Statistical Analysis Plan

Clinical Trial Protocol Identification No.	EMR 200095-006
Title:	A Phase Ib/II Multicenter, Randomized, Open Label Trial to Compare Tepotinib (MSC2156119J) Combined with Gefitinib Versus Chemotherapy as Second-line Treatment in Subjects with MET Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation and Having Acquired Resistance to Prior EGFR-Tyrosine Kinase Inhibitor (EGFR-TKI) Therapy
Trial Phase	Phase Ib
Investigational Medicinal Product(s)	Tepotinib and Gefitinib
Clinical Trial Protocol Version	30 September 2016 / Version 7.0 03 November 2016 / Version 7.1 local Japan 06 April 2017 / Version 7.2 (Local for Canada)
Statistical Analysis Plan Author	PPD
Statistical Analysis Plan Date and Version	10 July 2017 /Version 2.0
Statistical Analysis Plan Reviewers	PPD, PPD PPD, Trial Biostatistician

1 Signature Page

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A Phase Ib/II Multicenter, Randomized, Open Label Trial to Compare Tepotibib Combined with Gefitinib Versus Chemotherapy as Second line Treatment in Subjects with MET Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation and Having Acquired Resistance Prior EGFR-Tyrosine Kinase Inhibitor (EGFR-TKI) Therapy

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2 Table of Contents

3 List of Abbreviations and Definition of Terms

AE	Adverse Event
ACS	Abnormal, Clinically Significant
ANCS	Abnormal, Not Clinically Significant
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUC_{0-t}	Area Under the Concentration-time Curve from Time Zero to the Last Quantifiable Concentration
BOR	Best Overall Response
C_{av}	Average Plasma Concentration
CI	Confidence interval
CL/F	Apparent Systemic Clearance
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CR	Complete Response
CTP	Clinical Trial Protocol
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DLT	Dose-Limiting Toxicity
DM	Data Management
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
HGF	Hepatic Growth Factor

LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
$MR_{(AUC0-t)}$	Metabolite to Parent Ratio based on AUC_{0-t}
$MR_{(Cmax)}$	Metabolite to Parent Ratio based on C_{max}
MRI	Magnetic Resonance Imaging
MW	Molecular Weight
NCI	National Cancer Institute
NE	Not Evaluable
NSCLC	Non-small Cell Lung Cancer
PD	Progressive Disease
CCI	[redacted]
PR	Partial Response
PK	Pharmacokinetic
PT	Preferred Term
PTF	Peak Trough Fluctuation Ratio (in %)
$R_{acc(AUC)}$	Accumulation Factor for AUC_{τ}
$R_{acc(Cmax)}$	Accumulation Factor for C_{max}
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Events
SAF	Safety Analysis
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SEM	Standard Error of the Mean
SI	International System of Units
SMC	Safety Monitoring Committee
SOC	System Organ Class

τ	Dosing Interval
t_{lag}	Time Prior to the First Quantifiable Concentration
t_{max}	Time of Maximum Plasma Concentration
TEAE	Treatment Emergent Adverse Event
CCI	[redacted]
ULOQ	Upper Limit of Quantification
WHO	World Health Organisation

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
0.1	18NOV2013	PPD	Not Applicable – First Version
0.2	23DEC2013		Internal Review
0.3	14MAY2014		Sponsor Feedback for cMET-004 SAP relevant sections
0.4	2014		Rewrite to fit Merck Serono template; Remove cumulative presentations from all SMC meetings per cMET-004 sponsor decision
1.0	09Jun2016		Rewrite to fit Merck Serono template; Update to protocol_V5
2.0	10July2017		Update for dry run comments and protocol v7.0/7.1/7.2 and, PK analysis, and biomarker analysis. Correction for parameter CTCAE grading

5 Purpose of the Statistical Analysis Plan

The purpose of this Statistical Analysis Plan (SAP) is to document technical and detailed specifications for the safety monitoring committee (SMC) and final analysis of data collected for the Phase Ib sections of protocol EMR200095-006. 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.

This SAP is based on clinical trial protocol (CTP) version 7.0, dated 30 September 2016, version 7.1 local Japan, dated 03 November 2016, version 7.2 local Canada, dated 06 April 2017, SMC charter version 1.0, dated Dec2013, and is prepared in compliance with ICH E9.

6 Summary of Clinical Trial Features

Trial Objectives	**Primary Objectives** • To determine the recommended Phase II dose (RP2D) of tepotinib when used in combination with gefitinib (at the approved standard dose of 250 mg) when administered orally once daily over a 21-day cycle in subjects with MET diagnostic-positive status (MET+) advanced NSCLC. **Secondary Objectives** • To characterize the pharmacokinetics (PK) of tepotinib when given in combination with gefitinib; • To characterize the PK of gefitinib when given in combination with tepotinib;

	• To assess the safety and tolerability of tepotinib in combination with gefitinib; • To evaluate preliminary antitumor activities of tepotinib in combination with gefitinib. **Exploratory Objectives** CCI • To assess biomarkers that may correlate with antitumor activity, including, but not limited to, markers of the Mesenchymal-Epithelial Transition Factor Gene (c-Met) pathway activation (e.g., phospho-c-Met, hepatocyte growth factor [HGF] levels, and c-Met mutations), and other relevant oncogenic pathways.
Trial design and plan	The Phase Ib stage of the study comprises 2 parts, the standard "3+3" dose escalation cohorts, and an additional cohort for subjects from the mainland China sites. This Phase Ib part that contains the "3+3" dose escalation cohorts is a multicenter, open label, dose escalation phase. A standard "3+3" dose escalation design with a dose escalation and a dose confirmation phase will be used. The criteria for dose escalation and de-escalation rules are based on the occurrence of dose-limiting toxicities (DLTs) during Cycle 1. Other clinically relevant safety issues, as well as emerging PK data, should also be considered as necessary when making dosing decisions. A Safety Monitoring Committee (SMC) will perform periodic safety review and will be responsible for making the decision to escalate (or de-escalate) the dose level after all subjects in the preceding cohort have completed the first cycle of treatment and subject data during this cycle have been evaluated. The anticipated dose cohorts of tepotinib are 300 and 500 mg once daily. Gefitinib will be coadministered at standard dose (250 mg once daily). Rich PK sampling will be performed in Phase Ib to characterize the PK of tepotinib and gefitinib. In addition, and separate from the "3+3" trial cohorts, up to 3 evaluable subjects will be enrolled in a separate cohort at one dose level below the RP2D at selected sites in mainland China.

Planned number of subjects	Approximately 15 to 18 subjects following a "3+3" dose escalation design, and an additional up to 3 evaluable subjects from the mainland China sites.
Schedule of visits and assessments	Subjects will be screened for up to 28 days prior to study treatment. Informed consent will be obtained prior to performing any trial assessment. Subjects will receive tepotinib in combination with gefitinib once daily until progressive disease (PD)/intolerable toxicities/withdrawal from treatment. In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Cases that may be considered for treatment beyond progression include subjects with slow ("smoldering") progression after an initial partial response (PR)/complete response (CR), provided there are no clinical symptoms related to underlying cancer disease and no new lesions. All cases must be discussed and agreed with the sponsor, and documented in the appropriate designated electronic case report form (eCRF) section. The investigator has to ensure that all safety data are collected, as per protocol, in the same manner as before progression, with the exception of the QoL questionnaires, which shall not be collected for this subject group. RECIST Version 1.1 radiographical assessment will follow institutional practice guidelines, however, tumor assessment information will not be recorded in the eCRF and there will be no further documentation collected except AEs for any new lesion and/or clinical symptoms of PD after first PD. Discontinuation of treatment beyond PD is based upon the development of clinical symptoms, emergence of new lesions or the discretion of the treating physician. For analysis of the primary endpoint, only the first progression event is used. Subjects who stop all trial treatments will have an End of Treatment visit within 14 days of the last dose, the completion of treatment cycle, or the day when it is determined to permanently discontinue the study treatment. A Safety Follow-up visit will occur at 30 days $\pm$ 3 days after the last dose for safety monitoring. If a subject withdraws from the treatment for reasons other than PD, additional follow up visits for tumor assessments will be performed until disease progression.
Inclusion and exclusion criteria	**Inclusion Criteria** For inclusion in Phase Ib, all of the following inclusion criteria must be fulfilled: 1. Histologically or cytologically confirmed advanced NSCLC, <u>regardless</u> of histology subtype, which failed on gefitinib for reasons other than toxicity or compliance;

2. Availability of a fresh or archived pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples). For subjects who have had at least 1 prior anticancer treatment, a biopsy obtained between failure of the most recent anticancer treatment and enrollment is mandatory;

3. MET+ status, as determined by the central laboratory, i.e. c-Met overexpression as determined by immunohistochemistry (IHC) (i.e., IHC 2+ or IHC 3+) and/or c-Met amplification as determined by in situ hybridization (ISH);

4. Signed, written informed consent by subject or legal representative prior to any study-specific screening procedure;

5. Male or female, ⩾ 18 years of age (or minimum age of legal consent consistent with local regulations, if minimum is > 18 years of age);

6. Measurable disease in accordance with RECIST Version 1.1;

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Exclusion Criteria

Subjects are not eligible for Phase Ib if they fulfill any of the following exclusion criteria:

Cancer Related

1. Symptomatic metastasis of brain and/or CNS, uncontrolled with antiepileptics and requiring steroids, unless treated and stable without steroids for at least 10 days within 4 weeks prior to the first dose of trial treatment;

2. Any unresolved toxicity more than National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 4.0) Grade 2 from previous anticancer therapy;

3. Estimated life expectancy < 3 months;

4. Need for transfusion within 14 days prior to the first dose of trial treatment;

5. Prior chemotherapy, biological therapy, radiation therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of trial treatment.

Laboratory Values and Organ Function

1. Inadequate hematological function:
   - Hemoglobin < 8.5 g/dL
   - Neutrophils < 1.5×10^9/L
   - Platelets < 100×10^9/L;

2. Inadequate liver function:
   - Total bilirubin > 1.5 × upper limit of normal (ULN)
   - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 3 × ULN;

   For subjects with liver metastases:
   - Total bilirubin > 1.5 × ULN
   - AST/ALT > 5 × ULN

3. Known pre-existing interstitial lung disease;

4. Inadequate renal function:
   - Renal impairment as evidenced by serum creatinine ≥ 1.5 × ULN, or creatinine clearance (CrCl) < 60 mL/min calculated by the Cockcroft-Gault formula (24 hour CrCl might be requested by the investigator for confirmation, if calculated CrCl is < 60 mL/min. In such case, subjects with 24 hour CrCl < 60 mL/min should be excluded)

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

5. Subjects who have ongoing medical history of acute pancreatitis and/or chronic pancreatitis, with concomitant elevated lipase and/or amylase, clinical symptoms, and/or imaging studies that are indicative of the diagnosis (subjects in mainland China only) .

General

1. Impaired cardiac function
   - Left ventricular ejection fraction (LVEF) < 45% defined by echocardiography (a screening LVEF assessment without history of congestive heart failure [CHF] is not required)
   - Serious arrhythmia
   - Unstable angina pectoris
   - CHF New York Heart Association (NYHA) III and IV (APPENDIX 1)
   - Myocardial infarction within the last 12 months prior to trial entry
   - Signs of pericardial effusion;

	2. Hypertension uncontrolled by standard therapies (not stabilized to <150/90 mmHg); 3. Contraindication to the administration of gefitinib; 4. Medical history of liver fibrosis/cirrhosis; 5. Past or current history of neoplasm other than NSCLC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years; 6. Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the tested product; 7. Major surgery within 28 days prior to Day 1 of trial treatment; 8. Known human immunodeficiency virus positivity; 9. Substance abuse, active infection, or other acute or chronic medical or psychiatric condition or laboratory abnormalities that might increase the risk associated with study participation at the discretion of investigators; 10. Female subjects who are pregnant or lactating, or men and women of reproductive potential not willing or not able to employ a highly effective method of birth control/contraception to prevent pregnancy until the end of study. A highly effective method of contraception is defined as those, alone or in combination, that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. This requirement begins 2 weeks before receiving the first trial treatment and ends 3 months after receiving the last treatment; 11. Known hypersensitivity to any of the trial treatment ingredients; 12. Legal incapacity or limited legal capacity; 13. Any other reason that, in the opinion of the principal investigator, precludes the subject from participating in the trial; 14. Participation in another interventional clinical trial (except those subjects who were solely involved in other trials where the investigation product was gefitinib, erlotinib, or afatinib) within the 30 days prior to first dose.

Investigational Medicinal Product(s): dose/mode of administration/ dosing schedule	For "3+3" dose escalation cohorts, tepotinib will be administered orally at 300 or 500 mg (or potentially, at a lower dose level, depending on the decision of the SMC) once daily, in combination with gefitinib at 250 mg. For the additional up to 3 evaluable subjects from the mainland China sites, tepotinib will be administered orally one dose level below the RP2D once daily, in combination with gefitinib at 250 mg.
Planned treatment duration per subject	Subjects may continue to receive tepotinib+gefitinib once daily until PD, intolerable toxicity, or withdrawal from treatment. In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Discontinuation of treatment beyond PD is at the discretion of the treating physician. If the subject develops new lesions or clinical symptoms, the benefit of continuing treatment with the study drugs should be discussed with the sponsor.
Primary endpoints	• Incidence of subjects experiencing at least 1 DLT in Cycle 1. (i.e., 21 days after the first dose of trial medication); • Incidence and type of other adverse events (AEs).
Secondary endpoint(s)	The secondary endpoints of the trial are as follows. Secondary endpoints related to safety: • Drug exposure; • Incidence and type of Treatment-Emergent Adverse Events (TEAEs) toxicity grades as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0): treatment related TEAEs, serious AEs (SAEs), treatment related SAEs, TEAEs with toxicity Grade $\geqslant$ 3, treatment related TEAEs Grade $\geqslant$ 3, and TEAEs leading to permanent treatment discontinuation; • Incidence and reasons for deaths within 33 days after the last dose of study drug; • Safety laboratory tests graded by NCI-CTCAE (version 4.0); • Vital signs, 12-lead electrocardiogram (ECG) changes, physical examination, including change in body weight, and ECOG PS. Other secondary endpoints include:

	• Tumor response as measured by objective response (OR) and disease control based on RECIST Version 1.1; • PK: AUC_{0-t}, AUC_{0-tau}, C_{max}, C_{avg}, C_{min}, t_{max}, $AUC_{0-\infty}$, CL/F, V_z/F, V_{ss}/F, λ_z and $t_{1/2}$ (when appropriate).
Exploratory endpoints	CCI • Exploratory biomarkers include biomarkers that may correlate with antitumor activity, including, but not limited to, markers of c-Met pathway activation (e.g., phospho-c-Met, HGF levels, and c-Met mutations), other relevant oncogenic pathways.

7 Sample Size/Randomization

The total number of subjects in the "3+3" dose escalation cohorts is approximately 15 to 18, on the basis of the "3+3" dose escalation method with 2 dose cohorts: 3 or 6 in the dose escalation cohort and a potential for 3 or 12 subjects in dose confirmation cohort (if dose de-escalation does not occur). The final sample size depends on the number of subjects who experience DLTs at each dose level, safety and emerging PK data and decision from the SMC meeting.

In addition, separately from the "3+3" dose escalation cohorts, up to an additional 3 evaluable subjects will be enrolled in the mainland China sites.

Randomization will not occur in both part of Phase Ib studies.

8 Overview of Planned Analyses

In addition to "3+3" Dose Escalation Cohorts, an additional cohort for subjects from the mainland China sites is included to meet a request from the Chinese Food and Drug Administration (CFDA) following clinical trial amendment review. Up to 3 evaluable subjects will be enrolled in the mainland China sites separately and will be tested at tepotinib one dose level below the RP2D once daily. The aim of this cohort is to collect preliminary data of the safety and PK of tepotinib administered in combination with gefitinib in subjects from mainland China sites.

