. Subjects in the DLT analysis set will be allocated to the dose level initially received during Cycle 1.

Safety analyses other than those for the dose finding process and efficacy analyses will be performed on the ITT/Safety analysis set.

Selected efficacy analyses will be repeated for subgroups.

If confidence intervals 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, 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 first administration of study drug will serve as the baseline measurement.

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

Statistical analyses will be performed by the Merck Serono Global Biostatistics Department and/or CRO. The computer program SAS® System (Version 9.1 or higher; PPD) or R (Version 2.10.1 or higher) will be used.

Details of the statistical analyses will be presented in a SAP.

8.5.2 Analysis of Primary Endpoints

For Phase Ib, the primary endpoint will be summarized as the number and proportion of subjects experiencing a DLT occurring during Cycle 1.

Information regarding safety and PK data beyond Cycle 1 will also be taken into consideration to confirm the RP2D.

For Phase II, the primary endpoint is PFS status, evaluated by the proportion of subjects who are progression-free at 12 weeks or later according to RECIST Version 1.1. Subjects are considered to be 'progression-free' if the subject has a tumor assessment of CR, partial response, or SD (according to RECIST Version 1.1) 12 weeks after start of treatment or later. In any other case, the subject is not considered to be 'progression-free'. The proportion of subjects progression-free at 12 weeks will be estimated, including a 90% confidence interval. The numerator of the estimated rate is the number of subjects in the ITT/safety population progression-free at 12 weeks and the denominator is the number of all subjects in the respective analysis population.

The design and hypothesis testing is based on the binomial distribution. The null hypothesis that the rate of progression-free subjects at 12 weeks is $\leq 15\%$ will be tested against a one-sided alternative.

If 12 or more subjects are considered progression-free at 12 weeks, the null hypothesis will be rejected and the trial will have met its primary endpoint. The test keeps a one-sided type-I error of 5%.

8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Time-to-Event Endpoints

TTP will be measured as the time (in months) from the date of first study drug administration to the date of radiological confirmation of PD performed according to RECIST Version 1.1. Deaths or subjects without radiological progression at time of analysis will be censored at the date of last tumor assessment.

PFS is defined as the time (in months) from first study drug administration to either first observation of PD or occurrence of death due to any cause within 12 weeks of the last tumor assessment, whichever occurs first. If no progression or death is observed, or if death without previously documented PD is observed more than 12 weeks after last tumor assessment without progression, PFS will be censored at the date of last tumor assessment or first administration of MSC2156119J, whichever occurs later.

TTSP as a subject-reported outcome is defined as the time (in months) from first study drug administration to the date of deterioration of symptoms assessed by FHSI-8 (defined as at least a 4-point increase, i.e., higher score, compared with baseline value), or deterioration to ECOG performance score 4, or death.

OS will be measured as the time (in months) from first study drug administration to the date of death. For subjects not known to be deceased at time of analysis, OS time will be censored at the last date the subject was known to be alive. If this date is after the data cutoff, subjects will be censored at the date of data cutoff.

TTP, PFS, TTSP and OS will be analyzed by Kaplan-Meier estimates as appropriate.

8.5.3.2 Objective Tumor Response, Disease Control, and AFP

Objective tumor response will be evaluated by the best overall response (BOR) rate, defined as the proportion of subjects having achieved CR or partial response according to RECIST Version 1.1 as the BOR from the date of first study drug administration until first occurrence of radiological PD.

Disease control will be evaluated by the disease control rate, defined as the proportion of subjects having achieved CR or partial response or SD according to RECIST Version 1.1 as the BOR from the date of first study drug administration until first occurrence of radiological PD. In case SD is the BOR, SD must be observed at the end of Cycle 2 or later.

Biological response will be evaluated as the rate of subjects with a decrease in AFP level of > 20% by Cycle 2 compared with baseline.

BOR rate, disease control rate, and the rate of subjects with AFP response will be summarized along with two-sided, 90% confidence intervals.

8.5.3.3 PK Parameters

For PK parameters being assessed as secondary endpoints, PK variables will be analyzed descriptively for each treatment and administration separately. Descriptive statistics include N, arithmetic mean, geometric mean, standard deviation, SEM, median, minimum, maximum and 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 the lower limit of quantification will be taken as zero for descriptive statistics of concentrations.

For PK parameters, individual plasma concentration-time profiles (linear and semi-logarithmic scales) will be plotted by treatment. Mean plasma concentrations per treatment and administration will be plotted with standard deviations using schedule time points. The weight-normalized PK parameters will be calculated if appropriate.

Formal statistical hypotheses have not been planned for PK parameters. Any statistical tests that might be performed will be considered exploratory. All analyses will be based on the PK analysis set.

The PK population includes all subjects who have received MSC2156119J and who had at least one blood sample drawn that provides drug concentration data for PK evaluation. Results of the population PK analysis approach may be reported separately. Further details of PK analyses will be provided in the SAP.

8.5.4 Safety Analyses

Any treatment emergent AEs will be summarized, i.e., those events that are 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 will be characterized by time on treatment, number of initiated and completed cycles, actual cumulative dose (mg) and compliance (%).

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using NCI-CTCAE (Version 4.0) toxicity grade. The incidence of treatment-emergent AEs, SAEs, related AEs and SAEs, AEs of Grade ≥ 3 by NCI-CTCAE, related AEs of Grade ≥ 3 by NCI-CTCAE, AEs leading to permanent treatment discontinuation will be summarized by MedDRA system organ classes and preferred terms. AE 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.

Descriptive summaries of actual (absolute) laboratory values and changes from baseline will be presented. Laboratory results will be classified by grade according to NCI-CTCAE, Version 4.0. The worst on-treatment grades after the first dose of trial treatment will be summarized. Shifts in NCI-CTCAE grades from baseline to worst on-treatment grade and from baseline to end of treatment (day of final dose of MSC2156119J) will be presented.

