# Appendix 16.1.9 Documentation of Statistical Methods

- Statistical Analysis Plan for Phase Ib, Version 1.0, Amend 1.0; 08 May 2017
- Statistical Analysis Plan for Phase II, Version 1.1; 12 February 2018

# Statistical Analysis Plan for Phase Ib

| | |
|---|---|
| **Clinical Trial Protocol Identification No.** | EMR 200095-004 |
| **Title:** | A Multicenter, Treated, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy Versus Sorafenib in Asian Subjects with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function |
| **Trial Phase** | Phase Ib/II |
| **Investigational Medicinal Product(s)** | MSC2156119J (Tepotinib) |
| **Clinical Trial Protocol Version** | 24 Mar 2017/Version 4.0 |
| **Statistical Analysis Plan Author** | PPD |
| **Statistical Analysis Plan Date and Version** | 30 Dec 2016/ Version 1.0<br>08 May 2017/ Final Amend 1.0 |
| **Statistical Analysis Plan Reviewers** | PPD, Senior Statistical Reviewer, PPD<br>PPD, Trial Biostatistician, Merck Serono<br>PPD, PPD, Merck Serono<br>PPD, PPD, Merck Serono<br>PPD, PPD, Merck Serono |

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# 1 Signature Page

**Statistical Analysis Plan for Phase Ib:** EMR 200095-004

A Multicenter, Treated, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy Versus Sorafenib in Asian Subjects with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function

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# 1 Signature Page

**Statistical Analysis Plan for Phase Ib:** EMR 200095-004

A Multicenter, Treated, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy Versus Sorafenib in Asian Subjects with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function

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# 2 Table of Contents

# 3 List of Abbreviations and Definition of Terms

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| AST | Aspartate Aminotransferase |
| ATP | Adenosine Triphosphate |
| AUC | Area Under the Curve |
| $AUC_{0-t}$ | Area Under the Concentration-time Curve from Time Zero to the Last Quantifiable Concentration |
| $C_{av}$ | Average Plasma Concentration |
| CHF | Congestive Heart Failure |
| CI | Confidence Interval |
| CL/F | Apparent Systemic Clearance |
| $C_{max}$ | Maximum Plasma Concentration |
| c-Met | Mesenchymal-Epithelial Transition Factor Gene |
| $C_{min}$ | Minimum Plasma Concentration |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMS | Clinical Trial Management System |
| CV | Coefficient of Variation (%) |
| DBP | Diastolic Blood Pressure |
| DLT | Dose-Limiting Toxicity |
| DNA | Deoxyribonucleic Acid |
| DS | Drug Substance |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GeoCV | Geometric Coefficient of Variation |
| GeoMean | Geometric Mean |
| GGT | Gamma-Glutamyl Transpeptidase |
| GMP | Good Manufacturing Practice |
| HBeAg | Hepatitis B extracellular antigen |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HR | Hazard ratio |
| HIV | Human Immunodeficiency Virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISH | In Situ Hybridization |
| ITT | Intent-to-Treat |
| IVRS | Interactive Voice Response System |
| LCSS | Lung Cancer Symptom Scale |
| LLOQ | Lower Level of Quantification |
| LVEF | Left Ventricular Ejection Fraction |
| 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 $C_{max}$ |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| MW | Molecular Weight |

| | |
|---|---|
| NCI | National Cancer Institute |
| OR | Objective Response |
| OS | Overall Survival |
| PD | Progressive Disease |
| Pd | Pharmacodynamics |
| PET | Positron Emission Tomography |
| PFS | Progression Free Survival |
| P-gp | P-Glycoprotein |
| PGx | Pharmacogenomics |
| PK | Pharmacokinetics |
| PoC | Proof of Concept |
| PP | Per Protocol |
| PR | Partial Response |
| PT | Prothrombin Time |
| PTF | Peak Trough Fluctuation Ratio (in %) |
| $R_{acc(AUC)}$ | Accumulation Factor for $AUC_{\tau}$ |
| $R_{acc(Cmax)}$ | Accumulation Factor for $C_{max}$ |
| RBC | Red Blood Cells |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic Acid |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Stable Disease |
| SEM | Standard Error of the Mean |
| SMC | Safety Monitoring Committee |
| StD | Standard Deviation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $\tau$ | Dosing Interval |
| $t_{1/2}$ | Half-Life |
| TEAE | Treatment-Emergent Adverse Event |
| TKI | Tyrosine Kinase Inhibitor |

| | |
|---|---|
| $t_{lag}$ | Time Prior to the First Quantifiable Concentration |
| $t_{max}$ | Time to Maximum Concentration |
| TNM | Tumor, Lymph Nodes, Metastasis |
| TTSP | Time to Symptom Progression |
| UDP | Uridine 5'-Diphospho |
| ULN | Upper Limit of Normal |
| $V/_f$ | Volume of Distribution |
| $V_{ss/f}$ | Volume of Distribution at Steady State |
| $V_{z/f}$ | Apparent Volume of Distribution Associated to the Terminal Phase |
| WBC | White Blood Cells |
| $\lambda z$ | Terminal Phase Rate Constant |

# 4 Modification History

| Unique Identifier for SAP Version | Date of SAP Version | Author | Changes from the Previous Version |
|---|---|---|---|
| Final V1.0 | 02Dec2016 | PPD | Not Applicable – First Version |
| Amend v1.0 | 26Mar2017 | PPD | Add CCI sections and update per dry run comments |
| Final Amend V1.0 | 08May2017 | PPD | Update review comment |

# 5 Purpose of the Statistical Analysis Plan

The purpose of this SAP is to document technical and detailed specifications for the phase Ib final analysis of data collected for protocol EMR 200095-004 Version 4.0 dated 24Mar2017 and Version 4.1 dated 27Mar2017 for Korea only. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). 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 CSR but not identified in this prospective SAP will be clearly identified in the CSR.

The SAP is based upon section 8 (Statistics) of the trial protocol and is prepared in compliance with ICH E9.

# 6 Summary of Clinical Trial Features

| | |
|---|---|
| **Trial Objectives** | **Primary Objectives**<br>• To confirm the recommended Phase II dose (RP2D) of MSC2156119J administered orally once daily at a 21-day cycle in subjects with advanced hepatocellular carcinoma (HCC) and Child-Pugh class A liver function. The target RP2D in HCC subjects is the RP2D as determined in the global first-in-man (FIM) trial, i.e., 500 mg once daily<br>**Secondary Objectives**<br>• To characterize the single and multiple dose pharmacokinetics (PK), preliminary antitumor activity, and biochemical response of MSC2156119J in Asian subjects with HCC and Child-Pugh class A liver function<br>**Exploratory Objectives** |

| | |
|---|---|
| | • CCI [redacted] |
| **Trial design and plan** | Phase Ib will be an open label, single arm trial at selected sites in mainland China, South Korea, and Taiwan.<br><br>The classical "3+3" design will be applied for sites in South Korea and Taiwan, with a dose escalation phase and a dose confirmation phase. In addition and separate from the "3+3" trial cohorts, the SMC may recommend to add up to an additional 12 subjects in 1 or more dose cohorts at dose levels at or above the RP2D, and up to 3 subjects will be enrolled in a separate cohort at selected sites in mainland China. |
| **Planned number of subjects** | Up to 21 subjects, including 18 subjects from South Korea and Taiwan following a "3+3" dose escalation method. The SMC may recommend to enroll up to an additional 12 subjects in one or more dose cohorts at dose levels at or above the RP2D. Up to an additional 3 subjects from the mainland China sites. |
| **Schedule of visits and assessments** | Subjects will be screened for up to 14 days prior to study treatment. Informed consent will be obtained prior to performing any trial assessment.<br><br>MSC2156119J (Phase Ib) will be administered once daily over a 21-day cycle, which may repeat until disease progression (as determined by the investigator), intolerable toxicity, or withdrawal from the trial.<br><br>For Phase Ib, scheduled visits during the treatment period will occur on Days 1, 2, 8, and 15 of Cycle 1; Days 1, 8, and 15 of Cycle 2; and Day 1 of Cycles ≥ 3.<br><br>At each scheduled visit during the treatment period, physical examination/weight, vital signs (except as noted below), hematology, coagulation, chemistry, adverse events (AEs), and concomitant medication assessments will be performed.<br><br>Subjects will also be assessed at the discontinuation of the trial medication. Study drug post-treatment follow-up visit will be performed within 30 ± 3 days after the last dose for subjects who discontinue the trial medication. Survival data (subject survival and anticancer therapies) in Phase Ib will be collected every 3 months (± 2 weeks) after the dose of study drug. Subjects will be contacted by telephone. |

| | |
|---|---|
| **Primary endpoints** | • Incidence of subjects experiencing at least 1 dose limiting toxicity (DLT) within the first administration cycle (i.e., 21 days after the first dose)<br><br>• Incidence and type of other AEs |
| **Secondary endpoint(s)** | Secondary efficacy endpoints are:<br><br>• Progression-free survival (PFS) assessed by investigator. PFS time is defined as the time (in months) from first administration to either first observation of disease progression or occurrence of death due to any cause within 84 days of either first administration or the last tumor assessment.<br><br>• Overall survival (OS) time. OS time is defined as the time (in months) from first administration to the date of death.<br><br>• TTP assessed by investigator. TTP is defined as the time (in months) from first administration to date of the observation of radiological PD assessed by the investigator.<br><br>• Objective response (OR). OR is defined as complete response (CR) or partial response (PR) as the best overall response according to local radiological assessments from first administration to first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1.<br><br>• Disease control. Disease control is defined as CR, PR, or stable disease (SD) as the best overall response according to local radiological assessments from the date of first administration to the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after first administration.<br><br>Secondary safety endpoints are:<br><br>• Drug exposure.<br><br>• Incidence and type of AEs (all grades as per the National Cancer Institute's (NCI)-CTCAE version 4.0): all treatment emergent adverse events (TEAEs), related TEAEs, treatment emergent serious adverse events (SAEs), related treatment emergent SAEs, TEAEs of NCI-CTCAE (version |

| | |
|---|---|
| | 4.0) with Grade ≥ 3, related TEAEs ≥ Grade 3, and TEAEs leading to permanent/temporary treatment discontinuation.<br>• Incidence and reasons for deaths, including deaths within 33 days after the last dose of study drug.<br>• Safety laboratory tests graded by NCI-CTCAE (version 4.0).<br>• Vital signs; 12-lead ECG changes; physical examinations, including change in body weight; and ECOG PS. |
| **Pharmacokinetics** | • PK endpoint : area under the curve from time zero to time t (AUC0-t), area under the plasma concentration versus time curve within 1 dosing interval (AUC0-tau), maximum concentration (Cmax), average plasma concentration within 1 dosing interval (Cav), observed minimum plasma concentration (Cmin), time to maximum concentration (tmax), area under the curve from time zero to infinity following last administration (AUC0-∞), apparent clearance (CL/f), apparent volume distribution associated to the terminal phase (Vz/f), volume of distribution at steady state (Vss/f), area under the curve terminal phase rate constant (λz), and half-life (t1/2) when appropriate |
| **Exploratory endpoints** | • CCI [redacted] |

# 7 Sample Size

For Phase Ib, the total number of subjects in this trial is up to 21. Of these subjects, up to 18 will be enrolled based on the "3+3" dose-escalation method with 2 dose cohorts: 3 to 6 subjects in the first dose cohort and 3 to 12 subjects in the second dose cohort (if dose de-escalation does not occur). In addition, separate from the "3+3" dose escalation cohorts, the SMC may recommend to enroll up to an additional 12 subjects in 1 or more dose cohorts at or above the RP2D, and up to 3 subjects will be enrolled in the mainland China sites. The final sample size will depend on the number of subjects who experience DLTs observed at each dose level, the number of dose levels explored, the safety data, and the decision from the SMC meeting.

# 8 Overview of Planned Analyses for Phase Ib

The methods described in this document will be applied to the preparation of tables, figures and listings (TLFs) for the Phase Ib CSR. Statistical analyses will be performed using cleaned electronic clinical report form (eCRF) data collected.

This SAP will cover the final analysis only.

# 9 Changes to the Planned Analyses in the Clinical Trial Protocol

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

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# 10 Protocol Deviations and Analysis Sets

## 10.1 Definition of Protocol Deviations

Protocol deviations describe how close the study has been conducted according to the protocol as expected per GCP. Some of these deviations may be significant contributors to analysis bias.

Important protocol deviations are a subset of 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.

The following, but not limited to, are defined as important protocol deviations:

- 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 an excluded concomitant medication;
- Deviation from GCP.

A data review will be held to discuss and update the definition of important protocol deviations so as to determine the evaluability of the subjects prior to database lock.

## 10.2 Definition of Analysis Sets and Subgroups

**Screening Analysis Set**

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

**DLT Analysis Set:**

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

**Safety Analysis Set (SAF)**

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

The SAF will be used for summaries of demographic and baseline characteristics, as well as for summary of safety and efficacy data per dose and in total. And analyses performed on the SAF will consider subjects as treated.

**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 * tepotinib median $t_{max}$, etc.) affecting PK. This analysis set will be used for summaries of the PK data for tepotinib and its metabolites. If a subject undergoes a tepotinib dose change after Cycle 1 Day 1, their PK data will no longer be included in the PK Analysis Set from the time of the change.

All PK data will be included in listings regardless of whether or not they are included in the PK analysis set.

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# 11 General Specifications for Statistical Analyses

All statistical analyses will be performed using SAS® version 9.2.

Unless otherwise indicated baseline characteristic data will be presented separately for the treatment cohorts and for overall, safety data and efficacy data will be presented separately for the treatment cohorts and overall.

**Data handling after cut-off date:**

In general, if a cut-off date is set, data obtained after the cut-off will not be displayed in any listings or used for summary statistics, e.g. laboratory values of samples taken after data cut-off, AE with onset date after data cut-off, death, etc. will not be included in any analysis or listing. The only exceptions are the date of death and the date last known to be alive from the "Subject Follow-up" eCRF.

In particular, the following steps will be taken to derive and report some eCRF data that might be potentially affected by the cutoff date:

- If the last known alive date is after the cutoff date, the date will be updated to the cutoff date.
- If the death date is after the cutoff date, the death date will be set to missing, and the last known alive date will be updated to the cutoff date.

Stop dates are not affected by this rule, e.g. a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed

**Pooling of centers:**

Because of the high number of participating centers and the anticipated small number of subjects treated in each center data will be pooled across centers.

**Significance level:**

All statistical analysis mentioned in this SAP are in a descriptive manner, no formal tests are to be performed. If confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 90%, unless otherwise in this SAP specified.

**Presentation of continuous and qualitative variables:**

Continuous variables will be summarized using the following descriptive statistics unless otherwise specified (see Section **Error! Reference source not found.**), i.e.

- number of subjects (N), number of subjects with non-missing values
- mean, standard deviation
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum, and maximum,

Categorical variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the sample size of the population of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

**Trial day and treatment day:**

Trial day/ Treatment day are defined relative to the date of first administration of trial drug. Day 1 is defined as the day of the first administration, the day before is defined as Trial day –1 (no Trial day 0 is defined).

- Trial day or treatment day =
    - date of event – the date of first administration, if date of event < the date of first administration
    - or date of event – the date of first administration + 1 , if date of event ≥ the date of first administration

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Trial Day or Treatment Day, and any corresponding durations will be presented as missing. Rules of handling missing dates relevant to efficacy will specified in the subsequent sections.