Statistical analyses of the Phase Ib data will be carried out in a descriptive manner and will be performed using eCRF data in general. Data will be analyzed after 21 days dosing of the last subject. The DLT population is the underlying data set for the MTD determination. Safety analyses will be performed according to the as-treated principle. Safety data will be descriptively analyzed on the Safety Analysis Set. AEs will be coded according to the Medical Dictionary for Regulatory

Activities (MedDRA) Version 20.0 and reported by system organ class (SOC) and preferred term (PT). The severity of AEs will be graded using NCI-CTCAE (Version 4.0) toxicity grades.

Efficacy analyses will be performed on the Safety Analysis Set. The analysis of demographics and baseline characteristics will be obtained from the Safety Analysis Set.

8.1 Sequence of Analysis

A Safety Monitoring Committee (SMC) will be responsible for making the decision to escalate (or de-escalate) the dose level after all subjects in the preceding cohort have completed the first cycle of treatment and all subjects' data during this cycle have been evaluated. Final analysis will be performed after completion of the dose confirmation phase.

The SMC will not be responsible for safety evaluation of the up to 3 evaluable subjects in the additional cohort of subjects from the mainland China sites. Sponsor experts including, but not limited to, medical responsible, safety responsible and pharmacokineticist, as well as the coordinating investigator, will review the safety profile of the up to 3 evaluable subjects in the additional cohort.

8.2 Safety Monitoring Committee

For subjects in the "3+3" dose escalation cohorts, data pertaining to all suspected unexpected serious adverse reactions (SUSARs) and potential DLTs will be sent to the Safety Monitoring Committee (SMC) on a continual basis. SMC mandatory members will be identified before trial initiation and will include 1 or more investigator(s), the Medical Responsible, a pharmacokineticist, and a safety representative from the sponsor. Ad hoc members will be consulted as needed and may include, but are not restricted to, the biostatistician, or the treating investigator in the case of particular safety findings.

The SMC will be responsible for making the decision of dose escalation (or de-escalation) to a new dose level or expansion of enrollment at the same dose level after all subjects in the preceding cohort have completed Cycle 1 and all events during this cycle have been fully evaluated.

When 3 subjects have completed Cycle 1 at each dose cohort, new enrollment to this trial is paused in each of the dose cohorts. A full safety data set (all AEs, laboratory data, electrocardiogram (ECG) data, and vital signs) and available PK data will be submitted to the SMC, which evaluates the data and confirms the DLT incidence. For the definition of a DLT, refer to Section8.2.1. Depending on the incidence of DLTs, the SMC will determine whether to recruit additional subjects, or de-escalate to next dose level, or discontinue the study. The ad hoc SMC meetings can be performed at any time in case a safety concern should arise.

Further details of the safety monitoring process are specified in the dedicated SMC charter version 1.0, dated December 2013.

8.2.1 Definition of DLT

The period of DLT observation is during Cycle 1 for each subject.

Using the NCI-CTCAE (Version 4.0), a DLT is defined as any of the following toxicities that occur at any dose level and judged to be related to Tepotinib Combined with Gefitinib by the investigator and/or the sponsor:

Grade 4 neutropenia for more than 7 days;

Grade ⩾ 3 febrile neutropenia for more than 1 day;

Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with non-traumatic bleeding;

Grade ⩾ 3 uncontrolled nausea/vomiting and/or diarrhea despite adequate and optimal treatment;

Grade ⩾ 3 any non-hematological AE, except the aforementioned gastrointestinal events and alopecia; however, a DLT is defined specifically for the following cases:

- Grade ⩾ 3 liver AE requiring a recovery period of more than 7 days to the baseline or to Grade 1 (This criterion is not limited to the liver function tests. Other liver AE e.g., jaundice or hepatic encephalopathy suggestive of liver failure should be also considered);
- Grade ≥ 3 lipase and/or amylase elevation with confirmation of pancreatitis, either based on clinical or radiological signs will be considered as DLT. An isolated lipase and/or amylase elevation of ≥ Grade 3 without clinical or radiological evidence of pancreatitis will not be classified as DLT (for related topics, see APPENDIX 2).

8.3 Final Analysis

All final analyses identified in this SAP will be performed by PPD PPD following sponsor authorization of this SAP, database lock and sponsor authorization of the analysis sets.

A data review meeting will be held prior to database lock. In addition, no database can be locked until this SAP has been approved.

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 λ_z, considering the apparent terminal half-life of tepotinib and its metabolites. Therefore, all PK parameters dependent on λ_z will not be determined, i.e. $AUC_{0-\infty}$, $\%AUC_{extra}$, CL/F (single dose); $t_{1/2}$, Vz/F, and Vss/F.

The biomarker analysis sets will not be used. Instead all biomarker analyses will be performed on the Safety Set. For all analyses of categorical biomarkers a missing category will be included for all subjects where the biomarker was not determined or is not evaluable.

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 the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication;
- Deviation from GCP.

Important protocol deviations will be determined for all subjects by either site monitoring or medical review.

All the important protocol deviations will be included in Study Data Tabulation Model (SDTM) datasets. 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 prior to database lock.

10.2 Definition of Analysis Sets and Subgroups

All Screening Analysis Set

The All Screening Analysis set includes all subjects who have provided the 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 discontinue the trial prematurely during Cycle 1 for reasons other than a DLT and do not receive at least 80% (i.e., < 17 treatment days) of planned cumulative doses of tepotinib+gefitinib during Cycle 1 for reasons other than AEs or DLTs will be replaced.

The DLT Analysis Set will be used for evaluation of the number of subjects experiencing any DLTs at the end of each cohort and for the assessment of the RP2D in Cycle 1. Subjects who have

been replaced during the Cycle 1 or who belong to the additional cohort for subjects from the mainland China sites will be excluded from the DLT analysis set.

Safety Analysis Set (SAF)

The SAF set includes all subjects who have received at least 1 dose of tepotinib or gefitinib. Subjects replaced for evaluation of DLT and subjects who are from mainland China sites will still be included in the SAF set if they are treated at least once.

In addition to safety analysis, the efficacy analysis will be analyzed using all subjects in the SAF set.

PK Analysis Set

The PK Analysis Set includes all subjects who have received at least one dose of tepotinib and who had at least one post dose blood sample drawn that provides drug concentration data for PK evaluation and was not impacted by a protocol deviation or other event (eg, vomiting within the time frame of 2 * tepotinib median t_{max}, etc.) affecting PK. This analysis set will be used for summaries of the PK data for tepotinib and its metabolites, as well as for gefitinib. If a subject undergoes a tepotinib dose change after Cycle 1 Day 1, their PK data (for both tepotinib and gefitinib treatment) 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.

For baseline biomarker analyses, the Safety Analysis Set will be used. For all analyses of categorical biomarkers missing categories will be included for all subjects where biomarker results are not available. If applicable, two missing categories will be applied to distinguish between subjects where the biomarker was not determined and those where the biomarker data was not evaluable

11 General Specifications for Statistical Analyses

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 in the derived data sets 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.

Definition of reference start date, end dates, and study day:

Reference start date should coincide with Cycle 1 Day 1 and is defined as the day on which the first dose of study treatment was taken by the subject.

Reference end date is defined as the day of the last dose of study treatment.

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

- If the date of the event is on or after the reference date then: Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date then: Study Day = (date of event – reference date).

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

Retests, unscheduled visits and early termination data:

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to best/worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the worst available measurement for that visit will be used for by-visit summaries. Scenarios whereby subjects have a retest will be looked at on a case by case basis, with discussion with the medical team to decide which measurement should be used.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

Definition of baseline:

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered as baseline, but AEs and medications commencing on the reference start date will be considered post-baseline.

End of treatment:

Unless otherwise specified, end of treatment (EOT) is defined as the earliest non-missing measurement taken after reference end date. EOT measurements in general should be recorded at the "End of Treatment" visit.

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.

Calculation of duration:

Duration will be calculated by the difference of start and stop date + 1 if not otherwise specified.

Conversion factors:

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Missing data:

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

Incomplete AE-related dates will be handled as follows:

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

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

In individual subject data listings the documented date as given in the eCRF will be reported (e.g., __May2013 in case of day missing, but month and year available). No imputed values will be presented in the Clinical Trial Report. In all other subject data listings, imputed values will be presented. In those listings imputed date of death, last date known to be alive, start of AE and relationship of AE to study treatment will be flagged.

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

Windowing conventions:

No visit windowing will be performed for this study.

Statistical tests and significance level:

All data will be described using presentations of descriptive statistics only. No formal statistical analyses will be conducted in this study and significance level is not applicable.

Software version:

All analyses will be conducted using SAS (PPD) version 9.2 or higher.

Pooling of centers:

Because of the high number of participating centers and the anticipated small number of subjects in each center, data will be pooled across centers. Centre pooling will be carried out across all centers for use in statistical summaries for this study.

Examination of subgroups:

No formal subgroup summaries will be presented in this study.

Presentation of continuous and qualitative variables:

Appendix 3 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by PPD .

Continuous variables will be summarized using the following descriptive statistics unless otherwise specified (see Section 16.3.3):

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

Qualitative variables will be summarized by counts and percentages.

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

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: All Screening Analysis Set

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

Subjects will remain in the study until death, progression disease, loss to follow-up, or withdrawal of consent. Subjects are free to withdraw from the study at any time without giving their reason(s).

The following will be summarized overall and per treatment group when applicable:

- Total number of subjects screened (All screened subjects)
- Number of screen failure subjects (overall and grouped by primary reason for screen failure) and number of subjects allocated to treatment
- Number of subjects who discontinued the treatment after allocated to treatment, grouped by dose level and main reason separately for each treatment component
- Number of subjects who discontinued the trial after allocated to treatment, grouped by dose level and main reason

12.2 Protocol Deviations

Population: Safety Analysis Set

All protocol deviations, including inclusion/exclusion criteria deviations and deviations during the trial, will be listed, even if they are believed not to influence any of the results

12.2.1 Important Protocol Deviations

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 in categories: <65 years, >=65 years (65 -< 75, 75 -< 85, >= 85 years)
- Sex: male, female
- Race: Asian, other
- Region: Mainland China, South Korea, Taiwan, Singapore
- Nicotine use/Smoking status: never used, regular user, occasional user, former user.
- ECOG PS at baseline: 0, 1

Vital Signs at baseline:

- Height (cm): summary statistics
- Weight (kg): summary statistics
- BMI (kg/m2): summary statistics

Specifications for computation:

- Age (years): (date of given informed consent - date of birth) / 365.25, presented to 1 decimal place (dp).
- BMI (kg/ m2) = weight (kg) / height (m)2

13.2 Medical History

The medical history will be summarized from the "Medical History" and "Medical History Details" eCRF pages, using MedDRA version 20.0, preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category.

Ongoing 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.

Both previous and ongoing medical history will be listed.

13.3 Disease History

Disease history is collected on Disease History eCRF data. Information on disease history collected at the pre-treatment evaluation visit will be presented. Summary statistics will be presented for

- Site of Primary tumour
- Time since initial diagnosis (years)
- Tumor histophathologic/cytologic type: squamous, adenocarcinoma, large cell, bronchoalveolar, other
- Histologic tumor grade/differentiation: well differentiated, moderately differentiated, poorly differentiated, not applicable
- TNM classification at initial diagnosis and at study entry
- Metastasis sites at initial diagnosis and at study entry
- EGFR genetic mutation status: wild type, mutated, not available/feasible
- T790M Mutation Status: Positive, Negative

Specifications for computation:

- Time since initial diagnosis (years) = (date of informed consent – date of diagnosis) / 365.25, presented to 1 decimal place.

13.4 Medication History of Oncology

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

Summary statistics will be presented for

- Prior anti-cancer drug therapy
  - Any prior anti-cancer drug therapy
  - Type of systemic therapy
  - Intent of therapy
  - Previous TKI therapies
  - Line of previous TKI therapies
  - Immediate prior TKI therapies
  - Previous chemo therapies
  - Best response
- Prior anti-cancer radiotherapy
  - Any prior anti-cancer radiotherapy
  - Type of therapy

- Intent of therapy
- Best response

- Prior anti-cancer surgery
  - Any prior anti-cancer surgery
  - Number of prior anti-cancer surgeries
  - The surgery was curative in intent (yes/ no)
  - Outcome of surgery

Medication history for prior anti-cancer therapy and surgery information, including drug therapies, radiotherapy, and surgeries will be listed separately.

Specification for computation:

Previous TKI therapies are those collected by "Prior Anti-Cancer Drug Therapies Details" eCRF and listed in below table per the review of the most current database:

SDTM.CM.CMDECOD	SDTM.CM.CMTRT	Reported to Outputs (same as CMDECOD by default)
AFATINIB	Afatinib	
ERLOTINIB	Erlotinib	
ERLOTINIB HYDROCHLORIDE	Tarceva	ERLOTINIB
GEFITINIB	Gefitinib	
	Iressa	
	Iressa Gefitinib	
INVESTIGATIONAL DRUG	AUY922	AUY922
	AZD9291 Third generation EGFR TKI.	AZD9291
	AZD9291 Third generation EGR TKI	AZD9291
	INC280	INC280

CMDECOD will be reported by default. The drugs with different names but with same category would be merged together, for example CMDECOD =''ERLOTINIB' or 'ERLOTINIB HYDROCHLORIDE' will be combined into one category 'ERLOTINIB'. Drugs without commercial name such as CMDECOD ='INVESTIGATIONAL DRUG', the modified eCRF reported name will be used for categories.

Lines of previous TKI anti-cancer therapies are those lines collected by "Prior Anti-Cancer Drug Therapies Details" eCRF and containing one or more TKI therapies. The sequence number (SDTM.CM.CMGRPID) for the last previous TKI line will be categorized and summarized.

An immediate prior TKI therapy is the one which meets: 1) the corresponding line is the last one reported in the "Prior Anti-Cancer Drug Therapies Details" eCRF, 2) the therapy is a TKI therapy.

Previous chemo therapies are those collected by "Prior Anti-Cancer Drug Therapies Details" eCRF with a CMDECOD value listed as below per the review of the most current database:

SDTM.CM.CMDECOD	SDTM.CM.CMTRT	Reported to Outputs (same as CMDECOD by default)
CARBOPLATIN	Carboplatin	
	cardoplatin	
CISPLATIN	CISPLATIN	
DOCETAXEL	docetaxel	
	Taxotere	
	TOXOTERE	
ETOPOSIDE	Etoposide	
GEMCITABINE	gemcitabine	
GEMCITABINE HYDROCHLORIDE	GEMTAN	GEMCITABINE
	GEMZAR	GEMCITABINE
IRINOTECAN	Irinotecan	
PACLITAXEL	paclitaxel	
	Taxol	
PEMETREXED	pemetrexed	
PEMETREXED DISODIUM	Alimta	PEMETREXED
	Alimta pemetrexed	PEMETREXED
UFTORAL	Tegafur-uracil	
VINORELBINE	vinorelbine	
VINORELBINE TARTRATE	Navelbine	VINORELBINE

13.5 Baseline Biomarkers Measured in Tumor Tissue

All baseline biomarker variables will be listed.

13.5.1 Baseline Biomarker Variables

13.5.1.1 Baseline tumor c-Met Expression

The following scores will be provided by the pathologist, based on c-Met expression raw data measured by IHC in pre-treatment or archived tumor biopsies:

- Met score at baseline (possible values: 0, 1+, 2+, 3+)

In general, measurements flagged as non-evaluable will not be taken into account for analysis.

13.5.1.2 Baseline tumor c-Met Amplification

The following parameters will be provided for FISH analysis of pre-treatment or archived tumor biopsies:

- FISH analysis:

- c-Met / CEP7 copy number ratio
- Mean gene copy number

In general, measurements flagged as non-evaluable will not be taken into account for analysis.

