Integrated Analysis Plan

Clinical Trial Protocol No.	MS 200095-0022
Title	A Phase II, single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplification (VISION)
Trial Phase	II
Investigational Medicinal Product(s)	Tepotinib (MSC2156119J)
Clinical Trial Protocol Version	17 January 2020 / Version 8.0 09 February 2021 / Version 8.1 – Local China
Integrated Analysis Plan Author	PPD
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Integrated Analysis Plan Reviewers	PPD PPD, IQVIA PPD, PPD, IQVIA PPD, PPD, IQVIA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck China PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck Healthcare KGaA PPD, PPD, Merck China PPD, PPD Merck Healthcare KGaA PPD, PPD, Merck S.L. Spain

1 Signature Page

Integrated Analysis Plan: MS200095-0022

A Phase II, single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplification (VISION)

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2 Table of Contents

3 List of Abbreviations and Definition of Terms

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CDISC	Clinical Data Interchange Standards Consortium
cfDNA	Cell Free DNA
CI	Confidence Interval
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
ctDNA	Circulating Tumor DNA
CV	Coefficient of variation
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Co-operative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EM	Exploratory Medicine
EOT	End of treatment
FU	Follow-Up
GBS	Global Biostatistics
GCP	Good Clinical Practice
GCN	Gene copy number
IAP	Integrated Analysis Plan
ICD-O	International Classification of Diseases for Oncology
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IPD	Important Protocol Deviations

IRC	Independent Review Committee
ITT	Intention to Treat
LBx-	Liquid Biopsy negative
LBx+	Liquid Biopsy positive
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ND	Non-determined
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression free Survival
PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient Reported Outcome
PSCR	Prescreening population
PT	Preferred Term
QOL	Quality of Life
QTcF	Fridericia's formula for corrected QT interval
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
TBx	Tumor Tissue Biopsy
TBx-	Tumor Tissue Biopsy negative
TBx+	Tumor Tissue Biopsy positive
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Screening Analysis Set

SD	Stable Disease
SDG	Standardized Drug Groupings
SEM	Standard Error of the Mean
SMI	Small Molecule Inhibitor
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary

4 Modification History

Unique Identifier for IAP Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	7th September 2017	PPD	First final version
2.0	10 July 2019	PPD	Changes in header; Addition of Met amplification cohort; redefined details on objectives based on liquid and biopsy testing results; redefine details on secondary endpoints analysis; increase of number of primary analysis sets; increase of number of analyses; sample size justification for the added cohort; changes in subgroup definition; changes in CRO name (IQVIA previously known as Quintiles); redefine PK analyses; addition of EORTC QLQ-LC13 longitudinal analysis.
3.0	12 August 2019	PPD	Changes: Protocol Version; section 5 and 8 added analysis with 19th July 2019 cut-off; Section 9 added the additional analysis for potential regulatory submission
4.0	05 February 2020	PPD	Changes: • Protocol version 6.0 and 7.0 implemented (i.e. analysis of Cohort C added) • Sections 6 and 7 removed to simplify the document, considering they were identical to the protocol • Statistical analyses on per protocol analysis set were removed since considered not relevant any more • New document to list outputs requested for each delivery (including IDMCs) cross-referenced in Appendix 1. • Subgroups derivation added and increased the number of subgroups of interest. • Analysis of questionnaire data detailed to evaluate the effect of the study drug on patient reported outcomes • Improved description of outputs to be created • Listing of batch and kit numbers added • Rederivation of some hematology, biochemistry and ECG parameters added • Minor typos corrected • Appendix 2 removed since deemed not necessary and redundant
5.0	22 July 2020	PPD	Changes: • Section 7.1 added to describe COVID-19 related outputs. • Added four new subgroups of interest.

Unique Identifier for IAP Version	Date of IAP Version	Author	Changes from the Previous Version
			• Added analyses for the subjects with first dose before 2nd of October 2019 in addition to those considering first dose before 2nd of April 2019 wherever applicable. Clarified what analysis should be performed on the SAF or ITT analysis set or both. • Updated section 10.2.1, clinically important protocol deviations added. • Updated section 11.2 to add new outputs on prior anti-cancer drug therapies.
6.0	14 April 2021	PPD	• Updated section 6 to describe new analyses needed for US and China authorities. • Updated section 8 with new subgroups for age 3 (threshold 80 years of age), China and China race • Updated section 9 removing specific subsets of subjects of interest, reflecting the maturity of Cohort A data • New disposition table (section 10), exposure table (section 13) • New efficacy analyses on SAF population (section 14) added to comply with requests from regulatory authorities • New categories to analyze duration of response added at section 14.2.2 • New plot added in order to visually present PFS reached under this treatment and PFS reached under tepotinib treatment at section 14.2.4 • Shift tables by China status for clinical laboratory evaluations, vital signs and ECGs have been added on section 15 to further investigate safety on Chinese subjects
7.0	23 September 2021	PPD	• Update section 6 to combine analyses of global Cohort C and Cohort C (China extension); refer to Cohort C as Cohort C (global enrollment phase or China extension); remove specific 9-month analysis for subjects enrolled in mainland China; add 3-month follow-up analysis for initial China submission • Added COVID-19 vaccinations outputs in section 7.1 • Added reference to outputs to be produced by Chinese status/for subjects enrolled in mainland China only in multiple sections.
8.0	31 March 2022	PPD	• Section 8.1: now all the PDs (including minor) to be kept in the SDTM • Section 8.2: updated wording for Chinese status • Section 11.2: Added analysis of duration of prior anti-cancer drug therapy regimens and Sankey plot to describe the flow of prior anti-cancer drug therapies.