Changes from baseline to minimum and maximum on-treatment values will be summarized descriptively for vital signs (body temperature, heart rate, and blood pressure) and body weight. Similarly, change from baseline to worst on-treatment value will be summarized descriptively for the QTc interval.

Clinically significant, abnormal findings from 12-lead ECG during treatment phase 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 performance score will be summarized descriptively by visit.

8.5.4.1 Analyses to Support Dose-Escalation Decisions

Within each dose level and upon completion of Cycle 1 (i.e., the first 21 days) of treatment by the last subject, data and analyses for Cycle 1 will be presented to the SMC for a decision on dose escalation. These will include listings of AEs graded according to NCI-CTCAE and DLTs, listings of laboratory data, as well as subject demographics, disease history, and treatment compliance in Cycle 1. Additionally, data from all other cycles for subjects dosed at previous dose levels must

be provided for each SMC meeting. Any protocol violation that could affect the DLT determinations will be monitored and reported. The full data to be presented will be documented in detail in the SMC charter.

8.5.5 Analysis of Exploratory Endpoints

CCI [redacted]

8.6 Interim Analysis

The SMC will evaluate safety data for the purpose of determining dose escalation in Phase Ib. In Phase II, safety data will be evaluated after 12 and 24 subjects received study drug in Cycle 1. In addition, administrative interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

Each 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 are included into the trial.

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the United States Food and Drug Administration (FDA) for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all subinvestigators 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.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent 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, as above. This delegation of tasks should clearly be documented on the site delegation log.

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 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.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after 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 (tumor tissue, blood, deoxyribonucleic acid [DNA], and ribonucleic acid [RNA]) 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]

[redacted]

[redacted]

9.4 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 CRO. 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.

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 will follow the standard processes established for the investigators.

In cases where the investigator is not available, PPD provides the appropriate means to contact a PPD 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 PPD physician to assist with the medical emergency.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

9.6 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 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

9.7 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.

10 Trial Management

10.1 Case Report Form Handling

The investigator or designee will be responsible for entering trial data in the eCRF provided by the CRO/sponsor. It is the investigator's responsibility to ensure the accuracy of the data entered in the eCRFs, on the SAE Report Form, and on the AESI Report Form.

The data will be entered into a validated database. The CRO 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 procedures, and quality assurance procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the investigators at the completion of the trial.

10.2 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 EMR 200095-005),
- Date of subject's inclusion into the trial (i.e., date of giving 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 trial, and
- Date of and reason for early withdrawal of the subject from the trial or from MSC2156119J, 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, CT or MRI, ECG recordings, laboratory value listings, a subject diary for the compliance to MSC2156119J 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
- Information on AEs [e.g., seriousness, severity, outcome, duration of event (start and end date) and causality to MSC2156119J]
- Reason for providing concomitant medications/therapies (if applicable)
- Assessment of antitumor effect including tumor measurements

10.3 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. 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.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

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

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(s), 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.

10.5 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 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 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.

10.6.2 Publication

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 pre-submission 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.

11 References

1 Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008 May 21; 100(10):698-711.

2 Rimassa L, Porta C, Borbath I, Daniele B, Salvagni S, Van Laethem JL, et al. Tivantinib (ARQ 197) versus placebo in patients (Pts) with hepatocellular carcinoma (HCC) who failed one systemic therapy: Results of a randomized controlled phase II trial (RCT). J Clin Oncol. 30, 2012 (suppl; abstr 4006).

3 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45(2):228-47.

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

5 A'Hern RP. Sample size tables for exact single-stage phase II designs. Statist. Med. 2001; 20:859-66.

12 Appendices

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

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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 B: 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 patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients 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 C: Scoring System for Met Immunohistochemistry

Diagnostic	Clinical Score	Scoring Criteria
Positive	3+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with strong intensity (best seen using the 4-5x objective lens)
	2+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with moderate intensity (best seen using the 10x and 20x objective lens)
Negative	1+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with weak intensity but < 50% tumor cells with moderate or high intensity (best seen using the 40x objective lens)
	0	Samples with no staining, or with < 50% tumor cells with membrane and/or cytoplasmic staining (could be combination of any staining intensities)

Appendix D: 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 the table below.

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 E: 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	0	1	2	3	4
CNS7	I have pain in my	0	1	2	3	4
HI7	I feel	0	1	2	3	4
Hep2	I am bothered by jaundice or yellow color to my	0	1	2	3	4
Hep8	I have discomfort or pain in my stomach area	0	1	2	3	4

Appendix F: 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 past 7 days.**

	PHYSICAL WELL-BEING	**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 <u>past 7 days</u>.

	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	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>.

	<u>ADDITIONAL CONCERNS</u>	**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	0	1	2	3	4
C3	I have control of my	0	1	2	3	4
C4	I can digest my food	0	1	2	3	4
C5	I have diarrhea	0	1	2	3	4
C6	I have a good	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my	0	1	2	3	4

Cx6	I am bothered by	0	1	2	3	4
H17	I feel	0	1	2	3	4
An7	I am able to do my usual	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my	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	0	1	2	3	4
Hep 5	I have had a change in the way food	0	1	2	3	4
Hep 6	I have had	0	1	2	3	4
HN 2	My mouth is	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