13.5.1.3 Baseline tumor HGF Expression

The following score will be provided by the pathologist based on HGF expression raw data measured by IHC in pre-treatment or archived tumor biopsies:

- CAF HGF H-score, at baseline (continuous)
- HGF H-score, at baseline (continuous)

In general, measurements flagged as non-evaluable will not be taken into account for analysis.

The baseline HGF H-scores will not be analyzed for correlation/association to efficacy parameters.

Moreover, the HGF H-scores will be categorized in the following way:

- the variable baseline HGF H-score group [0 vs. any value] will have the following levels: H-score 0; H-score >0; H-score not done, H-score not evaluable

13.5.2 Descriptive Summaries of Baseline Biomarkers

13.5.2.1 Baseline tumor c-Met Expression

Baseline Met score will be summarized descriptively in a frequency table

Moreover, raw c-Met expression data will be presented in listings.

13.5.2.2 Baseline tumor c-Met Amplification Status

Baseline c-Met/CEP7 copy number ratio, mean gene copy number will be summarized descriptively using summary statistics. In addition, the following categories will be summarized:

- Mean Gene Copy Number: <5, >=5, >=6
- c-Met/CEP7 copy number ratio: <2, >=2
- FISH Status: FISH+ (either Mean Gene Copy Number >=5 or c-Met/CEP7 copy number ratio >=2), FISH-

Moreover, c-Met amplification data will be presented in listings.

13.5.2.3 Correlation between tumor Baseline c-Met Expression and Amplification Status

The correlation/association between c-Met expression and amplification status will be analyzed by presenting a cross-tabulation table. Cross-tabulation tables will only be presented by dose levels.

13.5.2.4 Baseline tumor HGF expression Status

Baseline HGF score (CAF HGF H-score, and Cytoplasmic HGF H-score) will be summarized descriptively using summary statistics.

Moreover, raw HGF from pre-treatment tumor biopsies will be presented in listings.

13.6 Other Baseline Characteristics

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

14 Previous or Concomitant Medications/Procedures

Population: Safety Analysis Set

14.1 Previous and concomitant medications

All terms will be coded using World Health Organization (WHO) Drug Dictionary version March 2017. Medications will be presented using the Anatomical Therapeutic Chemical (ATC) classification system, under level 2 and preferred names. Procedures will be reported by system organ class (SOC) and preferred term (PT) using MedDRA version 20.0. Reasons for previous medications/procedures will also be presented.

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

- 'Previous' medications or procedures are those which started and stopped prior to the first dose of study treatment.
- 'Concomitant' medications or procedures are those which:
  - started prior to, on or after the first dose of study treatment and started no later than 33 days following end of study treatment;
  - AND ended on or after the date of first dose of study treatment or were ongoing at the end of the study.
- 'Post' medications or procedures are those which started more than 33 days following the last dose of study treatment.

All medication/ treatment procedures will be listed.

14.2 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
- Type of systemic therapy
- Best response

Anti-cancer treatment after treatment termination will be listed.

15 Treatment Compliance and Exposure

Population: Safety Analysis Set

Compliance and exposure to both study treatment tepotinib and gefitinib will be presented for the SAF set for Cycle 1 as well as overall.

Study treatment tepotinib and gefitinib are given once daily (OD) and it is assumed that the subject should take medication from the morning of Cycle 1 Day 1, the visit day at which their medication is initially dispensed, to the morning before their scheduled medication return date.

The date of first tepotinib and gefitinib administration will be taken from the eCRF "Treatment Administration MSC2156119J Details" and "Treatment Gefitinib Administration Details" forms respectively. The date of last tepotinib and gefitinib treatment will be taken from the eCRF "Treatment Termination for MSC2156119J" and "Treatment Termination for Gefitinib" forms respectively.

The extent of compliance and exposure to tepotinib and gefitinib will be presented by the following summaries:

- Duration of exposure (weeks);
- Cumulative dose (mg);
- Dose intensity (mg/day);
- Relative dose intensity (%):
  - The breakdown of relative dose intensity (<60%, 60% - <80%, 80% - <90%, 90% - <110%, >110%) will be summarized by treatment group if patients have multiple Relative dose intensity.
- The number of dose reductions:

- Number and percentage of patients 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.

- The number of dose delays (dose temporary discontinuation):
  - Number and percentage of patients 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 patients have multiple dose temporary discontinuations.
  - Cumulative duration of dose temporary discontinuation (days) will be summarized.

Specifications for computation:

- Duration of exposure: dose reduction and dose delay are not taken into account for the calculation of duration of exposure
- Cumulative dose = the sum of the total dosage that the subject received in a time period
- Dose intensity (mg/day) = cumulative dose (mg) / duration on exposure (days)
- Relative dose intensity (%) = (actual dose (mg) / planned dose (mg))*100
- 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.
- Dose delay is defined as a change to drug interrupted, i.e. “0” dose level.

16 Endpoint Evaluation

16.1 Primary Endpoint Analyses

Population: DLT Analysis Set

The primary objective of this study is to investigate the incidence of subjects experiencing at least 1 DLT within the first treatment cycle (i.e. 21 days after first dose). Please refer section 8.2.1 for the definition of DLT. The primary endpoint is taken from the “Adverse Events Details” form on the eCRF and is recorded as “Is this adverse event a dose limiting toxicity?”

In addition to the DLT endpoint, the incidence and type of other AEs will also be assessed. These variables are also taken from the “Adverse Events Details” form.

No imputation for missing data will be performed for the DLT variable.

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

Tumor assessment will be performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The baseline tumor assessment is scheduled to be performed during the screening period. Tumor response evaluations will be then be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) and other modalities at the end of every 2 cycles (Cycles 3, 5, 7, 9, 11, 13, and every 4 cycles thereafter until PD).

Tumor assessments will be performed at EOT for subjects whose last tumor assessment was performed ⩾ 6 weeks before Cycle 17 and ⩾ 12 weeks afterwards prior to this visit and has no radiological PD in previous visits.

The secondary endpoint analyses associated to safety are listed in section 17.

Summary statistics will be presented for all parameters listed below for the SAF set.

16.2.1 Tumor response

Tumor response as measured by objective response (OR) and disease control based on RECIST Version 1.1. OR is defined as CR or PR as the best overall response according to local radiological assessments from the first administration of the trial treatment to the first observation of PD. Responses do not require confirmation according to RECIST Version 1.1; disease control is defined as CR, PR, or SD as the best overall response according to local radiological assessments from the date of the first administration of the trial treatment to the first observation of PD. In the case of SD, measurements must have met the SD criteria at least once after entry at a minimum interval of 42 days after the first administration of the trial treatment.

In addition to a summary of best overall response by dose level for all subjects, summaries will be provided by the following baseline biomarkers:

- c-Met score: 2+, 3+
- Mean Gene Copy Number: <5, >=5
- c-Met/CEP7 copy number ratio: <2, >=2
- FISH Status: FISH+ (either Mean Gene Copy Number >=5 or c-Met/CEP7 copy number ratio >=2), FISH-

16.3 Other Endpoint Analyses

Population: Safety Analysis Set

16.3.1 Duration of Response

The duration of overall response in months in subjects with a CR or PR is defined as the time from first assessment of CR/PR to the first time disease progression or death is documented. If a subject has not progressed or died at the time of analysis, the duration of objective response will be censored on the date of last disease assessment.

The duration of stable disease in months is defined as the time from the first dose to the first occurrence of PD or death. If a subject has not progressed or died at the time of analysis, the duration of SD will be censored on the date of last disease assessment.

The following summarizes will be reported in this study for SAF set.

- Duration of stable disease with or without censoring included
- Duration of overall response with or without censoring included
- The number of censored subjects

The time and duration of response per subject will be displayed in a swimmer graph in subjects with CR/PR. Flags for cMet status and immediate prior EGFR TKI therapy will be provided.

16.3.2 Target Lesion Diameter

The change from baseline in target lesion diameter will be summarized using descriptive statistics. The sum of the diameters will be used for all target lesions measured at each evaluation. The absolute change from baseline will also be summarized.

The individual maximal percentage reduction in sum of the diameters relative to baseline will be presented overall using a Waterfall plot which will include flags for cMet status and immediate prior EGFR TKI therapy.

The percent change from baseline of sum of diameters in target lesions as well as the first progressive disease with the type of the rational lesion (target/non-target/new) will be displayed against time point (weeks) in a line plot. The time point of a tumor assessment is defined as the earliest scan date of the respective visit. The baseline percent change is considered “0” on day 0. Flags for cMet status and immediate prior EGFR TKI therapy will be provided.

16.3.3 Pharmacokinetics

Population: PK Analysis Set

Tepotinib and metabolite (MSC2571107A and MSC2571109A) concentrations in plasma will be listed and presented in tables and descriptively summarized by dose level, day and scheduled time point. Gefitinib concentrations in plasma will be listed and presented in tables and descriptively summarized by 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 16.3.3.2. 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. Individual plasma concentration-time profiles (linear and semi-logarithmic scales) of gefitinib will be plotted by day; these profiles (i.e.both days) 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 four analytes separately (i.e., tepotinib and its metabolites, and gefitinib). Mean plasma concentrations of tepotinib and metabolites (MSC2571107A and MSC2571109A) 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 four analytes (i.e., tepotinib, metabolites [MSC2571107A and MSC2571109A] and gefitinib), 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 (MSC2571107A, MSC2571109A) from study EMR200095-006 phase Ib part will be analyzed jointly with data from studies EMR200095-001, -002, -003, -004, -005 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.

16.3.3.1 Pharmacokinetic Endpoints

The following pharmacokinetic endpoints will be analyzed:

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

16.3.3.2 Estimation of Individual Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by the PPD PK group using standard non-compartmental methods, actual elapsed sampling times, and the actual administered dose. The PK parameters listed below will be calculated for tepotinib and metabolites (MSC2571107A and MSC2571109A) and for gefitinib 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_{τ}	The area under the concentration-time curve over the dosing interval from T_1=0 h (predose) to T_2=τ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down). For Cycle 1 Day 1, AUCτ will be calculated as a partial area within the defined time range. For Cycle 1 Day 15, AUC_{τ} will be calculated at steady state from the pre-dose time point to the dosing interval time. AUC_{τ} will be calculated based on the observed concentration at the actual observation time, as long as actual time deviation is less than +/-10% at τ. If actual time deviation is equal to or greater than 10%, AUC_{τ} will be reported as missing.
CL/F	Apparent systemic clearance (calculated for tepotinib and gefitinib only), as Dose/AUC_{τ}. Calculated on Cycle 1 Day 15 only. For tepotinib, Dose is the tepotinib free base dose (i.e., adjusted for salt form). 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). For gefitinib, the dose administered is the free base form, so no dose adjustment is required.
AUC_{0-t}/Dose	Dose-Normalized AUC_{0-t} (calculated for tepotinib only). Normalized using actual dose(i.e., unadjusted for salt form).

AUC_{τ}/Dose	Dose-Normalized AUC_{τ} (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 = $100*(C_{max}-C_{min})/C_{av}$

Potential drug accumulation for tepotinib and its metabolites and for gefitinib will be evaluated by means of individual accumulation ratios for AUC_{τ} and C_{max} [$R_{acc(AUC)}$ and $R_{acc(Cmax)}$ respectively], that will be calculated by dividing the values obtained after multiple dose (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 Day 1) 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 λ_z, considering the apparent terminal half-life of tepotinib and its metabolites, and gefitinib. Therefore, all PK parameters dependent on λ_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_{τ} /Dose and C_{max}/Dose) by dose level

- Scatter plots on individual AUC_{τ} and C_{max} versus Dose on a linear scale.

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

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

16.3.4 On-Treatment Biomarkers in Tumor Tissue

On-treatment tumor biopsy is scheduled at any time between Cycle 1, Day 15 and the beginning of Cycle 3. If a tumor shows progression after initial response to Tepotibib, a final biopsy is highly desirable when progression is diagnosed.

Due to on-treatment biopsies are optional and probably no on-treatment sample was provided, no analysis will be applied for on-treatment biomarkers in tumor tissue.

If on-treatment result is available, it will be presented in listing only.

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.

The primary endpoint DLT is a safety endpoint, refer to Section 16.1 for further information.

Safety analyses will be performed according to the as-treated principle. Safety data will be descriptively analyzed on the Safety Analysis Set.

17.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 and reported by system organ class (SOC) and preferred term (PT). The severity of AEs will be graded using NCI-CTCAE (Version 4.0) toxicity grades. The investigator will be responsible for assigning the Common Toxicity Criteria (CTC) grades for AEs.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity within the first dosing day of study treatment until 33 days (inclusive) after the last dose of study treatment. AE occurring after the first treatment will always be considered as TEAE regardless of whether its onset date beyond the 33 days if it is assessed as drug related by investigator. 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.

The mechanisms for handling incomplete AE-related dates are described in Section 11.

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 set, will be presented.

Unless otherwise stated adverse events will be presented by SOC and PT in alphabetical order and also broken down further by maximum severity (refer to Section 17.1.2) and relationship (refer Section 17.1.3) to study treatment.

All listings will include all TEAEs and Non-TEAEs. All analyses described in Section 17.1.1 will be based on TEAEs if not otherwise specified.

17.1.1 All Adverse Events

The frequency tables in whole time period as well as incidence rates of individual AEs will be prepared for follows:

- TEAEs
- Tepotinib or Gefitinib related AEs
- Serious AEs (refer to Section 17.2.2)
- Tepotinib or Gefitinib related serious AEs
- AESIs (refer to Section 17.2.3)
- Tepotinib or Gefitinib related AESIs
- AEs by NCI-CTCAE severity grade (3/4)
- Tepotinib or Gefitinib related AEs by NCI-CTCAE severity grade (3/4)
- AEs leading to Tepotinib or Gefitinib permanent/temporary termination (refer to Section 17.1.4)
- AEs leading to death
- Tepotinib or Gefitinib related death

Furthermore, the following overall frequency tables will be provided:

- TEAEs by severity
- Relationship to Tepotinib or Gefitinib
- Actions taken with Tepotinib or Gefitinib
- Outcomes of TEAE

17.1.2 Severity

Severity is response for the item “Toxicity grade” on the “Adverse Events Details” form of the eCRF.

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.

17.1.3 Relationship to Study Treatment

Relationship to Tepotinib or Gefitinib will be identified as the response to the item "Relationship with MSC2156119J" or "Relationship with Gefitinib" on the "Adverse Events Details" form of the eCRF.

17.1.4 Adverse Events Leading to Treatment Discontinuation

TEAEs leading to permanent discontinuation of Tepotinib or Gefitinib will be identified as those records with a response of "Drug Withdrawal" to the item "Action(s) taken with MSC2156119J" or "Action(s) taken with Gefitinib" on the "Adverse Events Details" form of the eCRF.

TEAEs leading to temporary discontinuation of Tepotinib or Gefitinib will be identified as those records with a response of "Drug interrupted" to the item "Action(s) taken with MSC2156119J" or "Action(s) taken with Gefitinib" on the "Adverse Events Details" form of the eCRF.

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

17.2.1 Deaths

All deaths and deaths within 33 days after last dose of study treatment as well as reasons for death will be tabulated based on the information from the "Death" form of the eCRF.
Summaries will be presented for:

- Number of deaths
- Number of deaths within 33 days after last dose of treatment
- Autopsy Performed: Yes, No, or Unknown
- Primary reason for death: Disease progressions, Adverse event related to study treatment, Adverse event not related to study treatment, Other, or Unknown

17.2.2 Serious Adverse Events

Serious adverse events (SAEs) are those events with a response of "Yes" for the item "Serious Adverse Event" on the "Adverse Events Details" form of the eCRF.

17.2.3 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) is defined as AEs of asymptomatic lipase and/or amylase elevations of Grade $\geqslant$ 3.

Listing of subjects experienced any grade elevation of lipase / amylase will be provided.