**Definition of baseline:**

In general the last non-missing measurement prior to or on the day of first administration will serve as the baseline measurement.

**Definition of on-treatment value:**

On-treatment data refers to assessment values collected after the first study drug administration of any trial drug and within 33 days (inclusive) after the last study drug administration.

**Unscheduled visits and end of treatment data:**

Unscheduled measurements and end of treatment data will contribute to worst case value.

Listings will include all scheduled, unscheduled and end of treatment data.

End of treatment data will be presented separately by its nominal visit name in the by-visit summaries.

**Visit Windowing conventions:**

No visit windowing will be performed for this study. The by-visit summaries are based on subjects who have available data or who are expected to have available data only. Subjects who are expected to have available data are subjects who are still in the trial at the visit, that is, the planned visit date is <= the discontinuation date of the "Study Procedure Termination" eCRF form.

**Definition of duration:**

Duration will be calculated by the difference of start and stop date + 1 if not otherwise specified. For example, survival time (days) = date of death - the date of first administration + 1.

**Common calculations:**

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

**Conversion factors:**

Unless specified, Conversion of days to months /years will be defined as:

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

**Handling of missing data:**

Unless otherwise specified, missing data will not be replaced.

In all subject data listings imputed values will be presented and the respective imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd".

For the derivation of new date variables the following rules will apply:

- Partial birth dates will be handled this way: day will be imputed as 15 if it is missing, and month imputed as June if missing. If both of day and month are missing, they will be imputed as July 1st. If year is missing then the date will not be imputed.
- For imputing missing parts of dates for the efficacy analyses the missing day in a date will be imputed as the 15th of the month, if month and year is documented. This includes also dates of start of follow-up therapy.
- In case the last administration date is incomplete the date of last administration will be taken from the Treatment Termination eCRF page.
- 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.
- In all other cases missing or incomplete dates will not be imputed if not indicated otherwise.

# 12 Trial Subjects

This section includes specifications for reporting subject disposition and treatment/trial discontinuations.

## 12.1 Disposition of Subjects and Discontinuations

*Population: Screening Analysis Set*

All subjects who provide informed consent will be accounted for in this study. Subject disposition and withdrawals will be presented for the screening analysis set.

The following summaries will be provided for overall and each dose level when applicable:

- Total number of subjects screened (i.e. subjects who gave informed consent)
- Number of subjects who completed the screening phase, but discontinued from the trial prior to the date of first administration
- Number of subjects who did not complete the screening phase grouped by the main reasons, that is, screening failures
- Number of subjects treated
- Number of subjects who completed the treatment. A subject who completed treatment is defined as the subject died or the subject has been assessed as having progressive disease
- Number of subjects who discontinued the study treatment after the first administration, grouped by the main reason
- Number of subjects in survival follow up

## 12.2 Protocol Deviations

### 12.2.1 Important Protocol Deviations

*Population*: *Safety Analysis Set*

Important protocol deviations will be based upon the Clinical Trial Management System (CTMS) data and determined for all subjects by medical review processes. All the important protocol deviations will be included in Study Data Tabulation Model (SDTM) datasets, if identified by means of medical review. The Analysis Data Model (ADaM) datasets will be derived from SDTM and include all important protocol deviations.

A data review will be held to discuss and update the definition of important protocol deviations so as to determine the evaluability of the subjects prior to database lock.

The following outputs will be provided:

- Summary of important protocol deviations

# 13 Demographics and Other Baseline Characteristics

*Population: Safety Analysis Set*

Demographic data and other baseline characteristics will be presented using summary statistics for continuous variables and frequency tables for categorical variables.

## 13.1 Demographics

Demographic characteristics will be summarized using the following information from the Screening/Baseline visit CRF pages.

Demographic characteristics:

- Age (years): summary statistics, age will be presented to 1 decimal place.
- Age in categories: <65 years, >=65 years (65 -< 75, 75 -< 85, >= 85 years)
- Gender: male, female
- Race: Asian, other
- Region: Taiwan, South Korea, Mainland China
- Pooled region of site: Greater China (i.e. mainland China and Taiwan), outside of Greater China

Specifications for computation of age (years):

(date of given informed consent - date of birth + 1) / 365.25

## 13.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using Medical Dictionary for Regulatory Activities (MedDRA), current version, preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

## 13.3 Other Baseline Characteristics, Anti-Cancer Therapy and Surgery

### 13.3.1 Disease History

Information on disease history collected on the "Disease History" eCRF form at the pre-treatment evaluation visit will be presented. Summaries and listings will be presented for

- Site of Primary Tumor
- Time since initial diagnosis (months)

Time since initial diagnosis (months) = (date of informed consent – date of initial diagnosis+1) / 30.4375.

- Time since first occurrence of metastatic or locally advanced disease(months)
  Time since first occurrence of metastatic or locally advanced disease (months) = (date of informed consent – date of the first occurrence of metastatic or locally advanced disease +1) / 30.4375.
- BCLC Stage at Initial Diagnosis: 0, A, B, C, D
- BCLC Stage at Study Entry: 0, A, B, C, D
- Tumor histology
  - Macroscopic
  - Microscopic
  - Vascular invasion
  - Grading
- Metastatic sites at the first diagnosis
- Metastatic sites at the study entry

### 13.3.2 Other Baseline Characteristics

The following baseline characteristics will be summarized for this study:

- Height (cm)
- Weight (kg)
- BMI ($kg/m^2$): BMI ($kg/m^2$) is derived as weight (kg) / height $(m)^2$
- Nicotine and alcohol consumption
- ECOG at baseline
- Alpha-fetoprotein (AFP) elevation at the baseline: >=200 IU/ml, <200 IU/ml

  Elevated AFP refers to a state where AFP is above the reference range.
- Viral serology at baseline
  - HBsAg: negative vs. positive
  - Anti-HBc: negative vs. positive
  - HBeAg: negative vs. positive
  - Anti-HCV: negative vs. positive
  - HBV carrier: HBeAg is positive but HBsAg, anti-HBc and anti-HCV are all negative.

Baseline characteristics with respect to hematology/biochemistry, vital signs, ECG will be part of Section 17.

### 13.3.3 Prior Anti-Cancer Therapy and Surgery

Prior anti-cancer therapy and surgery information, including drug therapies, radiotherapy, local-regional therapies and surgeries will be summarized.

- Prior anti-cancer drug therapy
    - Any prior anti-cancer drug therapy (yes/ no)
    - Type of systemic therapy
    - Intent of therapy
    - Prior anti-cancer therapy drugs, preferred terms will be presented alphabetically
    - Number of prior anti-cancer therapy lines
    - Number of prior anti-cancer therapy lines for locally advanced/metastatic/palliative disease
    - Sequence number of previous TKI therapy lines

      Lines of previous TKI anti-cancer therapies are those lines collected on the "Prior Anti-Cancer Drug Therapies Details" eCRF and containing one or more TKI therapies. The TKI therapies will those whose type of systemic therapy="Kinase inhibitors".
    - The sequence number of the immediate TKI therapy line

      An immediate prior TKI therapy is the one which meets: 1) the corresponding line is the last one reported on the "Prior Anti-Cancer Drug Therapies Details" eCRF, 2) the therapy is a TKI therapy.
    - Best response
- Prior anti-cancer radiotherapy
    - Any prior anti-cancer radiotherapy
    - Intent of therapy
    - Number of prior anti-cancer radiotherapies
    - Best response
- Prior anti-cancer local-regional therapy
    - Any prior anti-cancer local-regional therapy
    - Type of therapy
    - Intent of therapy
    - Number of prior anti-cancer local-regional therapy
    - Outcome of therapy
- Prior anti-cancer surgery
    - Any prior anti-cancer surgery
    - Prior anti-cancer surgeries, preferred terms will be presented alphabetically
    - Number of prior anti-cancer surgeries
    - The surgery was curative in intent (yes/ no)

- Outcome of surgery

[redacted]

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[redacted]

## 14 Previous and Concomitant Medications/Procedures

*Population: Safety Analysis Set*

## 14.1 Previous and concomitant medications:

The medications recorded on the "Concomitant Medication Details" eCRF form will be used as data source.

All terms will be coded using the most current World Health Organization Drug Dictionary (WHO Drug) version at the time of database lock. Medications will be presented using the Anatomical Therapeutic Chemical (ATC) classification system. Numbers of subjects with concomitant medications/ treatment procedures will be presented overall and by ATC 2nd level, preferred terms.

Missing or partial dates for medications will not be imputed. In the case where it is not possible to define a medication as prior or concomitant, the event will be classified by the worst case; i.e. prior and concomitant.

- Previous medications are medications other than trial drugs, which are taken before first administration of trial drug.
- Concomitant treatments are medications other than trial drugs, which are taken by subjects any time on-treatment (on or after the first day of any trial drug treatment for each subject) or within 33 days after last dose of trial drug.

## 14.2 Concurrent procedures

Procedures collected from the "Concomitant Procedures" eCRF will be used as the data source.

Number of subject with concurrent procedures, i.e, those on-treatment procedures (prior, on or after the first day of trial treatment or within 33 days after last dose of trial treatment) will be summarized overall and by reason and preferred name.

All medication/ treatment procedures will be listed.

## 14.3 Anti-Cancer Treatment after Treatment Termination

New anticancer therapy will be recorded for subjects who discontinue from the treatment for reasons other than PD at the additional follow-up visits. The following summaries will be presented for anti-cancer treatment after discontinuation:

- Any anti-cancer treatment after discontinuation (yes/ no)
- Type of systemic therapy
- Anti-cancer therapy drugs after treatment termination: preferred terms will be presented alphabetically
- Time to start of new anti-cancer treatment after discontinuation (weeks): derived as the duration in weeks from first administration to the earliest start date of anti-cancer drugs after discontinuation
- Best response

# 15 Treatment Exposure

*Population: Safety Analysis Set*

The extent of exposure to MSC2156119J will be presented by the following summaries:

- Duration of therapy (weeks):

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

  Interruptions, compliance, and dose changes are not taken into account for the calculation of duration of therapy.
- Cumulative dose (mg):

  The cumulative dose per subject in a time period is the sum of the total dosage that the subject received.

- Dose intensity (mg/day):

$$\text{Dose intensity (mg/day)} = \left(\frac{\text{cumulative dose (mg)}}{\text{duration of therapy (days)}}\right)$$

- Relative dose intensity (%):

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Dose intensity (mg/day)}}{\text{planned dose intensity(mg/day)}}\right) * 100$$

  It will be summarized as continuous variables and also categorized into groups as the following:

  - < 60%
  - 60% - <80%
  - 80% - <90%
  - 90% - 110%
  - >110%
- Dose reductions: Dose reduction is defined as a change to a non-zero dose level lower than that planned in the protocol. A change from a less-than-planned non-zero dose level to another less-than-planned non-zero dose level will be considered as a new dose reduction.
  - Number and percentage of subjects with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / 3 / ≥4) will be summarized by treatment group.
  - Cumulative duration of dose reductions (days) will be summarized.
- Dose temporary discontinuation: Dose temporary discontinuation is defined as a change to dose interrupted, i.e. “0” dose level.
  - Number and percentage of subjects with interrupted study drug administration and maximum length of temporary discontinuation (1-2 days, 3-7 days, ≥8 days) i.e.

the worst case will be summarized by treatment group if subjects have multiple dose temporary discontinuations.
- Cumulative duration of dose temporary discontinuation (days) will be summarized.

# 16 Endpoint Evaluation

## 16.1 Primary Endpoint Analyses

*Population: DLT Analysis Set.*

**Number of subjects experiencing at least 1 DLT within the first treatment cycle**

DLTs are those AEs collected in the "Adverse Events Details" eCRF and with "Is this adverse event a dose limiting toxicity?" flagged as "Yes".

The following will be provided for DLTs during cycle 1 (i.e. first 21 days) for each dose level and overall:

- Incidences of DLTs
- Listing of DLTs

**Incidence and type of other AEs** will be specified in Section 17.1.

## 16.2 Secondary Endpoint Analyses

*Population: Safety Analysis Set*

### 16.2.1 Progression-free Survival (PFS) Assessed by Investigator

Progression Free Survival is defined as the time from first administration date to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death), for subjects with an event after two or more missing tumor assessments (i.e. 84 days). Subjects who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the start date unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

PFS (months) = [date of event or censoring– first administration date +1]/30.4375

The censoring and event date options to be considered for the PFS are presented in table 1.

Table 1: PFS Events/censoring rules

| Scenario | Date of event/censoring | Outcome |
|---|---|---|

| | | |
|---|---|---|
| Radiological PD observed within 12 weeks of the last valid tumor assessment or first treatment administration | Date of PD | Event |
| Death without previously confirmed PD is observed within 12 weeks of the first administration or the last valid tumor assessment | Date of death | Event |
| No baseline or post-baseline assessment | Date of first administration | Censored |
| Event after 2 or more missing assessments, including death which is not within 12 weeks of the first administration or the last tumor assessment, whatever occurs later | Date of last known tumor assessment or date of first administration, whatever occurs later | Censored |
| Lost to follow-up / withdraw consent without PD/death observed, including subjects with a last tumor assessment date >12 weeks prior to the analysis cut-off date | Date of last known tumor assessment or date of first administration, whatever occurs later | Censored |
| Ongoing in the study without an event, that is, no PD/death event observed within 84 of the cut-off date from the last adequate tumor assessment for this still-in-trial subject (administrative censoring) | Date of last known tumor assessment or date of first administration, whatever occurs later | Censored |

* Note: Not evaluable (NE) or Missing is not considered as a valid tumor assessment.

Kaplan-Meier survival curves (product-limit estimates) will be presented by treatment cohort together with a summary of associated statistics (25th quintile, median and 75th quintile survival time, 2-months, 4-months KM estimates and estimates for every 2 months thereafter as applicable) including the corresponding two-sided 90% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982), and CIs for the survival function estimates at above defined time points will be derived directly from the Kaplan-Meier estimates (CONFTYPE=LOGLOG in proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. SAS procedure LIFETEST will be used to obtain Kaplan-Meier estimates and plots.

Frequency (number and percentage) of subjects with each event type (PD or death) and censoring reasons will be presented. Censoring reasons are as follows:

- Event after 2 or more missing assessments
- No baseline assessment
- No post baseline assessments
- Withdrawal of consent / Lost to follow-up
- Ongoing in the study without an event due to the cutoff

The PFS time or censoring time and the reasons for censoring will also be presented in a subject listing.

### 16.2.2 Time-to-Progression (TTP) Assessed by Investigator

TTP is defined as the time (in months) from the date of first administration to the first observation of PD (as assessed by investigator):

PFS (months) = (date of 1st PD – the date of first administration+ 1) / 30.4375.

Similar event/censoring rules will be applied except that the death will not be considered as a TTP event and instead will be censored at the last available tumor assessment. Analysis methods analogous to the ones for PFS will employed.

### 16.2.3 Overall Survival (OS)

Overall survival is defined as the time from start date to the date of death due to any cause. Subjects last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– first administration date +1]/30.4375

Censoring reasons are as follows:

- Alive
- Withdrawal of consent
- Lost to follow-up

Censoring rules:

- Alive subjects will be censored at the last date known to be alive.
- If the subject is still in the trial at the cutoff of the analysis and found alive within 90 days of the cutoff date, it is considered administrative censoring, otherwise non-administrative censoring.
- Non-administrative censoring will be included in the "lost to follow-up" category if no other detailed reason specified.

