Appendix 16.1.9 Documentation of Statistical Methods

Appendix 16.1.9.1 Phase Ib SAP

- Version 1.0 dated 16 September 2016

Appendix 16.1.9.2 Phase II SAP

- Version 1.0 dated 15 March 2018

Statistical Analysis Plan – Phase Ib

Clinical Trial Protocol Identification No.	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
Trial Phase	Phase Ib/II
Investigational Medicinal Product(s)	tepotinib (MSC2156119J)
Clinical Trial Protocol Version	13 June 2016 / Version 6.0
Statistical Analysis Plan Author	PPD
Statistical Analysis Plan Date and Version	16 September 2016 / Version 1.0
Statistical Analysis Plan Reviewers	PPD, Senior Biostatistics Reviewer, PPD PPD, Biostatistician, Merck Biopharma PPD, Biostatistician, Merck Biopharma PPD, Medical Responsible, EMD Serono PPD, Clinical Pharmacologist, Merck Biopharma PPD, PPD, Merck Biopharma PPD, PPD, Merck Biopharma PPD, PPD, Merck Biopharma PPD, Pharmacometry, Merck Biopharma PPD, PPD, Merck Biopharma

[redacted]

1 Signature Page

Statistical Analysis Plan: EMR 200095-005

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

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2 Table of Contents

3 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
AFP	Alpha-Fetoprotein
ALBI	Albumin-Bilirubin
AUC	Area Under the Curve
AUC_{0-t}	Area Under the Concentration-time Curve from Time Zero to the Last Quantifiable Concentration
AUC_{τ}	Area Under the Concentration-time Curve Over the Dosing Interval
BOR	Best Overall Response
CAF	Cancer-Associated Fibroblast
C_{av}	Average Plasma Concentration
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CR	Complete Response
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
ICH	International Conference on Harmonization
IHC	Immunohistochemistry

IMP	Investigational Medicinal Product
ISH	In Situ Hybridization
ITT	Intent-to-Treat
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
$MR_{(AUC0-t)}$	Metabolite to Parent Ratio based on AUC_{0-t}
$MR_{(Cmax)}$	Metabolite to Parent Ratio based on C_{max}
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
ORR	Overall Response Rate
OS	Overall Survival
Pd	Pharmacodynamics
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
PT	Preferred Term
PTF	Peak Trough Fluctuation Ratio (in %)
Q1	Quartile 1
Q3	Quartile 3
$R_{acc(AUC)}$	Accumulation Factor for AUC_{τ}
$R_{acc(Cmax)}$	Accumulation Factor for C_{max}
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure

SD	Stable Disease
SEM	Standard Error of the Mean
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOLD	Sum of Longest Diameter
TEAE	Treatment Emergent Adverse Event
TNM	Tumor, Lymph Nodes, Metastasis
t_{lag}	Time Prior to the First Quantifiable Concentration
t_{max}	Time of Maximum Plasma Concentration
TTP	Time to Progression
CCI	[redacted]
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary
τ	Dosing Interval

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	16September2016	Danielle Lamy	N/A

5 Purpose of the Statistical Analysis Plan

The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for the phase Ib portion of clinical trial protocol (CTP) EMR 200095-005. Results of the final analysis described in this SAP will be included in the Clinical Trial Report (CTR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CTR but not identified in this prospective SAP will be clearly identified in the CTR.

The SAP is based on section 8 (Statistics) of the CTP dated 13 June 2016/version 6.0 and protocol amendments and is prepared in compliance with International Conference on Harmonization (ICH) E9.

6 Summary of Clinical Trial Features

Table A: Clinical Trial Features Summary

Trial Objectives	**Primary Objective** • Determine the recommended Phase II dose (RP2D) of tepotinib 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. **Secondary Objectives** • Characterize the single and multiple dose pharmacokinetics (PK) of tepotinib. • Assess antitumor activity and biochemical response of tepotinib. • Evaluate safety and tolerability of tepotinib. **Exploratory Objectives** • CCI [redacted]

	CCI [redacted]
Primary Endpoint	Incidence of dose limiting toxicities (DLTs) in Cycle 1
Secondary Endpoints	• PK parameters [area under the curve (AUC) parameters including AUC_{0-t}, AUC_{0-tau}, $AUC_{0-\infty}$, 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, progression free survival (PFS) time, overall survival (OS) time, and biological response as measured by alpha-fetoprotein (AFP)] • Safety parameters (drug exposure; incidence and type of treatment-emergent AEs (TEAEs); incidence and reasons for deaths, including deaths within 33 days after the last dose of tepotinib; vital signs; electrocardiogram (ECG) changes; hematology, chemistry, and urinalysis parameters; physical examination including change in body weight; and Eastern Cooperative Oncology Group (ECOG) performance status (PS).
Exploratory Endpoints	• CCI [redacted]
Methodology	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. Subjects will receive tepotinib 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	Up to 18 subjects in 2 dose cohorts
Safety Monitoring Committee Meetings	A safety monitoring committee (SMC) will be responsible for monitoring the safety of subjects and making decisions about dose escalation (or de-escalation) and including additional participants for dose confirmation. The SMC will meet: 1. During the dose escalation phase to determine whether the dose should be escalated or de-escalated after all subjects in the first cohort have completed Cycle 1 and all events have been fully evaluated 2. During the dose confirmation phase after the initial 3 dose confirmation subjects have completed Cycle 1 to decide whether to enroll 9 additional subjects at the same dose level or to de-escalate 3. After all subjects have completed Cycle 1 to determine whether to continue with the recommended phase II dose

7 Sample Size/Randomization

The determination of the sample size of up to 18 subjects followed the "3+3 rule," a well-established current methodology in the design of dose-finding trials in oncology.

Randomization is not applicable.

8 Overview of Planned Analyses

This SAP covers the analyses for efficacy and safety for the final analysis. All analyses will be performed using cleaned data. There are no interim analyses planned. Administrative interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

8.1 Sequence of Analyses

The final analysis will be performed after all subjects discontinue treatment and complete the safety follow-up visit. The final analysis will occur once all trial data is in-house, all data queries are resolved, and the database is fully locked.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

The following are changes to the planned analyses in the clinical trial protocol:

- Physical examination results at baseline will not be presented since these are not collected on the electronic case report form (eCRF).
- Relative dose intensity will be summarized rather than treatment compliance.
- CCI [redacted]

Otherwise, the statistical methods as described in the protocol will be adopted.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations include:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria;
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn;
- Subjects that receive the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication;
- Deviation from good clinical practice.

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

Important protocol deviations will be determined for all subjects by either site monitoring, medical review processes or programming based on the inclusion/exclusion criteria or other criteria presented in the protocol.

All important protocol deviations will be documented in CDISC datasets whether identified through site monitoring, medical review or programming. Important protocol deviations to be identified are specified in Appendix I and will be presented in a summary table and data listing.

10.2 Analysis Sets

Screening Analysis Set

The Screening Analysis Set includes all subjects who signed the Informed Consent Form (ICF). The Screening Analysis Set will be used for disposition and baseline characteristic summaries for selected biomarkers.

Intent-to-Treat/Safety (ITT/SAF) Analysis Set

The ITT/SAF Analysis Set includes all subjects who have been administered at least one dose of tepotinib. The ITT/SAF Analysis Set will be used for all safety and efficacy analyses aside from the primary endpoint analysis.

DLT Analysis Set

The DLT Analysis Set includes all subjects who completed Cycle 1 and who received at least 80% of planned cumulative doses of tepotinib in Cycle 1 and subjects who experienced a DLT during Cycle 1. The DLT Analysis Set will be used for the primary endpoint analysis.

Subjects who do not receive at least 80% of the planned dosage during Cycle 1 for reasons other than DLT are deemed as not fully evaluable for the DLT assessment and will be replaced, and will thus be excluded from the DLT Analysis Set.

PK Analysis Set

The PK Analysis Set includes all subjects who have received at least one dose of tepotinib and who had at least one post dose blood sample drawn that provides drug concentration data for PK evaluation and was not impacted by a protocol deviation or other event (eg, vomiting within the time frame of 2 * median t_{max}, etc.) affecting PK. If a subject undergoes a dose change after Cycle 1 Day 1, their data will no longer be included in the PK Analysis Set from the time of the change.

Analyses	Screening Analysis Set	ITT/SAF Analysis Set	DLT Analysis Set	PK Analysis Set
Disposition	✓			
Demographics		✓		
Baseline Assessments	✓ selected biomarkers	✓		
Past and Concomitant Therapies		✓		
Compliance and Exposure		✓		
Primary			✓	
Secondary		✓		
CCI				
Pd		✓		

Analyses	Screening Analysis Set	ITT/SAF Analysis Set	DLT Analysis Set	PK Analysis Set
PK				✓
Safety and Tolerability		✓		

11 General Specifications for Statistical Analyses

Non-compartmental computation of pharmacokinetic parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).

All analyses (production of tables, listings and figures as well as calculation of PK parameters, if appropriate) will be performed using SAS® Software version 9.2 or higher (Statistical Analysis System, SAS-Institute, Cary NC, USA).

Last date known to be alive:

The following dates will be used to determine the last date known to be alive prior to or at data cut-off:

- All patient assessment dates (laboratory blood draws, vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Last known alive date collected on the 'Subject Status/Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates

Unscheduled visits:

Data collected at unscheduled visits will not be included in by-visit summaries of data but may contribute to baseline value derivations and analyses in which post-baseline data is considered (e.g. best/worst on-treatment value).

End of Treatment visits:

End of Treatment visits will be included as a separate time point in by-visit summaries of data and may also contribute to analyses in which post-baseline data is considered (e.g. best/worst on-treatment value).

Significance level:

No statistical testing (i.e. p-values) will be performed. Confidence intervals will be two-sided with a confidence probability of 90%, unless otherwise specified.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics if not otherwise specified, i.e.

- number of subjects (N), number of subjects with non-missing values
- mean, standard deviation
- median, first quartile (Q1) - third quartile (Q3)
- minimum and maximum

Qualitative variables will be summarized by counts and percentages with percentages based on the number of subjects in the analysis set of interest, unless otherwise specified. Counts of missing observations will be included in the denominator and presented as a separate category in shift from baseline summaries. In general, percentages will be reported to 1 decimal place unless greater precision is deemed appropriate.

Table presentation:

Tables for time-to-event analyses, including time to progression, progression free survival, and overall survival will be presented with one overall column. Unless otherwise stated, all other tables will be presented by dose level and overall.

By-visit displays:

By visit summaries will include all planned visits until the last visit with at least 3 ongoing subjects.

Definition of baseline:

In general, the last measurement prior to first administration of trial treatment will serve as the baseline measurement. For ECG parameters, the average of up to three measurements at the last visit prior to the first administration of trial treatment will serve as the baseline measurement.

Definition of duration:

Duration will be calculated as the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first trial treatment administration + 1), if not otherwise specified.

The time since an event (e.g. time since first diagnosis) will be calculated as the reference date minus the date of the event.

Conversion factors:

The following conversion factors will be used to convert days into months or years:

- 1 month = 30.4375 days
- 1 year = 365.25 days.

Definition of treatment day:

Treatment day is defined relative to the start date of trial treatment. Treatment day 1 is the date of first administration of trial treatment, and the day before is defined as Treatment day -1 (no Treatment day 0 is defined).

Definition of on-treatment period:

The on-treatment period is defined as the time from the first trial treatment administration to the last trial treatment administration date + 33 days.

Definition of completion of a cycle:

A cycle is considered complete if the treatment end date minus the treatment start date plus one is greater than or equal to the following:

Cycle 1 (week 1 – 3)	21
Cycle 2 (week 4 – 6)	42
Cycle 3 (week 7 – 9)	63
Cycle 4 (week 10 – 12)	84
…	…
Cycle x (week (x-1)*3+1 – x*3)	x*21

Handling of missing data:

Unless otherwise specified in this SAP, all data will be evaluated as reported and no imputation of missing values will be done. In subject data listings imputed values will be presented (if applicable), and the imputed information will be flagged.

Missing statistics (i.e. when they cannot be calculated) will be presented as “nd” (i.e. not done). For example, if n=1, the measure of variability (standard deviation) cannot be computed and will be presented as “nd”.

Partial dates are allowed for some of the date fields as collected on the eCRF. Partial dates will not be imputed unless they pertain to previous/concomitant medications or adverse events as described in sections 14 and 17.1, respectively.

12 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

Analysis Set: Screening

Subjects will remain in the study until progressive disease, intolerable toxicity, death, or withdrawal of consent. Subjects are free to withdraw from the study at any time without giving their reason(s).

The following will be summarized for all screened subjects:

- Number of subjects screened
- Number of subjects who discontinued from the trial prior to treatment (overall and grouped by primary reason for discontinuation)
- Number and percentage of treated subjects. (i.e. those with at least one dose of trial treatment)
- Number and percentage of subjects who completed treatment (i.e. experienced death or disease progression)
- Number and percentage of subjects who discontinued treatment (overall and grouped by primary reason for discontinuation)
- Number and percentage of subjects who discontinued study procedures (overall and grouped by primary reason for discontinuation)
- Number and percentage of subjects who discontinued survival follow-up (overall and grouped by primary reason for discontinuation)

Percentages for the summaries above will be based on the ITT/SAF analysis set.

Number of subjects in the Screening analysis set along with number and percentage of subjects in the ITT/SAF, DLT, and PK analysis sets will be presented in a separate standalone summary.

The number of subjects from each region, country and clinical site will be summarized for the screening, ITT/SAF, DLT, and PK analysis sets.

12.2 Protocol Deviations

12.2.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations will be provided (separately for pre-/post inclusion deviations):

- Frequency table per reason of important protocol deviations by dose level and overall
- Listing of important protocol deviations

12.2.2 Reasons Leading to the Exclusion from an Analysis Set

This section does not apply to this trial as there is no per protocol analysis set defined for this study.

13 Demographics and Other Baseline Characteristics

Analysis Set: ITT/SAF

If not stated otherwise, summaries will be presented for the ITT/SAF Analysis Set. Baseline characteristics with respect to vital signs, physical examinations, electrocardiogram (ECG) results, and hematology/biochemistry will be part of Section 17 (Safety Evaluation).

13.1 Demographics

Demographic characteristics will be summarized using the following information.

- Demographic characteristics
  - Sex:
    - Male
    - Female
  - Race:
    - White
    - Black or African American
    - Asian
    - Other
  - Age (years): summary statistics
  - Age categories:
    - < 65
    - ≥ 65 - < 75
    - ≥ 75 - < 85
    - ≥ 85

- Country of site
  - Belgium
  - France
  - Germany
  - Italy

Specifications for computation:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day only: For the derivation only, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
  - In case of missing day and month: For the derivation only, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used

The integer part of the calculated age will be used for reporting purposes.