Appendix G: Phase Ib Schedule of Dosing and Assessments

	Screening	Cycle 1[a] Day				Cycle 2 Day[b]			Cycle ≥ 3[c] Day	EoT[d]	Post-treatment F/U Visit[e]	Survival F/U[f]
DAY	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**			
MSC2156119J dosing		QD										
Written informed consent	X											
Drug dispensation		X				X			X			
Demography, height	X											
Medical history	X											
Smoking status and alcohol use	X											
Tumor biopsy	X[g]	X[h]			X[i]					X[j]		
Physical examination/weight[bb]	X	X[k]	X	X	X	X	X	X	X	X	X	
ECOG status[bb]	X	X[k]				X			X	X	X	
Vital signs[l]	X	X[k]	X	X		X	X		X	X	X	
ECG[m, bb]	X	X[n]			X[n]	X[o]			X[o]	X	X	
Hematology and coagulation[p, bb]	X	X[k]	X	X	X	X	X	X	X	X	X	
Chemistry[q, bb]	X	X[k]	X	X	X	X	X	X	X	X	X	
Urinalysis[r, bb]	X	X[k]				X			X	X	X	
HBV Panel and anti-HCV antibodies[s]	X											
Viral Load of HBV/HCV[t, bb]	X	X[k]										
Pregnancy test (if applicable)[u, bb]	X	X				X			X	X	X	
Tumor assessment (RECIST Version 1.1 and mRECIST)[v, bb]	X								X[w]	X[x]		
Tumor assessment (^{18}F-FDG PET CT scan)[bb]		X[o]							X[y]			
Serum AFP[bb]	X	X[k]				X			X	X		
PK blood samples[z]		X			X							
CCI [redacted] /Pd		X[o]			X[o]			X[o]		X		

	Screening	Cycle 1[a] Day				Cycle 2 Day[b]			Cycle ≥ 3[c] Day	EoT[d]	Post-treatment F/U Visit[e]	Survival F/U[f]
DAY	-28 to 0	1	2	8	15	1	8	15	1			
CCI												
Patient 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	
Record date and reason for discontinuation from trial procedures and whether subject will continue for survival follow-up											X	
Record reason for withdrawal from survival follow-up												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=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EoT=end of treatment; ^{18}F-FDG-PET=^{18}F fluoro-D-glucose positron emission tomography; 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; HCV=hepatitis C virus; IMP=investigational medicinal product; INR=international normalized ratio; mRECIST=modified Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; Pd=pharmacodynamic; CCI ; PK=pharmacokinetic; PT=prothrombin time; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors.

a: The visit on Cycle 1 Day 8 may be performed within ± 1 day, and the visit on Cycle 1 Day 15 may be performed within ± 2 days, to accommodate unforeseen delays, holidays, or vacations.

b: All visits and assessments from Cycle 2 onwards may be performed ± 5 days to accommodate unforeseen delays, holidays, or vacations.

c: From Cycle 9 onward, the frequency of visits will be changed to every 6 weeks and every 12 weeks after Cycle 13. Visits from Cycle 3 onward may occur within ± 5 days of Day 1 of the applicable cycle.

d: 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 treatment. This visit should be performed on the last day of treatment but may be performed up to 7 days after the last day of treatment and prior to the start of subsequent anticancer therapy.

e: Post-treatment Follow-up visit, performed 30 ± 3 days after the last treatment for subjects who discontinue trial treatment permanently, including subjects who have completed an End of Treatment Visit. If another anticancer therapy will be started before the end of this period (30 days), this visit should be conducted prior to start of this therapy. Subjects who discontinue trial treatment for reasons other than disease progression, withdrawal of consent, loss to follow-up, or death will continue to have tumor assessments according to the same schedule as subjects who remain on the trial treatment until disease progression, withdrawal of consent, starting a new anticancer therapy, or death. A Trial Procedure Termination eCRF will be completed for all subjects when no further trial evaluations are expected (with the exception of potential survival follow-up).

f: Survival follow-up, to be performed every 3 months ± 2 weeks. The Survival F/U Termination eCRF will be completed after survival follow-up has been discontinued.

g: Provision of a pretreatment tumor biopsy taken within 28 days before the day of first dosing is mandatory. Either a formalin-fixed (formalin fixation is mandatory) paraffin-embedded block with tumor tissue (preferred) or at least 15 unstained slides must be sent to the central laboratory prior to enrollment. An associated pathology report must also be sent with the sample. CCI CCI .

h: Optional (frozen), for subjects for whom a second biopsy for CCI was not obtained at screening.

i: On-treatment biopsy (optional; frozen); for subjects for whom an optional pretreatment frozen biopsy for CCI was obtained; can be taken any day between Cycle 1 Day 15 and Cycle 3 Day 1.

j: Optional tumor biopsy for subjects with disease progression, to be taken on the last day of treatment or as soon as possible until up to 7 days after the last day of treatment and prior to start of subsequent anticancer treatment. Samples must be formalin fixed.

k: Only if last assessments were performed > 7 days.

l: Heart rate, diastolic and systolic blood pressure after 5 minutes in a supine position. On days when ECGs are taken, vital signs should be taken immediately prior to each ECG recording.

m: Subjects will undergo 12-lead ECGs after the subject has rested immediately after measurement of vital signs. ECGs will be taken in triplicate within 2 minutes at each assessment time point. Vital signs (heart rate, systolic and diastolic blood pressure, in a supine position) should be taken immediately prior to each ECG recording after supine position of 5 minutes.

n: ECGs are recorded after at least 5 minutes rest in supine position at predose and at 4, 10 and 24 hours postdose in Cycle 1. ECG recordings should be performed directly before PK sampling time-points on days when both assessments are performed (the 24-hour postdose ECG is to be performed predose on the following day).

o: Predose only. Tumor assessment may be performed up to 5 days prior to Day 1 of the respective cycle but must be performed before the start of the cycle.

p: Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet, and coagulation (PT, aPTT, and INR).

q: BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, creatinine clearance, sodium, potassium, calcium, magnesium and glucose.