17.3 Clinical Laboratory Evaluation

Urinalysis assessments

Dipstick urinalysis assessments will be conducted by sites. Sites will decide whether or not sending urine samples to central laboratory for microscopic examination.

The following information will be provided:

- Dipstick urinalysis assessments outcome by visit: normal, abnormal
- List of abnormal microscopic examination findings

Biochemistry, hematology and coagulation

Laboratory values (including corresponding normal ranges) from central laboratory will be used for summary statistics and shift tables. Only subjects with post baseline laboratory values will be included in these analyses. Data will be provided by the central laboratory using the International System of Units (SI) and all presentations will use SI units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLOQ), or "> X", i.e. above the upper limit of quantification (ULOQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Laboratory results will be classified according to the NCI-CTC Version 4.0. Please refer to Appendix 4 for gradable parameters. Additional laboratory results that are not part of NCI-CTC will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the laboratory normal ranges). For details of the reference ranges for each individual laboratory parameter, refer to Appendix 5. Parameters that have both LLOQ and ULOG will be split into high and low. For example, glucose will be presented by "glucose high" and "glucose low" separately.

Quantitative data will be examined for trends using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time.

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 values at any post-baseline visit will be tabulated for each visit by treatment. Shift tables of baseline versus the worst value will be presented. Abnormalities classified according to NCI-CTCAE toxicity grading version 4.0 will be described using the worst grade. In case of missing data at the end of the treatment period, the last known post-baseline value will be carried forward.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of the worst on treatment value according to normal range criteria

- Shift from baseline to worst on treatment value according to normal range criteria
- Shift from baseline to highest NCI-CTC grade

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.

17.4 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Body Temperature (˚C)
- Pulse Rate (bpm)
- Systolic Blood Pressure (SBP) (mmHg) in seated position
- Diastolic Blood Pressure (DBP) (mmHg) in seated position
- Respiratory Rate (breaths/min)
- Weight (kg)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit (for quantitative measurements)
- Waterfall plot for maximum percentage increase/decrease
- Categorical change from baseline to worst change for vital signs, excluding weight, will be grouped as follows:

Body temperature increase from baseline <37 °C; 37 - <38 °C; 38 - <39 °C; 39 - <40 °C; >=40 °C	< 1°C , 1-<2°C , 2-<3°C, ≥ 3 °C
Pulse rate increase from baseline <100 bpm ; ⩾ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Pulse rate decrease from baseline <100 bpm ; ⩾ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
SBP increase from baseline <140 mmHg; ⩾ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline <140 mmHg; ⩾ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP increase from baseline <90 mmHg; ⩾ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from baseline <90 mmHg; ⩾ 90 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg

Respiration rate increase from baseline <20 bpm ; ⩾ 20 bpm	≤5 bpm, >5 – 10 bpm, >10 bpm
Respiration rate decrease from baseline <20 bpm ; ⩾ 20 bpm	≤5 bpm, >5 – 10 bpm, >10 bpm

- Categorical changes in body weight from baseline to measurements during the treatment phase classified according to the NCI-CTCAE (version 4.0):

Variable				
Weight Gain	<5% from baseline	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline
Weight Loss	<5% from baseline	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline

17.5 ECG Evaluations

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 ordinal categorical ECG assessment result, the worst result among the 3 results will be used. If both abnormal with clinically significant and abnormal without clinically significant appeared, the worst case is abnormal with clinically significant. Rhythm will only be listed.

The following ECG parameters will be reported for this study based on the SAF set:

- PR Interval (msec)
- QRS Interval (msec)
- QTcB Interval (msec)
- QTcF Interval (msec)
- RR (msec)
- Overall assessment of ECG: Normal; Abnormal, not clinically significant; Abnormal, clinically significant

Specifications for computation:

$$QTcF\ (\text{msec}) = \frac{QT\ (msec)}{\sqrt[3]{RR\ (msec)/1000}}$$

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Frequency and percentages for result of ECG by visit

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

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

- Categorical change from baseline to worst change 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) Abnormal (i.e.>450ms)	<=0 ms >0 - <=30ms >30 - <=60ms >60ms

- Incidence of QTcF prolongations:

Parameter	Prolongations
QTcF	>450ms >480ms >500ms
Absolute QTcF change	>30ms >60ms

17.6 Physical Examination

A listing of subjects completing physical examinations results will be presented, however clinically significant and abnormal findings will be reported as AEs.

17.7 Other Safety Assessments

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be summarized descriptively by visit.

Pregnancy test data will only be listed.

18 Benefit Risk Assessment

Not applicable for this study.

19 References

ICH E9 Guidelines

ICH E14 Guidelines

Clinical Study Protocol EMR 200095-006 Phase Ib//II

Annotated Study Book for Study Design: EMR200095-006 Phase Ib (Electronic CRF)

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 Appendices

APPENDIX 1. NEW YORK HEART ASSOCIATION (NYHA) CRITERIA

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

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

APPENDIX 2. ASYMPTOMATIC ELEVATION OF SERUM LIPASE AND/OR AMYLASE

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

All cases of asymptomatic lipase and/or amylase elevations of Grade ≥ 3 will be reported as Adverse Events of Special Interest (AESI) to the sponsor (or delegate) in an expedited fashion.

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

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

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

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

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

APPENDIX 3. PROGRAMMING CONVENTIONS FOR OUTPUTS

PPD Output Conventions

Outputs will be presented according to the PPD general guidelines and template for outputs conventions.

Dates & Times

Depending on data available, dates and times will take the form DDMMMYYYY HH:MM:SS.

Spelling Format

US English.

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Long Name	Short Name
Screening	SCR
Cycle 1 Day 1	C1D1
Cycle 1 Day 2	C1D2
Cycle 1 Day 8	C1D8
Cycle 1 Day 15	C1D15
Cycle 2 Day 1	C2D1
Cycle 2 Day 8	C2D8
Cycle 2 Day 15	C2D15
Cycle 3 Day 1	C3D1
Cycle 4 Day 1	C4D1
…	…
Cycle X Day 1	CXD1
Safety Follow-up	SFU

Listings

- All listings will be ordered by the following (unless otherwise indicated in the template):
- Treatment received, by ascending dose group

- Centre-Subject ID,
- Date (where applicable),
- For listings where screen failure subjects are included, these will appear in a category after the treatment groups labelled ‘Screen Failure’.

APPENDIX 4. LIST OF LABORATORY ASSESSMENTS

Hematology and Coagulation Parameters

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

Biochemistry

Parameter
Blood urea nitrogen (BUN)
Creatinine
ALT
AST
GGT
Total bilirubin
Direct fraction of bilirubin (if total bilirubin is abnormal)
Lipase
Amylase
Total protein
Albumin
Alkaline phosphatase
Creatinine clearance[a]
Sodium
Potassium
Calcium
Magnesium
Glucose

a. If calculated creatinine clearance during screening is < 60 mL/min, then 24-hour urine creatinine clearance might be requested by the investigator

for confirmation of renal impairment; must be performed at the central laboratory.

- 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	>2.9	>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	>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	<3.0	<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 or BL if BL>ULN	>ULN+20 or BL+20 if BL>ULN	>ULN+40 or BL+40 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, LLN=Lower limit of normal ranger.

APPENDIX 5. LABORATORY REFERENCE RANGES

SI Units

Range Values

Analyte	Sex	Age	Reference	Units	L1	H1	L2	H2	D-	D+
Haematology										
WBC	Both	>=16Y	4.1-12.3	x10E9/L	<2.0	>35.0				
Haemoglobin	Female	12-65Y	116-162	g/L	<80	>200				
		66-100Y	110-161	g/L	<80	>200				
	Male	18-65Y	130-175	g/L	<80	>200				
		66-100Y	130-177	g/L	<80	>200				
Haematocrit	Female	12-65Y	0.35-0.47	V/V	<0.20	>0.60				
		66-100Y	0.33-0.46	V/V	<0.20	>0.60				
	Male	18-65Y	0.40-0.52	V/V	<0.20	>0.60				
		66-100Y	0.37-0.50	V/V	<0.20	>0.60				
RBC	Female	12-65Y	3.8-5.5	x10E12/L						
		66-100Y	3.8-5.4	x10E12/L						
	Male	12-65Y	4.1-5.9	x10E12/L						
		66-100Y	4.0-5.8	x10E12/L						
Platelet count	Both	0-110Y	140-450	x10E9/L	<50	>999				
Chemistry										
Sodium	Both	>=0Y	135-147	mmol/L	<130	>155				
Potassium	Both	0-109Y	3.3-5.1	mmol/L	<3.0	>6.0				
BUN/Urea	Both	18-60Y	2.14-7.14	mmol/L						
		61-110Y	2.86-8.21	mmol/L						
Creatinine	Female	>=16Y	44-80	umol/L		>318				
	Male	>=16Y	62-106	umol/L		>442				
Glucose	Both	16-59Y	4.1-5.9	mmol/L		>13.9				
		>=60Y	4.6-6.4	mmol/L		>13.9				
Calcium	Both	12-65Y	2.10-2.58	mmol/L	<1.75	>3.13				
		66-90Y	2.20-2.55	mmol/L	<1.75	>3.13				
		91-109Y	2.05-2.40	mmol/L	<1.75	>3.13				
Magnesium	Both	>=16Y	0.65-1.05	mmol/L		>1.25				
Protein total	Both	>3Y	60-80	g/L						
Albumin	Both	>=16Y	35-52	g/L	<20					
Bilirubin total	Both	1-90Y	3-21	umol/L						
		91-109Y	3-15	umol/L						
ALT	Female	>=17Y	<=33	IU/L		>165				
	Male	>=17Y	<=41	IU/L		>205				
AST	Female	>=16Y	<=31	U/L		>155				
	Male	>=16Y	<=37	U/L		>185				

Protocol Name EMR200095-006_Phase I CONFIDENTIAL Refer to PMP0086

SI Units

Range Values

Analyte	Sex	Age	Reference	Units	L1	H1	L2	H2	D-	D+
Chemistry										
GGT	Female	>=16Y	5-36	U/L		>180				
	Male	>=16Y	8-61	U/L		>305				
Alkaline phosphatase	Female	>=18Y	35-104	IU/L		>520				
	Male	>=18Y	40-129	IU/L		>645				
Amylase total	Both	>=1Y	28-100	U/L		>200				
Lipase	Both	>=16Y	13-60	U/L		>120				
Est. Creatinine Clearance (C&G)	Both	>=16Y	>=60	mL/min						
Urinalysis										
Urine microscopy	Both	>=0Y	NORMAL							
Coagulation										
Prothrombin time	Both	>=0Y	9.4-12.5	Seconds						
INR	Both	>=0Y	0.80-1.20							
aPTT	Both	1-110Y	20.6-39.9	Seconds						

Exclusion Values

Analyte	Sex	Age	Ethnic Origin	Visit	Criteria	Flag
Est. Creatinine Clearance (C&G)	Both	>=18Y	All	SCREENING DAY-28 TO -1	<60 mL/min	EX
AST	Female	>=16Y	All	SCREENING DAY-28 TO -1	>93 U/L	EX
AST	Male	>=16Y	All	SCREENING DAY-28 TO -1	>111 U/L	EX
ALT	Female	>=17Y	All	SCREENING DAY-28 TO -1	>99 IU/L	EX
ALT	Male	>=17Y	All	SCREENING DAY-28 TO -1	>123 IU/L	EX
Bilirubin total	Both	>=18Y	All	SCREENING DAY-28 TO -1	>31 umol/L	EX
Creatinine	Female	>=16Y	All	SCREENING DAY-28 TO -1	>=119 umol/L	EX
Creatinine	Male	>=16Y	All	SCREENING DAY-28 TO -1	>=159 umol/L	EX
Haemoglobin	Female	12-65Y	All	SCREENING DAY-28 TO -1	<85 g/L	EX
Haemoglobin	Male	18-65Y	All	SCREENING DAY-28 TO -1	<85 g/L	EX
Haemoglobin	Female	66-100Y	All	SCREENING DAY-28 TO -1	<85 g/L	EX
Haemoglobin	Male	66-100Y	All	SCREENING DAY-28 TO -1	<85 g/L	EX
Platelet count	Both	>=18Y	All	SCREENING DAY-28 TO -1	<100 x10E9/L	EX

Appendix 16.1.9 Documentation of Statistical Methods

- EMR200095-006 Phase Ib Statistical Analysis Plan
- EMR200095-006 Phase II Integrated Analysis Plan

Integrated Analysis Plan

Clinical Trial Protocol Identification No.	EMR 200095-006
Title:	A Phase Ib/II Multicenter, Randomized, Open Label Trial to Compare Tepotinib (MSC2156119J) Combined with Gefitinib Versus Chemotherapy as Second-line Treatment in Subjects with MET Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation and Having Acquired Resistance to Prior EGFR-Tyrosine Kinase Inhibitor (EGFR-TKI) Therapy
Trial Phase	Phase Ib/II
Investigational Medicinal Product(s)	Tepotinib (MSC2156119J) and Gefitinib
Clinical Trial Protocol Version	27 November 2017 / Version 8.0
Integrated Analysis Plan Author	PPD
Integrated Analysis Plan Date and Version	24Jan2019 / v2.0
Integrated Analysis Plan Reviewers	PPD, PPD, PPD PPD, Medical Writer, PPD PPD, Trial Biostatistician, Merck PPD, PPD, Merck PPD, PPD, Merck PPD, Medical Responsible, Merck PPD, PPD, Merck PPD, PPD, Merck

[redacted]

Signature Page

Integrated Analysis Plan: EMR 200095-006

A Phase Ib/II Multicenter, Randomized, Open Label Trial to Compare Tepotinib (MSC2156119J) Combined with Gefitinib Versus Chemotherapy as Second-line Treatment in Subjects with MET Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation and Having Acquired Resistance to Prior EGFR-Tyrosine Kinase Inhibitor (EGFR-TKI) Therapy

PPD

Trial Biostatistician

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD, Biostatistician

Merck KGaA

Frankfurter Strasse 250, 64293 Darmstadt, Germany

Table of Contents

1 List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Events of Special Interest
ASBI	Average Symptomatic Burden Index
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BOR	Best overall response
BSA	Body Surface Area
CI	Confidence Interval
c-Met	Mesenchymal-Epithelial Transition Factor Gene
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CV	Coefficient of Variation (%)
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EGFR-TKI	EGFR-Tyrosine Kinase Inhibitors
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	End of Treatment
CCI	[redacted]
GCN	Gene Copy Number
GCP	Good Clinical Practice

HGF	Hepatic Growth Factor
HRQoL	Health-Related Quality of Life
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
ISH	in situ hybridization
IRC	Independent Review Committee
ISH	In Situ Hybridization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LCSS	Lung Cancer Symptom Scale
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary For Regulatory Activities
MET+	MET Diagnostic-positive (status)
NCI	National Cancer Institute
NE	Inevaluable
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
Pd	Pharmacodynamics
PFS	Progression Free Survival
CCI	[redacted]
PR	Partial Response
PRO	Patient Reported Outcome
PS	Performance Status
PT	Prothrombin Time
Q1, Q3	First Quartile, Third Quartile
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors

RP2D	Recommended Phase II Dose
SAF	Safety Analysis Set
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Stable Disease
SDTM	Study Data Tabulation Model
SI	International System of Units
SOC	System Organ Class
SOLD	Sum of Longest Diameters
StD	Standard Deviation
$t_{1/2}$	Half-Life
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
t_{max}	Time to Maximum Concentration
TNM	Tumor, Lymph Nodes, Metastasis
TTSP	Time to Symptom Progression
V/F	Volume of Distribution
V_{ss}/F	Volume of Distribution at Steady State
VAS	Visual Analogue Scale
λz	Terminal Phase Rate Constant
WHO-DD	WHO Drug Dictionary

2 Modification History

Unique Identifier for IAP Version	Date of IAP Version	Author	Changes from the Previous Version
Final V1.0	02Mar2018	PPD	Not Applicable – First Version
Final V2.0	24Jan2019		Introduction of 18-months follow-up analysis Addition of further analyses for the subgroup of patients with gene amplification and/or increased c-Met GCN by ISH

3 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the primary analysis, the 18-months follow-up analysis and the final analysis of data collected during Phase II part of protocol EMR 200095-006 only. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP 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 IAP will be clearly identified in the CSR.