The last known alive date will be the latest date of the alive dates (refers to Table 2)

Table 2: Data source of alive dates

| eCRF or Dataset | CRF Items or Variables |
|---|---|
| Subject Status / Survival Follow-Up | Last known alive date, follow-up date |
| SDTM.SV | the latest dates of SVSTDTC, SVENDTC |
| Adverse Events | Start date, end date |
| Concomitant Medications | Start date, end date |
| Drug Administration | Start date, end date |
| End of Assessment Visit | Completion/discontinuation date |

| | |
|---|---|
| Additional Follow-Up / Progression Disease | Progression date |
| Anti-Cancer Treatment After Discontinuation | Start date, end date |

Analyses analogous to the ones for FPS will be performed, expect that the survival rate will be estimated at 3-month, 6-month and for every 3 months thereafter as applicable.

## 16.2.4 Antitumor Activity Assessed by Investigator

**Best Overall Response**

Best overall response (BOR) is defined as the best result obtained among all tumor assessment visits from baseline until end of treatment or determination of PD, excluding assessments after tumor surgery.

Not Evaluable (NE) is not considered a valid measurement. Overall response of NE will be changed to PD if subsequent scan is a PD. As a consequence, a BOR of NE will only be assigned if NE is the only one treatment assessment (for instance, a subject having assessments of NE and PD will be assigned BOR of PD).

Subjects with BOR of non-CR/non-PD (possible only for subjects without measurable disease at baseline) are not considered as having achieved objective response, nor clinical benefit.

The following will be provided:

- The number and percentage of subjects with a best overall response (BOR) of CR, PR, SD, PD, non-CR/non-PD, and NE will be tabulated.
- The number and percentage of subjects will be tabulated over time grouped by the overall response.
- The number and percentage of subjects will be tabulated by cMet status (Positive (2+ or 3+) /Negative (0 or 1+) /Indeterminate/Missing) for best overall response.
- Bar chart with time to response and duration of study treatment

**Objective Response Rate (ORR)**

The objective response rate is defined as the proportion of subjects having achieved complete response (CR) or partial response (PR) as the BOR according to radiological assessments from the date of first administration to end of treatment. Responses do not require confirmation according to RECIST v1.1.

The ORR will be presented for each dose level including the corresponding 90% Newcombe-Wilson CIs.

**Disease Control Rate (DCR)**

The disease control rate is defined as the proportion of subjects having achieved CR, PR, or stable disease (SD) as the BOR according to radiological assessments from first administration until end of study treatment the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after first administration.

The DCR and its 90% Newcombe-Wilson CI will be calculated.

Other secondary endpoints are provided in other sections:

- Exposure refers to Section 15.
- Other safety secondary endpoints refers to Section 16.1.

### 16.2.5 Pharmacokinetics

*Analysis Set: PK*

Tepotinib and metabolite (MSC2571109A and MSC2571107A ) concentrations in plasma will be listed and presented in tables and descriptively summarized by dose level, day and scheduled time point. Descriptive statistics will include 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 Section **Error! Reference source not found.**. Descriptive statistics of PK parameters will additionally show the geometric mean (GeoMean), the geometric CV percentage (GeoCV%), and the 95% confidence interval (CI) for the geometric mean.

Individual plasma concentration-time profiles (linear and semi-logarithmic scales) of tepotinib and its metabolites will be plotted by dose level and day; these profiles (i.e. all three analytes) will be overlaid in one plot per subject. Spaghetti plots overlaying all subjects' concentration-time profiles (linear and semi-logarithmic scales) will be plotted by dose level and day for each of the 3 analytes separately (i.e., tepotinib, MSC2571109A and MSC2571107A ). Mean plasma concentrations of tepotinib and metabolites (MSC2571109A and MSC2571107A) overlaid will also be plotted by dose level and day on linear (±standard deviation) and semi-logarithmic scales using scheduled time points. Mean concentration time profiles, separately by analyte and dose level, will also be displayed for each of the 3 analytes (i.e., tepotinib, MSC2571109A and MSC2571107A), overlaying both Day 1 and Day 15 in one plot.

At the dose level which includes the mainland Chinese subgroup, data will be summarized for Chinese subjects alone, non-Chinese subjects alone, and Chinese and non-Chinese subjects combined, in all descriptive summary tables and plots described above.

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 (MSC2571109A, MSC2571107A) from study EMR200095-004 phase Ib part will be analyzed jointly with data from studies EMR200095-001, -002, -003, -005, -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.

### 16.2.5.1 Pharmacokinetic Endpoints

The following pharmacokinetic endpoints will be analyzed:

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

### 16.2.5.2 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 (MSC2571109A and MSC2571107A) 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. At the dose level received by the Chinese subgroup, data will be summarized for Chinese subjects alone, non-Chinese subjects alone, and Chinese and non-Chinese subjects combined.

| | |
|---|---|
| $C_{max}$ | 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 |
| $AUC_{\tau}$ | The area under the concentration-time curve over the dosing interval from $T_1$=0 h (predose) to $T_2$=$\tau$ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down). For Cycle 1 Day 1, AUC$\tau$ will be calculated as a partial area within the defined time range. For Cycle 1 Day 15, $AUC_{\tau}$ will be calculated at steady state from the pre-dose time point |

| | |
|---|---|
| | to the dosing interval time. $AUC_{\tau}$ will be calculated based on the observed concentration at the actual observation time, as long as actual time deviation is less than +/-10% at $\tau$. If actual time deviation is equal to or greater than 10%, $AUC_{\tau}$ will be reported as missing. |
| CL/F | Apparent systemic clearance (calculated for tepotinib only), as Dose/$AUC_{\tau}$, where Dose is the tepotinib free base dose (i.e., adjusted for salt form). Calculated on Cycle 1 Day 15 only. The tepotinib free base dose is calculated as: Actual dose * MW(free base)/MW(salt), where MW(free base) is the molecular weight (MW) of free base (i.e., 492.57), and MW(salt) is the MW of the hydrochloride hydrate salt (i.e., 547.05) |
| $AUC_{0-t}$/Dose | Dose-Normalized $AUC_{0-t}$ (calculated for tepotinib only). Normalized using actual dose (i.e., unadjusted for salt form). |
| $AUC_{\tau}$/Dose | Dose-Normalized $AUC_{\tau}$ (calculated for tepotinib only). Normalized using actual dose (i.e., unadjusted for salt form). |
| $C_{max}$/Dose | Dose-Normalized $C_{max}$ (calculated for tepotinib only), Normalized using actual dose (i.e., unadjusted for salt form). |
| PTF | The peak trough fluctuation ratio within a complete dosing interval at steady state in %, calculated on Cycle 1 Day 15 only. PTF = $100*(C_{max}-C_{min})/C_{av}$ |
| Vss/F | For Cycle 1 Day 15 |

Potential drug accumulation for tepotinib and its metabolites will be evaluated by means of individual accumulation ratios for $AUC_{\tau}$ and $C_{max}$ [$R_{acc(AUC)}$ and $R_{acc(Cmax)}$ respectively], that will be calculated by dividing the values obtained after multiple dose (i.e. on Cycle 1 Day 15) by the values obtained after single dose (i.e. 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 for tepotinib and its metabolites by dividing the value obtained for each metabolite by the value obtained for the parent (i.e. MSC2571107A/tepotinib and MSC2571109A/tepotinib) after correction for MW differences between parent and metabolite (MW of tepotinib free base is 492.57, MW of MSC2571107A is 506.56, and MW of MSC2571109A is 506.56), separately for single dose (i.e. Cycle 1 Day1) and multiple dose (i.e. 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 $\lambda_z$, considering the apparent terminal half-life of tepotinib and its metabolites. Therefore, all PK

parameters dependent on $\lambda_z$ will not be determined, i.e. $AUC_{0-\infty}$, $\%AUC_{extra}$, CL/F (single dose); $t_{1/2}$, 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.

For tepotinib and its metabolites, dose proportionality will be presented graphically by day as follows:

- Boxplots for dose-normalized PK parameters ($AUC_\tau$ /Dose and $C_{max}$/Dose) by dose level
- Scatter plots on individual $AUC_\tau$ 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.

## 16.3 Other Endpoint Analyses

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

## 17 Safety Evaluation

*Population: Safety Analysis Set*

## 17.1 Adverse Events

*Population: Safety Analysis Set*

Treatment emergent adverse events: those events with onset dates occurring within the treatment periods, i.e, starts on or after the earliest dosing date of any study treatment and prior to the latest dosing date of any trial treatment + 33 days (inclusive). AE occurring after the first administration will always be considered as TEAE regardless of whether its onset date beyond the 33 days if it is assessed as trial-drug related by investigator.

"Timing related to study treatment" from the AE eCRF will be used to judge whether the AE is a TEAE when the AE onset date is the same day as the day of first administration.

In the case where it is not possible to define an AE as being treatment emergent or not, the AE will be classified as treatment emergent as the most conservative approach.

Summaries for the number of subjects in total and within each dose level will be presented, for each of the categories described in the sub-sections below.

Listings will include all TEAEs and Non-TEAEs. Summary tables described in Section 17.1, 17.2.2 and 17.2.3 will be based on TEAEs if not otherwise specified.

No formal statistical comparisons are planned.

### 17.1.1 All Adverse Events

AEs will be coded using the most current version of MedDRA dictionary. The investigator will be responsible for assigning the Common Toxicity Criteria (CTC) grades for AEs, using the most current version of NCI-CTCAE.

Incidence rates (frequencies and percentages) of individual AEs, that is, the number of subjects experiencing events AEs in each PT or SOC, and the proportion relative to the number of subjects in the SAF analysis set, will be presented.

Unless otherwise stated adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

The relationship to a trial treatment, as indicated by the investigator, is classified as "not related" or "related". TEAEs with a related or missing relationship to the trial treatment will be regarded as "related" to the trial treatment. If a subject reports the same AE more than once within that SOC/PT, the AE will be categorized as "unrelated" only when all relationship records are "unrelated", otherwise it will be classed as "related" in the corresponding relationship summaries.

Severity is classified as grade 1, 2, 3, 4, 5 (increasing severity) by referencing the most current NCI-CTCAE 4.0 (publication date: 28May2009). If a subject reports a TEAE more than once within that SOC/PT, the AE with the worst case severity will be used in the corresponding severity summaries. In case a subject had events with missing and non-missing severities, the maximum of the non-missing severities will be displayed. In case all the TEAEs of a subject are all with missing severities then grade 3 (severe) will be used unless there is any evidence that it should be grade 4 or 5.

An overview summary of TEAEs will be provided by dose level for cycle 1 (i.e. first 21 days from drug administration) and all cycles:

- TEAEs
- Related TEAEs
- Serious TEAEs
- Serious related TEAEs
- TEAEs of grade ≥ 3 by NCI-CTCAE
- Related TEAEs of grade ≥ 3 by NCI-CTCAE
- TEAEs of special interest (refer to Section 17.2.3)
- Related TEAEs of special interest
- TEAEs leading to death (AEs with grade 5 or outcome "fatal" if grade 5 not applicable)
- Related TEAEs leading to death (AEs with grade 5 or outcome "fatal" if grade 5 not applicable)
- TEAEs leading to temporary discontinuation of study treatment
- TEAEs leading to permanent discontinuation of study treatment

- TEAEs leading to study discontinuation

Also the following tables will be presented by SOC, PT in alphabetical order for TEAEs for cycle 1 and all cycles:

- Incidence of TEAEs
- Incidence of related TEAEs
- Incidence of TEAEs by worst severity (CTCAE grade)
- Incidence of related TEAEs by worst severity (CTCAE grade)
- Incidence of TEAEs with CTCAE grade >= 3
- Incidence of treatment related TEAEs with CTCAE grade >= 3

### 17.1.2 Adverse Events Leading to Treatment Discontinuation

*Population: Safety Analysis Set*

AEs leading to permanent or temporary discontinuation of study treatment are those AEs whose actions taken with study treatment is reported as "drug withdrawn" or "drug interrupted" in the "Adverse Events Details" eCRF. The following will be presented by SOC and PT in alphabetical order:

- Incidence of TEAEs leading to permanent discontinuation of study treatment
- Incidence of TEAEs leading to temporary discontinuation of study treatment

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

*Population: Safety Analysis Set*

### 17.2.1 Deaths

All deaths, deaths within 33 days after last dose of trial treatment as well as reason for death, will be tabulated based on information from the "Death" eCRF.

Summaries will be presented for:

- Number of deaths
- Number of deaths within 33 days after last dose of treatment (i.e. Death date – date of last dose <=33 days)
- Primary reason of death
    - Disease progressions
    - Adverse event related to study treatment
    - Adverse event not related to study treatment
    - Other
    - Unknown

All deaths for *screening analysis set* will be listed:

- In addition, date and cause of death will be provided in individual subject data listing together with selected dosing information (date of first / last administration, dose intensity, etc).
- Including columns for:
  - AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)
  - flag for death within 33 days of last study treatment administration

### 17.2.2 Serious Adverse Events

SAEs are those events with a response of "Yes" for the item "Serious Adverse Event" on the "Adverse Events Details" eCRF. Serious TEAE, serious related TEAEs and a full list of all SAEs will be presented:

- Incidence of Serious TEAEs by SOC and PT
- Incidence of Serious Related TEAEs by SOC and PT
- Incidence of Serious TEAEs leading to death by SOC and PT
- Listing of all SAEs.

### 17.2.3 Adverse Event of Special Interest

AE of Special Interest (AESI) is defined as AEs of asymptomatic lipase and/or amylase elevations of Grade ≥ 3. The following are collected and will be presented:

- Incidence of treatment emergent AESIs by SOC and PT
- Incidence of related treatment emergent AESIs by SOC and PT
- Any lipase or amylase increase will be listed with a column flagging the ones meeting AESI definition, as noted in Section 17.2.3.

## 17.3 Clinical Laboratory Evaluation

*Population: Safety Analysis Set*

Laboratory values (including corresponding normal ranges) from Central Lab will be used for summary statistics and shift tables.

Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, High). The number of subjects with clinical laboratory values below, within, or above normal ranges at baseline compared to worst on-treatment endpoint will be tabulated for each test by dose level. Shift tables of baseline versus worst on-treatment endpoint will be presented.

Thus the following tabulations will be provided for each dose level:

- Actual and changes from baseline to each scheduled visit over time
- Number of subjects with shifts from normal baseline to worst on-treatment result above/below normal limit. Please refer to the AdaM template 2.0 to find parameters to be

split into high and low. For example, glucose will be presented by "glucose high" and "glucose low" separately.

- Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will be shown in a data listing.
- Listing of any lipase or amylase increase.

Laboratory results will also be classified according to the most current version of NCI-CTC Version as provided by the central laboratory. Parameters with available NCI-CTC grades will be summarized as the following:

- Shifts in toxicity grading baseline to highest on-treatment: The worst on-treatment grade will be summarized by NCI-CTC grade (0, 1, 2, 3, 4, any). Please refer to the AdaM template 2.0 to find parameters to be split into high and low. For example, glucose will be presented by "glucose high" and "glucose low" separately.