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

s: HBV panel and anti-HCV antibodies: HBsAg, HBeAg, anti-HBc, and anti-HCV.

t: HBV viral load is only for subjects with hepatitis B at screening; HCV viral load is only for subjects with hepatitis C at screening.

u: Only for women of childbearing potential. A serum pregnancy test will be completed prior to dose administration at screening and at the Post-treatment Follow-up Visit. Urine pregnancy tests will be completed prior to dose administration on Day 1 of each cycle, and if clinically indicated at any other visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

v: Complete tumor assessment of all lesions by radiographic or other modality (using RECIST Version 1.1 and secondarily using mRECIST for HCC). 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 two cycles (i.e., before start of next odd-numbered cycle) until Cycle 13 and every 4 cycles thereafter.

w: To be performed on Day 1 of Cycles 3, 5, 7, 9, 11, 13 and every 4 cycles thereafter until disease progression or study drug discontinuation. Tumor assessment may be performed up to 5 days prior to Day 1 of the respective cycle, but must be performed before the start of the cycle.

x: Only if last tumor assessment was performed ≥ 6 weeks ago

y: Cycle 3 Day 1 only. Tumor assessment may be performed up to 5 days prior to Day 1 of the respective cycle but must be performed before the start of the cycle.

z: Samples will be taken predose, and at 0.25 hours ± 5 min, 0.5 hours ± 5 min, 1 hour ± 5 min, 2 hours ± 15 min, 4 hours ± 15 min, 8 hours ± 30 min, 10 hours ± 30 min, and 24 hours ± 30 min postdose (the 24-hour postdose sample is to be drawn predose on the following day).

CCI

bb: Assessment can be repeated at the investigator's discretion at unscheduled visits to assess the safety and tolerability of the IMP.

Appendix H: Phase II Schedule of Dosing and Assessments

	Screening	Cycle 1[a] Day				Cycle 2 Day[b]			Cycle ≥ 3[c] Day	EoT[d]	Post-treatment F/U Visit[e]	Survival F/U[f]
DAY	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**			
MSC2156119J dosing		QD										
Written informed consent	X											
Drug dispensation		X				X			X			
Demography, height	X											
Medical history	X											
Smoking status and alcohol use	X											
Tumor biopsy	X[g]									X[h]		
Physical examination/weight[z]	X	X[i]	X	X	X	X	X	X	X	X	X	
ECOG status[z]	X	X[i]				X			X	X	X	
Vital signs[j]	X	X[i]	X	X		X	X		X	X	X	
ECG[k, z]	X	X[l]			X[l]	X[m]			X[m]	X	X	
Hematology and coagulation[n, z]	X	X[i]	X	X	X	X	X	X	X	X	X	
Chemistry[o, z]	X	X[i]	X	X	X	X	X	X	X	X	X	
Urinalysis[p, z]	X	X[i]				X			X	X	X	
HBV Panel and anti-HCV antibodies[q]	X											
Viral Load of HBV/HCV[r, z]	X	X[i]										
Pregnancy test (if applicable)[s, z]	X	X				X			X	X	X	
Tumor assessment (RECIST Version 1.1 and mRECIST)[t, z]	X								X[u]	X[v]		
Tumor assessment (^{18}F-FDG PET CT scan)[z]		X[m]							X[w]			
Serum AFP[z]	X	X[i]				X			X	X		

CCI [redacted]

	Screening	Cycle 1[a] Day				Cycle 2 Day[b]			Cycle ≥ 3[c] Day	EoT[d]	Post-treatment F/U Visit[e]	Survival F/U[f]
DAY	**-28 to 0**	**1**	**2**	**8**	**15**	**1**	**8**	**15**	**1**			
CCI /Pd		X[m]			X[m]			X[m]		X		
CCI												
Patient survival and anticancer therapies												X
FHSI-8 and FACT-HP	X	X				X	X	X	X	X	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	
Record date and reason for discontinuation from trial procedures and whether subject will continue for survival follow-up											X	
Record reason for withdrawal from follow-up												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=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; EoT=end of treatment; ^{18}F-FDG-PET=^{18}F fluoro-D-glucose positron emission tomography; FACT-HP=Functional Assessment of Cancer Therapy-Hepatobiliary; FHSI-8=Functional Assessment of Cancer Therapy 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; HCV=hepatitis C virus; IMP=investigational medicinal product; INR=international normalized ratio; mRECIST=modified Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; Pd=pharmacodynamic; CCI ; CCI ; PT=prothrombin time; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors.

a: The visit on Cycle 1 Day 8 may be performed within ± 1 day, and the visit on Cycle 1 Day 15 may be performed within ± 2 days, to accommodate unforeseen delays, holidays, or vacations.

b: All visits and assessments from Cycle 2 onwards may be performed ± 5 days to accommodate unforeseen delays, holidays, or vacations.

c: From Cycle 9 onward, the frequency of visits will be changed to every 6 weeks and every 12 weeks after Cycle 13. Visits from Cycle 3 onward may occur within ± 5 days of Day 1 of the applicable cycle.

d: 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 treatment. This visit should be performed on the last day of treatment but may be performed up to 7 days after the last day of treatment and prior to the start of subsequent anticancer therapy.

e: Post-treatment Follow-up visit, performed 30 ± 3 days after the last treatment for subjects who discontinue trial treatment permanently, including subjects who have completed an End of Treatment Visit. If another anticancer therapy will be started before the end of this period (30 days), this visit should be conducted prior to start of this therapy. Subjects who discontinue trial treatment for reasons other than disease progression, withdrawal of consent, loss to follow-up, or death will continue to have tumor assessments according to the same schedule as subjects who remain on the trial treatment until disease progression, withdrawal of consent, starting a new anticancer therapy, or death. A Trial Procedure Termination eCRF will be completed for all subjects when no further trial evaluations are expected (with the exception of potential survival follow-up).

f: Survival follow-up, to be performed every 3 months ± 2 weeks. The Survival F/U Termination eCRF will be completed after survival follow-up has been discontinued.