Site codes will be used for the determination of the subject's country of site.

13.2 Medical History

Medical history will be summarized as the numbers and percentages of subjects by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. PT and SOC will be determined using the latest version of MedDRA. Medical history data will be summarized by dose level and overall. A subject will be counted only once within a given SOC and within a given PT, even if he/she had the same medical history event at different times. The data will be displayed in terms of frequency tables ordered by primary SOC and PT in alphabetical order. Medical history data will come from the "Medical History Details" eCRF page.

13.3 Disease History

Information on disease history collected prior to dosing is found on the "Disease History" eCRF. The following will be summarized by dose level and overall:

- Site of primary tumor at study entry
- Time since initial diagnosis (years) defined as (the first trial treatment date – the date of initial diagnosis) / 365.25
- Time since first occurrence of metastatic or locally advanced disease (months) defined as (the first trial treatment date – the date of first occurrence of metastatic or locally advanced disease) / 30.4375
- Tumor, lymph nodes, metastasis (TNM) classification at initial diagnosis

- TNM classification at study entry
- Tumor Histology
    - Macroscopic Category (Massive/Nodular/Diffuse/Other)
    - Microscopic Category (Trabecular/Pseudoglandular/Compact/Scirrous/ Fibrolamellar/Clear Cell/Sclerosing/Sarcomatoid/Inflammatory HCC or Lympho-Epithelial-Like Carcinoma/Other)
    - Vascular Invasion (Yes/No/Not Available)
    - Grading (1/2/3/4/Not Available)

13.4 Other Baseline Characteristics

The following baseline characteristics will be reported for this study:

- ECOG PS: 0 or 1
- c-Met Status: Immunohistochemistry (IHC) 0, IHC 1+, IHC 2+, IHC 3+
- c-Met Status: In Situ Hybridization (ISH): ISH+, ISH-
- HGF: Cancer-Associated Fibroblast (CAF)
- HGF: Cytoplasmic
- Alcohol use status: Never used, Regular user, Occasional user, or Former user
- Nicotine use status: Never used, Regular user, Occasional user, or Former user
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m^2)
- Vascular invasion and/or extrahepatic spread: Presence or Absence
- AFP elevation at baseline: ≥ 200 IU/mL or < 200 IU/mL
- Prior local-regional therapy: Yes or No
- Albumin-Bilirubin (ALBI) Grade (1): 1, 2, or 3

Specifications for computation:

- ALBI Grade (1):
    - Calculate the linear predictor y: $y = (\log_{10}(\text{bilirubin}) * 0.66) + (\text{albumin} * -0.085)$ where bilirubin is in µmol/L and albumin is in g/L
    - Compare y to the following cut points:

- ALBI Grade 1: $y \leq -2.60$
- ALBI Grade 2: $-2.60 < y \leq -1.39$
- ALBI Grade 3: $y > -1.39$

- BMI (kg/m^2) = weight (kg)/[height (m)]^2

13.5 Prior Anti-Cancer Therapies

Information related to prior anti-cancer therapies were collected on the "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details", "Prior anti-Cancer Local-Regional Therapy Details", and "Prior Anti-Cancer Surgery Details" eCRF pages. Prior anti-cancer therapy related data will be listed.

14 Previous or Concomitant Medications/Procedures

Analysis Set: ITT/SAF

Summaries for previous and concomitant medications/procedures will be presented by dose level and overall.

Concomitant treatments are medications, other than trial medications, taken by subjects any time during the on-treatment period.

Previous medications are medications, other than trial medications and pre-medications for trial treatment, which are started before first administration of trial treatment.

Previous and concomitant medications will be summarized from the "Concomitant Medications Details" eCRF page.

In cases where date values do not allow unequivocal allocation of a medication to concomitant or previous medication, the medication will be considered as both a concomitant and previous medication.

Summaries of previous and concomitant medications will include the number and percentage of subjects by ATC classification level 2 and PT, as given from the latest version of the World Health Organization Drug Dictionary (WHO-DD). A subject will be counted only once within a given ATC class and within a given PT, even if he/she received the same medication at different times. If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. Summary tables will be sorted alphabetically by ATC class and PT. In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under the "Unavailable ATC classification" category.

All **concurrent procedures**, which were undertaken any time on trial, were collected on the eCRF page "Concomitant Procedure Details". The number and percentage of subjects with any

concurrent procedure, a concurrent procedure starting prior to the first dose of treatment, and a concurrent procedure starting after the start of treatment but within 33 days after the last dose of trial treatment will be presented.

15 Treatment Compliance and Exposure

Analysis Set: ITT/SAF

All dosing calculations and summaries will be based on the "Cohort Treatment MSC2156119J Administration Details" eCRF page.

Handling of missing data:

If the actual dose is missing, the planned dose level as entered in the eCRF will be used.

Cumulative Dose

The cumulative dose (mg) of tepotinib per subject is the sum of the actual dose levels that the subject received (i.e. total dose administered [mg]).

Duration

For the purposes of deriving dose intensity, the duration of therapy (in weeks) during the trial is defined as:

$$\text{Duration}=\left(\frac{\text{last dose date - first dose date + 1}}{7}\right)$$

The duration of therapy (in months) during the trial is defined as:

$$\text{Duration}=\left(\frac{\text{last dose date - first dose date + 1}}{30.4375}\right)$$

Dose Intensity

The dose intensity and the relative dose intensity will be calculated for each subject across all cycles assuming a 3-week cycle duration. Dose intensity (mg/cycle) is defined as

$$\text{Dose intensity}=\left(\frac{\text{Cumulative dose}}{(\text{duration of therapy (in weeks)})/3}\right)$$

Relative Dose Intensity

Relative dose intensity, a measure of compliance, is defined as the dose intensity divided by the planned dose per cycle.

Number of Cycles Completed
The number of cycles a subject completed will be calculated as follows:

$$\text{Number of cycles completed} = \text{floor}\left(\frac{(\text{last dose date} - \text{first dose date} + 1)}{21}\right)$$

Number of Cycles Initiated
The number of cycles a subject initiated will be calculated as follows:

$$\text{Number of cycles initiated} = \text{ceiling}\left(\frac{(\text{last dose date} - \text{first dose date} + 1)}{21}\right)$$

The following will be summarized:

- Total number of initiated vs. completed cycles on treatment
- Duration (months)
- Cumulative dose (mg)
- Dose intensity (mg/cycle)
- Relative dose intensity (%) during Cycle 1 and overall

Dose reductions

A dose reduction is defined as a change from the planned dose level to one of the 2 lower dose levels below the recommended phase II dose (RP2D) (See CTP Section 6.2.3). The number of subjects with at least one dose reduction will be summarized by frequency and percentage per planned dose level. The minimum dose of the trial treatment will be derived per subject and categorized according to categories of reduced to 300 mg and reduced to 200 mg.

Dosing Interruptions

A dose interruption is defined as having missed 1 or more planned daily doses. Dosing interruptions will be summarized by planned dose level for the number of subjects with an interruption lasting either 1-2 days, 3-7 days, 8-14 days, and greater than 14 days (The longest interruption and cumulative days of interruption are summarized for each subject.)

Investigational Medicinal Product (IMP) Allocation

A listing of batch numbers of IMP and the subjects receiving IMP from the specific batch will be presented.

16 Endpoint Evaluation

16.1 Primary Endpoint Analysis

Analysis Set: DLT

The primary endpoint of this study is the incidence of DLTs occurring during Cycle 1. DLTs are collected on the "Adverse Events Details" form on the eCRF and are recorded as the answer ("Yes", "No", or "Not Applicable") to "Is this adverse event a dose limiting toxicity?" A DLT is defined as a toxicity of interest judged to be related to tepotinib by the investigator and/or the sponsor using the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Per the NCI-CTCAE, 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.

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.

The DLT summary table will present the following for the DLT analysis set:

- the number and proportion of subjects who experienced a DLT during Cycle 1 with corresponding two-sided exact Clopper Pearson (2) 90% confidence intervals (CIs)
- DLTs during Cycle 1 by SOC and PT

There will be no imputation of missing data for the DLT variable. A listing of DLT adverse event data will include subject identifier, dose level, and all relevant variables from the Adverse Event Details eCRF page.

16.2 Secondary Endpoint Analyses

Analysis Set: ITT/SAF

Tumor assessment will be performed by the investigator primarily according to the RECIST version 1.1 and secondarily according to the modified RECIST (mRECIST) for HCC (see CTP appendices J and K). The baseline tumor assessment is scheduled to be performed during the screening period. Tumor response evaluations will then be assessed by computed tomography (CT) or magnetic resonance imaging (MRI), whichever was used at the baseline tumor assessment, at the end of every 2 cycles (i.e. before the start of Cycles 3, 5, 7, 9, 11, 13, and every 4 cycles thereafter until PD). Tumor assessments will be performed at the end of treatment visit for subjects whose last tumor assessment was performed ≥ 6 weeks prior.

16.2.1 Efficacy Endpoints

16.2.1.1 Time to Progression (TTP)

TTP will be measured as the time (in months) from the date of first trial treatment administration to the date of radiological confirmation of PD performed according to RECIST Version 1.1. TTP will be censored at the date of last adequate tumor assessment for subjects that do not experience progression or subjects that experience progression after 2 or more subsequent missing tumor assessments. Subjects that are missing a baseline tumor assessment and/or all post-baseline tumor assessments will be censored at the first date of study drug administration.

The date of event/censoring is defined as follows:

Status		Censoring	Date of event / censoring
Progressed	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD or first study drug administration	Event	Date of PD
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first study drug administration, whatever is later

Didn't progress	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first study drug administration, whatever is later

TTP (months) = (date of PD/censoring – date of first trial treatment administration + 1)/30.4375

The number and percentage of individuals with progression will be presented per dose level. Kaplan-Meier (i.e. product-limit) estimates of the minimum, maximum, and median TTP will be presented overall along with 90% CIs for the median calculated according to Brookmeyer and Crowley (3). In addition, the pattern of censoring will be summarized overall (e.g., censoring due to death, study withdrawal, lost to follow-up, censoring due to data cut-off).

The number of subjects at risk for progression vs. those who have experienced progression along with Kaplan-Meier estimates of survival probability at 3, 6, and 12 months will be estimated with corresponding 90% CIs derived using the log-log transformation according to Kalbfleisch and Prentice (4) (i.e. conftype = loglog default option in SAS LIFETEST procedure).

A Kaplan-Meier plot of TTP and a listing of relevant TTP data will be provided.

16.2.1.2 Progression Free Survival (PFS)

PFS time is defined as the time from the date of first treatment administration to

- the date of the first documentation of objective PD or
- death due to any cause,

whichever occurs first.

PFS time will be censored at the date of last adequate tumor assessment for subjects who

- do not have an event (PD or death within 12 weeks of last tumor assessment) or
- have an event after two or more subsequent missing tumor assessments.

PFS time will be censored on the date of first study treatment for subjects who do not have

- a baseline tumor assessment or
- any post-baseline tumor assessments,

unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

The date of event/censoring is defined as follows:

Status		Censoring	Date of event / censoring
Progressed or died	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD or first study drug administration	Event	Minimum(Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first study drug administration, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD or date of first study drug administration, whatever is later

PFS (months) = (date of event/censoring – date of first trial treatment administration + 1)/30.4375

The analysis of PFS will be performed using Kaplan-Meier methods with the same approach for TTP described above.

The primary analysis of PFS will be based on RECIST Version 1.1 criteria. The primary analysis of PFS will be repeated based on mRECIST for HCC as an exploratory analysis.

16.2.1.3 Overall Survival (OS) Time

OS time is defined as the time (in months) from the date of first treatment administration to the date of death.

The date of event/censoring is defined as follows:

Survival Status	Source	Censoring	Date of event/censoring
Died	Death CRF	Event	Date of death
Alive (no date of death)	To be determined as defined in section 11	Censored	Last date known to be alive (defined in section 11)

OS (months) = (date of death/censoring – date of first trial treatment administration + 1)/30.4375

The analysis of OS will be performed using Kaplan-Meier methods with the same approach for TTP described above.

16.2.1.4 Best Overall Response

The best overall response (BOR) is the best response recorded from the start of treatment until disease progression. The BOR across all time points will be established applying the confirmation criteria based on RECIST 1.1, taking confirmation requirements into account as presented in Table 16.1. CR/PR may be claimed only if the corresponding criteria in Table 16.1 are met at a subsequent time point (28 days later). The time gap of two consecutive tumor response evaluations is the difference of two dates (i.e. the earliest scan date of target lesions associated with each assessment visit). SD may be claimed only if the SD criteria are met at least once after first administration at a minimum interval of 6 weeks. The time interval for SD will be calculated as (date of overall response - first dosing date of any of trial drug +1). The confirmation of response must not necessarily be at the next scan, but could be at any subsequent scan before PD. For instance, if a subject has PR-SD-PR or PR-NE-PR at consecutive tumor assessments, the BOR would qualify for PR (1). The number and percentage of subjects with BOR of CR, PR, SD, PD and not NE (not evaluable) will be summarized by the following:

- Dose level and overall
- c-Met status (IHC), dose level, and overall
- c-Met status (ISH), dose level, and overall

A figure displaying the BOR for each subject along with their percent change from baseline in AFP value will be displayed against time (weeks) in a line plot by the following baseline categories: < 200 ug/L, >= 200 ug/L, < 400 ug/L, and >= 400 ug/L. The BOR for each subject as assessed by RECIST 1.1 will be indicated in the figure.

A swimmer plot summarizing exposure information and response data will be presented by dose level and c-Met status (IHC/ISH). The BOR for each subject as assessed by RECIST 1.1 will be indicated in the figure.

Table 16.1 – Best Overall Response when Confirmation of CR and PR is Required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD

CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD provided minimum criteria for SD duration met, otherwise NE
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
SD	Any	SD provided minimum criteria for SD duration met, otherwise PD
PD	Any	PD
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend whether minimum duration for SD was met. However, sometime CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Objective tumor response

Objective tumor response will be evaluated by the objective response rate (ORR). The ORR is the proportion of subjects having achieved a BOR of CR or PR. The ORR will be established applying the criteria based on RECIST 1.1.

ORR will be summarized along with corresponding two-sided exact Clopper-Pearson (2) 90% CIs by the following:

- Dose level and overall
- c-Met status (IHC), dose level, and overall
- c-Met status (ISH), dose level, and overall

Disease Control

Disease control will be evaluated by the disease control rate, defined as the proportion of subjects having achieved a BOR of CR, PR, or SD.