## 17.4 Vital Signs

*Population: Safety Analysis Set*

Weight will be classified according to the NCI-CTCAE (version 4.0) criteria. Please find the CTCAE grading rules from the appendix.

The maximum changes of vital sign measurements screening/baseline to maximum on-treatment changes after start of 1st treatment will be grouped as follows:

| Vital Sign Parameter | Increase/ decrease | Baseline category | Change from baseline category |
|---|---|---|---|
| Temperature | Increase | <37 °C,<br>37 - <38 °C<br>38 - <39 °C<br>39 - <40 °C<br>>=40 °C | < 1°C ,<br>1-<2°C ,<br>2-<3°C,<br>≥ 3 °C |
| Heart rate | Increase | <100 bpm ;<br>≥ 100 bpm | ≤20 bpm,<br>>20 – 40 bpm,<br>>40 bpm |
| | Decrease | <100 bpm ;<br>≥ 100 bpm | ≤20 bpm,<br>>20 – 40 bpm,<br>>40 bpm |
| SBP | Increase | <140 mmHg;<br>≥ 140 mmHg | ≤20 mmHg,<br>>20 – 40 mmHg,<br>>40 mmHg |
| | Decrease | <140 mmHg;<br>≥ 140 mmHg, | ≤20 mmHg,<br>>20 – 40 mmHg, |

| | | | |
|---|---|---|---|
| | | | >40 mmHg |
| DBP | Increase | <90 mmHg;<br>≥ 90 mmHg | ≤20 mmHg,<br>>20 – 40 mmHg,<br>>40 mmHg |
| | Decrease | <90 mmHg;<br>≥ 90 mmHg | ≤20 mmHg,<br>>20 – 40 mmHg,<br>>40 mmHg |
| Respiration rate | Increase | <20 bpm ;<br>≥ 20 bpm | ≤5 bpm,<br>>5 – 10 bpm,<br>>10 bpm |
| | Decrease | <20 bpm ;<br>≥ 20 bpm | ≤5 bpm,<br>>5 – 10 bpm,<br>>10 bpm |

The following summaries will be prepared for vital sign parameters as grouped above considering only subjects with post baseline values:

- Change from baseline to worst on-treatment CTCAE toxicity grade for weight
- Maximal Shifts (changes in categories)

## 17.5 ECG

*Population: Safety Analysis Set*

All ECG readings will be recorded as 12-lead resting ECGs in triplicates. The average of these 3 results will be used for inclusion in the reporting of this study for numeric parameters. If some of the 3 results are missing, the average of available results will be used. For categorical data, the worst result among the 3 results will be used.

The Fridericia's Correction (QTcF) is derived as follows:

- Fridericia's Correction (ms): $QTcF\ (\text{ms}) = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$

  In case RR is not available $RR\ (ms) = 1000 * \frac{60}{HR\ (bpm)}$ will be used.

The following summaries will be provided for ECG data:

- Summary over time for numeric parameters: only subjects at the visit will be summarized.
- Categorical shift from baseline to worst on-treatment value for the QTcB and QTcF: the baseline and the worst on-treatment value will be grouped as follows:

| Parameter | Baseline category | Worst on treatment value |
|---|---|---|

| | | |
|---|---|---|
| QTcB, QTcF | <=450ms<br>>450 - <=480ms<br>>480 - <=500ms<br>>500ms | <=450ms<br>>450 - <=480ms<br>>480 - <=500ms<br>>500ms |

- Categorical change from baseline to worst on-treatment value for the QTcB and QTcF: the baseline and the worst change from baseline value will be grouped as follows:

| Parameter | Baseline category | Worst change from baseline |
|---|---|---|
| QTcB, QTcF | Normal (i.e.<=450ms)<br>Abnormal (i.e.>450ms) | <=0 ms<br>>0 - <=30ms<br>>30 - <=60ms<br>>60ms |

## 17.6 Other Safety Evaluations

*Population: Safety Analysis Set*

The following will be provided for the ECOG performance status:

- Summary of ECOG over time: ECOG will be classified as 0, 1, 2, 3, 4, 5. Only subjects at the visit will be summarized.

# 18 Reporting Conventions

The mock shells will be provided in a separate document *EMR200095-004 Phase Ib CSR Mock Shells*.

# 19 References

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

# 20 Appendix

- Non-CRF Data are listed as:

| **Data to be Analyzed** | **Collected by** |
|---|---|
| Protocol deviations | Clinical Trial Management System (CTMS). |
| Laboratory data | Central Lab |

- Laboratory parameters with CTCAE grading are:

| **Lab Test Name** | | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
|---|---|---|---|---|---|

| **Chemistry** | | | | | |
|---|---|---|---|---|---|
| Total Bilirubin (umol/L) | Increase | >ULN | >1.5ULN | >3ULN | >10ULN |
| Aspartate Aminotransferase (U/L), SGOT | Increase | >1xULN | >3xULN | >5xULN | >20xULN |
| Alanine Aminotransferase (U/L), SGPT | Increase | >1xULN | >3xULN | >5xULN | >20xULN |
| Sodium (mmol/L) Low | Decrease | <LLN | **NA** | <130 | <120 |
| Sodium (mmol/L) High | Increase | >ULN | >150 | >155 | >160 |
| Calcium (mmol/L) Low (Albumin corrected), (Not total calcium) | Decrease | <LLN | <2 | <1.75 | <1.5 |
| Calcium (mmol/L) High (Albumin corrected), (Not total calcium) | Increase | >ULN | >2.88 | >3.12 | >3.38 |
| Magnesium (mmol/L) Low | Decrease | <LLN | <0.5 | <0.35 | <0.3 |
| Magnesium (mmol/L) High | Increase | >ULN | **NA** | >1.25 | >3.3 |
| Creatinine (umol/L) | Increase | >BL or ULN | >1.5BL or 1.5ULN | >3BL or 3ULN | >6ULN |
| Albumin (g/L) | Decrease | <LLN | <30 | <20 | **NA** |
| Alkaline phosphatase (U/L) | Increase | >1xULN | >2.5xULN | >5xULN | >20xULN |
| Amylase (U/L) | Increase | >1xULN | >1.5xULN | >2xULN | >5xULN |
| Lipase (U/L) | Increase | >ULN | >1.5xULN | >2xULN | >5xULN |
| Glucose (mmol/L) Low | Decrease | <LLN | <3.1 | <2.2 | <1.7 |
| Glucose (mmol/L) High | Increase | >ULN | >8.9 | >13.9 | >27.8 |
| Gamma Glutamyl Transferase (U/L) | Increase | >1ULN | >2.5xULN | >5xULN | >20xULN |
| Potassium (mmol/L) Low | Decrease | **NA** | <LLN | <3 | <2.5 |
| Potassium (mmol/L) High | Increase | >ULN | >5.5 | >6 | >7 |
| Creatinine Clearance, C&G (mL/min) | Decrease | **NA** | <60 | <30 | <15 |
| **Hematology** | | | | | |
| Hemoglobin (g/L) Low | Decrease | <LLN | <100 | <80 | **NA** |
| Hemoglobin (g/L) High | Increase | >ULN | >ULN+20 | >ULN+40 | **NA** |
| Platelet (10E9/L), PLT | Decrease | <LLN | <75 | <50 | <25 |
| Leukocytes (10E9/L) Low | Decrease | <LLN | <3 | <2 | <1 |
| Leukocytes (10E9/L) High | Increase | **NA** | **NA** | >100 | **NA** |

| | | | | | |
|---|---|---|---|---|---|
| Neutrophils (10E9/L), Absolute Neutrophils Count , ANC | Decrease | <LLN | <1.5 | <1 | <0.5 |
| Lymphocytes (10E9/L) Low | Decrease | <LLN | <0.8 | <0.5 | <0.2 |
| Lymphocytes (10E9/L) High | Increase | **NA** | >4 | >20 | **NA** |
| **Coagulation** | | | | | |
| | | | | | |
| Activated Partial Thromboplastin Time (sec) | Increase | >1ULN | >1.5ULN | >2.5ULN | **NA** |
| Prothrombin Intl. Normalized Ratio | Increase | >BL or ULN | >1.5BL or 1.5ULN | >2.5BL or 2.5ULN | **NA** |

* BL=Baseline, ULN=Upper limit of normal range.

- Vital sign parameters with CTCAE grading are:

| **Vital Sign Parameter** | | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
|---|---|---|---|---|---|
| Weight Loss (kg) | Decrease | 5 - <10% from BL | 10 - <20% from BL | >=20% from BL | **NA** |
| Weight Gain (kg) | Increase | 5 - <10% from BL | 10 - <20% from BL | >=20% from BL | **NA** |

* BL=Baseline.

# Statistical Analysis Plan

| | |
|---|---|
| **Clinical Trial Protocol Identification No.** | EMR 200095-004 |
| **Title:** | A Multicenter, Randomized, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy Versus Sorafenib in Asian Patients with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function |
| **Trial Phase** | Phase Ib/II |
| **Investigational Medicinal Product(s)** | MSC2156119J (Tepotinib) |
| **Clinical Trial Protocol Version** | 19 May 2017/Version 4.0 |
| **Statistical Analysis Plan Author** | PPD |
| **Statistical Analysis Plan Date and Version** | 12 Feb 2018/Final Version 1.1 |
| **Statistical Analysis Plan Reviewers** | PPD, Senior Statistical Reviewer, PPD<br>PPD, Trial Biostatistician, Merck Serono<br>PPD, PPD, Merck SeronoCharles<br>PPD, PPD, Merck Serono |

[redacted]
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# 1 Signature Page

**Statistical Analysis Plan:** EMR 200095-004

A Multicenter, Randomized, Phase Ib/II Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of MSC2156119J as Monotherapy versus Sorafenib in Asian Patients with MET+ Advanced Hepatocellular Carcinoma and Child-Pugh Class A Liver Function

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## 2 Table of Contents

# 3 List of Abbreviations and Definition of Terms

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| AST | Aspartate Aminotransferase |
| ATP | Adenosine Triphosphate |
| CHF | Congestive Heart Failure |
| CI | Confidence Interval |
| c-Met | Mesenchymal-Epithelial Transition Factor Gene |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRO | Contract Research Organization |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of Variation (%) |
| DBP | Diastolic Blood Pressure |
| DLT | Dose-Limiting Toxicity |
| DNA | Deoxyribonucleic Acid |
| DS | Drug Substance |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transpeptidase |
| GMP | Good Manufacturing Practice |
| HBeAg | Hepatitis B extracellular antigen |
| HBsAg | Hepatitis B surface antigen |
| HBc | Hepatitis B core antigen |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HR | Hazard Ratio |

| | |
|---|---|
| HIV | Human Immunodeficiency Virus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IMP | Investigational Medicinal Product |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISH | In Situ Hybridization |
| IVRS | Interactive Voice Response System |
| LCSS | Lung Cancer Symptom Scale |
| LLQ | Lower Level of Quantification |
| LVEF | Left Ventricular Ejection Fraction |
| MedDRA | Medical Dictionary For Regulatory Activities |
| mITT | Modified Intent-to-Treat |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| OR | Objective Response |
| OS | Overall Survival |
| PD | Progressive Disease |
| CCI [redacted] | [redacted] |
| PET | Positron Emission Tomography |
| PFS | Progression Free Survival |
| P-gp | P-Glycoprotein |
| PGx | Pharmacogenomics |
| PK | Pharmacokinetics |
| PoC | Proof of Concept |
| PP | Per Protocol |
| PR | Partial Response |

| | |
|---|---|
| PT | Prothrombin Time |
| RBC | Red Blood Cells |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic Acid |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic Blood Pressure |
| SD | Stable Disease |
| SEM | Standard Error of the Mean |
| SMC | Safety Monitoring Committee |
| StD | Standard Deviation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | Treatment-Emergent Adverse Event |
| TKI | Tyrosine Kinase Inhibitor |
| TNM | Tumor, Lymph Nodes, Metastasis |
| TTSP | Time to Symptomatic Progression |
| UDP | Uridine 5'-Diphospho |
| ULN | Upper Limit of Normal |
| WBC | White Blood Cells |

# 4 Modification History

| Unique Identifier for SAP Version | Date of SAP Version | Author | Changes from the Previous Version |
|---|---|---|---|
| Final V1.0 | 13 Jul 2017 | PPD | Not Applicable – First Version |
| Final V1.1 | 12 Feb2018 | PPD | • Update one criteria of -the definition of Per-Protocol Analysis Set from 'Completed at least 80% of the planned dose for at least one cycle, except for patients discontinue due to early death or progression' to 'Dosed for at least 80% of the planned dosing days for at least one cycle, except for patients discontinue due to early death or progression'<br>• Clarify long term follow-up -analysis which will be included in CSR addendum in section 11'Safety data collected after the cut-off date for final analysis from the subjects who will still be on trial treatment will be reported through patient profile in an addendum to the clinical study report.'<br>• Add subgroup "Baseline HBV or HCV status" to the part of 'Subgroup of interest'<br>• Add section 16.3.5 of Tumor Shrinkage by IRC<br>• Add section 16.3.6 of Tumor Shrinkage by Investigator<br>• Modify subgroup analysis of TTP and PFS from only for 'predefined biomarker' subgroups to all predefined subgroups section 16.2.1 and 16.2.3 |
| | | | |

# 5 Purpose of the Statistical Analysis Plan

The purpose of this SAP is to document technical and detailed specifications for the primary and final analysis of data collected for the phase II of the protocol EMR 200095-004 version 4.0 dated 19May2017. Results of the analyses 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 upon section 8 (Statistics) of the trial protocol and is prepared in compliance with ICH E9.