g: Provision of a pretreatment tumor biopsy taken within 28 days before the day of first dosing is mandatory. Either a formalin-fixed (formalin fixation is mandatory) paraffin-embedded block with tumor tissue (preferred) or at least 15 unstained slides must be sent to the central laboratory prior to enrollment. An associated pathology report must also be sent with the sample. The pretreatment biopsy will be analyzed for MET+ status before any other screening procedures are performed; only subjects with MET+ tumors will undergo the remaining screening procedures.

h: Optional tumor biopsy, to be taken on the last day of treatment or as soon as possible until up to 7 days after the last day of treatment, and prior to start of subsequent anticancer treatment. Samples must be formalin fixed.

i: Only if last assessments were performed > 7 days.

j: Heart rate, diastolic and systolic blood pressure after 5 minutes in a supine position. On days when ECGs are taken, vital signs should be taken immediately prior to each ECG recording.

k: Subjects will undergo 12-lead ECGs after the subject has rested immediately after measurement of vital signs. ECGs will be taken in triplicate within 2 minutes at each assessment time point. Vital signs (heart rate, systolic and diastolic blood pressure, in a supine position) should be taken immediately prior to each ECG recording after supine position of 5 minutes.

l: ECGs are recorded after at least 5 minutes rest in supine position at predose and at 4 hours postdose in Cycle 1. ECG recordings should be performed directly before PK sampling time-points on days when both assessments are performed.

m: Predose only. Tumor assessment may be performed up to 5 days prior to Day 1 of the respective cycle but must be performed before the start of the cycle.

n: Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet, and coagulation (PT, aPTT, and INR).

o: BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, creatinine clearance, sodium, potassium, calcium, magnesium and glucose.

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

q: HBV panel and anti-HCV antibodies: HBsAg, HBeAg, anti-HBc, and anti-HCV.

r: HBV viral load is only for subjects with hepatitis B at screening; HCV viral load is only for subjects with hepatitis C at screening.

s: Only for women of childbearing potential. A serum pregnancy test will be completed prior to dose administration at screening and at the Post-treatment Follow-up Visit. Urine pregnancy tests will be completed prior to dose administration on Day 1 of each cycle, and if clinically indicated at any other visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

t: Complete tumor assessment of all lesions by radiographic or other modality (using RECIST Version 1.1 and secondarily using mRECIST for HCC). 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 two cycles (i.e. before start of next odd-numbered cycle) until Cycle 13 and every 4 cycles thereafter.

u: To be performed on Day 1 of Cycles 3, 5, 7, 9, 11, 13 and every 4 cycles thereafter until disease progression or study drug discontinuation. Tumor assessment may be performed up to 5 days prior to Day 1 of the respective cycle, but must be performed before the start of the cycle.

v: Only if last tumor assessment was performed ≥ 6 weeks ago.

w: Cycle 3 Day 1 only. Tumor assessment may be performed up to 5 days prior to Day 1 of the respective cycle but must be performed before the start of the cycle.

CCI [redacted]

z: Assessment can be repeated at the investigator's discretion at unscheduled visits to assess the safety and tolerability of the IMP.

Appendix I: Blood Sampling Schedule for PK/Pd

Phase Ib

Cycle	Day	Time points H = hours after dosing	PK	Pd/CCI	CCI
			4 mL	20 mL (2 x 10 mL)	
Cycle 1	Day 1	Predose	X	X	
		H 0.25 (± 5 min)	X		
		H 0.5 (± 5 min)	X		
		H 1 (± 5 min)	X		
		H 2 (± 15 min)	X		
		H 4 (± 15 min)	X		
		H 8 (± 30 min)	X		
		H10 (± 30 min)	X		
		H24 (± 30 min)	X[a]		
Cycle 1	Day 15	Predose	X	X	
		H 0.25 (± 5 min)	X		
		H 0.5 (± 5 min)	X		
		H 1 (± 5 min)	X		
		H 2 (± 15 min)	X		
		H 4 (± 15 min)	X		
		H 8 (± 30 min)	X		
		H10 (± 30 min)	X		
		H24 (± 30 min)	X[a]		
Cycle 2	Day 15	Predose		X	
	EoT			X	

Abbreviations: EoT, end of treatment; H, hour; Pd, pharmacodynamic; CCI; PK, pharmacokinetic.
[a] The 24-hour postdose sample will be taken predose on the following day
All predosing samples should be taken within 60 minutes before each treatment administration

Phase II

Cycle	Day	Time points H = hours after dosing	CCI	Pd CCI 20 mL (2 x 10 mL)	CCI
Cycle 1	Day 1	Predose		X	
		H 4 (± 15 min)			
Cycle 1	Day 15	Predose		X	
Cycle 2	Day 1	Predose			
		H 4 (± 15 min)			
Cycle 2	Day 15	Predose		X	
	EoT			X	

Abbreviation: EoT, end of treatment; H, hour; Pd, pharmacodynamic; CCI ; CCI .
All predosing samples should be taken within 60 minutes before each treatment administration

Appendix J: Response Evaluation Criteria in Solid Tumors (RECIST) Version 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 one 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 organs, 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, sagittal, 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 ≥ 10 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 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.

Partial response: 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 partial response 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. Case report forms (CRFs) 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 partial response, 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 partial response 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 partial response 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 applies 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 overall response (BOR) 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 BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's BOR 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 partial response or CR is needed to deem either one the 'BOR'.

The BOR is determined once all the data for the subject is known. Best response determination in trials where confirmation of complete or partial response 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, partial response at second assessment, and PD on last assessment has a BOR of partial response). 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	Partial response
CR	Not Evaluated	No	Partial response
Partial response	Non-PD or not all evaluated	No	Partial response
SD	Non-PD or not all evaluated Non-PD	No	SD
Not all evaluated		No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* CR = complete 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 partial response-NE-partial response 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 partial response 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 overall response is measured from the time measurement criteria are first met for CR/partial response (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 K: Modified Response Evaluation Criteria in Solid Tumors (mRECIST) for Hepatocellular Carcinoma (HCC)

The text below was obtained from the following reference: Lencioni, R and Llovet, JM. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Semin Liver Dis 2010;30:52-60.