Disease control rate will be summarized along with corresponding two-sided exact Clopper-Pearson (2) 90% CIs by the following:

- Dose level and overall
- c-Met status (IHC), dose level, and overall
- c-Met status (ISH), dose level, and overall

16.2.1.5 Sum of Longest Diameters (SOLD)

The sum of longest diameters of viable target lesions is collected on the "Sum of Longest Diameters" eCRF page. The relative change in SOLD of target lesions from baseline will be calculated as follows:

((SOLD of the target lesions at post-baseline – SOLD of target lesions at baseline) / SOLD of target lesions at baseline) *100

The relative change from baseline of SOLD in target lesions as well as occurrence of initial progressive disease with rationale evaluation type (target lesion/non-target lesion/new lesion) will be displayed against time point (weeks since treatment initiation) in a spider plot. The baseline relative change is considered "0" on day 1. Dose level and c-Met status (IHC/ISH) will be distinguished by different colors, line types, and/or symbols. Reference lines at +20% and -30% will be shown.

Best relative change in SOLD of target lesions from baseline will be calculated as follows for all subjects that present a measurable tumor at baseline and at least one post-baseline tumor assessment:

((the lowest SOLD of target lesions at post-baseline – SOLD of target lesions at baseline) / SOLD of target lesions at baseline) *100

The best relative change from baseline in SOLD will be displayed using waterfall plots. One plot will be color coded for dose level and c-Met status (IHC) and one will be color coded for dose level and c-Met status (ISH). Reference lines at +20% and -30% will be shown.

Summary statistics for the SOLD values and their change from baseline over time will be presented by the following in separate tables:

- Dose level and overall
- c-Met status (IHC), dose level, and overall
- c-Met status (ISH), dose level, and overall

If sufficient HGF data is available, scatter plots of baseline HGF (both CAF and cytoplasmic) versus the best (minimum) on treatment SOLD value by dose level will be presented.

SOLD data including absolute and relative change from baseline values will be listed.

16.2.1.6 Biological Response

Biological response is defined as the proportion of subjects with a decrease in AFP level of more than 20% at the Cycle 3 assessment, or the last assessment for subjects that terminated treatment prior to the Cycle 3 assessment, as compared with baseline. AFP level is measured at screening, Cycle 1 Day 1 (only if the screening measurement was done more than 7 days prior), Day 1 of every cycle thereafter, and the End of Treatment visit.

Biological response will be summarized, including corresponding two-sided exact Clopper-Pearson (2) 90% CIs, by the following in separate tables:

- Dose level and overall
- c-Met status (IHC), dose level, and overall
- c-Met status (ISH), dose level, and overall

If sufficient HGF data is available, scatter plots of best (minimum) on treatment AFP value versus both baseline HGF (CAF and cytoplasmic) will be provided.

Biological response will be flagged on the tumor marker listing. (See Section 17.3.)

16.2.2 Pharmacokinetics

Analysis Set: PK

Tepotinib and metabolite (MSC2571107A and MSC2571109A) concentrations in plasma will be listed and presented in tables and descriptively summarized by dose level, day and scheduled time point using N, arithmetic mean, standard deviation , standard error of the mean (SEM), median, minimum, maximum, and coefficient of variation (CV) (%). For descriptive statistics of concentration data, values below the lower limit of quantification (LLOQ) will be assigned values as defined in 16.2.2.2. Descriptive statistics of PK parameters will additionally show the geometric mean (GeoMean), the geometric CV percentage (GeoCV%), and the 95% CI for the geometric mean.

Individual plasma concentration-time profiles (linear and semi-logarithmic scales) will be plotted by dose level and day, overlaying tepotinib and its metabolites (i.e. all three analytes) in one plot per subject. Spaghetti plots overlaying all subjects' individual analyte concentrations (linear and semi-logarithmic scales) will be plotted by dose level and day for each of the three analytes separately. Mean plasma concentrations of all three analytes overlaid will also be plotted by dose level and day on linear (±standard deviation) and semi-logarithmic scales using schedule time points. Mean concentration time profiles per each analyte separately and by dose level will also be displayed, overlaying both Day 1 and Day 15 in one plot.

A listing of PK blood sample collection times by individual as well as derived sampling deviations will be provided.

PK profiles of tepotinib and its active metabolites (MSC2571107A, MSC2571109A) from study EMR200095-005 phase Ib part will be analyzed jointly with data from studies EMR200095-001, -002, -003, -004, -006 and -007 by a non-linear mixed effect approach. The plasma concentration time profiles after single or multiple dose administration of tepotinib in healthy volunteers and solid tumor patients will be evaluated with compartment models. Covariates of demographics, lab values, disease status and co-medication will be tested in order to identify any intrinsic and extrinsic factors that are predictive of PK inter-individual variability. More details are given in a separate Data Analysis Plan for Pooled Population Pharmacokinetic Analysis. The results will be reported separately.

16.2.2.1 Pharmacokinetic Endpoints

The following pharmacokinetic endpoints will be analyzed:

- Plasma PK parameters of tepotinib and metabolites MSC2571107A and MSC2571109A: the definition of the parameters and the planned analysis is described in the subsequent sections

16.2.2.2 Estimation of Individual Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by the PPD PK group using standard non-compartmental methods, actual elapsed sampling times, and the actual administered dose. The PK parameters listed below will be calculated for tepotinib and metabolites MSC2571107A and MSC2571109A in plasma, when applicable, based on frequent PK sampling as applied in phase Ib. PK parameters will be summarized by PK analyte, dose level, and day.

C_{max}	Maximum observed concentration
t_{max}	Time of C_{max}
AUC_{0-t}	Area under the concentration-time curve from time zero to the last quantifiable concentration
t_{lag}	t_{lag} is the time prior to the first quantifiable (non-zero) concentration [for Cycle 1 Day 1 only]
C_{av}	The average concentration at steady state, calculated on Cycle 1 Day 15 only. $C_{av} = AUC_{\tau} / \tau$ (AUC_{0-t} if necessary).
C_{min}	The minimum observed concentration during a complete dosing interval, calculated on Cycle 1 Day 15 only
AUC_{τ}	The area under the concentration-time curve over the dosing interval from T_1=0 h (predose) to T_2=τ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down).

	For Cycle 1 Day 1, AUCτ will be calculated as a partial area within the defined time range. For Cycle 1 Day 15, AUC_τ will be calculated at steady state from the pre-dose time point to the dosing interval time. AUC_τ will be calculated based on the observed concentration at the actual observation time, as long as actual time deviation is less than +/-10% at τ. If actual time deviation is equal to or greater than 10%, AUC_τ will be reported as missing.
AUC_{0-t}/Dose	Dose-Normalized AUC_{0-t}. Normalized using actual dose.
AUC_τ/Dose	Dose-Normalized AUC_τ. Normalized using actual dose.
C_{max}/Dose	Dose-Normalized C_{max}, Normalized using actual dose.
PTF	The peak trough fluctuation ratio within a complete dosing interval at steady state in %, calculated on Cycle 1 Day 15 only. PTF = $100*(C_{max}-C_{min})/C_{av}$

Potential drug accumulation will be evaluated by means of individual accumulation ratios for AUC_τ and C_{max} ($R_{acc(AUC)}$ and $R_{acc(Cmax)}$ respectively, that will be calculated by dividing the values obtained after multiple dose [e.g. on Cycle 1 Day 15] by the values obtained after single dose [e.g. Cycle 1 Day1]) and summarized descriptively for each dose level.

Individual metabolite to parent ratios for AUC_{0-t} and C_{max} ($MR_{(AUC0-t)}$ and $MR_{(Cmax)}$ respectively), will be calculated by dividing the value obtained for each metabolite by the value obtained for the parent (i.e. MSC2571107A/tepotinib and MSC2571109A/tepotinib), separately for single dose (e.g. Cycle 1 Day1) and multiple dose (e.g. Cycle 1 Day 15), and summarized descriptively for each dose level and day.

The dosing and sampling scheme in this study does not allow the reliable estimation of λ_z, considering the apparent terminal half-life of tepotinib and its metabolites. Therefore, all PK parameters dependent on λ_z will not be determined, i.e. $AUC_{0-\infty}$, $\%AUC_{extra}$, CL/F; $t_{1/2}$, Vz/F, and Vss/F.

Other parameters may be added as appropriate.

The calculation of the AUCs will be performed using the mixed log-linear trapezoidal method (linear up, log down). The actual (unrounded) time of blood sampling will be used for PK evaluation. In cases where the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data. The pre-dose samples will be considered as if they had been taken simultaneously with the administration. Plasma concentrations below LLOQ before the last quantifiable data point will be taken as zero for calculating the AUC (ie, embedded BLQ values will be set to zero). Plasma concentrations below LLOQ after the last quantifiable data point will be set to 'zero'.

PK parameters will be evaluated and listed for all subjects who provide sufficient concentration-time data. Formal statistical hypotheses have not been planned for PK parameters. Any statistical tests that might be performed will be considered exploratory.

Dose proportionality will be presented graphically by day as follows:

- Boxplots for dose-normalized PK parameters (AUC_τ /Dose and C_{max}/Dose) by dose level
- Scatter plots on individual AUC_τ and C_{max} versus Dose on a linear scale.

PK Parameters are to be rounded for reporting as appropriate. In export datasets, PK parameters will be provided with full precision, and will not be rounded.

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

17 Safety Evaluation

Analysis Set: ITT/SAF

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs. The analysis for the primary endpoint, incidence of DLTs during Cycle 1, is specified in Section 16.1.

17.1 Adverse Events

Adverse Event definitions:

- **Treatment emergent adverse events (TEAEs):** A TEAE is defined as an adverse event with a start date on or after the date of first dose of tepotinib and up to 33 days after the last treatment administration (the last possible day for the end of trial visit) unless considered drug treatment-related by the investigator, in which case it is classified as a TEAE despite occurring more than 33 days after the last treatment administration. If the onset date of the AE is the same as the date of the first dose, the AE will not be regarded as treatment-emergent if the onset of the AE was before first study drug administration (according to the information provided on the AEs CRF page).
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the "Adverse Event Details" eCRF page, Serious Adverse Event = Yes).
- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the "Adverse Event Details" eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (i.e. no answer to the question "Relationship with study treatment").

- **Adverse Events Leading to Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the "Adverse Event Details" eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the "Adverse Event Details" eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Adverse Events of Special Interest (AESI):** adverse events of special interest (amylase increase ≥ grade 3 or lipase increase ≥ grade 3)

All analyses described in Section 17.1 will be based on TEAEs if not otherwise specified. The AE listing will include all AEs (whether treatment-emergent or not). A listing of adverse events of special interest (AESIs) will also be provided.

In AE listings, a flag will indicate whether the AE occurred before, during, or after the treatment emergent period.

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of trial treatment then the onset date will be replaced by the minimum of start of trial treatment and AE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the later case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.
- Further information after cut-off (like fatal outcome) might be taken from Safety data base and included separately into CTR.

17.1.1 All Adverse Events

Adverse events will be summarized in terms of frequency tables by worst NCI-CTCAE grade, primary SOC body term as the Body System category and PT as the event category in alphabetical order. Both PT and SOC will be assigned using the latest version of MedDRA.

Each subject will be counted only once within each SOC and PT. If an adverse event is reported for a given subject more than once during treatment, the worst (i.e. maximum) severity and the strongest relationship to trial treatment will be summarized.

In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

An adverse events summary table will be provided. The rows of the summary table will show the overall number and percentage of subjects for each of the following:

- Any TEAE
- Trial treatment related TEAEs
- Serious TEAEs
- Non-serious TEAEs
- Trial treatment related serious TEAEs
- Any TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Trial treatment related TEAEs by NCI-CTCAE severity grade (≥3, ≥4)
- TEAEs of special interest (AESI)
- TEAEs leading to permanent treatment discontinuation
- Trial treatment related TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death
- Trial treatment related TEAEs leading to death

Additionally, frequency tables by primary SOC and PT will be presented by dose level and overall for the above, except for (related) TEAEs leading to death, which will be presented in a listing.

17.1.2 Adverse Events Leading to Treatment Discontinuation

See section 17.1.1.

17.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

17.2.1 Deaths

All deaths and deaths within 33 days after last dose of trial treatment and deaths within 60 days after first trial treatment, as well as reason for death, will be tabulated based on information from the "Death" and "Survival Follow-Up" eCRFs.

In addition, date and primary reason for death will be provided in an individual subject data listing along with selected dosing information (date of first / last administration of trial treatment). The listing will include a column for AEs with a fatal outcome and will identify deaths that occurred within 33 days of that subject's last administration of trial treatment and within 60 days after first trial treatment.

17.2.2 Serious Adverse Events

Please refer to Section 17.1.1. A subject listing of all SAEs will be provided in addition to the table described in Section 17.1.1.

17.3 Clinical Laboratory Evaluation

Laboratory results are assessed at a local laboratory and will be classified using NCI-CTCAE Version 4.0. Values that are below the limit of detection will be imputed as half of the detection limit.

The following will be presented:

- Tables with descriptive statistics and boxplots for both chemistry and hematology values and their changes from baseline by visit
- An eDISH (evaluation of drug-induced serious hepatotoxicity) plot for total bilirubin and ALT
- For NCI-CTCAE gradable chemistry and hematology parameters:
    - Tables for the worst grade (≥0, ≥3, or ≥4) during the on-treatment period using counts and percentages by laboratory parameter
    - Tables showing shifts from baseline to highest (worst) on-treatment grade (0, 1, 2, 3, or 4) For those parameters which are graded for increase as well as decrease such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately.
- For non NCI-CTCAE gradable chemistry and hematology parameters:
    - Tables displaying shifts from baseline to abnormal values for the maximum and minimum post-baseline values based on reference range (Low, Normal, or High)

The following hematology parameters were collected:

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count
- Differential WBC
- Platelet count

The following chemistry parameters were collected:

- Blood urea nitrogen (BUN)
- Urea
- Creatinine
- AST
- ALT
- Gamma-glutamyl transpeptidase (GGT)
- Total bilirubin
- Direct bilirubin (if total is abnormal)
- Lipase
- Amylase
- Total Protein
- Albumin
- Alkaline Phosphatase
- Creatinine Clearance
- Sodium
- Potassium
- Calcium
- Magnesium
- Glucose

The following laboratory parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information:

- Coagulation: prothrombin time, activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR)
- Pregnancy Tests: serum and urine
- Urinalysis: glucose, ketones, blood, pH, proteins, nitrites, leukocytes, red blood cell count, white blood cell count

- HBV panel and anti-HCV (hepatitis C virus) antibodies: HBsAg (hepatitis B surface antigen), HBeAg (hepatitis B e antigen), anti-HBc (anti-hepatitis B core antigen), and anti-HCV
- Viral load of HBV/HCV (only for subjects with hepatitis B at screening)
- Tumor markers: serum AFP

Listings of laboratory results will be provided for all laboratory parameters. These listings will be sorted by parameter and visit for each subject. Laboratory values that are outside of the normal range will be flagged and corresponding normal ranges will be provided.

17.4 Vital Signs

Vital sign data was collected on the "Vital Signs" eCRF page. For the definition of baseline, see Section 11.