# 6 Summary of Clinical Trial Features

| | |
|---|---|
| **Trial Objectives** | **Primary Objectives**<br>● To evaluate efficacy as measured by time to progression (TTP) of Tepotinib as monotherapy in the first-line treatment compared with sorafenib in patients with MET+ advanced HCC and Child-Pugh class A liver function. |

| | |
|---|---|
| | **Secondary Objectives**<br>● To evaluate the safety and tolerability of Tepotinib versus sorafenib<br>● To evaluate antitumor activity of Tepotinib versus sorafenib<br>**Exploratory Objectives**<br>● To evaluate patient reported outcomes (PROs) of Tepotinib compared with sorafenib. PROs will be assessed using FACT-HP questionnaire.<br>● CCI [redacted] |
| **Trial design and plan** | Phase II will be a randomized, open label, active controlled trial to evaluate the efficacy, safety, and PK of Tepotinib as first-line treatment versus sorafenib in patients with MET+, Barcelona Clinic Liver Cancer (BCLC) Stage B or C, systemic treatment naive advanced HCC and Child-Pugh class A liver function. Phase II is planned to be conducted at 45 to 55 sites in mainland China, South Korea, Taiwan, and other Asian countries.<br><br>Patients will receive either Tepotinib once daily (at the recommended Phase II dose (RP2D) determined from Phase Ib) or 400 mg sorafenib twice daily until disease progression, intolerable toxicity or consent withdrawal from the trial. |
| **Planned number of patients** | Approximately 140 patients were planned to be randomized on a 1:1 basis to receive Tepotinib or sorafenib. The sponsor subsequently decided to stop prescreening after 40 TTP events (confirmed by the IRC) or on 15 August 2017, whichever occurs first. |
| **Schedule of visits and assessments** | Patients will be screened for up to 14 days prior to trial treatment. Informed consent will be obtained prior to performing any trial assessment.<br><br>Tepotinib (Phase II) will be administered once daily over a 21-day cycle and sorafenib (Phase II) will be administered twice daily over a 21-day cycle, |

| | |
|---|---|
| | which may repeat until disease progression (as determined by the investigator), intolerable toxicity, or withdrawal from the trial.<br><br>For Phase II, scheduled visits during the treatment period will occur on Days 1, 8, and 15 of Cycle 1; Days 1 and 8 of Cycle 2; and Day 1 of Cycles ≥ 3.<br><br>At each scheduled visit during the treatment period, physical examination/weight, vital signs, hematology, coagulation, chemistry, adverse events (AEs), and concomitant medication assessments will be performed.<br><br>Patients will also be assessed at the discontinuation of the trial medication. Trial drug post-treatment follow-up visit will be performed within 30 ± 3 days after the last dose for patients who discontinue the trial medication. Survival data (patient survival and anticancer therapies) will be collected every 3 months (± 2 weeks) after the dose of trial drug. Patients will be contacted by telephone.<br><br>Subjects undergoing prescreening at the prescreening stop date may still be enrolled into the trial, if eligible. Subjects receiving study treatment may continue treatment after discussion with their Investigator. Subjects who decide to continue treatment will continue on their originally randomized treatment, at their most recent dose according to the protocol. Safety monitoring and data collection will continue without modification through to the end of treatment assessment. |
| **Primary endpoints** | • TTP assessed by an Independent Review Committee (IRC). TTP is defined as the time (in months) from randomization to date of the observation of radiological progressive disease (PD) assessed by an IRC. |
| **Secondary endpoint(s)** | • Secondary efficacy endpoints are:<br>• Progression-free survival (PFS) based on tumor assessed by the IRC. PFS time is defined as the time (in months) from randomization to either first observation of disease progression or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment.<br>• PFS based on tumor assessment by investigator. PFS time is defined as the time (in months) from randomization to either first observation of radiologically confirmed PD by the investigator or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment.<br>• Overall survival (OS) time. OS time is defined as the time (in months) from randomization to the date of death.<br>• TTP assessed by investigator. TTP is defined as the time (in months) from randomization to date of the observation of radiological PD assessed by the investigator. |

| | |
|---|---|
| | • Time-to-symptomatic progression (TTSP). TTSP is defined as the time (in months) from the date of randomization to the date of deterioration of symptoms assessed by FHSI-8, defined as the total score increase by at least 4 points compared with the baseline value, or deterioration to ECOG PS of 4.<br>• Objective response (OR) based on tumor assessment by IRC. OR is defined as complete response (CR) or partial response (PR) as the best overall response according to radiological assessments as adjudicated by the IRC from randomization to first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1.<br>• OR based on tumor assessment by the investigator. OR is defined as CR or PR as the best overall response according to radiological assessments as adjudicated by the investigator from randomization to first occurrence of PD. Responses do not require confirmation according to RECIST v 1.1.<br>• BOR (Best Overall Response) based on tumor assessment by the IRC. BOR is defined as the best result obtained among all tumor assessments adjudicated by the IRC from baseline until end of treatment or determination of PD, excluding assessments after tumor surgery.<br>• BOR (Best Overall Response) based on tumor assessment by the investigator. BOR is defined as the best result obtained among all tumor assessments adjudicated by the investigator from baseline until end of treatment or determination of PD, excluding assessments after tumor surgery<br>• Disease control based on tumor assessment by the IRC. Disease control is defined as CR, PR, or stable disease (SD) as the best overall response according to radiological assessments as adjudicated by the IRC from the date of randomization to the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization.<br>• Disease control based on tumour assessment by the investigator. Disease control is defined as CR, PR, or SD as the best overall response according to radiological assessments as adjudicated by the investigator from the date of randomization to the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization. |
| **Safety Endpoints** | • Drug exposure<br>• Incidence and type of AEs (all grades as per NCI-CTCAE version 4.0): all treatment emergent adverse events (TEAEs), related TEAEs, treatment emergent SAEs, related treatment emergent SAEs, TEAEs of NCI-CTCAE (version 4.0) with Grade ≥ 3, related TEAEs ≥ Grade |

| | |
|---|---|
| | 3, and TEAEs leading to temporary/permanent treatment discontinuation<br>• Incidence and reasons for deaths, including deaths within 33 days after the last dose of study Drug<br>• Safety laboratory tests graded by NCI-CTCAE (version 4.0)<br>• Vital signs; 12-lead ECG changes; physical examinations, including change in body weight; and ECOG PS. |
| **Exploratory endpoints** | • PRO assessments of Tepotinib compared with sorafenib will be assessed using the FACT-HP questionnaire.<br>• CCI [redacted] b<br>• CCI [redacted]<br>• CCI [redacted]<br>• CCI [redacted] |

## 7 Sample Size/Randomization

The initial sample size planning required 100 TTP events (assessed by an IRC) to ensure 80% power with a two-sided significance level of 10% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio (HR) of 0.6. Assuming a median TTP in Asian patients for the sorafenib arm of 2.8 months, an HR of 0.6 represents a 1.87 month increase, resulting in a median TTP of 4.67 months for the Tepotinib arm. One formal interim futility analysis with O'Brien-Flemming method as futility boundary calculation was planned to be performed after observation of 50% of TTP events. With the additional assumption of accrual period of 12 months and follow up period of 6 month, and an overall drop-out rate of 17.4%, a total number of 140 patients with MET+ HCC will be randomized (1:1 basis) to receive Tepotinib or sorafenib.

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

Randomization will be performed centrally by using an IVRS. A stratified permuted block randomization procedure will be employed using the following strata:

- BCLC Stage: Stage B versus Stage C

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

# 8 Overview of Planned Analyses

**Cut-off date**

This SAP covers the analyses for efficacy and safety based on the data cut-off.

- The cut-off date for the primary analysis will be determined by the date after 40 reported TTP events (confirmed byIRC) for the modified Intent-To-Treat (mITT) Population or 15th August 2017, whichever occurs first.
- The final analysis will be conducted approximately 6 months after the last subject is first dosed.

Due to cleaning activities final number of events might deviate from the planned number. The data applied with the cut-off date will not be adjusted retrospectively in this case.

This SAP will cover the primary and final analysis. Separate SAPs will be provided covering the following analyses:

- Safety analyses for IDMCs

## 8.1 Primary Analysis

The primary analysis will be conducted when 40 TTP events (confirmed byIRC) reported for mITT population or 15 August 2017, whichever occurs first. Final Analysis

The final statistical analysis is planned to be conducted approximately 6 months after the last subject is first dosed.

Data review meetings will be held prior to database lock for both primary and final analysis.

# 9 Changes to the Planned Analyses in the Clinical Trial Protocol

The following change was made in the planned analysis between the study protocol and the SAP prior to database lock:

- The following additional criteria added to the definition of PP analysis set:
  - The absence of any clinical important protocol deviations with respect to factors likely to affect the efficacy of treatment.
  - Data review will be held to determine the evaluability of the subjects prior to the database lock.
  - Change the criteria of ‘complete at least 1 cycle of treatment’ to ‘completed at least 80% of the planned dose for at least one cycle, except for patients discontinue due to early death or progression’.

- Kaplan-Meier estimates for TTP will be presented by 2 months, 4 months and every 2 months instead of 6 month, 12 month and every 6 month.

CCI [redacted]

# 10 Protocol Deviations and Analysis Sets

## 10.1 Definition of Protocol Deviations

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 receive study medication despite not satisfying the inclusion criteria or violating exclusion 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 GCP

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

- Important protocol deviations include
    - Deviations from the inclusion and exclusion criteria
    - Deviations post inclusion
- Subset of these important protocol deviations are clinically important if leading to the exclusion of the subject from the PP set (see section 10.2).

All important protocol deviations should be documented in CDISC datasets whether identified through sites monitoring or medical review. Please refer to Protocol Deviation Guide for more details.

## 10.2 Definition of Analysis Sets and Subgroups

**Screening Analysis Set (SCR)**

The screening (SCR) analysis set includes all patients who have signed the main informed consent (i.e., screening failures plus patients enrolled).

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

The intention-to-treat (ITT) analysis set in Phase II part of this trial consists of all subjects who were randomized to study treatment. Subjects will be allocated as randomized.

**Modified Intent-to-Treat Analysis Set (mITT)**

The modified intention-to-treat (mITT) analysis set will include all patients with MET+ HCC who were randomized to trial treatment. Subjects with IHC c-Met status 1+ or 'not assessable' on re-scoring will be excluded from the primary analysis set. The mITT Analysis Set will be used to assess the tumor activity and the efficacy of the compound. Analyses performed on the mITT set will take into account patients' allocation to treatment groups as randomized.

**Per-Protocol Analysis Set (PP)**

The per-protocol (PP) analysis set is defined as all mITT patients who meet the following criteria:

- Histologically or cytologically confirmed hepatocellular carcinoma
- Correct treatment allocation according to randomization or dose selection
- Measurable or evaluable disease at baseline
- Dosed for at least 80% of the planned dosing days for at least one cycle, except for patients discontinue due to early death or progression
- Received only permitted medications or procedures according to this protocol
- The absence of any clinical important protocol deviations (see Section 12.2). The exclusion from PP set will be determined in case-by-case scenario, and will be confirmed by a blind data review meeting prior to the database lock.

PP analysis set data will be presented according to as-randomized principle.

If the PP analysis set includes at least 90% of patients in the mITT analysis set, additional efficacy analyses on the PP analysis set will be omitted as the differences in the results based upon these two analysis sets are expected to be negligible.

CCI [redacted]

[redacted]

**Safety Analysis Set (SAF)**

The safety (SAF) analysis set includes all patients who have received at least 1 dose of Tepotinib or sorafenib. The SAF analysis set will be used for all summaries of safety data. Analyses performed on the safety analysis set will consider patients as treated. As an example, if a patient was randomized to control arm, but received active treatment throughout the trial rather than control treatment, the patient's safety data should be reported under active treatment.

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An overview of analysis sets and analyses is given in Table 1:

Table 1: Analysis Sets

| Analyses | Modified Intent-to-Treat Analysis Set | Per Protocol Analysis Set | Safety Analysis Set |
|---|---|---|---|
| Baseline Assessments | ✓ | | ✓ |
| Past, Concomitant and Post Therapies | ✓ | | |
| Medical History | ✓ | | ✓ |
| Compliance and Exposure | | | ✓ |
| Efficacy: Primary | ✓ | ✓ | |
| Efficacy: Secondary | ✓ | ✓ | |
| Safety Analysis | | | ✓ |

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**Subgroup of interest**

Subgroup analyses will be performed on subgroups as defined below.

For the purpose of including baseline variables into Cox's proportional hazards model the following subgroup variables are to be used. For variables with more than two categories, an indicator variable will be defined for each category except for the first category, which defines the reference always. The following subgroups will be defined:

- Type of MET+ (please refer to Section 13.3.2)
  - moderate [2+] (reference level)
  - strong [3+]
- Gene amplification status
  - mean gene copy number <5 (reference level)
  - mean gene copy number ≥ 5
- Age
  - age < 65 years (reference level)
  - age ≥ 65 years
- Gender
  - male (reference level)

  - female
- Geographic region (please refer to Section 13.1)
  - Greater China
  - outside of Greater China (reference level)
- BCLC stage
  - Stage B (reference level)
  - Stage C
- Vascular invasion and/or extrahepatic spread
  - presence
  - absence (reference level)
- The underlying disease or medical condition related to etiology (please refer to Section 13.3.2):
  - HBV
  - Other (reference level)
- Baseline HBV or HCV status
  - Either HBV or HCV positive
  - Both HBV and HCV negative

- AFP elevation at the baseline (please refer to Section 13.3.2)
  - yes
  - no (reference level)
- Prior local-regional therapy:
  - yes
  - no (reference level)
- Baseline tumor HGF group
  - 0 (reference level)
  - Other
- Baseline plasma shedded cMet group
  - above the median
  - below/at the median (reference level)
- Baseline plasma IL-8 group
  - above the median

  - below/at the median (reference level)
- Baseline plasma HGF Group
  - above the median
  - below/at the median (reference level)
- Baseline plasma HGF Group
  - above upper quartile (25% quantile)
  - below/at the upper quartile (25% quantile) (reference level)
- Type of IHC c-Met status (based on ITT population):
  - 1+ (reference level)
  - 2+
  - 3+

The analysis of individual subgroups will be done in a case there are enough observations in each subgroup (i.e. more than 10 subjects in any treatment group). A summary for a number of patients in each subgroup will be produced.

# 11 General Specifications for Statistical Analyses

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

**Data handling after cut-off date:**

In general, if a cut-off date is set, data obtained after the cut-off will not be displayed in any listings or used for summary statistics, e.g. laboratory values of samples taken after data cut-off, AE with onset date after data cut-off, death, etc. will not be included in any analysis or listing. In particular, the following steps will be taken to derive and report some eCRF data that might be potentially affected by the cutoff date:

- If the start date of a visit, or a prior, concomitant and post medication/procedure/treatment, or an adverse event is before or on the cutoff date, and the stop date is after the cutoff date, the stop date will be set to the cutoff date, and
  - For the medication/procedure/treatment, it will be considered in the status of ongoing.
  - For the adverse event, its outcome will be considered as ongoing.
- If the last known alive date is after the cutoff date, the date will be updated to the cutoff date.
- If the death date is after the cutoff date, the death date will be set to missing, and the last known alive date will be updated to the cutoff date.

**Pooling of centers:**

Because of the high number of participating centers and the anticipated small number of patients treated in each center data will be pooled across centers, and the factor center will not be considered in statistical models or for subgroup analyses.

**Significance level:**

If confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 90%, unless otherwise in this SAP specified.

**Presentation of continuous and qualitative variables:**

Continuous variables other than PK will be summarized using the following descriptive statistics, i.e.

- number of patients (N), number of patients with non-missing values
- mean, standard deviation
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum, and maximum,

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Categorical variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of patients of the sample size of the population of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

**Trial day and treatment day:**

Trial day is defined relative to the date of randomization. Day 1 is defined as the day of the randomization, the day before is defined as Trial day –1 (no Trial day 0 is defined).

- Trial day =
    - date of event – the date of randomization, if date of event < the date of randomization
    - or date of event – the date of randomization + 1 , if date of event ≥ the date of randomization

Treatment day will be calculated relative to the date of the first administration of trial treatment, treatment day 1 is defined as the first administration day.

- Treatment day = date of event – first administration day + 1

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Trial Day or Treatment Day, and any corresponding durations will be presented as missing. Rules of handling missing dates relevant to efficacy will be specified in the subsequent sections.

**Definition of baseline:**

In general the last non-missing measurement prior to or on the day of randomization will serve as the baseline measurement. If such a value is not available, the last measurement prior to or on the day of the first trial treatment administration will serve as the baseline measurement.

If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

**Definition of on-treatment value:**

On-treatment data refer to assessment values collected after the first trial drug administration of any trial treatment and within 33 days (inclusive) after the last trial drug administration.

**End of treatment (EOT) data**

Data reported at the EOT visit are not eligible for the baseline selection. EOT data will be presented in a separate visit in the by-visit summaries.