SUMMARY OF THE mRECIST ASSESSMENT OF RESPONSE: STANDARDIZING RESPONSE ASSESSMENT

1. IMAGE ACQUISITION

The administration of intravenous contrast is recommended for all computed tomography (CT) or magnetic resonance imaging (MRI) studies if not medically contraindicated. In contrast-enhanced studies, it is mandatory to obtain a dual-phase imaging of the liver. Every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run.

2. IMAGE INTERPRETATION

To properly use the proposed mRECIST for HCC to assess response rates and time to progression in HCC clinical trials and to ensure comparability across studies, uniform image acquisition parameters, rigorous quality control, and independent blinded multireader assessments are mandatory.

3. ASSESSMENT OF TUMOR LESION AT BASELINE

To be selected as a target lesion using mRECIST, a HCC lesion should meet all the following criteria:

- The lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI. It is important to point out that only well-delineated, arterially enhancing lesions can be selected as target lesions for mRECIST.

DEFINING TREATMENT RESPONSE AND TUMOR PROGRESSION

1. TARGET LESIONS RESPONSE

The mRECIST for HCC has introduced the following amendments to RECIST in the determination of tumor response for target lesions, which are summarized in Table 3.

Table 3 Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for Hepatocellular Carcimona Following the

American Association for the Study of Liver Disease-Journal of the National Cancer Institute Guideline

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

Abbreviations: HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors

2. NONTARGET LESION RESPONSE

According to mRECIST for HCC, tumor necrosis should be taken into account when assessing the response of nontarget lesions. The disappearance of intratumoral arterial enhancement in nontarget lesions should be considered equivalent to the disappearance of nontarget lesions, and therefore, should declare complete response of nontarget lesions. The persistence of intratumoral arterial enhancement in one or more nontarget lesions should be considered equivalent to persistence of one or more nontarget lesions, and therefore, should declare incomplete response / stable disease. The appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions should declare progressive disease.

Special recommendations for the assessment of tumor response in nontarget lesions in patients with HCC and cirrhosis can be made regarding the following points:

- Portal vein thrombosis. Malignant portal vein thrombosis should be considered a nonmeasurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment.

- Porta hepatis lymph node. Lymph nodes detected at the portal hepatis can be considered as malignant if the lymph node short axis is at least 20 mm.
- Pleural effusion and ascites. The mRECIST for HCC emphasizes that cytopathologic confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease.

3. NEW LESIONS

In the assessment of tumor progression, these concepts have been adopted by the mRECIST assessment proposal, considering some specificities for the frame of progression mode:

- A newly detected hepatic nodule will be classified as HCC—and therefore will be declared as evidence of progression—when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with washout in the portal venous or late venous phase.
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans.
- An individual radiologic event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

OVERALL RESPONSE ASSESSMENT

Any newly detected focal liver lesion that does not meet the criteria reported above should be considered equivocal and not conclusive for disease progression.

Appendix L: Examples of Drugs that Prolong QT Interval and Have a Risk of Torsades de Pointe

The following lists provide examples of drugs that prolong QT Interval and have a risk of Torsades de Pointe (http://crediblemeds.org/). Please note the following: This is not an exhaustive list. If you have questions on a drug product not included in this list, please consult the prescribing information for that product.

Amiodarone	Sparfloxacin
Anagrelide	Haloperidol
Arsenic trioxide	Halofantrine
Astemizole	Ibutilide
Azithromycin	Levomethadyl
Bepridil	Mesoridazine
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Cisapride	Ondansetron
Citalopram	Pentamidine
Clarithromycin	Pimozide
Cocaine	Probucol
Disopyramide	Procainamide
Dofetilide	Quinidine
Domperidone	Sevoflurane
Dronedarone	Sotalol
Droperidol	Sulpiride
Erythromycin	Terfenadine
Escitalopram	Thioridazine
Flecainide	Vandetanib

Appendix M: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Multicenter, Single Arm, Phase Ib/II Study to Evaluate Efficacy, Safety, and PK of MSC2156119J as Monotherapy in Subjects with MET+ Advanced Hepatocellular Carcinoma with Child Pugh Class A Liver Function Who Have Failed Sorafenib Treatment
IND Number:	CCI
EudraCT Number:	2013-002053-30
Clinical Trial Protocol Date / Version:	13 June 2016/Version 6.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

_____ _____

Signature Date of Signature

Name, academic degree	PPD
Function	PPD
	PPD
Institution	EMD Serono
Address	EMD Serono Research & Development Institute, Inc., 45A Middlesex Turnpike, Billerica, MA 01821, USA
Telephone number	PPD
E-mail address	PPD

Signature Page –Coordinating Investigator

Trial Title	A Multicenter, Single Arm, Phase Ib/II Study to Evaluate Efficacy, Safety, and PK of MSC2156119J as Monotherapy in Subjects with MET+ Advanced Hepatocellular Carcinoma with Child Pugh Class A Liver Function Who Have Failed Sorafenib Treatment
IND Number	CCI
EudraCT Number	2013-002053-30
Clinical Trial Protocol Date / Version	13 June 2016/Version 6.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree	PPD
Function	PPD
Institution	PPD
	PPD
Address	PPD
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

Signature Page – Principal Investigator

Trial Title	A Multicenter, Single Arm, Phase Ib/II Study to Evaluate Efficacy, Safety, and PK of MSC2156119J as Monotherapy in Subjects with MET+ Advanced Hepatocellular Carcinoma with Child Pugh Class A Liver Function Who Have Failed Sorafenib Treatment
IND Number	CCI [redacted]
EudraCT Number	2013-002053-30
Clinical Trial Protocol Version/Date	13 June 2016/Version 6.0
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, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information 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 to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic qualifications