Table 1. Categories of Change from Baseline for Vital Sign Parameters

Parameters, baseline categories	Categories of Change from Baseline
Body temperature increase < 37°C; 37 - <38°C; 38 - <39°C; 39 - <40°C; ≥ 40°C	< 1°C , 1-<2°C , 2-<3°C, ≥ 3 °C
Heart rate increase from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Systolic Blood Pressure (SBP) increase from baseline <140 mmHg; ≥ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline <140 mmHg; ≥ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
Diastolic Blood Pressure (DBP) increase from baseline <90 mmHg; ≥ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from baseline <90 mmHg; ≥ 90 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
Weight increase	<10%, ≥10%
Weight decrease	<10%, ≥10%

The following summaries will be prepared for vital sign parameters as grouped in Table 1:

- Maximal Shifts from baseline to worst-on treatment value (changes in categories, including total rows/columns)
- Listing of highest on-treatment change from baseline per subject
- Minimum and maximum absolute and change from baseline values

17.5 ECG

ECG results were collected on the "Electrocardiogram" eCRF page. Triplicate measurements are collected for all ECG parameters. The average of the triplicate measurements at each visit will be used for analysis purposes.

QTcF intervals will be derived as follows:

Fridericia's Correction (QTcF) $$QTc_f = \frac{QT}{\sqrt[3]{RR}}$$

where: RR = RR interval measured in seconds.

The worst shifts in the overall ECG assessment (e.g., normal, abnormal (not clinically significant), abnormal (clinically significant)) from baseline during the on-treatment period will be summarized. The incidence and percentage of subjects with clinically significant abnormalities at any time during the on-treatment period will be summarized by ECG parameter. The clinically significant abnormal criteria are provided in Table 2.

Table 2 Clinically Significant Criteria for ECG Test Results

Test	Clinically Significant Abnormality Criteria
PR Interval	≥ 220 msec and increase from baseline ≥ 20 msec
QRS Interval	≥ 120 msec
QTcF Interval - absolute	>450 msec, >480 msec, and >500 msec
QTcF Interval - change from baseline	Increase from baseline > 30 msec and ≤ 60 msec; Increase from baseline > 60 msec

A listing of 12-lead ECG data will be provided with all relevant information including derived variables.

17.6 ECOG Performance Status

ECOG PS data was collected on the "ECOG Performance Status" eCRF page, and will be summarized descriptively by visit. The ECOG PS is presented in Appendix A of the CTP.

18 Benefit Risk Assessment

A formal benefit-risk assessment will not be performed as part of the analysis.

19 References

1. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550-558.

2. Agresti A. Categorical Data Analysis (2nd Ed.). New Jersey: John Wiley & Sons, Inc. 2002: 18-20.

3. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics 1982;38:29-41.

4. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons 1980.

20 Appendices

Appendix 1 Important Protocol Deviations

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Inclusion criteria: **For the subject to be eligible for inclusion, each criterion must be checked 'YES':**					
Criterion 1: Histologically confirmed HCC	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 1.	PDEV01	Section 5.3.1	Medical review required
Criterion 2: Child Pugh Class A liver function score	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 2.	PDEV02	Section 5.3.1	Medical review required
Criterion 3: MET+ Status	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 3.	PDEV03	Section 5.3.1	Medical review required.
Criterion 4: Availability of a pretreatment tumor biopsy	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 4.	PDEV04	Section 5.3.1	Medical review required
Criterion 5: Male or female, 18 years of age or older	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 5.	PDEV05	Section 5.3.1	Medical review required
Criterion 6: Measureable disease in accordance with RECIST Version 1.1	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 6.	PDEV06	Section 5.3.1	Medical review required.
Criterion 7: ECOG PS of 0 or 1	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 7.	PDEV07	Section 5.3.1	Medical review required

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Criterion 8: Previously treated with sorafenib for >= 4 weeks and discontinued at least 14 days prior to Day 1 due to either intolerance or radiographic progression	Inclusion/Exclusion criteria	Subject did not meet inclusion criterion 8.	PDEV08	Section 5.3.1	Medical review required
Criterion 9: Signed and dated informed consent	Inclusion/Exclusion criteria	Subject did not meet inclusion criterion 9.	PDEV09	Section 5.3.1	Medical review required
Exclusion criteria: **For the subject to be eligible for inclusion, each criterion must be checked 'NO':**					
Criterion 1: Prior systemic anticancer treatment for advanced HCC (except for sorafenib)	Eligibility and Entry Criteria	Subject met exclusion criterion 1	PDEV10	Section 5.3.2	Medical review required.
Criterion 2: Prior treatment with any agent targeting the HGF/c-Met pathway	Eligibility and Entry Criteria	Subject met exclusion criterion 2	PDEV11	Section 5.3.2	Medical review required.
Criterion 3: Local-regional therapy within 4 weeks before Day 1	Eligibility and Entry Criteria	Subject met exclusion criterion 3	PDEV12	Section 5.3.2	Medical review required.

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Criterion 4: Laboratory Index at Baseline: • Hemoglobin ≤ 8.5 g/dl; • Neutrophils < 1.5 x 109/L; • Platelets < 60 x 109/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;	Eligibility and Entry Criteria	Subject met exclusion criterion 4	PDEV13	Section 5.3.2	Medical review required
Criterion 5: Past or current history of neoplasm other than HCC	Eligibility and Entry Criteria	Subject met exclusion criterion 5	PDEV14	Section 5.3.2	Medical review required
Criterion 6: Known central nervous system or brain metastasis (either symptomatic or untreated)	Eligibility and Entry Criteria	Subject met exclusion criterion 6	PDEV15	Section 5.3.2	Medical review required

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Criterion 7: Medical history of conditions that may hamper compliance and/or absorption of tested products	Eligibility and Entry Criteria	Subject met exclusion criterion 7	PDEV16	Section 5.3.2	Medical review required
Criterion 8: Clinically significant gastrointestinal bleeding within 4 weeks before trial entry	Eligibility and Entry Criteria	Subject met exclusion criterion 8	PDEV17	Section 5.3.2	Medical review required
Criterion 9: Peripheral neuropathy Grade >= 2	Eligibility and Entry Criteria	Subject met exclusion criterion 9	PDEV18	Section 5.3.2	Medical review required
Criterion 10: Impaired cardiac function	Eligibility and Entry Criteria	Subject met exclusion criterion 10	PDEV19	Section 5.3.2	Medical review required
Criterion 11: Uncontrolled hypertension by standard medication	Eligibility and Entry Criteria	Subject met exclusion criterion 11	PDEV20	Section 5.3.2	Medical review required
Criterion 12: Known human immunodeficiency virus	Eligibility and Entry Criteria	Subject met exclusion criterion 12	PDEV21	Section 5.3.2	Medical review required
Criterion 13: Known or suspected drug hypersensitivity to any ingredients of MSC2156119J	Eligibility and Entry Criteria	Subject met exclusion criterion 13	PDEV22	Section 5.3.2	Medical review required
Criterion 14: Female subjects must have negative pregnancy test prior to enrollment	Eligibility and Entry Criteria	Subject met exclusion criterion 14	PDEV23	Section 5.3.2	Medical review required
Criterion 15: Concurrent treatment with non-permitted drug	Eligibility and Entry Criteria	Subject met exclusion criterion 15	PDEV24	Section 5.3.2	Medical review required

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Criterion 16: Substance abuse, chronic medical or psychiatric condition or laboratory abnormalities that increase risk associated with trial participation	Eligibility and Entry Criteria	Subject met exclusion criterion 16	PDEV25	Section 5.3.2	Medical review required
Criterion 17: Prior treatment with MSC2156119J or other c-Met inhibitors	Eligibility and Entry Criteria	Subject met exclusion criterion 17	PDEV26	Section 5.3.2	Medical review required
Criterion 18: Participation in another interventional clinical trial within 28 days prior to Day 1	Eligibility and Entry Criteria	Subject met exclusion criterion 18	PDEV27	Section 5.3.2	Medical review required
Criterion 19: Previous anticancer treatment-related toxicities not recovered to Grade 0-1 or baseline	Eligibility and Entry Criteria	Subject met exclusion criterion 19	PDEV28	Section 5.3.2	Medical review required
Criterion 20: History of liver transplant	Eligibility and Entry Criteria	Subject met exclusion criterion 20	PDEV29	Section 5.3.2	Medical review required
Criterion 21: Active or uncontrolled infections except chronic HBV, chronic HCV, or both	Eligibility and Entry Criteria	Subject met exclusion criterion 21	PDEV30	Section 5.3.2	Medical review required
Criterion 22: Concurrent medical condition or disease that compromises trial conduct	Eligibility and Entry Criteria	Subject met exclusion criterion 22	PDEV31	Section 5.3.2	Medical review required
Non-permitted concomitant medication during the study	Prohibited Medications	Subjects that took non permitted medications and were not withdrawn	PDEV32	Section 6.5.2	Medical review required

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that became pregnant during the study and were not withdrawn	PDEV33	Section 5.5.1	Medical review required
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that had QTc > 500 msec or change of QTc from baseline > 60 msec and were not withdrawn	PDEV34	Section 5.5.1	Programmed to check if QTc > 500 msec or change from baseline > 60 msec
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that were not compliant with administration of MSC2156119J and were not withdrawn	PDEV35	Section 5.5.1	Medical review required
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects with documented progression of disease that were not withdrawn	PDEV36	Section 5.5.1	Medical review required
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that initiated other anticancer treatment and were not withdrawn	PDEV37	Section 5.5.1	Medical review required.
Subjects dosing error	Study Medication	Subject had dosing error.	PDEV38	Section 6.2	List if relative dose intensity over or equal to 110% or less than or equal to 90%.
PK Related Deviation	PK	Subject has deviation warranting exclusion from PK analysis set	PDEV39	NA	Review by PK scientist required
Any other protocol deviation which is deemed to be significant but has not been pre-specified in this table	Any	Any	PDEV99	NA	Medical review required.

Statistical Analysis Plan – Phase II

Clinical Trial Protocol Identification No.	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
Trial Phase	Phase Ib/II
Investigational Medicinal Product(s)	tepotinib (MSC2156119J)
Clinical Trial Protocol Version	13 June 2016 / Version 6.0
Statistical Analysis Plan Author	PPD
Statistical Analysis Plan Date and Version	15 March 2018 / Version 1.0
Statistical Analysis Plan Reviewers	PPD, PPD, PPD PPD, Biostatistician, Merck Biopharma PPD, Medical Responsible, EMD Serono PPD, Clinical Pharmacologist, Merck Biopharma PPD, PPD, Merck Biopharma PPD, PPD, Merck Biopharma PPD, PPD, Merck Biopharma PPD, Pharmacometry, Merck Biopharma PPD, PPD, Merck Biopharma PPD, PPD, Merck Biopharma

1 Signature Page

Statistical Analysis Plan: EMR 200095-005

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

PPD Trial Biostatistician: PPD

PPD

Signature

PPD

Date of Signature

PPD

PPD

Merck Biopharma Trial Biostatistician: PPD

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64293 Darmstadt, Germany

2 Table of Contents

3 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
AFP	Alpha-Fetoprotein
ALBI	Albumin-Bilirubin
ATC	Anatomical Therapeutic Chemical
BOR	Best Overall Response
CAF	Cancer-Associated Fibroblast
CI	Confidence Interval
CR	Complete Response
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
EWB	Emotional Well-Being
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Hep	Functional Assessment of Cancer Therapy - Hepatobiliary
FACT-HP	Functional Assessment of Cancer Therapy - Hepatobiliary
FDG	Fluoro-D-Glucose
FHSI-8	Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8
FWB	Functional Well-Being
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor

ICH	International Conference on Harmonization
IERC	Independent Endpoint Review Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
ISH	In Situ Hybridization
ITT	Intent-to-Treat
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NGS	Next Generation Sequencing
ORR	Overall Response Rate
OS	Overall Survival
Pd	Pharmacodynamics
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
PT	Preferred Term
PWB	Physical Well-Being
Q1	First quartile
Q3	Third quartile
QTcF	Fridericia's QT correction
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAF	Safety

SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SEM	Standard Error of the Mean
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOLD	Sum of Longest Diameter
SWB	Social Well-Being
TEAE	Treatment Emergent Adverse Event
TNM	Tumor, Lymph Nodes, Metastasis
TOI	Trial Outcome Index
TTP	Time to Progression
TTSP	Time to Symptomatic Progression
CCI	[redacted]
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	15 March 2018	PPD	First final version

5 Purpose of the Statistical Analysis Plan

The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for the phase II portion of clinical trial protocol (CTP) EMR 200095-005. Results of the final analysis described in this SAP will be included in the Clinical Trial Report (CTR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CTR but not identified in this prospective SAP will be clearly identified in the CTR.

The SAP is based on section 8 (Statistics) of the CTP dated 13 June 2016/version 6.0 and protocol amendments and is prepared in compliance with International Conference on Harmonization (ICH) E9.

6 Summary of Clinical Trial Features

Table A: Clinical Trial Features Summary (Phase II)

Trial Objectives	**Primary Objective** • Evaluate efficacy of tepotinib in subjects with MET+ advanced hepatocellular carcinoma (HCC) pretreated with sorafenib and Child Pugh class A liver function. **Secondary Objectives** • Evaluate the safety and tolerability of tepotinib • Evaluate antitumor activity and biochemical response of tepotinib **Exploratory Objectives** • CCI [redacted]

	CCI [redacted]
Primary Endpoint	• Progression-free survival (PFS) status at 12 weeks
Secondary Endpoints	• Efficacy parameters (PFS, objective tumor response, disease control, time to progression (TTP), overall survival (OS), time to symptomatic progression [TTSP; defined as time from first study drug administration to deterioration of symptoms as assessed by the Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8), or by deterioration to Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 4, or death], and biological response as measured by alpha-fetoprotein (AFP)) • Safety parameters (drug exposure; incidence and type of treatment-emergent adverse events (TEAEs); incidence and reasons for deaths, including deaths within 33 days after the last dose of tepotinib; vital signs; electrocardiogram (ECG) changes; hematology, chemistry, and urinalysis parameters; physical examination including change in body weight; and ECOG PS.
Pharmacokinetic Endpoints	CCI [redacted]
Exploratory Endpoints	• CCI [redacted]
Methodology	Phase II is a multicenter, single-arm, nonrandomized, study of the efficacy, safety, and CCI of tepotinib in subjects with MET+ advanced HCC pretreated with sorafenib and with Child Pugh class A liver function. Subjects will be given tepotinib at the recommended Phase II dose (RP2D) confirmed in Phase 1b. Subjects will receive tepotinib 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	48 subjects
Safety Monitoring Committee Meetings	A safety monitoring committee (SMC) will be responsible for monitoring the safety of subjects and making decisions about the safety of the subjects on trial. The SMC will meet and review the safety of tepotinib: 1. After 12 subjects have completed Cycle 1 2. After 24 subjects have completed Cycle 1

7 Sample Size/Randomization

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 tepotinib 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. 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.