**Unscheduled visits:**

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

**Definition of duration:**

Duration will be calculated by the difference between start and stop date + 1 if not otherwise specified. For example, survival time (days) = date of death - the date of randomization + 1.

**Common calculations:**

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

**Conversion factors:**

Unless specified, Conversion of days to months /years will be defined as:

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

**Handling of missing data:**

For the derivation of new date variables the following rules will apply:

- Partial birth dates will be handled this way: day will be imputed as 15 if it is missing, and month imputed as June if missing. If both of day and month are missing, they will be imputed as July 1st. If year is missing then the date will not be imputed.
- For imputing missing parts of dates for the efficacy analyses the missing day in a date will be imputed as the 15th of the month, if month and year is documented. This includes also dates of start of follow-up therapy.
- In case the last administration date is incomplete the date of last administration will be taken from the Treatment Termination eCRF page.
- 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 patient'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.
- In all other cases missing or incomplete dates will not be imputed if not indicated otherwise.

Unless otherwise specified, missing data will not be replaced.

In individual patient data listings (to be included in section 16.4 of the Clinical Trial Report) the documented date as given in the eCRF will be reported (e.g. __May2009 in case of day missing, but month and year available). In all other patient data listings imputed values (of dates captured on the eCRF) will be presented and the respective dates will be flagged as imputed.

Missing statistics, e.g. when they cannot be calculated, should be presented as “nd”. For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as “nd”.

All statistical analyses will be performed using SAS® version 9.3 or higher version.

Safety data collected after the cut-off date for final analysis from the subjects who will still be on trial treatment will be reported through patient profile in an addendum to the clinical study

report.

# 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

*Population: Screening Analysis Set*

All patients who provide informed consent will be accounted for in this study. Patient disposition and withdrawals will be presented for the screening analysis set.

The following summaries will be provided for overall and each treatment group when applicable:

- Number of patients prescreened, and screened among them
- Total number of patients screened (i.e. patients who gave informed consent)
- Number of patients who completed the screening phase, but discontinued from the trial prior to the date of randomization
- Number of patients who did not complete the screening phase grouped by the main reasons, that is, screening failures
- Number of randomized patients
- Number of patients randomized but not treated
- Number of patients who completed the treatment. A patient who completed treatment is defined as the patient died or the patient has been assessed as having progressive disease
- Number of randomized patients who discontinued the trial treatment after randomization, grouped by treatment and main reason
- Number of patients in survival follow up

Treatment randomized to, treatment treated, the first/last dosing date, completion/termination status, and analysis set allocated in will be presented to listing for the mITT analysis set.

## 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
- Listing of important protocol deviations

### 12.2.2 Reasons Leading to the Exclusion from an Analysis Set

Subjects who meet one of the criteria described in section 10.2 will be excluded from the PP. For these subjects, the reasons for exclusion will be summarized and listed;

- Frequency table per reason of exclusion from the PP population
- Listing of reasons of exclusion from the PP population

## 13 Demographics and Other Baseline Characteristics

*Population: mITT Analysis Set*

Demographic data and other baseline characteristics will be presented using summary statistics for continuous variables and frequency tables for categorical variables. Demographic characteristics will be based on mITT and SAF analysis sets.

### 13.1 Demographic

Demographic characteristics will be summarized using the following information from the Screening/Baseline visit eCRF pages.

Demographic characteristics:

- Age (years): summary statistics

  $$\text{Age (years)} = (\text{date of informed consent} - \text{date of birth} + 1) / 365.25$$

  Age will be presented to 1 decimal place.
- Age in categories:
  - <65 years
  - >=65 years (65 -< 75, 75 -< 85, >= 85 years)
- Gender: male, female
- Race: Asian
- Ethnicity: Japanese, not Japanese
- Pooled region of site:
  - Greater China (i.e. mainland China and Taiwan),
  - Outside of Greater China
- Region:
  - Mainland China
  - Taiwan
  - South Korea

### 13.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA, current version, preferred term (PT) as Event category and MedDRA system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

Ongoing medical histories are the ones recorded as "ongoing" in the "Medical History Details" eCRF form, otherwise will be classified as previous medical conditions. The following will be summarized:

- Ongoing medical conditions

## 13.3 Other Baseline Characteristics, Anti-Cancer Therapy and Surgery

### 13.3.1 Disease History

Information on disease history collected on the "Disease History" eCRF page at the pre-treatment evaluation visit will be presented. Summaries and listings will be presented for the followings:

- Site of Primary Tumor
- Time since initial diagnosis (years)
  Time since initial diagnosis (years) = (date of informed consent – date of initial diagnosis+1) / 365.25.
- Time since first occurrence of metastatic or locally advanced disease (years)

  Time since first occurrence of metastatic or locally advanced disease (years) = (date of informed consent – date of the first occurrence of metastatic or locally advanced disease +1) / 365.25.
- BCLC Stage at Initial Diagnosis: 0, A, B, C or D
- BCLC Stage at Study Entry: 0, A, B, C or D
- Tumor histology: Macroscopic Tumors, Microscopic Tumors, Vascular invasion, Tumor histology Grading
- Metastatic sites at the first diagnosis of advanced disease
- Metastatic sites at study entry

### 13.3.2 Other Baseline Characteristics

The following baseline characteristics will be summarized for this study:

- Height (cm)
- Weight (kg)
- BMI (kg/m$^2$): BMI (kg/m$^2$) is derived as weight (kg) / height (m)$^2$
- Nicotine and alcohol consumption
- ECOG at baseline

- MET+ Status
- Alpha-fetoprotein (AFP) elevation at the baseline: yes vs. no

  Elevated AFP refers to a state where AFP is above the reference range.
- The underlying disease or medical condition related to etiology - Hepatitis B Virus (HBV or HCV): positive vs. negative.

  HBV or HCV could be missing because the virus load at baseline was not collected.
  - HBV+ is defined as: The HBV DNA Virus load (IU/ml) is detectable /any numerical value (including HBV Virus load < 116 copy/ml);
  - HBV- is defined as: The HBV DNA Virus load (IU/ml) is target not detected;
  - HCV+ is defined as: The HCV RNA Virus load (IU/ml) is detectable /any numerical value;
  - HCV- is defined as: The HCV RNA Virus load (IU/ml) target not detected;
- Viral serology at baseline:

  HBsAg: negative vs. positive

  Anti-HBc: negative vs. positive

  HBeAg: negative vs. positive

  Anti-HCV: negative vs. positive

  HBV carrier: HBs Ag (+), HBeAg (-), anti-HBe (+), normal ALT (Within 40IU/ml), HBV DNA undetectable or < 2000IU/ml, anti-HCV should be negative

Baseline characteristics with respect to hematology/biochemistry, vital signs, ECG will be part of Section 17.

### 13.3.3 Prior Anti-Cancer Therapy and Surgery

Prior anti-cancer therapy and surgery information, including drug therapies, radiotherapy, local-regional therapies and surgeries will be summarized.

- The following will be summarized for prior anti-cancer drug therapy:
  - Any prior anti-cancer drug therapy (yes/ no)
  - Type of therapy
  - Intent of therapy
  - Prior anti-cancer therapy drugs, presented by preferred terms alphabetically
  - Number of prior anti-cancer therapy lines
  - Best response
- The following will be summarized for prior anti-cancer radiotherapy
  - Any prior anti-cancer radiotherapy (yes/ no)

- Intent of therapy
- Number of prior anti-cancer radiotherapies
- Best response

- The following will be summarized for prior anti-cancer local-regional therapy
  - Any prior anti-cancer local-regional therapy (yes/ no)
  - Type of therapy
  - Intent of therapy
  - Number of prior anti-cancer radiotherapies
  - Prior anti-cancer local-reginal therapy drugs, presented by preferred terms alphabetically
  - Best response
- The following will be summarized for prior anti-cancer surgery
  - Any prior anti-cancer surgery (yes/ no)
  - Number of prior anti-cancer surgeries
  - Prior anti-cancer surgeries, preferred terms will be presented alphabetically
  - The surgery was curative in intent (yes/ no)
  - Outcome of surgery

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# 14 Previous and Concomitant Medications/Procedures

*Population: mITT Analysis Set*

## 14.1 Previous and concomitant medications

The medications recorded on the "Concomitant Medication Details" eCRF form will be used as data source.

All terms will be coded using the most current World Health Organization Drug Dictionary (WHO Drug) version at the time of database lock. Medications will be presented using the Anatomical Therapeutic Chemical (ATC) classification system. Numbers of patients with concomitant medications/ treatment procedures will be presented overall and by ATC 2nd level, preferred terms.

Missing or partial dates for medications will not be imputed. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. considered as both previous and concomitant.

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

- Concomitant treatments are medications, other than trial treatments, which are taken by patients any time on-treatment (on or after the first day of any trial treatment for each patient) or within 33 days after last dose of trial treatment.

## 14.2 Concurrent procedures

All concurrent procedures, which were undertaken any time on trial, will be summarized according to the CRF page "Concurrent Procedures". Concurrent procedures will be classified by medical review.

Number of patient with concurrent procedures, i.e, those on-treatment procedures will be summarized per treatment arm and overall and by reason and preferred name.

All medication/ treatment procedures will be listed.

## 14.3 Anti-Cancer Treatment after Discontinuation

New anticancer therapy will be recorded for patients who discontinue from the treatment for reasons other than PD at the additional follow-up visits. The following summaries will be presented for anti-cancer treatment after discontinuation:

- Any anti-cancer treatment after discontinuation (yes/ no)
- Type of systemic therapy
- Anti-cancer treatment drugs after discontinuation, presented by preferred terms alphabetically

- Time to start of new anti-cancer treatment after discontinuation (months): derived as the duration from randomization to the earliest start date of anti-cancer drugs after discontinuation
- Best response

# 15 Treatment Compliance and Exposure

*Population: Safety Analysis Set*

The date of first drug administration will be taken from the "Tepotinib Administration Details" and "Sorafenib Administration Details" eCRF forms respectively. The date of last drug administration will be taken from the "Treatment Termination for Tepotinib" and "Treatment Termination for Sorafenib" eCRF forms respectively.

The extent of exposure to Tepotinib or sorafenib will be presented by the following summaries:

- Duration of therapy (weeks):

$$\text{Duration of therapy (weeks)} = \frac{\text{date of last dose - date of first dose+1}}{7}$$

  Interruptions, compliance, and dose changes are not taken into account for the calculation of duration of therapy.
- Cumulative dose (mg):

  The cumulative dose per patient in a time period is the sum of the total dosage that the patient received.

- Dose intensity (mg/day):

$$\text{Dose intensity (mg/day)} = \frac{\text{cumulative dose (mg)}}{\text{duration of therapy (days)}}$$

- Relative dose intensity (%):

$$\text{Relative dose intensity (\%)} = \frac{\text{Dose intensity (mg/day)}}{\text{planned dose intensity(mg/day)}} * 100$$

  It will be summarized as continuous variables and also categorized into groups as the following:

  - < 60%
  - 60% - <80%
  - 80% - <90%
  - 90% - 110%
  - >110%

# 16 Endpoint Evaluation

## 16.1 Primary Endpoint Analyses

*Population: mITT Analysis Set; PP Analysis Set as sensitivity analysis if less than 90% of mITT.*

**Definition of primary endpoint**

The primary endpoint is Time-to-Progression (TTP) as assessed by IRC according to RECIST 1.1 (Eisenhauer EA et al, 2009).

TTP is defined as the time (in months) from randomization to the first observation of PD (as assessed by IRC). The earliest scan date of target/non-target/new lesions will be used as the date of an overall response.

TTP (months) = (date of 1st PD – date of randomization+ 1) / 30.4375.

Start date of TTP:

- The date of randomization

Event date is the earliest date of the following events:

- Observed PD before the patient drops out. Overall response of "not evaluable" will be changed to PD if subsequent scan is a PD. PD data from "Overall response" in Assessment of Disease Based on Imaging eCRF will be used.
- PD assessed by imaging after the patient drops out. Imaging PDs collected in the "Survival Follow-Up / Progression Disease" eCRF will be used.

Censoring rules:

- Censored on the date of randomization if no baseline or post-baseline assessment.
- Censored at the date of death, if the patient died without documented PD.
- Censored on the date of last tumor assessment or the date of randomization, whatever occurs later, if:
  - Lost to follow-up / withdraw consent without PD observed (includes also patients whose last available radiological assessment is at least 42 days before data cut-off), or
  - No PD observed up to the cut-off date (administrative censoring)

An overview of event/censoring rules is given in table 2:

Table 2: General events/censoring rules

| | Date of event/censoring | Censored |
|---|---|---|
| **Events:** | | |

| | | |
|---|---|---|
| Radiological PD observed before the patient drops out. | Date of PD | No |
| Radiological PD assessed after the patient drops out. | Date of PD | No |
| **Censoring:** | | |
| No baseline or post-baseline assessment | Date of randomization | Yes |
| Lost to follow-up / withdraw consent without PD observed (includes also patients with a radiological assessment that is at least 42 days before data cut-off) | Date of last known tumor assessment or date of randomization, whatever occurs later | Yes |
| No PD observed up to the cut-off date (administrative censoring) | Date of last known tumor assessment or date of randomization, whatever occurs later | Yes |
| Died without documented PD | Date of death | Yes |

**Primary analysis**

The primary analysis will test the equality of TTP between treatment arms in the randomized part of Phase II, based on the mITT population, applying a two-sided stratified log-rank test at a significance level of $\alpha = 10\%$, taking into account the strata used for randomization, i.e., baseline BCLC stage. IVRS strata other than the eCRF strata will be used.

The following null-hypothesis is tested by the Cox's proportional hazards model stratified according to strata used for randomization:

$$H_0: \lambda_{experimental}(t) = \lambda_{control}(t)$$

$$H_1: \lambda_{experimental}(t) = \theta\lambda_{control}(t), \theta \neq 1,$$

where $\lambda(t)$ represents the hazard at time t and $\theta$ the unknown constant of proportionality of hazards in the allocated treatment groups in the randomized part. Ties will be handled by replacing the proportional hazards model by the discrete logistic model. With this ties option the Score-test in the Cox's proportional hazards model is identical to the log-rank test:

```
proc phreg data=xxx;
        strata BCLC;
        model TTE*TTE_censor(1) = treatment / ties = discrete rl;
        ods output globaltests=logRank_TTE (where=(test='Score'))
        parameterestimates = HR_TTE ;
run ;
Where:
TTE_censor = 1 if censored, 0 otherwise
Treatment  = 1 if in experimental arm, =0 if in control arm
TTE        = Time to event variable, for primary analysis it is TTP by IRC.
```

The hazard ratio $\theta$ and 90% CIs of Tepotinib compared to sorafenib will be calculated by Cox's proportional hazards model stratified by baseline BCLC (stage B vs stage C).

Kaplan-Meier curves (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics (25th quintile, median and 75th quintile survival time, 2-months, 4-months KM estimates and estimates for every 2 months thereafter as applicable) including the corresponding two-sided 90% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982), and CIs for the survival function estimates at above defined time points will be derived from the Kaplan-Meier estimates using the log-log transformation (CONFTYPE=LOGLOG in SAS PROC LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. Comparisons of survival rates will be performed from a Z-test using estimates and standard errors derived from the Kaplan-Meier method and Greenwood's formula. SAS procedure LIFETEST will be used to obtain Kaplan-Meier estimates and plots.