Position (job title)

Address of Institution

Telephone number

Fax number

E-mail address

Sponsor Responsible Persons not Named on the Cover Page

Name	PPD
Function	PPD
Institution	Merck KGaA
Address	Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number	PPD
Fax number	PPD
E-mail address	PPD

Name	PPD
Function	Project Biostatistician, PPD
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Appendix N: Protocol Amendments and List of Changes

Previous Protocol Amendments

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
1	N	20 January 2014	Global	Y
2	N	13 February 2015	Global	Y
3	N	28 May 2015	Local (USA)	Y
4	Y	20 July 2015	Global	Y

Amendment #1 20 January 2014, Global

Rationale

The purpose of this protocol amendment is:

- To update the Medical Responsible.
- To add and revise inclusion and exclusion criteria.
- To clarify permitted and non-permitted medications.
- To include minor corrections and clarifications to the clinical trial protocol.

The main changes to be made to the clinical trial protocol and the rationale for the changes are described below.

Rationale for the Changes in Inclusion/Exclusion Criteria

In the inclusion criteria, MET+ status in Phase Ib and Phase II was clarified.

An exclusion criterion was modified to exclude patients with existing QTc prolongation or with known risk factors for QTc prolongation. In addition, withdrawal criteria regarding QTc findings were added to the protocol.

The allowed highly effective methods of contraception in the exclusion criteria were revised to correspond to the Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CHMP/ICH/286/95, modification). In the schedule of assessments, a serum pregnancy test for women of child-bearing age was added to the Follow-up Visit, and a urine pregnancy test was included on Day 1 of each cycle.

Rationale for the Changes in Permitted Medicines and Non-permitted Medicines

Due to the potential interference of MSC2156119J with P-gp, the listing of examples of other substrates of P-gp that have a narrow therapeutic window was expanded to include new oral anticoagulants and cardiovascular drugs. Concomitant use of these drugs is still permitted, but they should be used with caution. In addition, enrollment was not allowed for subjects who receive treatment with dabigatran and/or aliskiren as specified in Section 6.5.2 of the protocol "non-permitted medicines." Moreover, an appendix to the protocol was added including non-permitted drugs that are known to prolong QTc and in addition are known to cause respective ventricular tachycardia. In addition, to provide appropriate close safety monitoring additional instructions were provided to investigators to consult with specialists as needed.

Major Scientific Changes

There are no major scientific changes in this amendment.

Administrative and Editorial Changes

The editorial changes in this amendment are listed above.

Amendment #2 13 February 2015, Global

Rationale

The purpose of this amendment is to add sites in the United States, to make administrative and editorial changes, and to make tumor biopsies optional with the exception of the pretreatment biopsies in Phase Ib and Phase II. The rationale for other administrative and editorial changes are listed below.

Major Scientific Changes

There are no major scientific changes in this amendment.

Administrative and Editorial Changes

The following administrative and editorial changes were made:

- The number of sites was increased, and the text was modified to include sites in the United States. EMD Serono Research & Development Institute, Inc. was added as the sponsor in the United States.
- The text for tumor biopsies was revised so that only the pretreatment biopsies in Phase Ib and Phase II will be mandatory. All other biopsies are optional.
- The planned trial period was updated.
- The important risks in Section 3.5 (Risk-Benefit Evaluation) were changed from asymptomatic elevation of pancreatic enzymes to asymptomatic elevation of lipases and/or amylases.
- Inclusion criteria in the synopsis were numbered for consistency with the body of the protocol. Exclusion criteria were also numbered in both the synopsis and body of the protocol.
- Inclusion criterion #1 was modified to remove "cytologicaly confirmed HCC."
- The nonclinical and clinical background of the IMP was replaced with a reference to the IB.
- Additional text on potential drug-drug interactions was added in Section 3.5 based on nonclinical data and subsequent assessment for clinical relevance that have become available since the previous version of the protocol.
- The list of non-permitted medications in Section 6.5.2 was modified to include colchicine and other drugs, for which the package insert/summary of product characteristics includes a contraindication for P-gp, BCRP, and/or OCT1 inhibiting drugs.
- The list of permitted medications in Section 6.5.1 was modified to state that concomitant medications that have a narrow therapeutic window and are known to be transported by BCRP, or OCT1 are permitted but should be used with caution.
- The windows for tumor assessment by ^{18}F-FDG PET CT scan and for PK assessments were added to the Schedules of Dosing and Assessments and the Blood Sampling Schedule for PK/Pd.

- The frequency of tumor assessments by RECIST and mRECIST in the Schedules of Dosing and Assessments was clarified.
- The exclusion criteria related to the laboratory index at baseline was clarified to indicate that the subject must not have either serum creatinine ≥ 1.5 x ULN or calculated creatinine clearance < 60 ml/min.
- The calculation of Day 1 for cycles after Cycle 1 was described.
- The coordinating investigator's and protocol lead's contact information were updated.
- The collection of smoking status and alcohol use was distinguished from medical history because they are collected on separate eCRF pages.
- It was clarified that concomitant procedures are collected in addition to concomitant medications.
- For consistency with Appendix I, it was clarified that blood samples collected for CCI [redacted] are also collected for Pd.
- The wording for ECG assessments was clarified, and the parameters were listed.
- The schedule of assessments was clarified to indicate that procedures can be repeated at unscheduled visits at the investigator's discretion to assess the safety and tolerability of the IMP.
- Descriptions were added of the eCRFs completed when no further trial evaluations are expected (with the exception of potential survival follow-up; Trial Procedure Termination eCRF) and after survival follow-up is discontinued (Survival Follow-up Termination eCRF). Figure 4 was added to show when these eCRFs would be completed and what assessments would be performed after the Post-treatment Follow-up Visit.
- It was stated that 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."
- Financial disclosure rules for the investigator were added to Section 9.1 because the trial is considered an FDA covered trial.
- The clinical trial manager was changed.
- Changes were made to align with the Sponsor's updated CTP template: synopsis headings were updated, the clinical trial registry was listed, language for safety assessments was updated in Section 7.4, signature pages were moved to an appendix, and all amendments were listed in the appendix.