Randomization is not applicable.

8 Overview of Planned Analyses

This SAP covers the analyses for efficacy and safety for the final analysis. Statistical analyses will be performed using cleaned electronic Case Report Form (eCRF) data. An administrative interim efficacy analysis, described in a separate analysis plan, was previously performed. Further administrative interim analyses at time points that are not specified in the protocol may be performed for internal planning purposes.

8.1 Sequence of Analyses

The final analysis will be performed at the end of the trial, 12 months after the last subject's first dose of tepotinib. The final analysis will occur once all trial data is in-house, all data queries are resolved, and the database is fully locked.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

The following are changes to the planned analyses in the clinical trial protocol:

- Physical examination results at baseline will not be presented since these are not collected on the eCRF. Relevant findings had to be entered on the medical history or adverse event eCRF page.

- Relative dose intensity will be summarized rather than treatment compliance.

- The Pd Analysis Set is not defined in this SAP since all Pd related analyses will be carried out on the intent-to-treat (ITT)/safety (SAF) analysis set.

- The deterioration of symptoms assessed by FHSI-8 is defined in accordance with the scoring guidance in appendix 2 as at least a 4-point decrease compared with the baseline value.

- Summaries of sum of longest diameter (SOLD) data are included but these are not explicitly mentioned in the protocol.

- Summaries of quality of life data are included but these are not explicitly mentioned in the protocol.

- Duration of response will be calculated and presented in data listings but this is not explicitly mentioned in the protocol.

- The underlying disease or medical condition related to etiology subgroups will be hepatitis C virus (HCV), and other as opposed to hepatitis B virus (HBV) and other as defined in the protocol.

- CCI [redacted]

- A decrease in AFP level of more than 20% at the Cycle 3 assessment, or the last assessment for subjects that terminated treatment prior to the Cycle 3 assessment, as compared with baseline.

Otherwise, the statistical methods as described in the protocol will be adopted.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations include:

- Subjects that are dosed on the study despite not satisfying the inclusion criteria;
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn;
- Subjects that receive the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication;
- Deviation from good clinical practice.

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion

Important protocol deviations will be determined for all subjects by either site monitoring, medical review processes or programming based on the inclusion/exclusion criteria or other criteria presented in the protocol.

All important protocol deviations will be documented in CDISC datasets whether identified through site monitoring, medical review or programming. Important protocol deviations to be identified are specified in Appendix 1 and will be presented in a summary table and data listing.

10.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set

The Screening Analysis Set includes all subjects who signed the Informed Consent Form (ICF). The Screening Analysis Set will be used for the display of disposition data. Rescreened subjects will be counted once in the Screening Analysis Set. For subjects who are rescreened, the most recent data will be presented in listings.

Intent-to-Treat/Safety Analysis Set

The ITT/SAF Analysis Set includes all subjects who have been administered at least one dose of tepotinib. The ITT/SAF Analysis Set will be used for all safety and efficacy analyses.

CCI [redacted]

[redacted]

Additional Subgroup Analysis Sets

The below subgroup analyses may be performed on the primary endpoint and some secondary endpoints. The subgroup analyses are exploratory in nature. The following subgroups will be defined:

- 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
- Underlying disease or medical condition related to etiology: HCV versus other
- AFP elevation at baseline: ≥ 200 IU/mL versus < 200 IU/mL
- Prior local-regional therapy: yes versus no
- Baseline c-Met Status: Immunohistochemistry (IHC): IHC 0, IHC 1+, IHC 2+, IHC3+
- Baseline c-Met Status: In Situ Hybridization (ISH): ISH+, ISH-
- Baseline Cancer-Associated Fibroblast (CAF) HGF: above the median, below/at the median, not done, not evaluable.
- Baseline Cytoplasmic HGF: above the median, below/at the median, not done, not evaluable
- Baseline Circulating HGF
    - Above the median, below/at the median, not done, not evaluable
    - Above upper quartile (25% quantile), below/at upper quartile, not done, not evaluable
- Baseline Shedded c-Met
    - Above the median, below/at the median, not done, not evaluable
    - Above upper quartile, below/at upper quartile, not done, not evaluable
- Baseline IL-8
    - Above the median, below/at the median, not done, not evaluable
    - Above upper quartile, below/at upper quartile, not done, not evaluable
- Baseline c-Met Amplification (ISH): c-Met amplification +, c-Met amplification –
- Baseline HCV Status: HCV versus non-HCV
- Baseline HBV Status: HBV versus non-HBV

- Baseline HBV/HCV Status: HBV or HCV versus neither HBV nor HCV

Analyses	Screening Analysis Set	ITT/SAF Analysis Set	CCI
Disposition	✓		
Demographics		✓	
Baseline Assessments		✓	
Past and Concomitant Therapies		✓	
Compliance and Exposure		✓	
Primary		✓	
Secondary		✓	
CCI			
CCI			
CCI			
Safety and Tolerability		✓	

11 General Specifications for Statistical Analyses

All analyses (production of tables, listings and figures) will be performed using SAS® Software version 9.2 or higher (Statistical Analysis System, SAS-Institute, Cary NC, USA).

Last date known to be alive:

The following dates will be used to determine the last date known to be alive prior to or at data cut-off:

- All subject assessment dates (laboratory blood draws, vital signs, performance status, ECG, tumor assessments, quality of life assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- Adverse Event (AE) start and end dates
- Last known alive date collected on the 'Subject Status/Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates

Unscheduled visits:

Data collected at unscheduled visits will not be included in by-visit summaries of data but may contribute to baseline value derivations and analyses in which post-baseline data is considered (e.g. best/worst on-treatment value).

End of Treatment visits:

End of Treatment visits will be included as a separate time point in by-visit summaries of data and may also contribute to analyses in which post-baseline data is considered (e.g. best/worst on-treatment value).

Significance level:

The significance level is 5% one-sided. The primary efficacy endpoint analysis is described in Section 16.1. Confidence intervals (CIs) will be two-sided with a confidence probability of 90%, unless otherwise specified.

Presentation of continuous and qualitative variables:

Continuous variables other than CCI will be summarized using descriptive statistics if not otherwise specified, i.e.

- number of subjects (N), number of subjects with non-missing values
- mean, standard deviation
- median, first quartile (Q1) - third quartile (Q3)
- minimum and maximum

Pharmacokinetic data (concentrations) will be summarized using N, arithmetic mean, standard deviation, median, minimum, maximum, and coefficient of variation (CV) (%).

Qualitative variables will be summarized by counts and percentages, with percentages based on the number of subjects in the analysis set of interest, unless otherwise specified. Counts of missing observations will be included in the denominator and presented as a separate category in shift from baseline summaries. In general, percentages will be reported to 1 decimal place unless greater precision is deemed appropriate.

By-visit displays:

By-visit summaries will include all planned visits until the last visit with at least 3 ongoing subjects.

Definition of baseline:

In general, the last measurement prior to first administration of trial treatment will serve as the baseline measurement. For ECG parameters, the average of up to three measurements at the last visit prior to the first administration of trial treatment will serve as the baseline measurement.

Definition of duration:

Duration will be calculated as the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first trial treatment administration + 1), if not otherwise specified.

The time since an event (e.g. time since first diagnosis) will be calculated as the reference date minus the date of the event.

Conversion factors:

The following conversion factors will be used to convert days into months or years:

- 1 month = 30.4375 days
- 1 year = 365.25 days.

Definition of treatment day:

Treatment day is defined relative to the start date of trial treatment. Treatment day 1 is the date of first administration of trial treatment, and the day before is defined as Treatment day -1 (no Treatment day 0 is defined).

Definition of on-treatment period:

The on-treatment period is defined as the time from the first trial treatment administration to the last trial treatment administration date + 33 days.

Definition of completion of a cycle:

A cycle is considered complete if the treatment end date minus the treatment start date plus one is greater than or equal to the following:

Cycle 1 (week 1 – 3)	21
Cycle 2 (week 4 – 6)	42
Cycle 3 (week 7 – 9)	63
Cycle 4 (week 10 – 12)	84
…	…
Cycle x (week (x-1)*3+1 – x*3)	x*21

Handling of missing data:

Unless otherwise specified in this SAP, all data will be evaluated as reported and no imputation of missing values will be done. In subject data listings, imputed values will be presented (if applicable), and the imputed information will be flagged.

Missing statistics (i.e. when they cannot be calculated) will be presented as "nd" (i.e. not done). For example, if n=1, the measure of variability (standard deviation) cannot be computed and will be presented as "nd".

Partial dates are allowed for some of the date fields as collected on the eCRF. Partial dates will not be imputed unless they are required for assignment of a medication to previous or concomitant or an adverse event to treatment emergent. The date imputation rules for adverse events are described in Section 17.1.

12 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

Analysis Set: Screening

Subjects will remain in the study until death, withdrawal of consent, or trial completion. Subjects are free to withdraw from the study at any time without giving their reason(s).

The following will be summarized for all screened subjects:

- Number of subjects screened (rescreened subjects will be counted once)
- Number of subjects rescreened
- Number of subjects who discontinued from the trial prior to treatment (overall and grouped by primary reason for discontinuation)
- Number and percentage of treated subjects. (i.e. those with at least one dose of trial treatment)
- Number and percentage of subjects who completed treatment (i.e. experienced death or disease progression)
- Number and percentage of subjects who discontinued treatment (overall and grouped by primary reason for discontinuation)
- Number and percentage of subjects who discontinued study procedures (overall and grouped by primary reason for discontinuation)
- Number and percentage of subjects who discontinued survival follow-up (overall and grouped by primary reason for discontinuation)

Percentages for the summaries above will be based on the ITT/SAF Analysis Set.

Number of subjects in the Screening Analysis Set along with number and percentage of subjects in the ITT/SAF and CCI Analysis Sets will be presented in a separate standalone summary.

The number and percentage of subjects from each region, country and clinical site will be summarized for the screening, ITT/SAF, and CCI Analysis Sets.

12.2 Protocol Deviations

12.2.1 Important Protocol Deviations

Analysis Set: ITT/SAF

The following summary table and listing of important protocol deviations will be provided:

- Frequency table per reason of important protocol deviations
- Listing of important protocol deviations

12.2.2 Reasons Leading to the Exclusion from an Analysis Set

This section does not apply to this trial as there is no per protocol Analysis Set defined for this study.

13 Demographics and Other Baseline Characteristics

Analysis Set: ITT/SAF

If not stated otherwise, summaries will be presented for the ITT/SAF Analysis Set. Baseline characteristics with respect to vital signs, ECG results, and hematology/biochemistry will be part of Section 17 (Safety Evaluation).

13.1 Demographics

Demographic characteristics will be summarized using the following information.

- Demographic characteristics
  - Sex:
    - Male
    - Female
  - Race:
    - White
    - Black or African American
    - Asian

  - Other
  - Unknown
- Age (years): summary statistics
- Age categories:
  - < 65
  - 65 - < 75
  - 75 - < 85
  - ≥ 85
- Country of site
  - Belgium
  - France
  - Germany
  - Italy
  - Spain
  - Switzerland
  - United States of America

Specifications for computation:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day only: For the derivation only, the day of informed consent and the day of birth will be set to 1 and the formula above will be used.
  - In case of missing day and month: For the derivation only, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used.

The integer part of the calculated age will be used for reporting purposes.

Site codes will be used for the determination of the subject's country of site.

A listing of demographics will be provided with all data (as collected on the "Demographics" eCRF page) and derived variables used in the above summary table.

13.2 Medical History

Medical history will be summarized as the numbers and percentages of subjects by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. PT and SOC will be determined using the latest version of MedDRA. A subject will be counted only once within a given SOC and within a given PT, even if he/she had the same medical history event at different times. The data will be displayed in terms of frequency tables ordered by primary SOC and PT in

alphabetical order. Medical history data will come from the "Medical History Details" eCRF page, and a listing including all relevant medical history data will be provided.

13.3 Disease History

Information on disease history collected prior to dosing is found on the "Disease History" eCRF. The following will be summarized:

- Site of primary tumor at study entry
- Time since first occurrence of metastatic or locally advanced disease (months) defined as (the first trial treatment date – the date of first occurrence of metastatic or locally advanced disease) / 30.4375
- Time since initial diagnosis (years) defined as (the first trial treatment date – the date of initial diagnosis) / 365.25Root cause of HCC as assessed by investigator: Hepatitis B virus (HBV), Hepatitis C virus (HCV), alcohol induced cirrhosis, other
- Tumor, lymph nodes, metastasis (TNM) classification at initial diagnosis
- TNM classification at study entry
- Tumor Histology
    - Macroscopic Category (Massive/Nodular/Diffuse/Other)
    - Microscopic Category (Trabecular/Pseudoglandular/Compact/Scirrous/ Fibrolamellar/Clear Cell/Sclerosing/Sarcomatoid/Inflammatory HCC or Lympho-Epithelial-Like Carcinoma/Other)
    - Vascular Invasion (Yes/No/Not Available)
    - Grading (1/2/3/4/Not Available)

A listing of disease history will be provided with all relevant data (as collected on the "Disease History" eCRF page) and derived variables used in the above summary table.