**Sensitivity analysis**

An un-stratified Cox model will be fitted, by which the hazard ratio θ, the 90% CIs and p- value will be calculated.

Multivariate analysis will be performed with a stepwise selection to assess the effect of predefined baseline covariates, which are the subgroup variables in Section 10.2 (except for baseline tumor HGF and baseline biomarker variables measured in plasma).

The model selection is performed without fitting the treatment group in the proportional hazards model. The values 0.15 and 0.40 will be used as the p-value for entry into the model inclusion and p-value for staying in the model, respectively exclusion criteria.

```
proc phreg data=Eff_mITT ;
        class all-subgroup variables;
        strata BCLC;
        model TTE*censor(1)= all-subgroup variables /ties=discrete rl selection=stepwise
        slentry=0.15 slstay=0.40 details;
        ods output globaltests=logRank(where=(test='Score')) parameterestimates=HR;
run ;
Where:
slentry= boundary for p-value of Score test for inclusion, other values than 0.15 can be
considered
slstay= boundary for p-value of Wald test for exclusion, other values than 0.40 can be considered
```

Once the selection procedure is finalized the model will be refitted with the strata and the treatment group, plus the selected covariates.

```
proc phreg data=xxx;
        strata BCLC;
        class all-selected-covariates;
        model TTE*TTE_censor(1) = treatment all-selected-covariates / ties = discrete rl;
        ods output globaltests=logRank_TTE (where=(test='Score'))
        parameterestimates = HR_TTE ;
run ;
Where:
TTE_censor = 1 if censored, 0 otherwise
Treatment = 1 if in experimental arm, =0 if in control arm
TTE    = Time to event variables, for primary analysis it is TTP by IRC..
```

Subgroup analyses will be performed separately for each of the predefined subgroup variables without stratification due to the potential low number of patients per subgroup category. Cox regression models will be fitted for TTP by IRC as the dependent variable and with a subgroup type, the treatment group assignment and with and without the treatment by subgroup type interaction as explanatory variables. Hazard ratio (including 90% confidence interval) of Tepotinib compared to sorafenib is computed per subgroup level. P-value for the interaction test (Likelihood Ratio test) will be provided together with the hazard ratios and confidence intervals of the interaction model parameter. Forest plots will be presented with hazard ratios and 90% CIs of treatment for the overall treatment effect and for each subgroup level.

Kaplan-Meier curves will be presented by treatment arm for each predefined biomarkers subgroups.

A cross table of TTP assessed by IRC vs TTP assessed by investigator will be summarized to check the consistency of two definitions. If the TTP assessed by IRC and the TTP assessed by investigator are at most 30 days apart, the two TTPs will be considered consistent.

TTP assessed by IRC assessed will be further explored considering the PP population if the number of patients in the PP population is less than 90% of the number of patients in the mITT population.

## 16.2 Secondary Endpoint Analyses

*Population: mITT Analysis Set; PP Analysis Set if less than 90% of mITT.*

### 16.2.1 Progression-free Survival (PFS) on tumor assessment by IRC

PFS time is defined as the time (in months) from randomization to either first observation of disease progression or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment. The 84-day time window represents the time span between scheduled tumor assessments. The earliest scan date of target/non-target/new lesions will be used as the date of an overall response.

PFS (months) = (date of 1$^{st}$ PD or death –date of randomization+ 1) / 30.4375.

Start date of PFS:

- The date of randomization

Event date is the earliest date of the following events:

- Observed PD before the patient drops out. Overall response of “not evaluable” will be changed to PD if subsequent scan is a PD. PD data from “Overall response” in Assessment of Disease Based on Imaging eCRF will be used.
- PD assessed by imaging after the patient drops out. Imaging PDs collected in the “Survival Follow-Up / Progression Disease” eCRF will be used.

- Death without previously documented PD is observed within 84 days of the date of randomization or last tumor assessment. The Death date is collected on the "Death" eCRF form.

Censoring rules:

- Censored on the date of randomization if no baseline or post-baseline assessment.
- Censored on the date of last tumor assessment or the date of randomization, whatever occurs later, if:
  - Death without previously documented PD is observed not within 84 days of the randomization or last tumor assessment, or
  - Lost to follow-up / withdraw consent without PD/death observed (including also patients whose last available radiological assessment is at least 84 days before data cut-off), or
  - No PD/death observed yet up to the cut-off date (administrative censoring)

An overview of PFS event/censoring rules is given in table 3:

Table 3: PFS Events/censoring rules

| | **Date of event/censoring** | **Censored** |
|---|---|---|
| **Events:** | | |
| Radiological PD observed before the patient drops out. | Date of PD | No |
| Radiological PD assessed after the patient drops out. | Date of PD | No |
| Death without previously documented PD is observed within 84 days of the randomization or the last tumor assessment | Date of death | No |
| **Censoring:** | | |
| No baseline or post-baseline assessment | Date of randomization | Yes |
| Death without previously documented PD is observed not within 84 days of the randomization or the last tumor assessment | Date of last known tumor assessment or date of randomization, whatever occurs later | Yes |
| Lost to follow-up / withdraw consent without PD/death observed (includes also patients with a radiological assessment that is at least 84 days before data cut-off) | Date of last known tumor assessment or date of randomization, whatever occurs later | Yes |
| No PD/death observed up to the cut-off date (administrative censoring) | Date of last known tumor assessment or date of randomization, whatever occurs later | Yes |

Analysis methods analogous to the ones of the primary endpoint will employed. Subgroup analyses will be performed for each of the subgroup variables. Kaplan-Meier curves will be presented by treatment arm for each predefined biomarker subgroup.

### 16.2.2 PFS based on tumor assessment by Investigator

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

### 16.2.3 Overall Survival (OS)

A preliminary analysis on OS may be performed when the primary analysis on TTP is analyzed. Final OS analysis will be carried out after the database lock.

Overall survival (OS) time is defined as the time (in months) from randomization to the date of death. For patients who do not have a date of death, the last date known to be alive will be used:

> OS (months) = (date of death or last date known to be alive – the date of randomization+ 1) / 30.4375.

Event date:

- Date of death if the death is before the cut-off date

For patients who do not have a date of death, the patient will be censored at the last known alive date, and will be categorized as:

- Administrative censoring: For patients whose last date known to be alive is within 90 days of cutoff date.
- Non-administrative censoring: For patients whose last date known to be alive is outside of 90 days before cutoff date.

The last known alive date will be the latest date of alive dates (refers to Table 4)

Table 4: Data source of alive dates

| **eCRF or Dataset** | **CRF Items or Variables** |
|---|---|
| Patient Status / Survival Follow-Up | Last known alive date, follow-up date |
| SDTM.SV | SVSTDTC, SVENDTC |
| Adverse Events | Start date, end date |
| Concomitant Medications | Start date, end date |
| End of Assessment Visit | Completion/discontinuation date |
| Additional Follow-Up / Progression Disease | Progression date |
| Anti-Cancer Treatment After Discontinuation | Start date, end date |

Analyses analogous to the ones for TTP will be performed, expect that the survival rate will be estimated at 3-month, 6-month and for every 3 months thereafter as applicable. Subgroup analyses

will be performed for each of the subgroup variables. Kaplan-Meier curves will be presented by treatment arm for each predefined biomarker subgroup.

### 16.2.4 TTP Assessed by Investigator

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

TTP (months) = (date of 1st PD –date of randomization+ 1) / 30.4375.

Analysis methods analogous to the ones of TTP assessed by IRC will employed.

### 16.2.5 Time-to-Symptomatic Progression (TTSP)

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

Start date of TTSP:

- The date of randomization

Event date is the date of the earliest deterioration.

Censoring rules:

- Censored on the date of randomization if no baseline or post-baseline assessment.
- Censored at the date of death, if the patient died without deterioration.
- Censored on the date of last FHSI-8 / ECOG assessment or the date of randomization, whatever occurs later, if:
  - Lost to follow-up / withdraw consent without deterioration observed (includes also patients whose last available FHSI-8 / ECOG assessment is at least 42 days before data cut-off), or
  - No deterioration observed up to the cut-off date (administrative censoring)

The FHSI-8 will be scored by the following scoring guideline (version 4):

**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**

Analyses analogous to the ones of TTP will be performed.

## 16.2.6 Antitumor Activity Assessed by IRC

**Best Overall Response**

Best overall response (BOR) is defined as the best result obtained among all tumor assessment visits from baseline until end of treatment or determination of PD, excluding assessments after tumor surgery.

Not Evaluable (NE) is not considered a valid measurement. Overall response of NE will be changed to PD if subsequent scan is a PD. As a consequence, a BOR of NE will only be assigned if NE is the only one treatment assessment (for instance, a patient having assessments of NE and PD will be assigned BOR of PD).

Patients with BOR of non-CR/non-PD (possible only for patients without measurable disease at baseline) are not considered as having achieved objective response, nor clinical benefit.

The following will be provided:

- The number and percentage of patients with a best overall response (BOR) of CR, PR, SD, PD, non-CR/non-PD, and NE will be tabulated.

- The number and percentage of patients will be tabulated over time grouped by the overall response.
- Bar chart with time to response and duration of trial treatment
- The number and percentage of patients will be tabulated by predefined biomarker subgroup and treatment group over time grouped by the best overall response.

**Objective Response Rate (ORR) based on tumor assessment by IRC**

The objective response rate is defined as complete response (CR) or partial response (PR) as the best overall response (BOR) according to radiological assessments as adjudicated by the IRC from randomization to first occurrence of PD.Responses do not require confirmation according to RECIST v1.1.

The Cochran-Mantel-Haenszel test will be performed for analysis using the randomization strata, i.e., type of Met+. The Cochran-Mantel-Haenszel will test the following two-sided hypothesis:

$H_0$: $\Psi = 1$

$H_1$: $\Psi \neq 1$

where $\Psi$ defines the common odds ratio across all strata.

The common Mantel-Haenszel odds ratio (OR) adjusted by strata and the corresponding 90% CIs using the variance formula for the log of the common odds ratio estimate will be presented. The odds ratio is defined as the odds of showing response with the investigational drug, divided by the odds of showing response with the control treatment, i.e. an odds ratio greater than one corresponds to a benefit of the investigational arm. The homogeneity of the odds ratio across strata will be checked by the Breslow-Day test, The null hypothesis of no association in any of the strata is tested against the alternative, which says that at least in one stratum there is an association between treatment effect and tumor response. Additional to the Mantel-Haenszel estimate, odds ratios per stratum are indicated with the corresponding exact confidence interval. The common odds ratio with no adjustment by strata and its 90% CI will be provided as well.

The ORR rate will be presented for each treatment group including the corresponding 90% Newcombe-Wilson CIs.

The best percent change (%) from baseline for the sum of longest diameters will be displayed in a waterfall plot.

**Disease Control Rate (DCR) by IRC**

The disease control rate is defined as the proportion of patients having achieved CR, PR, or stable disease (SD) as the BOR according to radiological assessments from randomization until end of trial treatment the first occurrence of PD. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization.

The DCR rate and its 90% Newcombe-Wilson CI will be calculated.

### 16.2.7 Antitumor Activity Assessed by Investigator

**Best overall response**

BOR is defined as the best result obtained among all tumor assessment visits by investigator from baseline until end of treatment or determination of PD, excluding assessments after tumor surgery.

**ORR based on tumor assessment by Investigator**

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

**DCR based on tumor assessment by the investigator**

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

## 16.3 Other Endpoint Analyses

CCI [redacted]

CCI [redacted]

[redacted]

## 16.3.2 Patient Reported Outcome

*Population: mITT Analysis Set*

**Functional assessment of cancer therapy-hepatobiliary (FACT-HP)**

The FACT-HP questionnaire will be scored by the FACT-Hep Scoring Guideline (version 4):

**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 WELL-BEING (PWB)** | GP1 | 4 | - | _____ | =_____ |
| | GP2 | 4 | - | _____ | =_____ |
| | 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 WELL-BEING (SWB)** | GS1 | 0 | + | _____ | = _____ |
| | GS2 | 0 | + | _____ | = _____ |
| | 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 WELL-BEING (EWB)** | GE1 | 4 | - | _____ | = _____ |
| | GE2 | 0 | + | _____ | = _____ |
| | 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 WELL-BEING (FWB)** | GF1 | 0 | + | _____ | = _____ |
| | GF2 | 0 | + | _____ | = _____ |
| | 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**

| 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

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

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

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

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

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

The absolute value and change from baseline of FACT-Hep Total score, Trial Outcome Index (TOI) score and FACT-G score will be summarized over time descriptively for each treatment group.

[redacted]

### 16.3.5 Tumor Shrinkage by IRC

*Population: Safety Analysis Set*

The percent change from baseline in target lesions assessed by IRC (sum of longest diameter for non-nodal lesions and short axis for nodal lesions, SOD) per time point will be derived for subjects with post baseline target lesion assessments as:

$$\text{Percent change from baseline} = 100 * (\frac{\text{SOD at visit } X}{\text{SOD at baseline}} - 1)$$

The earliest scan date of target lesions will be used as the date of SOD.

The best relative change in target lesions from baseline will be derived across all post-baseline assessments by IRC until documented disease progression as:

$$\text{Best relative change} = \textit{the mimimum value of percent change from baseline}$$

The following will be provided:

- Waterfall plot for the best relative change of SOD
- Waterfall plot for the best relative change of SOD by cMet status (Positive (2+ or 3+) /Negative (0 or 1+) /Indeterminate/Missing)
- The percent change from baseline in target lesions per time point will be displayed in a line plot and presented in a data listing as well as other relevant information.

### 16.3.6 Tumor Shrinkage by Investigator

The percent change from baseline in target lesions assessed by investigator (sum of longest diameter for non-nodal lesions and short axis for nodal lesions, SOD) per time point will be derived for subjects with post baseline target lesion assessments as:

$$\text{Percent change from baseline} = 100 * (\frac{\text{SOD at visit } X}{\text{SOD at baseline}} - 1)$$

The earliest scan date of target lesions will be used as the date of SOD.

The best relative change in target lesions from baseline will be derived across all post-baseline assessments by investigator until documented disease progression as:

$$\text{Best relative change} = \textit{the mimimum value of percent change from baseline}$$

Analysis methods analogous to the ones of tumor shrinkage assessed by IRC will employed.

## 17 Safety Evaluation

*Population: Safety Analysis Set*

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. Analyses will be performed using the Safety Analysis set.

Safety analyses will be done on the safety analysis set and according to the as-treated principle.

## 17.1 Adverse Events

*Population: Safety Analysis Set*

Treatment emergent adverse events: those events with onset dates occurring within the treatment periods, i.e, starts on or after the earliest dosing date of any trial treatment and prior to the latest dosing date of any trial treatment + 33 days (inclusive). AE occurring after the first administration will always be considered as TEAE regardless of whether its onset date beyond the 33 days if it is assessed as trial-drug related by investigator.

"Timing related to study treatment" from the AE eCRF will be used to judge whether the AE is a TEAE when the AE onset date is the same day as the day of first administration.

In the case where it is not possible to define an AE as being treatment emergent or not, the AE will be classified as treatment emergent as the most conservative approach.

Summaries for the number of patients in total and within each treatment group will be presented, for each of the categories described in the sub-sections below.