Amendment #3 28 May 2015, Local (USA)

The changes made to the clinical trial protocol are as follows:

- Continuation of MSC2156119J in the event of persistent Grade 3 amylase/lipase elevations without clinical or radiological evidence of pancreatitis is allowed only if there is objective evidence of benefit, rather than the potential for benefit. If any subjects experience Grade 4 pancreatitis, they may not be rechallenged with MSC2156119J at any dose.

- A justification was added for permitting dose interruptions for up to 21 days for AEs ≥ Grade 3, provided the AE goes down to ≤ Grade 1 or baseline, and there is objective evidence of benefit (as determined by the last RECIST CT scan).

- For the second dose cohort (500 mg), the SMC will decide on actions to be taken if 2 or more subjects out of the first 3 experience a DLT during the first treatment cycle. It was clarified that the decision of the SMC will be made by consideration of the DLTs, other clinically relevant safety data, and emerging PK data.

- As MSC2156119J will be continuously administered, overall information regarding safety and PK data beyond Cycle 1 will also be taken into consideration to confirm the RP2D.

Rationale

The purpose of this protocol amendment is to incorporate changes requested by the FDA.

Major Scientific Changes

There are no major scientific changes in this amendment.

Administrative and Editorial Changes

The date and version number of the protocol were revised as appropriate.

Amendment #4 20 July 2015, Global

The changes to be made to the clinical trial protocol are as follow:

- Continuation of MSC2156119J in the event of persistent Grade 3 amylase/lipase elevations without clinical or radiological evidence of pancreatitis is allowed only if there is objective evidence of benefit, rather than the potential for benefit. If any subjects experience Grade 4 pancreatitis, they may not be rechallenged with MSC2156119J at any dose.

- For the second dose cohort (500 mg), the SMC will decide on actions to be taken if 2 or more subjects out of the first 3 experience a DLT during the first treatment cycle. It was clarified that the decision of the SMC will be made by consideration of the DLTs, other clinically relevant safety data, and emerging pharmacokinetic (PK) data.

- As MSC2156119J will be continuously administered, overall information regarding safety and PK data beyond Cycle 1 will also be taken into consideration to confirm the RP2D.

- CCI [redacted].

- To update the list of permitted and non-permitted medicines to improve guidance for investigators and inform them better about drugs whose PK may be relevantly influenced by drug transporters such as P-gp, BCRP or OCT1 or drugs that are known to strongly influence the PK of other drugs via P-gp.

- To include administrative changes, minor corrections and clarifications to the clinical trial protocol.

Rationale for for updates to permitted and non-permitted medication

In vitro data indicate that tepotinib potentially inhibits P-gp, BCRP and OCT1. In addition tepotinib was also identified as a substrate of P-gp. The protocol is amended to introduce cautionary statements regarding strong P-gp inhibitors. We recommend that investigators either exchange strong P-gp inhibitors or, should they decide to proceed with administration, implement close safety monitoring.

While close safety monitoring is a measure to assess a potential increase in bioavailability of tepotinib by concomitant use of a strong P-gp inhibitor, the decrease of the bioavailability of tepotinib by concomitant administration of a potent P-gp-inducing drug cannot be clinically monitored. Therefore, investigators are asked to exclude drugs known to strongly induce P-gp.

Additionally, the selection of these drugs took into consideration the exclusion criteria of the protocol, thus, precluding further administration of anti-cancer or anti-retroviral (anti-HIV) drugs. Finally, to ensure the concomitant use of tepotinib with medications having a narrow therapeutic window and known to being P-gp, BCRP or OCT-1 substrates is avoided, Section 6.5.2 was amended by introducing a broader range of examples of drugs whose PK is potentially influenced by concomitant tepotinib via these drug transporters in order to better guide investigators and

inform them about drugs that are to be used with caution or are not taken in combination with tepotinib.

CCI [redacted]

CCI [redacted]

Rationale (follow-up commitment to ANSM request; July 7th 2015)

The sponsor committed to the ANSM in the context of the review amendment No.2/Protocol V3.0 to re-define the new information regarding permitted and non-permitted medicines (ie sections 6.5.1 and 6.5.2) that were introduced in Amendment No.2 as major substantial change (see below). To that effect the sponsor has added the section below to re-define these changes as substantial.

Major Scientific Changes (follow-up commitment as per ANSM request July 7th 2015)

The list of non-permitted medications in Section 6.5.2 was modified to include colchicine and other drugs, for which the package insert/summary of product characteristics includes a contraindication for P gp, BCRP, and/or OCT1 inhibiting drugs.

The list of permitted medications in Section 6.5.1 was modified to state that concomitant medications that have a narrow therapeutic window and are known to be transported by BCRP, or OCT1 are permitted but should be used with caution.

Administrative and Editorial Changes

The date and version number of the protocol were revised as appropriate.

Amendment #5 13 June 2016, Global

The changes made to the clinical trial protocol are as follows:

- It was added that administrative interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.
- To include administrative changes to the clinical trial protocol.

Rationale

The purpose of this protocol amendment is to permit the conduct of interim analyses for internal planning only.

Major Scientific Changes

There are no major scientific changes in this amendment.

Administrative and Editorial Changes

The sponsor medical responsible was changed and the corresponding details on the title page and signature page were updated to reflect this. The sponsor project biostatistician was changed and the corresponding details on the sponsor responsible persons page were updated. The address and contact details of the Coordinating Investigator were changed and the corresponding details on the title page and signature page were updated. The date and version number of the protocol were revised as appropriate.