13.4 Other Baseline Characteristics

The following baseline characteristics will be reported for this study:

- Height (cm) (collected on the "Vital Signs" eCRF page)
- Weight (kg) (collected on the "Vital Signs" eCRF page)
- Body Mass Index (kg/m^2) (derived as indicated below)
- ECOG PS: 0 or 1 (collected on the "ECOG Performance Status" eCRF page)
- FHSI-8 score (collected on the "FHSI-8" eCRF page)
- Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-HP) score (collected on the "FACT-HP" eCRF page)

- Nicotine use status: Never used, Regular user, Occasional user, or Former user (collected on the "Nicotine Consumption" eCRF page)
- Alcohol use: Yes or No (collected on the "Alcohol Consumption" eCRF page)
- AFP elevation at baseline: ≥ 200 IU/mL or < 200 IU/mL (collected on the "Tumor Markers" eCRF page)
- Prior local-regional therapy: Yes or No (collected on the "Prior Anti-Cancer Local-Regional Therapy" eCRF page)
- Albumin-Bilirubin (ALBI) Grade (1): 1, 2, or 3 (derived as indicated below)

Specifications for computation:

- ALBI Grade (1):
    - Calculate the linear predictor y: $y = (\log_{10}(\text{bilirubin}) * 0.66) + (\text{albumin} * -0.085)$ where bilirubin is in µmol/L and albumin is in g/L
    - Compare y to the following cut points:
        - ALBI Grade 1: $y \leq -2.60$
        - ALBI Grade 2: $-2.60 < y \leq -1.39$
        - ALBI Grade 3: $y > -1.39$
- Body mass index (kg/m^2) = weight (kg)/[height (m)]^2

13.5 Baseline Biomarkers in Tumor

The following baseline biomarkers will be reported for this study:

- c-Met Status: Immunohistochemistry (IHC) 0, IHC 1+, IHC 2+, IHC 3+ (collected as part of the immunology data at Q^2 Solutions, defined as indicated below)
- c-Met Status: In Situ Hybridization (ISH): ISH+, ISH- (derived as indicated below)
- Cancer-Associated Fibroblast (CAF) HGF Immunohistochemistry (IHC) (collected as part of the immunology data at Q^2 Solutions, defined as indicated below)
- Cytoplasmic HGF: Immunohistochemistry (IHC) (collected as part of the immunology data at Q^2 Solutions, defined as indicated below)

Specifications for computation:

- c-Met Status (IHC)

- IHC 0: No staining of tumor cells, or < 50% of tumor cells with membrane and/or cytoplasmic staining of any staining intensity (or combination of intensities)
- IHC 1+: ≥ 50% of tumor cells with at least weak (1+) membrane and/or cytoplasmic staining, but < 50% of tumor cells with moderate or strong membrane and/or cytoplasmic staining
- IHC 2+: ≥ 50% of tumor cells with at least moderate (2+) membrane and/or cytoplasmic staining, but <50% of tumor cells with strong membrane and/or cytoplasmic staining
- IHC 3+: ≥ 50% of tumor cells with strong (3+) membrane and/or cytoplasmic staining with strong intensity

- c-Met Status (ISH):
  - ISH+ if a subject has a mean gene copy number ≥ 5 or a MET:CEP7 ratio ≥ 2
  - ISH- if a subject has a mean gene copy number < 5 and a MET:CEP7 ratio < 2
  - For ISH+ cases, the mean gene copy number and the ratio should be reported
- CAF HGF (IHC):
  - Histo-score of expression with range (1-300)
- Cytoplasmic HGF (IHC):
  - Histo-score of expression with range (1-300)

Baseline biomarker status/values will be summarized using descriptive statistics in a frequency table. The correlation/association between c-Met expression (IHC) and amplification (ISH) status will be analyzed by presenting a cross-tabulation table.

Moreover, the demographics table will be repeated with the following baseline biomarker groups as to investigate distribution of demographic data in the baseline biomarker groups:

- table by baseline IHC group [IHC 0, IHC 1+, IHC 2+, IHC 3+]
- table by baseline ISH group [ISH+, ISH-]

CCI [redacted]

[redacted]

- CCI

:

13.7 Prior Anti-Cancer Therapies

Information related to prior anti-cancer therapies were collected on the "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details", "Prior Anti-Cancer Local-Regional Therapy Details", and "Prior Anti-Cancer Surgery Details" eCRF pages.

The number of subjects in each of the following anti-cancer therapy categories will be tabulated:

- Subjects with at least one type of prior anti-cancer treatment

- Subjects with at least one prior anti-cancer drug therapy
- Subjects with at least one prior anti-cancer radiotherapy
- Subjects with at least one prior anti-cancer local-regional therapy
- Subjects with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows:

- Number of subjects with at least one prior anti-cancer drug therapy
- Number of any prior anti-cancer therapy regimens: missing / 1 / 2 / 3 / ≥4
- Number of prior anti-cancer drug therapy for metastatic/locally advanced disease: missing / 1 / 2 / 3 / ≥4.
- Type of prior anti-cancer therapy: Cytotoxic Therapy / Endocrine Therapy / Monoclonal Antibodies Therapy / Small Molecules / Immunotherapy / Other
- Intent of Therapy: Neo-Adjuvant / Adjuvant / Metastatic or Locally advanced
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Not-Complete Response/Non-Progressive Disease (Non-CR/non-PD) / Not assessable / Unknown. Best response is derived from the last treatment regimen

The prior anti-cancer drugs will also be extensively detailed with the number and percentage of subjects by the drug class and PT in a table. A subject will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Listings of prior anti-cancer treatments and procedures will also be provided: a) listing of prior anti-cancer drug therapies, b) listing of prior anti-cancer radiotherapy, c) listing of prior anti-cancer local-regional therapy and d) listing of prior anti-cancer surgeries. These will include the subject identification number, and all the relevant collected data-fields on the corresponding eCRF pages. Prior anti-cancer drug therapies will be coded using the World Health Organization Drug dictionary (WHO-DD).

14 Previous or Concomitant Medications/Procedures

Analysis Set: ITT/SAF

14.1 Prior and Concomitant Medications/Procedures

Concomitant treatments are medications, other than trial medications, taken by subjects any time during the on-treatment period.

Previous medications are medications, other than trial medications and pre-medications for trial treatment, which are started before first administration of trial treatment.

Previous and concomitant medications will be summarized from the "Concomitant Medications Details" eCRF page.

In cases where date values do not allow unequivocal allocation of a medication to concomitant or previous medication, the medication will be considered as both a concomitant and previous medication. Incomplete concomitant or previous medication-related dates will be handled as described in section 17.1.

Summaries of previous and concomitant medications will include the number and percentage of subjects by Anatomical Therapeutic Chemical (ATC) classification level 2 and PT, as given from the latest version of the WHO-DD. A subject will be counted only once within a given ATC class and within a given PT, even if he/she received the same medication at different times. If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. Summary tables will be sorted alphabetically by ATC class and PT. In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under the "Unavailable ATC classification" category.

A listing of previous and concomitant medications will be created with the information collected on the "Concomitant Medications Details" eCRF page.

All **concurrent procedures**, which were undertaken any time on trial, were collected on the eCRF page "Concomitant Procedure Details". The number and percentage of subjects with any concurrent procedure, a concurrent procedure starting prior to the first dose of treatment, and a concurrent procedure starting after the start of treatment but within 33 days after the last dose of trial treatment will be presented.

A listing of concurrent procedures will be created with the information collected on the "Concomitant Procedures Details" eCRF page.

14.2 Subsequent Anti-Cancer Therapies/Procedures

Anti-cancer treatment after discontinuation will be provided in a data listing with data retrieved from "Anti-Cancer Treatment After Discontinuation Details", "Anti-Cancer Radiotherapy After Discontinuation", and "Anti-Cancer Surgeries After Discontinuation" eCRF pages.

15 Treatment Compliance and Exposure

Analysis Set: ITT/SAF

All dosing calculations and summaries will be based on the "MSC2156119J Administration Details" eCRF page.

Handling of missing data:

If the actual dose is missing, the planned dose level as entered in the eCRF will be used.

Cumulative Dose

The cumulative dose (mg) of tepotinib per subject is the sum of the actual dose levels that the subject received (i.e. total dose administered [mg]).

Duration

For the purposes of deriving dose intensity, the duration of therapy (in weeks) during the trial is defined as:

$$\text{Duration} \left(\frac{\text{last dose date} \quad \text{first dose date} + 1}{7}\right)$$

The duration of therapy (in months) during the trial is defined as:

$$\text{Duration} \left(\frac{\text{last dose date} \quad \text{first dose date} + 1}{30.4375}\right)$$

Dose Intensity

The dose intensity and the relative dose intensity will be calculated for each subject across all cycles assuming a 3-week cycle duration. Dose intensity (mg/cycle) is defined as

$$\text{Dose intensity} \left(\frac{\text{Cumulative dose}}{(\text{duration of therapy (in weeks)})/3}\right)$$

Relative Dose Intensity

Relative dose intensity, a measure of compliance, is defined as the dose intensity divided by the planned dose per cycle.

Number of Cycles Completed

The number of cycles a subject completed will be calculated as follows:

$$\text{Number of cycles completed} \quad \text{floor}\left(\frac{(\text{last dose date} - \text{first dose date} + 1)}{21}\right)$$

Number of Cycles Initiated

The number of cycles a subject initiated will be calculated as follows:

$$\text{Number of cycles initiated} \quad \text{ceiling}\left(\frac{(\text{last dose date} - \text{first dose date} + 1)}{21}\right)$$

The following will be summarized:

- Total number of initiated vs. completed cycles on treatment
- Duration (months)
- Cumulative dose (mg)
- Dose intensity (mg/cycle)
- Relative dose intensity (%)

Listings of treatment exposure and compliance will be created to present the information listed above for each subject.

Dose reductions

A dose reduction is defined as a change from the planned dose level to one of the 2 lower dose levels below the RP2D (See CTP Section 6.2.3). The number of subjects with at least one dose reduction will be summarized by frequency and percentage. The minimum dose of the trial treatment will be derived per subject and categorized as reduced to 300 mg or reduced to 200 mg.

Dosing interruptions

A dose interruption is defined as having missed 1 or more planned daily doses. Dosing interruptions will be summarized by planned dose level for the number of subjects with an interruption lasting either 1-2 days, 3-7 days, 8-14 days, and greater than 14 days (The longest interruption and cumulative days of interruption are summarized for each subject.)

Investigational Medicinal Product (IMP) Allocation

A listing of batch numbers of IMP and the subjects receiving IMP from the specific batch will be presented.

16 Endpoint Evaluation

16.1 Primary Endpoint Analysis

Analysis Set: ITT/SAF

Tumor assessments will be performed by the investigator primarily according to the RECIST Version 1.1 and secondarily according to the modified RECIST (mRECIST) for HCC (see CTP appendices J and K). The baseline tumor assessment is scheduled to be performed during the screening period. Tumor response evaluations will then be assessed by computed tomography (CT) or magnetic resonance imaging (MRI), whichever was used at the baseline tumor assessment, at the end of every 2 cycles (i.e. before the start of Cycles 3, 5, 7, 9, 11, 13, and every 4 cycles thereafter until PD). Tumor assessments will be performed at the end of treatment visit for subjects whose last tumor assessment was performed ≥ 6 weeks prior.

The primary endpoint of this study is PFS status at 12 weeks as assessed by the investigator according to RECIST Version 1.1. Progression-free is defined as a subject having a tumor assessment of Complete Response (CR), Partial Response (PR), Non-CR/non-PD, or Stable Disease (SD) 12 weeks after the start of treatment or later.

The number and percentage of individuals who experienced an event (PD or death) at or before 12 weeks will be presented along with the corresponding two-sided exact Clopper-Pearson (2) 90% CI.

The null hypothesis that the rate of progression-free subjects at 12 weeks is less than or equal to 15% will be tested against a one-sided alternative using a binomial exact test with an alpha value of 0.05.

The primary endpoint analyses will be repeated for the subgroups described in Section 10.

16.2 Secondary Endpoint Analyses

Analysis Set: ITT/SAF

16.2.1 Progression Free Survival (PFS)

PFS time is defined as the time from the date of first treatment administration to

- the date of the first documentation of objective PD or
- death due to any cause within 12 weeks of last tumor assessment,

whichever occurs first.

PFS time will be censored at the date of last adequate tumor assessment for subjects who

- do not have an event (PD or death within, less than or equal to 12 weeks of last adequate tumor assessment).

Last adequate tumor assessment is defined as the last tumor assessment result that is CR, PR, Non-CR/non-PD, or SD.

PFS time will be censored on the date of first study treatment for subjects who do not have

- a baseline tumor assessment or
- any post-baseline tumor assessments within, less than or equal to, 12 weeks of first administration of study treatment,

unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

The date of event/censoring is defined as follows:

Status		**Censoring**	**Date of event / censoring**
Progressed or died	Radiological PD or death within, less than or equal to 12 weeks of last adequate tumor assessment	Event	Minimum (Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR, Non-CR/non-PD, or SD or date of first study drug administration, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR, Non-CR/non-PD, or SD or date of first study drug administration, whatever is later

PFS (months) = (date of event/censoring – date of first trial treatment administration + 1)/30.4375

The analysis of PFS per investigator as assessed by RECIST 1.1 and mRECIST will be performed using the following methods:

Kaplan-Meier (i.e. product-limit) estimates of the minimum, maximum, and median PFS time will be presented overall along with 90% CIs for the median calculated according to Brookmeyer

and Crowley (3). In addition, the pattern of censoring will be summarized (e.g. censoring due to death, study withdrawal, lost to follow-up, censoring due to data cut-off).

The number of subjects at risk for death or PD vs. those who have died or experienced progression along with Kaplan-Meier estimates of survival probability at 3, 6, and 12 months will be estimated with corresponding 90% CIs derived using the log-log transformation according to Kalbfleisch and Prentice (4) (i.e. conftype = loglog default option in SAS LIFETEST procedure).

A Kaplan-Meier plot of PFS and a listing of PFS data will be provided. The PFS analyses based on RECIST 1.1described above will be repeated for the subgroups defined in Section 10.

16.2.2 Time to Progression (TTP)

TTP will be measured as the time (in months) from the date of first trial treatment administration to the date of radiological confirmation of PD performed according to RECIST Version 1.1. TTP will be censored at the date of last adequate tumor assessment for subjects that do not experience progression or subjects that experience progression after 2 or more subsequent missing tumor assessments. Subjects that are missing a baseline tumor assessment and/or all post-baseline tumor assessments will be censored at the first date of trial treatment administration.

The date of event/censoring is defined as follows:

Status		Censoring	Date of event / censoring
Progressed	Radiological PD	Event	Date of PD
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR, Non-CR/non-PD, or SD or date of first study drug administration, whatever is later
Didn't progress		Censored	Date of last tumor assessment with outcome CR, PR, Non-CR/non-PD, or SD or date of first study drug administration, whatever is later

TTP (months) = (date of PD/censoring – date of first trial treatment administration + 1)/30.4375

The analysis of TTP per investigator as assessed by RECIST 1.1 will be performed using Kaplan-Meier methods with the same approach for PFS described in Section 16.2.1. TTP per investigator as assessed by mRECIST will be analyzed using the same methods as the analysis of TTP per investigator as assessed by RECIST 1.1.

16.2.3 Time to Symptomatic Progression (TTSP)

TTSP will be measured as the time (in months) from the date of first trial treatment administration to the date of deterioration of symptoms assessed by FHSI-8 (defined as at least a 4-point decrease, i.e., lower score, compared with baseline value), or deterioration to ECOG performance score 4, or death. TTSP will be censored at the last FHSI-8 or ECOG assessment with a non-missing value as of the data cut-off date for subjects that do not experience symptomatic progression. Subjects that are missing a baseline FHSI-8 assessment and all post-baseline ECOG assessments will be censored at the first date of trial treatment administration. The FHSI-8 will be scored using the scoring guidelines (version 4.0) shown in Appendix 2.