The IAP is based on clinical trial protocol (CTP) version 8.0, dated 27 November 2017, version 8.1 local Japan, dated 27 November 2017, version 7.2 local Canada, dated 06 April 2017, and is prepared in compliance with International Conference on Harmonization E9.

4 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	To evaluate whether the efficacy in terms of progression free survival (PFS) of second-line tepotinib in combination with gefitinib is superior to pemetrexed+cisplatin/carboplatin in subjects with T790M negative, MET+ locally advanced or metastatic NSCLC harboring an epidermal growth factor receptor (EGFR) mutation and having acquired resistance to first-line EGFR-TKI therapy including gefitinib, erlotinib, icotinib, or afatinib.	Primary Endpoint • PFS assessed by Investigator in the randomized part	13.1
Secondary Objective	To evaluate the safety and tolerability of tepotinib in combination with gefitinib	Secondary Endpoints • Drug exposure • AEs	12, 14

	• Incidence and reasons for deaths within 30 (±3) days after the last dose of study drug • Laboratory tests • Vital signs, 12-lead ECG and others.	
To evaluate the efficacy of tepotinib in combination with gefitinib in T790M negative, MET+ subjects	Secondary Endpoints: • PFS by independent review committee (IRC) in the randomized part • OS • Tumor response and disease control.	13.2
To evaluate the antitumor activity of tepotinib in combination with gefitinib in T790M positive, MET+ subjects in a separate single-arm cohort (mainland China sites only)	Secondary Endpoints: • PFS assessed by Investigator and IRC in single-arm cohort • OS • Tumor response and disease control	13.2
To assess patient-reported outcomes (PROs) with respect to quality of life (QoL), as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, Version 3.0), and time-to-symptom progression (TTSP), as measured by Lung Cancer Symptom Scale (LCSS).	Secondary Endpoint: • EORTC QLQ-C30 • TTSP by LCSS	15.3

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Exploratory Objective	To investigate biomarkers of c-Met pathway activation and other relevant oncogenic pathways in serum and tumor tissue and their potential correlation with prognosis and the activity of tepotinib in combination with gefitinib	• Markers of c-Met pathway activation (eg, hepatic growth factor [HGF] levels, and c-Met mutations), other relevant oncogenic pathways	15.2

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5 Overview of Planned Analyses

Cut-off date

The primary analysis of the Phase II part will be conducted once all subjects have either been treated for at least 6 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first. This IAP covers the analyses for efficacy and safety based on the data cut-off for the primary analysis. Statistical analyses will be performed using cleaned eCRF data gained until the clinical cut-off date.

In addition, an analysis of the Phase II part will be conducted once all subjects have either been treated for at least 18 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first. This IAP covers the analyses for efficacy and safety based on the data cut-off for this 18-months follow-up analysis. This analysis will form the basis for the CSR. Statistical analyses will be performed using cleaned eCRF data gained until the clinical cut-off date.

The final analysis will be conducted once the last subject discontinued treatment and completed the subsequent safety follow-up visit. Statistical analyses will be performed using cleaned eCRF data without applying a cut-off date. Only limited analyses focusing on long-term follow-up, e.g. overall survival, will be conducted.

A data review meeting will be held prior to the database lock for each of the two analyses. In addition, no database can be locked and no randomization code should be unblinded until this IAP has been approved.

Sample Size

The initial sample size planning required 111 PFS events (assessed by Investigator) 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 of 0.6. Assuming a median PFS time of 5 months in the control arm, a hazard ratio of 0.6 represents a 3.3 months increase, resulting in a median PFS time of 8.3 months for the experimental arm. With other assumptions: 1) accrual period of 39 months and follow-up period of 9 months; 2) randomization ratio of 2:1 (experimental vs. control arm); 3) overall drop-out rate of ~15%; 4) 1 non-binding futility analysis with futility boundary $\alpha_0 = 0.81$ was planned to be performed after observation of 50% of PFS events. A total of approximately 156 subjects were planned to be randomized to receive tepotinib+gefitinib or pemetrexed+cisplatin/carboplatin. From study start to approval of Protocol Version 7.0, subjects were randomized at a 1:1 ratio to receive either tepotinib+gefitinib or pemetrexed+cisplatin. From the approval of Protocol Version 7.0 onwards, subjects were randomized at a 2:1 ratio to receive either tepotinib+gefitinib or pemetrexed+cisplatin/carboplatin.

The Sponsor subsequently decided to halt prescreening/enrollment. The sites were notified about the enrollment halt on 25 May 2017. The last subject was randomized on 12 June 2017. Until then 55 subjects had been randomized.

In the single-arm cohort of Phase II, up to 15 subjects with T790M positive, MET+ status were planned to be enrolled (mainland China sites only). All subjects enrolled under clinical trial protocol Version 2.0 with T790M positive status and randomization to the experimental arm will count into this single-arm cohort as well, meaning that the number of 15 subjects will be reduced by these subjects, and T790M positive subjects enrolled under clinical trial protocol Version 2.0 and T790M positive subjects from the mainland China sites enrolled under clinical trial protocol Version 3.0 will be analyzed as one group. By the time of the enrollment halt, all 15 subjects with MET+ T790M positive NSCLC had been enrolled.

Randomization

Randomization only occurred in the randomized part of Phase II and was performed centrally by using an interactive voice response system (IVRS).

From study start to approval of Protocol Version 7.0, subjects were randomized at a 1:1 ratio to either the experimental arm (tepotinib+gefitinib) or the control arm (pemetrexed+cisplatin). From the approval of Protocol Version 7.0 onwards, subjects were randomized at a 2:1 ratio to either the experimental arm (tepotinib+gefitinib) or the control arm (pemetrexed+cisplatin/carboplatin). A stratified permuted block randomization procedure was employed using the following strata:

- Type of MET+: protein overexpression immunohistochemistry (IHC) 2+ vs. protein overexpression IHC3+ vs. gene amplification and/or increased c-Met gene copy number (GCN), both by in situ hybridization (ISH).

- Prior EGFR-TKI treatment: gefitinib vs. erlotinib vs. icotinib vs. afatinib.

Please note that subjects with the co-existence of amplification and/or increased c-Met GCN as well as overexpression will be included in the amplification and/or increased c-Met GCN stratum.

Independent Data Monitoring Committee

A separate analysis plan covers periodic reviews to evaluate the safety of the subjects by the Independent Data Monitoring Committee (IDMC):

- Safety analysis when approximately 25% patient dosed to ensure continued subject safety.
- Additional safety analysis may occur on request of the IDMC or Merck Serono.

6 Changes to the Planned Analyses in the Clinical Trial Protocol

No further exploratory analyses based on per-protocol population will be performed and mentioned in this IAP.

Subgroup of histological subtype, ie, adenocarcinoma vs. non-adenocarcinoma, will be omitted due to the very small number of non-adenocarcinoma.

7 Protocol Deviations and Analysis Sets

7.1 Definition of Protocol Deviations

Protocol deviations describe how closely the study has followed the protocol as expected per Good Clinical Practice (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 the wrong treatment or an incorrect dose;
- Subjects that receive an excluded concomitant medication;
- Deviation from GCP.

Important protocol deviations will be based upon the Clinical Trial Management System data and determined for all patients by either site monitoring, medical review or programming. All important protocol deviations will be included in Study Data Tabulation Model (SDTM) datasets.

7.2 Definition of Analysis Sets and Subgroups

All Screening Analysis Set

The All Screening Analysis Set includes all subjects who have provided the informed consent (ie, screening failures plus subjects enrolled).

Intent-to-Treat Analysis Set (ITT) (Randomized part of Phase II only)

The ITT Analysis Set consists of all subjects in the randomized part of Phase II who were randomized to study treatment. Analyses performed on the ITT set will take into account subjects' allocation to treatment groups as randomized.

The ITT will be used for summaries of demographic and baseline characteristics as well as efficacy.

Safety Analysis Set (SAF)

The Safety Analysis Set includes all subjects who have received at least 1 dose of tepotinib, gefitinib, pemetrexed, cisplatin, or carboplatin.

The Safety Analysis Set will be used for all summaries of safety data. Subjects will be allocated as treated. As an example, if a subject was randomized to the investigational arm, but received treatment of the control arm throughout the trial rather than the investigational treatment, the subject's safety data should be reported under the control group.

In the single-arm cohort of Phase II, the Safety Analysis Set will also be used for summaries of demographic and baseline characteristics as well as efficacy.

An overview of analyses for ITT Analysis Set and SAF Analysis Set is given in Table 1:

Table 1: Analysis Sets

Analyses	ITT Set (randomized part)	SAF Set (randomized part)	SAF Set (single-arm cohort)
Baseline Assessments	✓		✓
Past, Concomitant and Post Therapies	✓		✓
Medical History	✓		✓
Compliance and Exposure		✓	✓
Efficacy: Primary	✓		✓
Efficacy: Secondary	✓		✓
Safety and Tolerability		✓	✓

QoL evaluable population

In the randomization part of Phase II, the QoL evaluable population includes all ITT subjects with a baseline and at least one evaluable on-treatment QoL questionnaire.

In the single-arm cohort of Phase II, the QoL evaluable population includes subjects in Safety Analysis Set with a baseline and at least one evaluable on-treatment QoL questionnaire.

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Pd Analysis Set

All subjects who have received at least 1 dose of study drug and have the baseline and at least 1 post-baseline Pd/Biomarkers assessment.

Subgroups of interest

Subgroup analyses will be performed on subgroups (depending on the actual size of the subgroup) as defined below:

- Age: < 65 years (reference level) vs. ≥ 65 years;
- Gender: male (reference level) vs. female;
- Type of MET: protein overexpression IHC2+ (reference level) vs. protein overexpression IHC3+;
- Type of MET: gene amplification and/or increased c-Met GCN by ISH (reference level) vs. neither gene amplification nor increased c-Met GCN;
- Smoking history: never smokers (reference level) vs. ever smokers;

Regarding baseline variables to be included into Cox's proportional hazards model the above parameterization is 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.

8 General Specifications for Statistical Analyses

Data handling after cut-off date:

Data obtained after the cut-off will not be displayed in any listings or used for summary statistics, eg, 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.

Stop dates are not affected by this rule, eg, 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:

To provide overall estimates of treatment effect, data will be pooled across centers. The factor center will not be considered in statistical models or for subgroup analyses because of the high

number of participating centers and the anticipated small number of subjects randomized in each center.

Significance level:

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

Presentation of continuous and qualitative variables:

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

In case the analysis refers only to certain visits percentages will be based on the number of subjects still present in the trial at that visit, unless otherwise specified.

Definition of baseline:

In general, the last measurement prior to or on the day of randomization / first administration of the trial treatment will serve as the baseline measurement.

Trial day / Treatment day:

Trial day / Treatment day are defined relative to the date of randomization / start of treatment. Trial day 1 (reference start date, except analyses of questionnaires) defines the day of randomization for the randomized part and day of first study treatment for the single-arm cohort, the day before is defined as Trial day –1 (no Trial day 0 is defined).

- Trial day =

- date of event – reference date + 1, if the date of the event is on or after the reference date.
- date of event – reference date, if the date of the event is prior to the reference date.

Treatment day will be calculated in accordance with treatment day 1. Treatment day 1 is defined as the date of first administration of any the following trial drugs (tepotinib, gefitinib, pemetrexed, or cisplatin/carboplatin).

Treatment day 1 will be considered as reference start date for analyses of questionnaires.

Definition of duration:

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

The time since an event occurs (eg, time since first diagnosis) will be calculated as reference date minus date of event.

Common calculations:

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

- Test Value at Visit X – Baseline Value

Conversion factors:

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

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

Definition of 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.

End of treatment:

Unless otherwise specified, end of treatment (EOT) is defined as the earliest non-missing measurement taken after reference end start date. EOT measurements in general should be recorded at the "End of Treatment" visit.

Retests, unscheduled visits and early termination data:

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to best/worst case value where required (eg, shift table).

In the case of a retest (same visit number assigned), the latest/worst available measurement for that visit will be used for by-visit summaries, unless otherwise specified.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

Handling of missing data:

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

- Partial birth dates will be handled this way:
    - Day will be imputed as 15 if missing, and month imputed as June if missing. If both the day and month are missing, they will be imputed as July first. If the year is missing then the date will not be imputed.

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

- For imputing missing parts of dates for the efficacy analyses the missing day in a date will be imputed as follows:
    - The fifteenth of the month, if month and year are documented. This also includes also dates of start of follow-up therapy.
    - In all other cases missing or incomplete dates will not be imputed if not indicated otherwise.
- If the last administration date is incomplete the date of last administration will be taken from treatment termination eCRF pages (“TREATMENT TERMINATION FOR MSC2156119J”, “TREATMENT TERMINATION FOR GEFITINIB”, “TREATMENT TERMINATION FOR PEMETREXED”, “TREATMENT TERMINATION FOR CISPLATIN”, or “TREATMENT TERMINATION FOR CARBOPLATIN”).

In individual subject data listings the documented date as given in the eCRF will be reported (eg, __May2013 in case of day missing, but month and year available). In subject data listings, imputed values will be presented (if applicable), and imputed information will be flagged.

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

Software version:

All analyses will be conducted using SAS (PPD PPD) version 9.2 or higher.

9 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.

9.1 Disposition of Subjects and Discontinuations

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.

Subjects will remain in the study until but not limited to death, progression of disease, loss to follow-up or withdrawal of consent. Subjects are free to withdraw from the study at any time without giving their reason(s).

If a subject withdraws consent from the optional pharmacogenomic assessments, they may continue on the trial.

The following summaries will be provided for all screened subjects within the randomized part/ single-arm cohort:

- Total number of subjects screened (i.e. subjects who gave informed consent)
- Number of subjects who discontinued from the trial prior to randomization (overall and grouped by the main reason, eg, Subject did not meet all eligibility criteria, Withdrew informed consent, Progressive disease, Death, Adverse Event, Lost to follow-up, Lost to follow-up) [For single-arm cohort, number of subjects who discontinued from the trial prior to treatment will be displayed.]
- Number of randomized subjects. (for single-arm cohort, number of enrolled subjects [i.e. those who gave informed consent and who were allocated to single-arm cohort] will be displayed)
- Number of subjects who completed the treatment in each treatment group.

  A subject who completed treatment is defined as follows:

  - the subject died, or
  - the subject has been assessed as having progressive disease

In addition, cisplatin treatment completed is defined as the subject has completed 6 cycles cisplatin/carboplatin treatment or has completed 4 cycles administration of cisplatin/carboplatin followed by pemetrexed maintenance.

- Number of subjects who discontinued the treatment after randomization, grouped by treatment arm and main reason separately for each treatment component (for single-arm cohort, number of subjects who discontinued the treatment after allocation to treatment)
- Number of randomized subjects who continued only in survival and disease follow-up after randomization, grouped by treatment arm (for single-arm cohort, number of enrolled subjects who continued only in survival and disease follow-up after treatment allocation will be displayed)
- Number of randomized subjects who discontinued the trial after randomization, grouped by treatment arm and main reason (for single-arm cohort, number of enrolled subjects who discontinued after treatment allocation will be displayed)

The number of subjects in each of the following analysis sets will be summarized. In addition, the percentage of analysis sets excepting screening analysis set will be presented with percentage based on the number of subjects in ITT Analysis Set.

- Screening Analysis Set
- Safety Analysis Set
- ITT Analysis Set
- QoL Evaluation Population
- CCI [redacted]
- Pd Analysis Set

In addition, analysis sets by site will be presented.