Listings will include all TEAEs and Non-TEAEs. Summary tables described in Section 17.1, 17.2.2 and 17.2.3 will be based on TEAEs if not otherwise specified.

No formal statistical comparisons are planned.

### 17.1.1 All Adverse Events

AEs will be coded using the most current version of MedDRA dictionary. The investigator will be responsible for assigning the Common Toxicity Criteria (CTC) grades for AEs, using the most current version of NCI-CTCAE.

Incidence rates (frequencies and percentages) of individual AEs, that is, the number of patients experiencing events AEs in each PT or SOC, and the proportion relative to the number of patients in the SAF analysis set, will be presented.

Unless otherwise stated adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

The relationship to the trial treatment, as indicated by the investigator, is classed as "not related" or "related". TEAEs with a related or missing relationship to the trial treatment will be regarded as "related". If a patient reports the same AE more than once within that SOC/PT, the AE will be categorized as "unrelated" only when all relationship records are "unrelated", otherwise it will be classed as "related" in the corresponding relationship summaries.

Severity is classified as grade 1, 2, 3, 4, 5 (increasing severity) by referencing the most current NCI-CTCAE 4.0 (publication date: 28May2009). If a patient reports a TEAE more than once within that SOC/PT, the AE with the worst case severity will be used in the corresponding severity summaries. In case a patient had events with missing and non-missing severities, the maximum of the non-missing severities will be displayed. In case all the TEAEs of a patient are all with missing severities then grade 3 (severe) will be used unless there is any evidence that it should be grade 4 or 5.

An overview summary of TEAEs will be provided by treatment group for cycle 1 and all cycles:

- TEAEs
- Related TEAEs
- Serious TEAEs
- Serious related TEAEs
- TEAEs of grade ≥ 3 by NCI-CTCAE
- Related TEAEs of grade ≥ 3 by NCI-CTCAE
- TEAEs of special interest (refer to Section 17.2.3)
- Related TEAEs of special interest
- TEAE leading to death (AEs with grade 5 or outcome "fatal" if grade 5 not applicable)
- Related TEAE leading to death (AEs with grade 5 or outcome "fatal" if grade 5 not applicable)
- TEAEs leading to dose reduction of trial treatment
- TEAEs leading to temporary discontinuation of trial treatment
- TEAEs leading to permanent discontinuation of trial treatment
- TEAEs leading to study discontinuation

Also the following tables will be presented by SOC, PT in alphabetical order for TEAEs:

- Incidence of TEAEs
- Incidence of TEAEs by worst severity (CTCAE grade)
- Incidence of related TEAEs
- Incidence of TEAEs with CTCAE grade >= 3
- Incidence of treatment related TEAEs with CTCAE grade >= 3

### 17.1.2 Adverse Events Leading to Treatment Discontinuation

AEs leading to permanent or temporary discontinuation of trial treatment are those AEs whose actions taken with trial treatment is reported as "drug withdrawn" or "drug interrupted" in the "Adverse Events Details" eCRF. The following will be presented by SOC and PT in alphabetical order:

- Incidence of TEAEs leading to dose reduction of trial treatment
- Incidence of TEAEs leading to permanent discontinuation of trial treatment
- Incidence of TEAEs leading to temporary discontinuation of trial treatment

## 17.2 Deaths, Other SAEs, and AEs of Special Interest

*Population: Safety Analysis Set*

### 17.2.1 Deaths

All deaths, deaths within 33 days after last dose of trial treatment, will be tabulated based on information from the "Death" eCRF.

Summaries will be presented for:

- Number of deaths
- Number of deaths within 33 days after last dose of treatment
- Primary reason of death
  - Disease progressions
  - Adverse event related to trial treatment
  - Adverse event not related to trial treatment
  - Other
  - Unknown

All deaths for *screening analysis set* will be listed:

- In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (date of first / last administration, dose intensity, etc).
- Including columns for:
  - AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)
  - flag for death within 33 days of last trial treatment administration

### 17.2.2 Serious Adverse Events

SAEs are those events with a response of "Yes" for the item "Serious Adverse Event" on the "Adverse Events Details" eCRF. Serious TEAE, serious related TEAEs and a full list of all SAEs will be presented:

- Incidence of serious TEAEs by SOC and PT
- Incidence of serious related TEAEs by SOC and PT
- Incidence of serious TEAEs leading to death by SOC and PT
- Incidence of related serious TEAEs leading to death by SOC and PT
- Listing of all SAEs

### 17.2.3 Adverse Event of Special Interest

AE of Special Interest (AESI) is defined as AEs of asymptomatic lipase and/or amylase elevations of Grade ≥ 3. The following are collected and will be presented:

- Incidence of treatment emergent AESIs by SOC and PT
- Incidence of related treatment emergent AESIs by SOC and PT

## 17.3 Clinical Laboratory Evaluation

*Population: Safety Analysis Set*

Laboratory values (including corresponding normal ranges) from Central Lab will be used for summary statistics and shift tables. Only patients with post baseline laboratory values will be included in these analyses.

Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, High). The number of patients with clinical laboratory values below, within, or above normal ranges at baseline compared to worst on-treatment results will be tabulated for each test by treatment groups. Shift tables of baseline versus worst on-treatment endpoint will be presented.

Thus the following tabulations will be provided for each treatment arm:

- Actual and changes from baseline to each scheduled visit over time
- Number of patients with shifts from baseline to worst on-treatment result above/below normal limit. Please refer to the AdaM template 2.0 to find parameters to be split into high and low. For example, glucose will be presented by "glucose high" and "glucose low" separately.
- Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will be shown in a data listing.
- Any lipase or amylase increase will be listed with a column flagging the ones meeting AESI definition, as noted in Section 17.2.3.

Laboratory results will also be classified according to the most current version of NCI-CTC Version as provided by the central laboratory. Parameters with available NCI-CTC grades will be summarized as the following:

- Number and percentage of subjects with any, NCI-CTC grade 0, 1, 2, 3, or 4 laboratory abnormalities under treatment – (worst case)
- /Shifts in toxicity grading from baseline to worst on-treatment grade: The worst on-treatment grade will be summarized by NCI-CTC grade (0, 1, 2, 3, 4, any). Please refer to the AdaM template 2.0 to find parameters to be split into high and low. For example, glucose will be presented by "glucose high" and "glucose low" separately.

| Parameter | Baseline category | Worst on trial value |
|---|---|---|
| Lab parameters with NCI-CTCAE grade | Grade 0<br>Grade 1<br>Grade 2<br>Grade 3<br>Grade 4<br>Any (Total) | Grade 0<br>Grade 1<br>Grade 2<br>Grade 3<br>Grade 4<br>Any (Total) |

## 17.4 Vital Signs

*Population: Safety Analysis Set*

Weight will be classified according to the NCI-CTCAE (version 4.0) criteria. Please find the CTCAE grading rules from the appendix.

| Parameter | Baseline category | Worst on trial value |
|---|---|---|
| Weight | Grade 0<br>Grade 1<br>Grade 2<br>Grade 3<br><br>Any (Total) | Grade 0<br>Grade 1<br>Grade 2<br>Grade 3<br>Any (Total) |

The maximum changes of vital sign measurements screening/baseline to maximum on-treatment changes after start of 1st treatment will be grouped as follows:

| Vital Sign Parameter | Increase/ decrease | Baseline category | Change from baseline category |
|---|---|---|---|
| Temperature | Increase | <37 °C,<br>37 - <38 °C<br>38 - <39 °C<br>39 - <40 °C<br>>=40 °C | < 1°C ,<br>1-<2°C ,<br>2-<3°C,<br>≥ 3 °C |
| Heart rate | Increase | <100 bpm ;<br>≥ 100 bpm | ≤20 bpm,<br>>20 – 40 bpm,<br>>40 bpm |
| | Decrease | <100 bpm ;<br>≥ 100 bpm | ≤20 bpm,<br>>20 – 40 bpm,<br>>40 bpm |
| SBP | Increase | <140 mmHg;<br>≥ 140 mmHg | ≤20 mmHg,<br>>20 – 40 mmHg,<br>>40 mmHg |
| | Decrease | <140 mmHg;<br>≥ 140 mmHg, | ≤20 mmHg,<br>>20 – 40 mmHg,<br>>40 mmHg |
| DBP | Increase | <90 mmHg;<br>≥ 90 mmHg | ≤20 mmHg,<br>>20 – 40 mmHg,<br>>40 mmHg |

| | | | |
|---|---|---|---|
| | Decrease | <90 mmHg;<br>≥ 90 mmHg | ≤20 mmHg,<br>>20 – 40 mmHg,<br>>40 mmHg |
| Respiration rate | Increase | <20 bpm ;<br>≥ 20 bpm | ≤5 bpm,<br>>5 – 10 bpm,<br>>10 bpm |
| | Decrease | <20 bpm ;<br>≥ 20 bpm | ≤5 bpm,<br>>5 – 10 bpm,<br>>10 bpm |

The following summaries will be prepared for vital sign parameters as grouped above considering only subjects with post baseline values:

- Change from baseline to worst on-treatment CTCAE toxicity grade for weight
- Maximal Shifts (changes in categories)

## 17.5 ECG

*Population: Safety Analysis Set*

All ECG readings will be recorded as 12-lead resting ECGs in triplicates. The average of these 3 results will be used for inclusion in the reporting of this study for numeric parameters. If some of the 3 results are missing, the average of available results will be used. For categorical data, the worst result among the 3 results will be used.

The following summaries will be provided for ECG data:

- The ECG overall assessment as reported by the investigator on the "Electrocardiogram" eCRF page will be summarized by time point/visit (Number and percentage of subject with result of ECG reported as Normal/Abnormal/Abnormal NCS/Abnormal CS)
- Summary over time for numeric parameters: only patients still stay at the visit will be summarized.
- Categorical shift from baseline to worst on-treatment value for QTcF: the baseline and the worst on-treatment value will be grouped as follows:

| Parameter | Baseline category | Worst on trial value |
|---|---|---|
| QTcF | <=450ms<br>>450 - <=480ms<br>>480 - <=500ms<br>>500ms | <=450ms<br>>450 - <=480ms<br>>480 - <=500ms<br>>500ms |

- Categorical change from baseline to worst on-treatment value for QTcF: the baseline and the worst change from baseline value will be grouped as follows:

| Parameter | Baseline category | Worst change from baseline |
|---|---|---|
| QTcF | Normal (i.e.<=450ms) | <=0 ms |

| | | |
|---|---|---|
| | Abnormal (i.e.>450ms) | >0 - <=30ms<br>>30 - <=60ms<br>>60ms |

## 17.6 Other Safety Evaluations

*Population: Safety Analysis Set*

The following will be provided for the ECOG performance status:

- Summary of ECOG over time: ECOG will be classified as 0, 1, 2, 3, 4, 5. Only patients still stay at the visit will be summarized.
- Shifts in ECOG performance status from baseline to worst on-treatment performance status will be summarized by treatment group

# 18 Reporting Conventions

The mock shells will be provided in a separate document *EMR200095-004 Phase II CTR Mock Shells*.

# 19 References

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

# 20 Appendix

- Non-CRF Data are listed as:

| Data to be Analyzed | Collected by |
|---|---|
| Protocol deviations | Clinical Trial Management System (CTMS). |
| Laboratory data | Central Lab |

- Laboratory parameters with CTCAE grading are:

| Lab Test Name | | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| **Chemistry** | | | | | |
| Total Bilirubin (umol/L) | Increase | >ULN | >1.5ULN | >3ULN | >10ULN |
| Aspartate Aminotransferase (U/L), SGOT | Increase | >ULN | >3xULN | >5xULN | >20xULN |
| Alanine Aminotransferase (U/L), AST | Increase | >ULN | >3xULN | >5xULN | >20xULN |
| Sodium (mmol/L) Low | Decrease | <LLN | **NA** | <130 | <120 |
| Sodium (mmol/L) High | Increase | >ULN | >150 | >155 | >160 |
| Calcium (mmol/L) Low (Albumin corrected), (Not total calcium) | Decrease | <LLN | <2 | <1.75 | <1.5 |
| Calcium (mmol/L) High (Albumin corrected), (Not total calcium) | Increase | >ULN | >2.9 | >3.1 | >3.4 |
| Magnesium (mmol/L) Low | Decrease | <LLN | <0.5 | <0.4 | <0.3 |
| Magnesium (mmol/L) High | Increase | >ULN | **NA** | >1.23 | >3.3 |
| Creatinine (umol/L) | Increase | >BL or ULN | >1.5BL or 1.5ULN | >3BL or 3ULN | >6ULN |
| Albumin (g/L) | Decrease | <LLN | <30 | <20 | **NA** |
| Alkaline phosphatase (U/L) | Increase | >ULN | >2.5xULN | >5xULN | >20xULN |
| Amylase (U/L) | Increase | >ULN | >1.5xULN | >2xULN | >5xULN |
| Lipase (U/L) | Increase | >ULN | >1.5xULN | >2xULN | >5xULN |
| Glucose (mmol/L) Low | Decrease | <LLN | <3.0 | <2.2 | <1.7 |

| | | | | | |
|---|---|---|---|---|---|
| Glucose (mmol/L) High | Increase | >ULN | >8.9 | >13.9 | >27.8 |
| Gamma Glutamyl Transferase (U/L) | Increase | >ULN | >2.5xULN | >5xULN | >20xULN |
| Potassium (mmol/L) Low | Decrease | <LLN | <LLN | <3 | <2.5 |
| Potassium (mmol/L) High | Increase | >ULN | >5.5 | >6 | >7 |
| Creatinine Clearance, C&G (mL/min) | Decrease | **NA** | <60 | <30 | <15 |
| **Hematology** | | | | | |
| Hemoglobin (g/L) Low | Decrease | <LLN | <100 | <80 | **NA** |
| Hemoglobin (gm/dL) High | Increase | >ULN or BL if BL>ULN | >ULN+2 or BL+2 if BL>ULN | >ULN+4 or BL+4 if BL>ULN | **NA** |
| Platelet (10E9/L), PLT | Decrease | <LLN | <75 | <50 | <25 |
| Leukocytes (10E9/L) Low | Decrease | <LLN | <3 | <2 | <1 |
| Leukocytes (10E9/L) High | Increase | **NA** | **NA** | >100 | **NA** |
| Neutrophils (10E9/L), Absolute Neutrophils Count , ANC | Decrease | <LLN | <1.5 | <1 | <0.5 |
| Lymphocytes (10E9/L) Low | Decrease | <LLN | <0.8 | <0.5 | <0.2 |
| Lymphocytes (10E9/L) High | Increase | **NA** | >4 | >20 | **NA** |
| **Coagulation** | | | | | |
| | | | | | |
| Activated Partial Thromboplastin Time (sec) | Increase | >1ULN | >1.5ULN | >2.5ULN | **NA** |
| Prothrombin Intl. Normalized Ratio | Increase | >BL or ULN | >1.5BL or 1.5ULN | >2.5BL or 2.5ULN | **NA** |

* BL=Baseline, ULN=Upper limit of normal range.

- Vital sign parameters with CTCAE grading are:

| **Vital Sign Parameter** | | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Weight Loss (kg) | Decrease | 5 - <10% from BL | 10 - <20% from BL | >=20% from BL | **NA** |
| Weight Gain (kg) | Increase | 5 - <10% from BL | 10 - <20% from BL | >=20% from BL | **NA** |

* BL=Baseline.