The date of event/censoring is defined as follows:

Status	Censoring	Date of event / censoring
Progressed	Event	Earliest date corresponding to deterioration of symptoms (decrease of 4 in FHSI-8 score from baseline, ECOG performance score of 4, or death)
Didn't progress	Censored	Latest date from last FHSI-8 assessment, ECOG assessment, or date of first study drug administration

TTSP (months) = (date of deterioration of symptoms/censoring – date of first trial treatment administration + 1)/30.4375

The analysis of TTSP will be performed using Kaplan-Meier methods with the same approach for PFS described in Section 16.2.1.

16.2.4 Overall Survival (OS) Time

OS time is defined as the time (in months) from the date of first treatment administration to the date of death due to any cause.

The date of event/censoring is defined as follows:

Survival Status	Source	Censoring	Date of event/censoring
Died	Death eCRF	Event	Date of death
Alive as of the data cutoff date (no date of death)	To be determined as defined in Section 11	Censored	Last date known to be alive (defined in Section 11)

OS (months) = (date of death/censoring – date of first trial treatment administration + 1)/30.4375

The analysis of OS will be performed using Kaplan-Meier methods with the same approach for PFS described in Section 16.2.1 and will be repeated for the subgroups described in Section 10. In addition, the pattern of censoring will be summarized (e.g. censoring due to death, study withdrawal, lost to follow-up, censoring due to data cut-off).

16.2.5 Best Overall Response (BOR)

The confirmed best overall response (BOR) is the best response recorded from the start of treatment until PD. The BOR across all time points will be established applying the confirmation criteria based separately on RECIST 1.1 and mRECIST, taking confirmation requirements into account as presented in Table 1. Subjects that do not have measureable disease at baseline may have a BOR of Non-CR/non-PD. This is determined by using Non-CR/non-PD in place of SD in Table 1. CR/PR may be claimed only if the corresponding criteria in Table 1 are met at a subsequent time point. The time gap of two consecutive tumor response evaluations is the difference of two dates (i.e. the earliest scan date of target lesions associated with each assessment visit). SD may be claimed only if the SD criteria are met at least once after first administration at a minimum interval of 42 days. The time interval for SD will be calculated as (date of overall response - first dosing date of trial drug +1). The confirmation of response must not necessarily be at the next scan, but could be at any subsequent scan before PD. For instance, if a subject has PR-SD-PR or PR-not evaluable (NE)-PR at consecutive tumor assessments, the BOR would qualify for PR. The number and percentage of subjects with BOR of CR, PR, SD, PD, Non-CR/non-PD and NE will be summarized once for BOR per investigator as assessed by RECIST 1.1 and again for BOR per investigator as assessed by mRECIST.

Tumor response data will be presented in a listing.

A figure displaying the BOR for each subject along with their percent change from baseline in AFP value will be displayed against time (weeks) in a line plot by the following baseline categories: < 200 ug/L, >= 200 ug/L, < 400 ug/L, and >= 400 ug/L. The BOR for each subject per investigator as assessed by RECIST 1.1 will be indicated in the figure.

A swimmer plot summarizing exposure information and response data will be presented by c-Met status (IHC/ISH). The BOR for each subject per investigator as assessed by RECIST 1.1 will be indicated in the figure. Another identical swimmer plot will be created, but it will display the BOR for each subject per investigator as assessed by mRECIST.

Table 1 – Best Overall Response when Confirmation of CR and PR is Required

Overall response First time point	Overall response Subsequent time point	Best overall response

CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD provided minimum criteria for SD duration met, otherwise NE
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend whether minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Objective tumor response

Objective tumor response will be evaluated by the objective response rate (ORR). The ORR is the proportion of subjects having achieved a BOR of CR or PR. The ORR will be established applying the criteria based on the investigator's assessment using RECIST 1.1. Subjects with a BOR of Non-CR/non-PD (possible only for subjects without measurable disease at baseline) are not considered as having achieved objective response. Therefore these subjects will be counted in the denominator of the rate but not the numerator.

ORR will be summarized along with corresponding two-sided exact Clopper-Pearson (2) 90% CIs.

The above analyses will be repeated using the ORR established by applying the criteria based on the investigator's assessment using mRECIST.

Disease Control

Disease control will be evaluated by the disease control rate, defined as the proportion of subjects having achieved a BOR, per investigator as assessed by RECIST 1.1, of CR, PR, or SD. In case SD is the BOR, SD must be observed at a minimum interval of 42 days after the first dose of study drug. Subjects with a BOR of Non-CR/non-PD (possible only for subjects without measurable disease at baseline) are not considered as having achieved a BOR of CR, PR, or SD . Therefore, these subjects will be counted in the denominator of the rate but not the numerator.

Disease control rate will be summarized along with corresponding two-sided exact Clopper-Pearson (2) 90% CIs.

The above analyses will be repeated using disease control rate defined as the proportion of subjects having achieved a BOR, per investigator as assessed by mRECIST of CR, PR, or SD. SD must be observed at the end of Cycle 2 or later.

Tumor assessments will also be assessed using an 18F-fluoro-D-glucose (FDG) positron emission tomography (PET) scan. All FDG-PET results will be presented in a data listing using data collected from the "Tumor Assessment Using 18F-Fluoro-D-Glucose (FDG) Positron Emission Tomography (PET)" eCRF page.

16.2.6 Duration of Response

The duration of response will be calculated for each subject with a response of CR or PR according to RECIST 1.1 and mRECIST as the time from first observation of response until first observation of documented disease progression or death when death occurs within 12 weeks of the last tumor assessment. For subjects with a response of CR or PR but neither documented disease progression nor death within 12 weeks after the last tumor assessment, the duration of response will be censored at the date of the last adequate tumor assessment.

Duration of response (weeks) = (date of PD or death – date of CR or PR + 1) / 7

Duration of response information will be included on the tumor response listing.

16.2.7 Biological Response

Biological response is defined as the proportion of subjects with a decrease in AFP level of more than 20% at the Cycle 3 assessment, or the last assessment for subjects that terminated treatment prior to the Cycle 3 assessment, as compared with baseline. AFP level is measured at screening, Cycle 1 Day 1 (only if the screening measurement was done more than 7 days prior), Day 1 of every cycle thereafter for which there is a visit, and the End of Treatment visit.

Biological response will be summarized, including corresponding two-sided exact Clopper-Pearson (2) 90% CIs.

If sufficient HGF data is available, scatter plots of best (minimum) on treatment AFP value versus both baseline HGF (CAF and cytoplasmic) will be provided.

Biological response will be flagged on the tumor marker listing. (See Section 17.3.)

16.3 Analysis on Subgroups

Subgroups for analysis are defined in Section 10. The analysis of the primary endpoint (number of progression free subjects at week 12) and PFS and OS will be presented by subgroups.

16.4 Other Endpoint Analyses

Analysis Set: ITT/SAF

16.4.1 Endpoint Analysis per Independent Endpoint Review Committee (IERC)

The PFS, TTP, and BOR per IERC for both RECIST 1.1 and mRECIST will be calculated as a sensitivity analysis to the primary and secondary endpoints. In case of different dates of scans within the same tumor assessment visit, the earliest scan date should be used as the date of tumor assessment.

Overall summary tables per the IERC for both RECIST 1.1 and mRECIST will be produced for PFS and TTP as described in Sections 16.2.1 and 16.2.2, respectively.

Contingency tables for both RECIST 1.1 and mRECIST will be created to compare the following tumor assessment results between IERC and investigators:

- BOR (NE / PD / SD / CR / PR / Non-CR/non-PD / CR + PR)

16.4.2 Sum of Longest Diameters (SOLD)

The sum of longest diameters (SOLD) of viable target lesions is collected on the "Sum of Longest Diameters" eCRF page. The relative change in SOLD of target lesions from baseline will be calculated as follows:

((SOLD of the target lesions at post-baseline – SOLD of target lesions at baseline) / SOLD of target lesions at baseline) *100

The relative change from baseline of SOLD in target lesions as well as occurrence of initial progressive disease with rationale evaluation type (target lesion/non-target lesion/new lesion) will be displayed against time point (weeks since treatment initiation) in spider plots. The baseline relative change is considered "0" on day 1. One plot will be color coded for c-Met status (IHC) and one will be color coded for c-Met status (ISH). Reference lines at +20% and -30% will be shown.

Best relative change in SOLD of target lesions from baseline will be calculated as follows for all subjects that present a measurable tumor at baseline and at least one post-baseline tumor assessment:

((the lowest SOLD of target lesions at post-baseline – SOLD of target lesions at baseline) / SOLD of target lesions at baseline) *100

The best relative change from baseline in SOLD will be displayed using waterfall plots. One plot will be color coded for c-Met status (IHC) and one will be color coded for c-Met status (ISH). Reference lines at +20% and -30% will be shown.

Summary statistics for the SOLD values and their change from baseline over time will be presented.

If sufficient HGF data is available, scatter plots of baseline HGF (both CAF and cytoplasmic) versus the best (minimum) on treatment SOLD value will be presented.

SOLD data including absolute and relative change from baseline values will be listed.

16.4.3 Health-related Quality of Life

Health-related quality of life will be assessed using the FHSI-8 and FACT-HP questionnaires. The data are collected on the "FHSI-8" and "FACT-HP" eCRF pages, respectively.

16.4.3.1 Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8)

FHSI-8 data will be summarized descriptively at baseline and at all scheduled administrations of the questionnaire during the study. FHSI-8 data values range from 0 to 32, with a higher score indicating better quality of life. The data is scored as described in the guidelines in Appendix 2. Changes in FHSI-8 scores from baseline will be summarized by visit. The percentage of subjects missing assessments will be summarized for each scheduled administration of the questionnaires. A listing including FHSI-8 data will be provided. Changes from baseline indicative of deterioration of symptoms (a decrease in overall score of greater than or equal to 4) will be flagged in the listing. The FHSI-8 is presented in Appendix E of the CTP.

16.4.3.2 Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-HP)

FACT-HP data includes, in addition to the generic core (FACT-G), an 18-item module that addresses specific aspects of hepatobiliary cancer. The objective of the FACT-G is to measure health-related quality of life of people with chronic illnesses through 27 items across 4 domains: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The FACT-HP adds 18 items related to disease-specific issues. The FACT-HP questionnaire will be scored by the FACT-Hep scoring guidelines (Version 4.0) in Appendix 3. All FACT-HP scales are scored so that a higher score represents better quality of life. The abbreviations FACT-HP and FACT-Hep both refer to the Functional Assessment of Cancer Therapy – Hepatobiliary questionnaire. The FACT-HP abbreviation is used in the CTP whereas FACT-Hep is used in the scoring guidelines as seen in Appendix 3.

Descriptive statistics for FACT-HP scores and changes from baseline will be summarized at all scheduled administrations of the questionnaires during the study. These scores will include the following:

- FACT-G total score
- FACT-Hep total score
- FACT-Hep Trial Outcome Index (TOI)
- PWB subscore
- SWB subscore
- EWB subscore
- FWB subscore
- Hepatobiliary Cancer Subscale score

The percentage of subjects missing assessments will be summarized for each scheduled administration of the FACT-HP questionnaire. A listing including the PWB, SWB, EWB, FWB, and hepatobiliary cancer subscale, FACT-G total, FACT-Hep total, and FACT-Hep TOI scores will be provided. The FACT-HP is presented in Appendix F of the CTP.

CCI [redacted]

CCI [redacted]

CCI [redacted]

17 Safety Evaluation

Analysis Set: ITT/SAF

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as AEs, laboratory tests and vital signs.

17.1 Adverse Events

Adverse Event definitions:

- **Treatment emergent adverse events:** A treatment emergent adverse event (TEAE) is defined as an adverse event with a start date on or after the date of first dose of tepotinib and up to 33 days after the last treatment administration (the last possible day for the end of trial visit) unless considered drug treatment-related by the investigator, in which case it is classified as a TEAE despite occurring more than 33 days after the last treatment administration. If the onset date of the AE is the same as the date of the first dose, the AE

will not be regarded as treatment-emergent if the onset of the AE was before first study drug administration (according to the information provided on the AEs CRF page).

- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the "Adverse Event Details" eCRF page, Serious Adverse Event = Yes).
- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the "Adverse Event Details" eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (i.e. no answer to the question "Relationship with study treatment").
- **Adverse Events Leading to Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the "Adverse Event Details" eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the "Adverse Event Details" eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Adverse Events of Special Interest (AESI):** adverse events of special interest (amylase increase ≥ grade 3 or lipase increase ≥ grade 3)

All analyses described in Section 17.1 will be based on TEAEs if not otherwise specified. The AE listing will include all AEs (whether treatment-emergent or not). A listing of AESIs will also be provided.

In AE listings, a flag will indicate whether the AE occurred before, during, or after the treatment emergent period.

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of trial treatment then the onset date will be replaced by the minimum of start of trial treatment and AE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.
- Further information after cut-off (like fatal outcome) might be taken from Safety database and included separately into CTR.

17.1.1 All Adverse Events

Adverse events will be summarized in terms of frequency tables by worst National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade, primary

SOC body term as the Body System category and PT as the event category in alphabetical order. Both PT and SOC will be assigned using the latest version of MedDRA.

Each subject will be counted only once within each SOC and PT. If an adverse event is reported for a given subject more than once during treatment, the worst (i.e. maximum) severity and the strongest relationship to trial treatment will be summarized.

In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

An adverse events summary table will be provided. The rows of the summary table will show the overall number and percentage of subjects for each of the following:

- Any TEAE
- Trial treatment-related TEAEs
- Serious TEAEsTrial treatment-related serious TEAEs
- Non-serious TEAEs
- Trial treatment-related non-serious TEAEs
- Any TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Trial treatment-related TEAEs by NCI-CTCAE severity grade (≥3, ≥4)
- TEAEs of special interest (AESI)
- Trial treatment related AESIs
- TEAEs leading to temporary treatment discontinuation
- Trial treatment-related TEAEs leading to temporary treatment discontinuation
- TEAEs leading to permanent treatment discontinuation
- Trial treatment-related TEAEs leading to permanent treatment discontinuation
- TEAEs leading to death
- Trial treatment related TEAEs leading to death

Additionally, frequency tables by primary SOC and PT will be presented for the above, except for (related) TEAEs leading to death, which will be presented in a listing.

17.1.2 Adverse Events Leading to Treatment Discontinuation

See Section 17.1.1.

17.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

17.2.1 Deaths

All deaths and deaths within 33 days after last dose of trial treatment and deaths within 60 days after first trial treatment, as well as "reason for death", will be tabulated based on information from the "Death" and "Survival Follow-Up" eCRFs.

In addition, date and primary reason for death will be provided in an individual subject data listing along with selected dosing information (date of first / last administration of trial treatment). The listing will include a column for AEs with a fatal outcome and will identify deaths that occurred within 33 days of that subject's last administration of trial treatment and within 60 days after first trial treatment.

17.2.2 Serious Adverse Events

Please refer to Section 17.1.1. A subject listing of all SAEs will be provided in addition to the table described in Section 17.1.1.