The results of the randomization algorithm (according to IVRS) will be summarized as follows using ITT analysis set for randomized part:

- The number of subjects randomized (IVRS) overall, by region, by country within region
- Number of randomized subjects by randomization strata (IVRS)
- Cross tabulation: subjects randomized (tepotinib+gefitinib, pemetrexed+carboplatin/cisplatin) vs. treated (tepotinib+gefitinib, pemetrexed+carboplatin/cisplatin)

9.1.1 Biomarker Screening

A summary table and listing of biomarker screening activities will be provided for the screening analysis set (regardless of study arm). The summary table will provide the following information:

- EGFR genetic mutation status:
  - Number of patients tested (100%), wild type, mutated, not available/feasible
- T790M status:

  - Number of patients tested (100%), positive, negative, not available/feasible
- MET status (IHC) - Protein overexpression
  - Number of patients tested (100%), IHC 0, IHC 1+, IHC 2+, IHC 3+, not available/feasible
- MET status (ISH) – Gene amplification (c-Met / CEP7 copy number ratio)
  - Number of patients tested (100%), < 2, ≥ 2, not available/feasible
- MET status (ISH) – Mean Gene Copy Number
  - Number of patients tested (100%), < 5, ≥ 5, not available/feasible
- MET status (ISH) – Gene amplification or Mean Gene Copy Number
  - Number of patients tested (100%), Gene amplification or Mean Gene Copy Number ≥ 5, Neither gene amplification nor Mean Gene Copy Number ≥ 5, not available/feasible

In addition for those with EGFR mutation, a summary table of MET status (ISH) by T790M status (positive, negative, not available/feasible) and MET status (IHC: IHC 0, IHC 1+, IHC 2+, IHC 3+, not available/feasible) will be provided for the screening analysis set (regardless of study arm). The summary table will provide the following information:

- MET status – Gene amplification (c-Met / CEP7 copy number ratio)
  - Number of patients tested (100%), < 2, ≥ 2, not available/feasible
- MET status – Mean Gene Copy Number
  - Number of patients tested (100%), < 5, ≥ 5, not available/feasible
- MET status – Gene amplification or Mean Gene Copy Number
  - Number of patients tested (100%), Gene amplification or Mean Gene Copy Number ≥ 5, Neither gene amplification nor Mean Gene Copy Number ≥ 5, not available/feasible.

9.2 Protocol Deviations

Population: ITT Analysis Set for the randomized part, Safety Analysis Set for the single-arm cohort unless otherwise specified.

9.2.1 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

9.2.2 Reasons Leading to the Exclusion from an Analysis Set

Not applicable for this study.

10 Demographics and Other Baseline Characteristics

Population: ITT Analysis Set for the randomized part, Safety Analysis Set for the single-arm cohort unless otherwise specified.

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

10.1 Demographics

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

Demographic characteristics:

- Gender: male, female
- Age (years)
- Age categories: < 65 years, ≥ 65 years (65-74, 75-84, ≥ 85 years)
- Region: Greater China (China and Taiwan), Outside of Greater China (other countries)
- Race: Asian, non-Asian

Height, Weight, Body Surface Area, and Body Mass Index:

- Height (cm)
- Weight (kg)
- Body Surface Area (BSA) (m^2)
- Body Mass Index (BMI) (kg/m^2)

Eastern Cooperative Oncology Group (ECOG) performance status: 0, 1

Smoking Status at Baseline:

- Nicotine use status: never used, regular user, occasional user, former user
- Smoking history: never smoked, ever smoked

Result of chest X-ray: normal, abnormal

Specifications for computation:

- Age (years): (date of given informed consent - date of birth+1) / 365.25, presented to 1 decimal place.
- BMI (kg/ m^2) = weight (kg) / [height (m)]^2
- BSA (m^2) = ([height (cm) x weight (kg)] / 3600)$^{1/2}$
- Site codes will be used for the determination of the subject's geographic region.

10.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or higher, preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category.

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

10.3 Disease History

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

Summary statistics will be presented for

- Site of Primary tumor: Upper lobe, lung; Middle lobe, lung (right lung only); Lower lobe, lung; Overlapping lesion of lung; Lung, not otherwise specified (NOS)
- Time since initial diagnosis (years)
- Time since first occurrence of advanced disease (years)
- Time since most recent disease progression (years)
- Tumor histophathologic/cytologic type: squamous, adenocarcinoma, large cell, bronchoalveolar, other
- Histologic tumor grade/differentiation: well differentiated, moderately differentiated, poorly differentiated, not applicable
- TNM classification at initial diagnosis and at study entry: display all options
- Metastasis sites at initial diagnosis and at study entry: display all options
- EGFR genetic mutation status: wild type, mutated, not available/feasible
- Location of EGFR sampling: primary/metastasis

Specifications for computation:

- Time since initial diagnosis (years) = (date of informed consent – date of diagnosis) / 365.25, presented to 1 decimal place.
- Time since first occurrence of advanced disease (years) = (date of informed consent – date of first occurrence of advanced disease) / 365.25, presented to 1 decimal place.
- Time since most recent disease progression (years) = (date of informed consent – date of most recent disease progression) / 365.25, presented to 1 decimal place.

10.4 Prior Anti-Cancer Treatments

Information related to prior anti-cancer therapies and surgeries were collected on "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details", and "Prior Anti-Cancer Surgeries Details" eCRF forms and will be summarized.

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

- Subjects with at least one type of prior anti-cancer treatment
- Subjects with at least one prior anti-cancer drug therapy
- Subjects with at least one prior anti-cancer radiotherapy
- Subjects with at least one prior anti-cancer surgery

Summary statistics will be presented for

- Prior anti-cancer drug therapy
    - Any prior anti-cancer drug therapy
    - Number of prior anti-cancer therapy regimen line: missing/ 1/ 2/ 3/ ≥ 4
    - Type of systemic therapy
    - Intent of therapy
    - Best response
- Prior anti-cancer radiotherapy
    - Any prior anti-cancer radiotherapy
    - Number of prior anti-cancer radiotherapy regimen line: missing/ 1/ 2/ 3/ ≥ 4
    - Type of therapy
    - Intent of therapy
    - Best response
- Prior anti-cancer surgery
    - Any prior anti-cancer surgery
    - Number of prior anti-cancer surgeries
    - The surgery was curative in intent (yes/ no)
    - Outcome of surgery

Prior anti-cancer drug therapies will be summarized in terms of frequency tables: ordered by preferred term from WHO Drug Dictionary (WHO-DD) in alphabetical order.

Listings of prior anti-cancer treatments and procedures will be provided: a) listing of prior anti- cancer drug therapies, b) listing of prior anti-cancer radiotherapy and c) listing of prior anti- cancer surgeries. These will include the subject identification number, and all the relevant collected data-fields on the corresponding eCRF form.

10.5 Baseline Biomarkers Measured in Tumor Tissue

10.5.1 Baseline Biomarker Variables

10.5.1.1 Baseline Tumor c-Met Expression

The following scores will be provided by the pathologist, based on c-Met expression raw data measured by IHC in pre-treatment or archived tumor biopsies:

- c-Met H-score, tumor cell cytoplasm, at baseline (continuous)
- c-Met H-score, tumor cell membrane, at baseline (continuous)
- Met score at baseline (possible values: 0, 1+, 2+, 3+)

In general, measurements flagged as non-evaluable will not be taken into account for analysis.

This score will be used in all tables, figures and listing where the 4-level Met score is presented (except listings of raw c-Met expression data).

10.5.1.2 Baseline Tumor c-Met Amplification

The following parameters will be provided for FISH analysis of pre-treatment or archived tumor biopsies:

- FISH analysis:
    - c-Met copy number
    - CEP7 copy number
    - c-Met / CEP7 copy number ratio
    - Mean Gene Copy Number
    - FISH status

FISH+, i.e. either Mean Gene Copy Number ≥ 5 or c-Met/CEP7 copy number ratio ≥ 2, will be considered as amplified.

In general, measurements flagged as non-evaluable will not be taken into account for analysis.

10.5.1.3 Baseline Tumor HGF Expression

The following score will be provided by the pathologist based on HGF expression raw data measured by IHC in pre-treatment or archived tumor biopsies:

- CAF HGF H-score, at baseline (continuous)
- Cytoplasmic HGF H-score, at baseline (continuous)

In general, measurements flagged as non-evaluable will not be taken into account for analysis.

The baseline HGF H-scores will not be analyzed for correlation/association to efficacy parameters.

Moreover, the HGF H-scores will be categorized in the following way:

- The variable baseline HGF H-score group [0 vs. any value] will have the following levels: H-score 0; H-score >0; H-score not done, H-score not evaluable

10.5.2 Descriptive Summaries of Baseline Biomarkers

10.5.2.1 Baseline Tumor c-Met Expression

Baseline Met score will be summarized descriptively in a frequency table.

Moreover, raw c-Met expression data from pre-treatment tumor biopsies will be presented in listings.

10.5.2.2 Baseline Tumor c-Met Amplification Status

Baseline FISH status, c-Met/CEP7 copy number ratio and mean gene copy number will be summarized descriptively using summary statistics. In addition, the following categories will be summarized:

- Mean Gene Copy Number: $< 5, \geq 5, \geq 6$
- c-Met/CEP7 copy number ratio: $< 2, \geq 2$
- FISH Status: FISH+ (either Mean Gene Copy Number ≥ 5 or c-Met/CEP7 copy number ratio ≥ 2), FISH-

10.5.2.3 Correlation between Baseline c-Met Expression and Amplification Status

The correlation/association between c-Met expression and amplification status will be analyzed by presenting a cross-tabulation table for Met score by c-Met amplification status. Cross-tabulation tables will only be presented by regimen.

10.5.2.4 Baseline tumor HGF expression Status

Baseline HGF score (CAF HGF H-score and Cytoplasmic HGF H-score) will be summarized descriptively using summary statistics.

Moreover, raw HGF from pre-treatment tumor biopsies will be presented in listings.

10.6 Baseline Biomarkers Measured in Plasma

10.6.1 Baseline Biomarker Variables

For exploratory analyses, levels of shedded cMet, IL-8 and HGF will be measured in plasma by ELISA assay at baseline (Cycle 1 Day 1 pre-dose) and several post-baseline time points.

For all correlation/association analyses based on baseline levels of shedded cMet, IL-8 and HGF the baseline levels will be categorized based on the median. The following categories will be used: above the median; below/at the median; not done; not evaluable.

Additionally, for HGF, a further categorization based on the upper quartile (25% quantile) will be introduced. For this analysis the following categories will be used: above the upper quartile; below/at the upper quartile; not done; not evaluable.

10.6.2 Descriptive Summaries of Baseline Biomarker Variables

Baseline levels of shedded cMet, IL-8 and HGF will be summarized descriptively using summary statistics. Moreover, frequencies of categorized baseline levels will be presented.

10.7 Other Baseline Characteristics

Tumor biopsy and MET status will be summarized for:

- Location of MET sampling: primary/metastasis
- T790M mutation status: positive, negative, indeterminate
- T790M status documented or determined by central laboratory, using the QIAGEN therascreen® EGFR RGQ PCR Kit);
- Location of T790M sampling: primary/metastasis

Baseline characteristics with respect to physical examinations, hematology/biochemistry, vital signs, and ECG will be part of Section 14 (Safety Analyses).

10.7.1 Baseline Tumor Lesions

Target lesion assessments at baseline will be summarized as:

- Number of subjects with at least one target lesion
- Number of target lesions: grouped as 1, 2, 3, …. Also summarized as continuous variable.
- Lesion site
- Lesion type: primary/recurrence, node, metastasis (1, 2, >2)
- Assessment method
- Sum of longest diameter for non-nodal lesions and short axis for nodal lesions

Non-target lesion assessments at baseline will be summarized as:

- Number of subjects with at least one non-target lesion
- Number of non-target lesions: grouped as 1, 2, 3, …. Also summarized as continuous variable.
- Lesion type: primary/recurrence, node, metastasis

- Assessment method

11 Previous and Concomitant Medications/Procedures

Population: ITT Analysis Set for the randomized part, Safety Analysis Set for the single-arm cohort unless otherwise specified.

11.1 Medications and Procedures

Medications recorded on the "Concomitant Medication Details" eCRF form and procedures on the "Concomitant Procedure Details" eCRF form will be used as data source.

Medications will be coded and presented using World Health Organization Drug Dictionary Enhanced Version March 2017 (or higher) Anatomic Therapeutic Chemical (ATC) class level 2 (ATC-2nd level). Procedures will be coded using MedDRA Version 20.0 or higher and reported using SOC and PT.

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

- 'Previous' medications or procedures are those which started prior to the first dose of study treatment.
- 'Concomitant' medications or procedures are those which:
    - started prior to, on or after the first dose of study treatment and started no later than 33 days following end of study treatment;
    - AND ended on or after the date of first dose of study treatment or were ongoing at the end of the study.
- 'Post' medications or procedures are those which started more than 33 days following the last dose of study treatment.

The number of patients with concomitant medications will be summarized per treatment arm and overall. The number of patients will also be presented by ATC-2nd level and preferred term from the WHO-DD dictionary.

The number of patients with concomitant procedures will be summarized per treatment arm and overall. The number of patients will also be presented by reason and by SOC and PT.

All medications/procedures will be listed.

11.2 Anti-Cancer Treatment after Discontinuation

Anti-cancer treatment after treatment termination obtained from "Anti-Cancer Treatment After Discontinuation Details" eCRF page will be summarized for the SAF set.

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

12 Treatment Compliance and Exposure

Population: Safety Analysis Set

The extent of exposure to tepotinib, gefitinib, pemetrexed, cisplatin and carboplatin will be presented for the Safety analysis set.

All dosing calculations and summaries will be based on "MSC2156119J ADMINISTRATION DETAILS", "GEFITINIB ADMINISTRATION DETAILS", "PEMETREXED ADMINISTRATION DETAILS" "CISPLATIN ADMINISTRATION DETAILS" "CARBOPLATIN ADMINISTRATION DETAILS" "ACCOUNTABILITY (DISPENSING AND RETURN) GROUP A", and "ACCOUNTABILITY GROUP B" eCRFs pages.

Handling of missing data:

- If the start date is missing, it is assumed that the first dose of trial drug is given at the reference start date. The reference start date will replace incomplete dates of the earliest administration of trial drugs.
- If the last dosing date is incomplete the date of last dosing will be taken from the Treatment Termination page.
- If BSA cannot be derived due to missing weight, data from the previous available visit will be used instead; if due to missing height at screening, then BSA will be missing. If no on-treatment BSA, then baseline BSA will be used.

The following summaries will be presented for each treatment component on the experimental arm (tepotinib+gefitinib, including single arm cohort) and the control arm (pemetrexed+cisplatin/carboplatin):

- Total number of infusions received for Pemetrexed, Cisplatin and Carboplatin separately:
  - 1, 2, 3, 4, ≥ 5
  - Descriptive summary (mean, SD, median, Q1, Q3, minimum, and maximum)
- Duration of therapy (weeks) :
  - For tepotinib or gefitinib: duration = $\left(\frac{\text{date of last dose-date of first dose+1}}{7}\right)$

- For pemetrexed, cisplatin or carboplatin: duration = $\left(\frac{\text{date of last dose-date of first dose+21}}{7}\right)$
- Interruptions, compliance, and dose changes are not taken into account for the calculation of duration of therapy as well.

- Cumulative dose (mg):
  - The cumulative dose (mg) per subject in a time period is the sum of the total dosage that the subject received.