17.3 Clinical Laboratory Evaluation

Laboratory results are assessed at a local laboratory and will be classified using NCI-CTCAE Version 4.0.

The following will be presented:

- Tables with descriptive statistics and boxplots for both chemistry and hematology values and their changes from baseline by visit
- An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot for total bilirubin and alanine aminotransferase (ALT)
- An eDISH plot for total bilirubin and aspartate aminotransferase (AST)
- For NCI-CTCAE gradable chemistry and hematology parameters:
    - Tables for the worst grade (≥0, ≥3, or ≥4) during the on-treatment period using counts and percentages by laboratory parameter
    - Tables showing shifts from baseline to highest (worst) on-treatment grade (0, 1, 2, 3, or 4) For those parameters which are graded for increase as well as

decrease such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately.

- For non NCI-CTCAE gradable chemistry and hematology parameters:
    - Tables displaying shifts from baseline to abnormal values for the maximum and minimum post-baseline values based on reference range (Low, Normal, or High)

The following hematology parameters were collected:

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count
- Differential white blood cell count
- Platelet count

The following chemistry parameters were collected:

- Blood urea nitrogen (BUN)
- Urea
- Creatinine
- ALT
- AST
- Gamma-glutamyl transpeptidase (GGT)
- Total bilirubin
- Direct fraction of bilirubin (if total is abnormal)
- Lipase
- Amylase
- Total Protein
- Albumin
- Alkaline Phosphatase
- Creatinine Clearance
- Sodium
- Potassium

- Calcium
- Magnesium
- Glucose

The following laboratory parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information:

- Coagulation: prothrombin time, activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR)
- Pregnancy Tests: serum and urine
- Urinalysis: glucose, ketones, blood, pH, proteins, nitrites, leukocytes, and microscopic examination if abnormal urinalysis results
- HBV panel and anti-HCV (hepatitis C virus) antibodies: HBsAg (hepatitis B surface antigen), HBeAg (hepatitis B e antigen), anti-HBc (anti-hepatitis B core antigen), and anti-HCV
- Viral load of HBV/HCV (only for subjects with hepatitis B or hepatitis C, respectively, at screening)
- Tumor markers: serum AFP

Listings of laboratory results will be provided for all laboratory parameters with corresponding normal ranges. These listings will be sorted by parameter and visit for each subject.

17.4 Vital Signs

Vital sign data was collected on the "Vital Signs" eCRF page. For the definition of baseline, see Section 11.

Table 2. Categories of Change from Baseline for Vital Sign Parameters

Parameters, baseline categories	Categories of Change from Baseline
Body temperature increase < 37°C; 37 - <38°C; 38 - <39°C; 39 - <40°C; ≥ 40°C	< 1°C , 1-<2°C , 2-<3°C, ≥ 3 °C
Heart rate increase from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Systolic Blood Pressure (SBP) increase from baseline	≤20 mmHg, >20 – 40 mmHg, >40 mmHg

<140 mmHg; ≥ 140 mmHg	
SBP decrease from baseline <140 mmHg; ≥ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
Diastolic Blood Pressure (DBP) increase from baseline <90 mmHg; ≥ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from baseline <90 mmHg; ≥ 90 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
Weight increase	<10%, ≥10%
Weight decrease	<10%, ≥10%

The following summaries will be prepared for vital sign parameters as grouped in Table 1:

- Maximal Shifts from baseline to worst-on treatment value (changes in categories, including total rows/columns)
- Listing of highest on-treatment change from baseline per subject
- Minimum and maximum absolute and change from baseline values

17.5 ECG

ECG results were collected on the "Electrocardiogram" eCRF page. Triplicate measurements are collected for all ECG parameters. The average of the triplicate measurements at each visit will be used for analysis purposes.

QTcF intervals will be derived as follows:

Fridericia's Correction (QTcF) $$QTc_f = \frac{QT}{\sqrt[3]{RR}}$$

where: RR = RR interval measured in seconds.

The worst shifts in the overall ECG assessment (e.g., normal, abnormal (not clinically significant), abnormal (clinically significant)) from baseline during the on-treatment period will be summarized. The incidence and percentage of subjects with clinically significant abnormalities at any time during the on-treatment period will be summarized by ECG parameter. The clinically significant abnormal criteria are provided in Table 3.

Table 3. Clinically Significant Criteria for ECG Test Results

Test	Clinically Significant Abnormality Criteria
PR Interval	≥ 220 msec and increase from baseline ≥ 20 msec
QTcF Interval - absolute	>450 msec, >480 msec, and >500 msec
QTcF Interval - change from baseline	Increase from baseline > 30 msec and ≤ 60 msec; Increase from baseline > 60 msec

A listing of 12-lead ECG data will be provided including information collected on the "Electrocardiogram" eCRF form and relevant derived variables.

17.6 ECOG Performance Status

ECOG PS data is collected on the "ECOG Performance Status" eCRF page, and the ECOG shift from baseline to highest score during the on-treatment period will be summarized. A listing including all ECOG PS information will be provided, and ECOG PS with a shift from ECOG PS = 0 or 1 to 2 or higher will be flagged. The ECOG PS is presented in Appendix A of the CTP.

18 Benefit Risk Assessment

A formal benefit-risk assessment will not be performed as part of the analysis.

19 References

1. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550-558.

2. Agresti A. Categorical Data Analysis (2nd Ed.). New Jersey: John Wiley & Sons, Inc. 2002: 18-20.

3. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics 1982;38:29-41.

4. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data, New York: John Wiley & Sons 1980.

20 Appendices

Appendix 1 Important Protocol Deviations

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Inclusion criteria: **For the subject to be eligible for inclusion, each criterion must be checked 'YES':**					
Criterion 1: Histologically confirmed HCC	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 1.	PDEV01	Section 5.3.1	Medical review required
Criterion 2: Child Pugh Class A liver function score	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 2.	PDEV02	Section 5.3.1	Medical review required
Criterion 3: MET+ Status	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 3.	PDEV03	Section 5.3.1	Medical review required
Criterion 4: Availability of a pretreatment tumor biopsy	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 4.	PDEV04	Section 5.3.1	Medical review required
Criterion 5: Male or female, 18 years of age or older	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 5.	PDEV05	Section 5.3.1	Medical review required
Criterion 6: Measureable disease in accordance with RECIST Version 1.1	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 6.	PDEV06	Section 5.3.1	Medical review required
Criterion 7: ECOG PS of 0 or 1	Eligibility and Entry Criteria	Subject did not meet inclusion criterion 7.	PDEV07	Section 5.3.1	Medical review required
Criterion 8: Previously treated with sorafenib for >= 4 weeks and discontinued at least 14 days prior to Day 1 due to either intolerance or radiographic progression	Inclusion/Exclusion criteria	Subject did not meet inclusion criterion 8.	PDEV08	Section 5.3.1	Medical review required
Criterion 9: Signed and dated informed consent	Inclusion/Exclusion criteria	Subject did not meet inclusion criterion 9.	PDEV09	Section 5.3.1	Medical review required
Exclusion criteria: **For the subject to be eligible for inclusion, each criterion must be checked 'NO':**					
Criterion 1: Prior systemic anticancer treatment for advanced HCC (except for sorafenib)	Eligibility and Entry Criteria	Subject met exclusion criterion 1	PDEV10	Section 5.3.2	Medical review required
Criterion 2: Prior treatment with any agent targeting the HGF/c-Met pathway	Eligibility and Entry Criteria	Subject met exclusion criterion 2	PDEV11	Section 5.3.2	Medical review required
Criterion 3: Local-regional therapy within 4 weeks before Day 1	Eligibility and Entry Criteria	Subject met exclusion criterion 3	PDEV12	Section 5.3.2	Medical review required

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Criterion 4: Laboratory Index at Baseline: • Hemoglobin ≤ 8.5 g/dl; • Neutrophils < 1.5 x 109/L; • Platelets < 60 x 109/L; • Total bilirubin > 3 mg/dl; • AST or 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;	Eligibility and Entry Criteria	Subject met exclusion criterion 4	PDEV13	Section 5.3.2	Medical review required
Criterion 5: Past or current history of neoplasm other than HCC	Eligibility and Entry Criteria	Subject met exclusion criterion 5	PDEV14	Section 5.3.2	Medical review required
Criterion 6: Known central nervous system or brain metastasis (either symptomatic or untreated)	Eligibility and Entry Criteria	Subject met exclusion criterion 6	PDEV15	Section 5.3.2	Medical review required
Criterion 7: Medical history of conditions that may hamper compliance and/or absorption of tested products	Eligibility and Entry Criteria	Subject met exclusion criterion 7	PDEV16	Section 5.3.2	Medical review required
Criterion 8: Clinically significant gastrointestinal bleeding within 4 weeks before trial entry	Eligibility and Entry Criteria	Subject met exclusion criterion 8	PDEV17	Section 5.3.2	Medical review required
Criterion 9: Peripheral neuropathy Grade >= 2	Eligibility and Entry Criteria	Subject met exclusion criterion 9	PDEV18	Section 5.3.2	Medical review required
Criterion 10: Impaired cardiac function	Eligibility and Entry Criteria	Subject met exclusion criterion 10	PDEV19	Section 5.3.2	Medical review required
Criterion 11: Uncontrolled hypertension by standard medication	Eligibility and Entry Criteria	Subject met exclusion criterion 11	PDEV20	Section 5.3.2	Medical review required

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Criterion 12: Known human immunodeficiency virus	Eligibility and Entry Criteria	Subject met exclusion criterion 12	PDEV21	Section 5.3.2	Medical review required
Criterion 13: Known or suspected drug hypersensitivity to any ingredients of MSC2156119J	Eligibility and Entry Criteria	Subject met exclusion criterion 13	PDEV22	Section 5.3.2	Medical review required
Criterion 14: Female subjects must have negative pregnancy test prior to enrollment	Eligibility and Entry Criteria	Subject met exclusion criterion 14	PDEV23	Section 5.3.2	Medical review required
Criterion 15: Concurrent treatment with non-permitted drug	Eligibility and Entry Criteria	Subject met exclusion criterion 15	PDEV24	Section 5.3.2	Medical review required
Criterion 16: Substance abuse, chronic medical or psychiatric condition or laboratory abnormalities that increase risk associated with trial participation	Eligibility and Entry Criteria	Subject met exclusion criterion 16	PDEV25	Section 5.3.2	Medical review required
Criterion 17: Prior treatment with MSC2156119J or other c-Met inhibitors	Eligibility and Entry Criteria	Subject met exclusion criterion 17	PDEV26	Section 5.3.2	Medical review required
Criterion 18: Participation in another interventional clinical trial within 28 days prior to Day 1	Eligibility and Entry Criteria	Subject met exclusion criterion 18	PDEV27	Section 5.3.2	Medical review required
Criterion 19: Previous anticancer treatment-related toxicities not recovered to Grade 0-1 or baseline	Eligibility and Entry Criteria	Subject met exclusion criterion 19	PDEV28	Section 5.3.2	Medical review required
Criterion 20: History of liver transplant	Eligibility and Entry Criteria	Subject met exclusion criterion 20	PDEV29	Section 5.3.2	Medical review required
Criterion 21: Active or uncontrolled infections except chronic HBV, chronic HCV, or both	Eligibility and Entry Criteria	Subject met exclusion criterion 21	PDEV30	Section 5.3.2	Medical review required
Criterion 22: Concurrent medical condition or disease that compromises trial conduct	Eligibility and Entry Criteria	Subject met exclusion criterion 22	PDEV31	Section 5.3.2	Medical review required
Non-permitted concomitant medication during the study	Prohibited Medications	Subjects that took non permitted medications and were not withdrawn	PDEV32	Section 6.5.2	Medical review required

	Category of Protocol Deviation	Description of Protocol Deviation	Deviation Code	Protocol Section	Proposed check / comment
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that became pregnant during the study and were not withdrawn	PDEV33	Section 5.5.1	Medical review required
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that had QTc > 500 msec or change of QTc from baseline > 60 msec and were not withdrawn	PDEV34	Section 5.5.1	Programmed to check if QTc > 500 msec or change from baseline > 60 msec
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that were not compliant with administration of MSC2156119J and were not withdrawn	PDEV35	Section 5.5.1	Medical review required
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects with documented progression of disease that were not withdrawn	PDEV36	Section 5.5.1	Medical review required
Subjects that developed withdrawal criteria while on the study but were not withdrawn	Other criteria	Subjects that initiated other anticancer treatment and were not withdrawn	PDEV37	Section 5.5.1	Medical review required.
Subjects dosing error	Study Medication	Subject had dosing error.	PDEV38	Section 6.2	List if relative dose intensity over or equal to 110% or less than or equal to 90%.
CCI					
Any other protocol deviation which is deemed to be significant but has not been pre-specified in this table For Clinically Important PD	Any	Any	PDEV98	NA	Medical review required

Appendix 2 FHSI-8 Scoring Guidelines

FACT Hepatobiliary Symptom Index (FHSI-8)

Scoring Guidelines (Version 4)

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Subscale	Item Code	Reverse item?		Item response	Item Score
FHSI-8	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-32	C2	4	-	_____	=_____
	CNS7	4	-	_____	=_____
	HI7	4	-	_____	=_____
	Hep2	4	-	_____	=_____
	Hep8	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 8: _____
Divide by number of items answered: _____ **=FHSI-8 score**

Appendix 3 FACT-HP Scoring Guidelines

FACT-Hep Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-Hep).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

FACT-Hep Scoring Guidelines (Version 4) – Page 2

Subscale	Item Code	Reverse item?		Item response	Item Score
HEPATOBILIARY	C1	4	-	_____	=_____
CANCER	C2	4	-	_____	=_____
SUBSCALE	C3	0	+	_____	=_____
(HCS)	C4	0	+	_____	=_____
	C5	4	-	_____	=_____
Score range: 0-72	C6	0	+	_____	=_____
	Hep1	4	-	_____	=_____
	Cns7	4	-	_____	=_____
	Cx6	4	-	_____	=_____
	HI7	4	-	_____	=_____
	An7	0	+	_____	=_____
	Hep2	4	-	_____	=_____
	Hep3	4	-	_____	=_____
	Hep4	4	-	_____	=_____
	Hep5	4	-	_____	=_____
	Hep6	4	-	_____	=_____
	HN2	4	-	_____	=_____
	Hep8	4	-	_____	=_____

Sum individual item scores:_____
Multiply by 18: _____
Divide by number of items answered: _____=**HC Subscale score**

To derive a FACT-Hep Trial Outcome Index (TOI):
Score range: 0-128

_____ + _____ + _____ =_____=**FACT-Hep TOI**
(**PWB** score) (**FWB** score) (**HCS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-Hep total score:
Score range: 0-180

_____ + _____ + _____ + _____ + _____ =_____=**FACT-Hep Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**HCS** score)