- Dose intensity:
  - For tepotinib or gefitinib (mg/days): Dose intensity = $\left(\frac{\text{cumulative dose (mg)}}{\text{duration of therapy (days)}}\right)$
  - For pemetrexed or cisplatin (mg/m2 per week): dose intensity = $\left(\frac{\text{cumulative dose/BSA (mg/m}^2\text{)}}{\text{duration of therapy (weeks)}}\right)$.
  - Where BSA is the available BSA at baseline by using height at screening.
  - For carboplatin: Dose intensity = $\left(\frac{\text{cumulative dose (mg)}}{\text{duration of therapy (weeks)}}\right)$

- Planned dose intensity:
  - Tepotinib = 500 mg/day, gefitinib= 250 mg/day
  - Pemetrexed = 500/3 mg/m2 per week, cisplatin=75/3=25 mg/m2 per week
  - Carboplatin = Target AUC(mg/mL×min) × (GFR (mL/min) +25)/3 mg per week
    - Where GFR (mL/min) = (C x (140 − age [years]) x weight [kg])/ (72 x serum creatinine (mg/dL)) and C = 0.85 for female subjects and C = 1.00 for male subjects (i.e. according to Cockcroft-Gault).

- Relative dose intensity (%)
  - Dose intensity/Planned dose intensity×100%
  - The breakdown of relative dose intensity (<60%, 60% - <80%, 80% - <90%, 90% - <110%, >110%) will be summarized.
- Compliance for tepotinib or gefitinib:
  - $\frac{\text{Sum of (total number of tablets dispensed}*\text{dosage of the tablets)}-\text{Sum of (total number of tablets returned}*\text{dosage of the tablets))}}{\text{planned dose level (mg)}*\text{duration of therapy (days)}}$ × 100%.
- Dose reductions:
  - A dose reduction is defined as any dose change to less than 90% of planned dose level. Dose omission is not considered as dose reduction.
    - The number of subjects with at least one dose reduction will be summarized by frequency and percentage.

- The derived minimum dose levels will be used to summarize dose reduction as follows:
  - Number of subjects per minimum dose level for each trial drug.
  - The minimum doses of the trial drugs will be derived per subject and categorized according to a 70-<90%, 50-<70%, and < 50% level of the planned dose.

- Overdose:
  - An overdose is defined as any dose greater than the planned daily dose level. Applied for tepotinib or gefitinib.
    - The number of subjects with at least one overdose will be summarized by frequency and percentage.
- Dose changes:
  - Dose changes are those collected by the "Administration Details" eCRF pages.
    - Number of subject with at least one occurrence of dose adjusted or no dose and the reason will be summarized.
- Therapy delays:
  - Delays of will be derived as following definition and can only be calculated only for subjects with at least 2 administrations. Delay within 3 days will not be considered as therapy delays.
  - For pemetrexed, cisplatin or carboplatin, delay is defined as
    - administrations as the number of days since the start of last infusion -21 and will be presented as follows: number of subjects with delayed infusions, and maximum length of delay (no delay, > 3-8 days, 9-15 days, ≥ 16 days) – worst case
    - administrations as the number of cycles since last cycle with intake and will be presented as follows: number of subjects with delayed administration, and maximum length of delay (no delay, 1 cycle, 2 cycles, ≥ 2 cycles) – worst case
  - For tepotinib or gefitinib, delay is defined as having missed 1 or more planned daily dose and will be presented as follows: number of subjects with delayed administrations, and maximum length of delay (no delay, 3-8 days, 9-15 days, ≥ 16 days) – worst case

13 Efficacy Analyses

Unless otherwise specified the ITT analysis set will be used for the randomized part and the SAF analysis set will be used for the single-arm cohort.

All treatment comparisons of efficacy are between experimental treatment and control treatment of randomized part. The single-arm cohort data will be only presented in descriptive manner.

13.1 Primary Endpoint Analyses

13.1.1 Primary Analyses of Progression Free Survival

Population: ITT Analysis Set for the randomized part

Definition of primary endpoint

The primary endpoint is PFS as assessed by the Investigator according to RECIST 1.1 (Eisenhauer EA et al, 2009).

PFS time is defined as the time (in months) from reference start date to either the first observation of PD (as assessed by Investigator) or death due to any cause within 84 days of either allocation of treatment or the last tumor assessment. The 84-day time window represents twice 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 1st PD or death – reference start date+ 1) / 30.4375.

Start date of PFS:

Event date is the earliest date of the following events:

- Observed PD before the subject 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.
- Death without previously documented PD is observed within 84 days of reference start date or last tumor assessment. Information on Death is collected on the "Death" form.

Censoring rules:

- Data cut-off will be applied first.
- Censored on the reference start date if no baseline or post-baseline assessment is available.
- Censored on the date of last tumor assessment or reference start date, whatever occurs later, if:
    - Death without previously documented PD is observed not within 84 days of reference start date or last tumor assessment, or
    - Lost to follow-up / withdraw consent without PD/death observed (includes also subjects with a radiological assessment that is at least 84 days before data cut-off), or
    - No PD/death 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

Status		Censoring	Date of event / censoring
Progressed or died	Radiological PD observed before the subject drops out.	Event	Date of PD
	Radiological PD assessed after the subject drops out.	Event	Date of PD
	Death without previously documented PD is observed within 84 days of reference start date or last tumor assessment	Event	Date of death
	Death without previously documented PD is observed not within 84 days of reference start date or last tumor assessment	Censored	Date of last known tumor assessment or reference start date, whatever occurs later
Neither progressed nor died	Lost to follow-up / withdraw consent without PD/death observed (includes also subjects with a radiological assessment that is at least 84 days before data cut-off)	Censored	Date of last known tumor assessment or reference start date, whatever occurs later
	No PD/death observed up to the cut-off date (administrative censoring)	Censored	Date of last known tumor assessment or reference start date, whatever occurs later
Other	No baseline or post-baseline assessment	Censored	Date of reference start date

Primary analysis

The primary analysis will test the equality of PFS time between treatment arms in the randomized part of Phase II, based on the ITT 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., type of MET+. 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 θ 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 option for handling ties the Score-test in the Cox's proportional hazards model is identical to the log-rank test:

```
proc phreg data=xxx;
        strata MET_TYPE EGFR-TKI_trt;
        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 (tepotinib+gefitinib), =0 if in control arm (pemetrexed + cisplatin/carboplatin)
TTE = Time to event variables, for primary, it's PFS by Investigator; for secondary, it will be OS, PFS by IRC .

The hazard ratio θ and the 90% CI for θ of tepotinib+gefitinib compared to chemotherapy (pemetrexed+cisplatin/carboplatin) will be calculated by Cox's proportional hazards model stratified by type of MET+ status and prior EGFR-TKI treatment.

Kaplan-Meier survival curves (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics (median PFS time, 3-and 6-month survival rate estimates and estimates for every 6 months thereafter as applicable) including the corresponding two-sided 90% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and CIs for the survival function estimates at above defined time points will be derived directly from the Kaplan-Meier estimates (CONFTYPE=LINEAR in proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. SAS Proc LIFETEST will be used to obtain Kaplan-Meier estimates.

Subgroup analysis

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

Multivariate analysis will be performed with a stepwise selection to assess the effect of baseline covariates predefined as subgroup of interest in section 10, namely: age (< 65 vs. ≥ 65 years, gender, histologic subtype, smoking history (never smokers vs ever smokers).

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

```
proc phreg data=Eff_ITT ;
        class all-subgroup variables ... ;
        model TTE×censoring(1)= all-group 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 analysis model is refitted with the strata and the treatment group, plus the selected covariates.

```
proc phreg data=xxx;
        strata MET_TYPE ;
        model TTE×TTE_censor(1) = treatment all-group variables ... / 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, it's OS; for secondary, it will be one of TTP by
                                                    IRC, TTP by Investigator, PFS or TTSP.
```

Subgroup analyses will be performed for each predefined baseline factor without stratification due to the potential low number of subjects per subgroup category. Cox regression models will be fitted for PFS as 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+gefitinib compared to chemotherapy (pemetrexed+cisplatin) is computed per subgroup level. The 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.

In addition, to the subgroup analyses defined above the following analyses will be conducted for the subgroup of patients with gene amplification and/or increased c-Met GCN by ISH:

Demographics and Other Baseline Characteristics

- Demographic characteristics
- ECOG performance status at baseline
- Smoking status at baseline
- Prior anti-cancer drug therapy
- Baseline FISH status, c-Met/CEP7 copy number ratio and mean gene copy number

Exposure

- Duration of therapy (weeks) for tepotinib and gefitinib
- Duration of therapy (weeks) for pemetrexed, cisplatin and carboplatin

Safety

- Overview of Treatment Emergent Adverse Events (TEAEs)

- Any Trial Drug Related TEAEs by SOC and PT
- Any Trial Drug Related TEAEs with CTCAE Grade >= 3 by SOC and PT

Time of Follow-Up (PFS)

In order to assess duration of follow-up for progression-free survival, Kaplan Meier estimates will be calculated using the following censoring rules (reverse censoring indicator):

The date of event / censoring is defined as follows:

Status		**Censoring**	**Date of event / censoring**
Progressed assessed by Investigator or died	Radiological PD observed before the subject drops out.	Censored	Date of PD assessed by Investigator
	Radiological PD assessed after the subject drops out.	Censored	Date of PD assessed by Investigator
	Death without previously documented PD is observed within 84 days of reference start date or last tumor assessment	Censored	Date of death
	Death without previously documented PD is observed not within 84 days of reference start date or last tumor assessment	Event	Date of last known tumor assessment or reference start date, whatever occurs later
Neither progressed by Investigator nor died	Lost to follow-up / withdraw consent without PD/death observed (includes also subjects with a radiological assessment that is at least 84 days before data cut-off)	Event	Date of last known tumor assessment or reference start date, whatever occurs later
	No PD/death observed up to the cut-off date (administrative censoring)	Event	Date of last known tumor assessment or reference start date, whatever occurs later
Other	No baseline or post-baseline assessment	Event	Date of reference start date

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for progression-free survival.

13.2 Secondary Endpoint Analyses

The secondary efficacy analyses considered below will be regarded as supportive to the primary analysis.

13.2.1 PFS Assessed by IRC

Population: ITT Analysis Set for the randomized part

A sensitivity analysis of the primary endpoint will be done by analyzing PFS as assessed by IRC, which is defined similar to PFS as assessed by Investigator (described in Section 13.1.1), but taking into consideration only radiological tumor assessments performed by the IRC. Analyses analogous to the ones of PFS by Investigator will be performed.

A cross table of PFS assessed by IRC vs PFS assessed by Investigator will be summarized to check the consistency of two definitions. The consistency is defined as the two PFS are at most 30 days apart (30 day included).

13.2.2 PFS in the Single Arm Cohort

Population: Safety Analysis Set for the single-arm cohort

PFS assessed by Investigator and IRC in the single-arm cohort will be conducted as described in Section 13.1.1. The analyses described in Section 14.1.1 will be repeated except subgroup analysis. The subgroup of interest will be omitted due to small sample size.

13.2.3 Overall Survival

Population: ITT Analysis Set for the randomized part, Safety Analysis Set for the single-arm cohort

Overall survival (OS) will be measured as the time (in months) between reference start date to treatment and the date of death. For subjects not known to be deceased at time of analysis, OS time will be censored at the last date the subject was known to be alive. If this date is after the data cut-off, subjects will be censored at the date of data cut-off.

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

The date of event / censoring for OS is defined as follow:

Survival Status		**Source**	**Censoring**	**Date of event/ censoring**
Died	Before cut-off	Death eCRF	Event	Date of death
	After cut-off	Death eCRF	Censored	Date of cut-off
Alive or Lost to Follow-up/ Withdrew Consent (no date of death)	After cut-off	Follow-up eCRF	Censored	Date of cut-off
	Otherwise	See below	Censored	Last date known to be alive

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

- All patient assessment dates (blood draws (laboratory, CCI), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Last date of contact collected on the 'Survival information' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates
- Randomization date
- Date of death if the death is before the cut-off date

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics (median survival time, 3 and 6-month survival rate estimates and estimates for every 6 months thereafter as applicable) including the corresponding two-sided 95% confidence intervals. The confidence intervals for the median will be calculated according to Brookmeyer and Crowley (1982) and confidence intervals for the survival function estimates at above defined time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980) (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula. Kaplan-Meier plots will also be presented.

The censoring and event status with respect to the scenarios from the above table will be summarized.

Duration of Follow-Up (OS)

In order to assess duration of follow-up for overall survival, Kaplan Meier estimates will be calculated using the following censoring rules (reverse censoring indicator):

The date of event / censoring for OS follow-up is defined as follows:

Survival Status		**Source**	**Censoring**	**Date of event/ censoring**
Died	Before cut-off	Death eCRF	Censored	Date of death
	After cut-off	Death eCRF	Event	Date of cut-off
Alive or Lost to Follow-up/ Withdrew Consent (no date of death)	After cut-off	Follow-up eCRF	Event	Date of cut-off
	Otherwise	See above for the OS	Event	Last date known to be alive

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for overall survival.

13.2.4 Antitumor Activity

Population: ITT Analysis Set for the randomized part, Safety Analysis Set for the single-arm cohort

Outputs for antitumor activity will be provided as assessed by Investigator as well as 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.

Inevaluable (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 tumor 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 BOR of CR, PR, stable disease (SD), PD, non-CR/non-PD, and NE will be tabulated.
- 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 CR or PR as the BOR according to radiological assessments from reference start date to end of treatment. 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+ and prior EGFR-TKI treatment. The Cochran-Mantel-Haenszel will test the following two-sided hypothesis:

H_0: $\Psi = 1$

H_1: $\Psi \neq 1$

where Ψ defines the common odds ratio across all strata.

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

The common Mantel-Haenszel odds ratio 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 the Breslow-Day test is that the odds ratio is the same for all strata, against the alternative that at least one pair of strata have a different odds ratio. 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.

Disease Control Rate (DCR)

The disease control rate is defined as the proportion of subjects having achieved CR, PR, or SD as the BOR according to local radiological assessments from randomization/the first administration until end of study treatment in the randomized part/the single-arm cohort. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 39 days after informed consent.

The DCR rate and its 90% Clopper-Pearson CI will be calculated.

Duration of Response

Duration of response is defined as the time from first documented CR or PR (whichever is first recorded) until time of progression as per Investigator assessment. The definition of the end of duration of response should be consistent with the definition of end of PFS. This definition applies only to subjects who experienced CR or PR.

Sum of Longest Diameters (SOLD)

The sum of longest diameters (SOLD) of viable target lesions is collected on the "Sum of Diameters (SOLD)" eCRF page. Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesions and short axis for nodal lesions, SOLD) per time point. It will be derived for subjects with post baseline target lesion assessment as:

$$\text{Percent change from baseline} = 100 * (\frac{\text{Sum of target lesion diameters at visit } X}{\text{sum of target lesion diameters at baseline}} - 1)$$

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

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

The following will be provided:

The SOLD and the percent change will be summarized over time.

Waterfall plot for the best relative change of the sum of the longest diameter for non-nodal lesions and short axis for nodal lesions

The percent change from baseline in target lesions per time point as well as other relevant information will be presented in a data listing. The earliest scan date of target lesions will be used as the date of SOLD.

14 Safety Analyses

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, for both randomized part and single-arm cohort.

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

14.1 Adverse Events

AEs will be coded using the MedDRA Version 20.0 or higher. The Investigator will be responsible for assigning the Common Toxicity Criteria grades for AEs (NCI-CTCAE), using the most current version of NCI-CTCAE. The severity of AEs will be graded using NCI-CTCAE (Version 4.0) toxicity grades. The Investigator will be responsible for assigning the Common Toxicity Criteria grades for AEs.

TEAE: 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 drug + 33 days (inclusive).

“Timing related to MSC2156119J”, “Timing related to Gefitinib”, “Timing related to Pemetrexed”, “Timing related to Cisplatin” and “Timing related to Carboplatin” from the eCRF AE form will be used to judge whether the AE is a TEAE when the AE onset date is the same day as first dosing date:

- Case 1, only 1 trial drug is dosed during the earliest dosing date: if “Timing related to MSC2156119J” or “Timing related to Gefitinib” (depending on which trial drug is dosed) in the AE eCRF is “Before” then the AE will not be considered a TEAE, otherwise a TEAE.
- Case 2, both 2 trial drugs are dosed the earliest dosing date: if “Timing related to MSC2156119J” and “Timing related to Gefitinib” both are “Before” then the AE will not be considered a TEAE, otherwise a TEAE.

If 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 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 14.1 and 14.2 will be based on TEAEs if not otherwise specified. Besides, one additional listing for adverse event will be presented based on All Screening Analysis Set.

Incomplete AE-related dates will be handled as follows:

- If the onset date is missing completely or missing partially but the onset month and year, or the onset year is 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.

No formal statistical comparisons are planned and p-values for AEs will not be generated.

14.1.1 All Adverse Events

AEs will be coded using the MedDRA Version 20.0 or higher. The Investigator will be responsible for assigning the Common Toxicity Criteria grades for AEs, using NCI-CTCAE V4.0.

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.

If an adverse event is reported for a given subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated.

The relationship to a trial drug, as indicated by the Investigator, is classed as “unrelated” or “related”. TEAEs with a related or missing relationship to the trial drug will be regarded as “related” to the trial drug. Any trial drug related TEAE are those TEAEs with a related or missing relationship to any of the trial drugs randomized/dosed to. 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 classed as Grade 1, 2, 3, 4, 5 (increasing severity) by referencing the NCI-CTCAE V4.0. 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, the 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:

- Any TEAEs
- Trial treatment related TEAEs:

  - related to any drug,
  - related to tepotinib
  - related to gefitinib
  - related to pemetrexed
  - related to cisplatin
  - related to carboplatin
- Any serious TEAE
- Any non-serious TEAE
- Trial treatment Serious related TEAEs
  - related to any drug,
  - related to tepotinib
  - related to gefitinib
  - related to pemetrexed
  - related to cisplatin
  - related to carboplatin
- Any TEAE of Grade ≥ 3 by NCI-CTCAE
- Trial treatment related TEAEs of Grade ≥ 3 by NCI-CTCAE
  - related to any drug,
  - related to tepotinib
  - related to gefitinib
  - related to pemetrexed
  - related to cisplatin
  - related to carboplatin
- TEAEs of special interest
- Related TEAEs of special interest
  - related to any drug,
  - related to tepotinib
  - related to gefitinib
  - related to pemetrexed
  - related to cisplatin
  - related to carboplatin
- TEAE leading to death (AEs with Grade 5 or outcome “fatal” if Grade 5 not applicable)

- Trial treatment related TEAE leading to death (AEs with Grade 5 or outcome "fatal" if Grade 5 not applicable)
    - related to any drug,
    - related to tepotinib
    - related to gefitinib
    - related to pemetrexed
    - related to cisplatin
    - related to carboplatin
- TEAEs leading to dose reduction of
    - any treatment
    - tepotinib
    - gefitinib
    - pemetrexed
    - cisplatin
    - carboplatin
- TEAEs leading to temporary discontinuation of
    - any treatment
    - tepotinib
    - gefitinib
    - pemetrexed
    - cisplatin
    - carboplatin
- TEAEs leading to permanent discontinuation of
    - any treatment
    - tepotinib
    - gefitinib
    - pemetrexed
    - cisplatin
    - carboplatin

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

- Incidence of TEAEs by SOC, PT
- Incidence of TEAEs by SOC, PT and worst severity (CTCAE Grade)

- Incidence of related TEAEs by SOC, PT
    - related to any drug,
    - related to tepotinib
    - related to gefitinib
    - related to pemetrexed
    - related to cisplatin
    - related to carboplatin
- Incidence of TEAEs with CTCAE Grade ≥ 3 by SOC and PT
- Incidence of any drug related TEAEs with CTCAE Grade ≥ 3 by SOC and PT
- Incidence of non-serious AEs excluding SAEs

14.1.2 Adverse Events Leading to Treatment Discontinuation

AEs leading to temporary or permanent discontinuation of study treatment will be identified as those AEs whose action taken with study treatment was reported as “drug interrupted” or “drug withdrawn” 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 any treatment by SOC, PT
- Incidence of TEAEs leading to temporary discontinuation of any treatment by SOC, PT
- Incidence of TEAEs leading to dose reduction of any treatment by SOC, PT

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

14.2.1 Deaths

All deaths, deaths within 33 days after last dose of trial drug, death within 60 days after first dose 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 trial treatment
- Number of deaths within 60 days after first dose of trial treatment
- Primary reason of death
    - Disease progressions
    - Adverse event related to study treatment
    - Adverse event not related to study treatment

- Other
- Unknown

- Primary reason of death within 33 days after last dose of trial treatment
- Primary reason of death within 60 days after first dose of trial treatment

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 trial treatment
  - flag for death within 60 days of first trial treatment

14.2.2 Serious Adverse Events

SAEs are those events with a response of "Yes" for the item "Serious Adverse Event" on the "Adverse Events Details" form of the 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 any drug related Serious TEAEs by SOC and PT
- Listing of all SAEs for the SAF set.
- Incidence of TEAEs leading to death by SOC and PT
- Incidence of any drug related TEAEs leading to death by SOC and PT
- Listing of all TEAEs leading to death for the SAF set.

14.2.3 Adverse Event of Special Interest

Adverse Events of Special Interests (AESIs) are those events with a response of "Yes" for the item "Is this an adverse event of special interest?" on the "Adverse Events Details" form of the eCRF.

The following are collected and will be presented:

- Incidence of treatment emergent AESIs by SOC and PT: All cases of asymptomatic lipase and/or amylase elevations of Grade ≥ 3 will be reported as AESI
- Incidence of any drug related treatment emergent AESIs by SOC and PT
- Any lipase or amylase increase will be listed for SAF set

14.3 Clinical Laboratory Evaluation

Urinalysis assessments

Dipstick urinalysis assessments will be conducted by sites. Sites will decide whether or not sending urine samples to central laboratory for microscopic examination.

The following information will be provided:

- Dipstick urinalysis assessments outcome by visit: normal, abnormal
- List of abnormal microscopic examination findings

Biochemistry, hematology and coagulation

Laboratory values (including corresponding normal ranges) from Central Lab will be used for summary statistics and shift tables. Only subjects with post baseline laboratory values will be included in these analyses. Data will be provided by the central laboratory using the International System of Units (SI) and all presentations will use SI units.

Quantitative data will be examined for trends using descriptive statistics (mean, standard deviation, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline to each visit over time.

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 treatment.

The following summaries will be displayed per cohort and all cohorts combined:

- Number and percentage of subjects by worst on-treatment values (Low, Normal, High). Please refer to the Analysis Data Model (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.
- Shift from baseline to highest and lowest on-treatment value.

For gradable parameters (according to NCI-CTCAE v4.0), the following summaries will be displayed per cohort and all cohorts combined:

- Number and percentage of subjects by worst on-treatment values (≥ Grade 1, ≥ Grade 3, ≥ Grade 4)
- Shift in toxicity grading from baseline to highest postbaseline toxicity

The following figures will also be provided:

- Boxplots of the laboratory values by timepoint
- Boxplots of the change from baseline by timepoint

14.4 Vital Signs

Information from the "Vital Signs" eCRF will be used.

The following vital parameters will be reported:

- Auricular Temperature (˚C)
- Temperature Conversions:
- Auricular temperature (˚C) = Oral temperature + 0.5 (˚C) = Rectal temperature (˚C) = Axillary temperature +1 (˚C)
- Respiratory Rate (breaths/min)
- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (bpm)
- Height (cm): only at baseline
- Weight (kg)
- BMI (kg/m^2)
- BSA (m^2)

The following summaries will be provided for vital signs data:

- Vital signs at baseline will be presented descriptively.
- Summary statistics over time: only subjects at the visit will be summarized.
- Categorical change from baseline to worst on-treatment value (i.e. the highest value for increase and the lowest value for decrease) for vital signs, excluding weight, will be grouped as follows:

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

SBP	Increase	< 140 mmHg; ≥ 140 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
	Decrease	< 140 mmHg; ≥ 140 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP	Increase	< 90 mmHg; ≥ 90 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, >40 mmHg
	Decrease	< 90 mmHg; ≥ 90 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
Respiration rate	Increase	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, >5 – 10 bpm, >10 bpm
	Decrease	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, >10 bpm

- Categorical changes in body weight from baseline to measurements during the treatment phase classified according to the NCI-CTCAE (version 4.0):

Variable	Grade 1	Grade 2	Grade 3
Weight Gain	5 - < 10% from baseline	10 - < 20% from baseline	≥ 20% from baseline
Weight Loss	5 - < 10% from baseline	10 - < 20% from baseline	≥ 20% from baseline

Weight changes from baseline ≤ 5% will be categorized as Grade 0.

- In addition to data listing for vital signs, an additional subject data listing will present all changes from baseline reported in the highest categories for auricular temperature, heart rate, systolic blood pressure, diastolic blood pressure, respiration rate and weight.

14.5 ECG

Information from the "Electrocardiogram" eCRF will be used.

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. Result of ECG will use the worst result among the 3 results, i.e. Normal; Abnormal, not clinically significant; Abnormal, clinically significant. Rhythm will only be listed.

The following ECG parameters will be reported for this study based on the SAF set:

- PR Interval (msec)
- QRS Interval (msec)
- QTcF Interval (msec)
- RR (msec)
- Result of ECG: Normal; Abnormal, not clinically significant; Abnormal, clinically significant

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Frequency and percentages for result of ECG by visit
- Categorical shift from baseline to worst on-treatment value for the QTcF: the baseline and the worst on-treatment value (i.e. the highest value) will be grouped as follows:

Parameter	Baseline category	Worst on treatment value
QTcF	≤450ms >450 - ≤480ms >480 - ≤500ms >500ms	≤450ms >450 - ≤480ms >480 - ≤500ms >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:
    - Worst absolute change from baseline= | worst on-treatment value – value at baseline |

Parameter	Baseline category	Worst absolute change from baseline
QTcF	Normal (i.e.≤450ms) Abnormal (i.e.>450ms)	≤0 ms >0 - ≤30ms >30 - ≤60ms >60ms

- Incidence of QTcF prolongations

Parameter	Prolongations
QTcF	>450ms >480ms >500ms
Absolute QTcF change	>30ms >60ms

14.6 Other Safety or Tolerability Evaluations

Physical Examination

Information from the "Physical Examination" eCRF will be used.

A listing of subjects completing physical examinations results will be presented. However clinically significant abnormal findings will be reported as AEs.

ECOG

Information from the "ECOG Performance Status" and "Pregnancy Test" eCRF pages will be used.

ECOG performance status and pregnancy will be listed separately.

15 Analyses of Other Endpoints

CCI [redacted]

15.2 Pharmacodynamics and CCI [redacted]

The changes of the circulating levels of shedded cMet, IL-8 and HGF under treatment might be indicative of anti-tumor activity. The biomarkers shedded cMet, IL-8 and HGF will be measured in plasma by ELISA assay:

The following variables will be calculated to measure on-treatment changes in marker levels for each of the three biomarkers (shedded cMet, IL-8 and HGF):

- absolute and fold change from baseline level to on-treatment levels.

Further exploratory endpoints may include:

CCI [redacted]

- Further exploratory biomarkers that may correlate with antitumor activity.

All pharmacodynamics and pharmacogenomics will be presented in data listings together with BOR for the respective patients.

15.3 Health Related Quality of Life

The PROs with respect to QoL, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, Version 3.0), Lung Cancer Symptom Scale (LCSS), and CCI will be analyzed. Information obtained from "Quality of Life Questionnaire", "Quality of Life EORTC QoL-C30", "European Quality of Life and 5 Dimensions", And "Lung Cancer Symptom Scale" of eCRF will be used.

In the randomization part of Phase II, QoL evaluable population includes all ITT subjects with a baseline and at least one evaluable on-treatment QoL questionnaire.

In the single-arm cohort of Phase II, QoL evaluable population includes subjects in Safety Analysis Set with a baseline and at least one evaluable on-treatment QoL questionnaire.

Evaluability

Questionnaires filled in during the first 5 days after the beginning of a treatment cycle (day of pemetrexed or cisplatin/carboplatin infusion) will be considered non-evaluable, as these questionnaires would be primarily influenced by the acute side-effects of chemotherapy. In addition, questionnaires filled in "on-treatment", but after the date of progression, will be considered non-evaluable.

The patterns of completion of questionnaires will be explored to investigate the magnitude of missing data and to explore the extent of intermittent missing data and monotone missing data.

The following will be provided for each assessment period and overall:

- The number of subjects with at least one evaluable QoL questionnaires
- Percentage compliance: 100 × (number of subjects with at least one evaluable QoL questionnaires)/(number of subjects with at least one evaluable QoL questionnaire expected)

The reasons for missing evaluable questionnaires will be presented by each assessment period.

15.3.1 Lung Cancer Symptom Scale

Definition of Average Symptomatic Burden Index (ASBI)

The ASBI is the mean of all six symptom scores treated as a single domain.

If 3 or more items are missing, the subject will be considered non-evaluable at that time point. For each symptom score, the distance from the left boundary to the point where the subject has marked the line is measured in millimeters. The total scale length is 100 mm.

Definition of Time-to-Symptom Progression

Symptom progression will be defined as an increase (worsening) of the ASBI score of 10% of the scale breadth (10 mm on a scale of 0-100 mm) from the baseline score on at least two consecutive assessments during the period when assessments are performed every 2 cycles and then every 4 cycles. Once the frequency of assessments is reduced to every 4 cycles, then an increase at only one assessment is required as proof of worsening.

TTSP will be defined as the time from date of Cycle 1 Day 1 until date of symptom progression. If symptom progression requires two consecutive assessments meeting the criteria of worsening, then the date of symptom progression will be taken as the date of the earlier of the two assessments. Subjects diagnosed with PD at time of death will be considered as having an uncensored TTSP defined as time between date of randomization/first administration of trial treatment and date of death.

The following parameters will be summarized by the mean and SD for each treatment arm and overall for each assessment period:

- Total Score
- ASBI
- Appetite
- Fatigue
- Cough
- Dyspnea: shortness of breath
- Hemoptysis: blood in sputum
- Pain
- Symptom distress: symptoms from lung cancer
- Activity level: ability to carry out normal activities
- Global quality of life

A two sample t-test to compare the two treatment arms will be provided for the randomized part.

The analysis will test the equality of TTSP between treatment arms in the randomized part of Phase II, based on the ITT 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., type of MET+ status and prior EGFR-TKI treatment.

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

15.3.2 EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire consists of 30 multiple choice questions that can be classified into following categories:

- Functional scales: physical, role, cognitive, emotional, social
- Symptom scales: fatigue, nausea and vomiting, pain
- A global health status scale
- Single items: dyspnea, loss of appetite, insomnia, constipation, diarrhea, financial difficulties.

First the average of the items that contribute to the scale is estimated; this is the raw score; then a linear transformation is used to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. Refer to Appendix 1 for details on scoring. Each scale and item will be summarized using summary statistics descriptively. Summary statistics (mean [and standard deviation], median, range and 95% CI) of raw and standardized scores will be reported for the scales of the European EORTC QLQ-C30 questionnaire. These summary statistics will be presented for observed and change from baseline scores.

Missing data will be handled in accordance with the scoring manual. Namely, for multi-item scales, if at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which are present for that respondent.

CCI [redacted]

CCI [redacted]

16 References

1. 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.

2. Jackman D, Pao W, Riely GJ, et al. Clinical Definition of Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non–Small-Cell Lung Cancer. JCO Jan 10, 2010:357-360; published online on November 30, 2009.

17 Appendix

17.1 Scoring the EORTC QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the RawScore, RS, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + \cdots + I_n)/n$$

Then for functional scales:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} * 100$$

and for Symptom scales/items and Global health status /QoL:

$$Score = \{(\mathrm{RS} - 1)/\mathrm{range}\} * 100$$

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