Unique Identifier for IAP Version	Date of IAP Version	Author	Changes from the Previous Version
			• Section 12: Added analysis of duration of subsequent anti-cancer drug therapy regimens, analysis of specific therapies of interest and Sankey plot to describe the flow of anti-cancer drug therapies after discontinuation of study treatment. • Added Section 14.3.7 to analyze central nervous system tumor response using RANO criteria • Clarified that analysis should be performed on the SAF analysis set. ITT analysis set only used for combinations of LBx and TBx status (positive or negative).

5 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the analysis of data collected for protocol MS200095-0022. 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 upon section 8 (Statistics) of the trial protocol and protocol amendments and is prepared in compliance with International Conference on Harmonization E9.

6 Overview of Planned Analyses

This IAP covers the analyses for efficacy and safety based on the data from the various cut-off dates.

Sequence of Analyses and corresponding cut-off dates

Part 1: Cohort A (METex14 skipping alterations)

During the course of the study the following sequence of analyses will be conducted on subjects enrolled in Part 1: Cohort A (METex14 skipping alterations), referred to as Cohort A from now onwards:

- Interim Futility Analysis: When 12 subjects in the TBx analysis set have completed 4 cycles (84 days +/- 3 days) or have prematurely discontinued trial treatment for any reason, whichever comes first. The attendance of the subject at the Cycle 5, Day 1 visit will be used to trigger the completion of 4 cycles for data cut-off purposes.
- Interim Analysis: When 12 subjects in the LBx analysis set have completed 4 cycles (84 days +/- 3 days) or have prematurely discontinued trial treatment for any reason, whichever comes first. The attendance of the subject at the Cycle 5, Day 1 visit will be used to trigger the completion of 4 cycles for data cut-off purposes.

- 18th February 2019 cut-off analysis: it will be conducted based on all patients enrolled by 18th February 2019 and include all visits and events observed by that date.
- 19th July 2019 cut-off analysis: it will be conducted based on all patients enrolled by 19th July 2019 and include all visits and events observed by that date.
- 6-month follow-up analysis: it will be conducted once at least 60 subjects are included in the LBx analysis set and at least 60 subjects are included in the TBx analysis set and have either been treated with tepotinib for at least 6 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first.
- 9-month follow-up analysis: it will be conducted once at least 60 subjects are included in the LBx analysis set and at least 60 subjects are included in the TBx analysis set and have either been treated with tepotinib for at least 9 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first. It will be used as the primary analysis for United States Food and Drug Administration (FDA).
- 15-month follow-up analysis: it will be conducted once at least 60 subjects are included in the LBx analysis set and at least 60 subjects are included in the TBx analysis set and have either been treated with tepotinib for at least 15 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first. This analysis has been introduced in accordance with feedback from the FDA.
- Final analysis: it will be conducted when all subjects, in the cohort A have discontinued trial drug and two-thirds of the subjects have died.
- Periodic Safety Reviews: Frequency as stipulated in the IDMC Charter or at request of the IDMC or Merck.
- In addition to the analyses described above, further interim analyses at time points that are not specified in the protocol may be performed.

If 3 or less confirmed responders are observed at the futility interim analysis on 12 subjects in the TBx analysis set, the enrolment of subjects into Cohort A, tested positive for METex14 skipping alterations TBx, but not in plasma ctDNA will be discontinued. No stopping criteria are defined for any other interim analysis.

Part 1: Cohort B (MET amplification)

During the course of the study, the following analyses will be conducted on subjects enrolled in Part 1: Cohort B (MET amplification), referred to as Cohort B from now onwards:

- Futility interim analysis: after 12 subjects in the LBx analysis set have completed 4 cycles (84 days) or have prematurely discontinued trial treatment for any reason;
- Primary analysis: of Cohort B (covering all analysis sets) will be conducted once all subjects in the LBx analysis set have either been treated with tepotinib for at least 6 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first;

- 9-month follow-up analysis: it will be conducted once all subjects in the LBx analysis set have either been treated with tepotinib for at least 9 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first.
- Final analysis: at the end of the Cohort B defined as the time point at which all subjects in the cohort have discontinued trial drug and two-thirds of the subjects have died;
- In addition to the analyses described above, further interim analyses at time points that are not specified in the protocol may be performed.

If 2 or less confirmed responders are observed at the futility analysis on 12 subjects in the LBx analysis set, the enrolment of subjects tested positive for MET amplification in plasma ctDNA will be discontinued.

Part 2: Cohort C (confirmatory part for METex14 skipping alterations) global and mainland China extension

During the course of the study, the following analyses will be conducted on all subjects enrolled in Part 2: Cohort C (confirmatory part METex14 skipping alterations), regardless of whether subjects were enrolled during the global enrollment phase (until the end of March 2021) or the China extension (until 20th May 2021):

- 3-month follow-up analysis for initial China submission will be conducted once all subjects enrolled in Cohort C (global enrollment phase or China extension) have either been treated with tepotinib for at least 3 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first
- Primary (9-month follow-up) analysis will be conducted once all subjects enrolled in Cohort C (global enrollment phase or China extension) have either been treated with tepotinib for at least 9 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first
- 18-month follow-up analysis will be conducted once all subjects enrolled in Cohort C (global enrollment phase or China extension) have either been treated with tepotinib for at least 18 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first. This analysis has been introduced in accordance with a specific FDA post-marketing requirement.
- Final analysis at the end of the Part 2: Cohort C, defined as the time point at which all subjects enrolled in Cohort C (global enrollment phase or China extension) have discontinued trial drug and two-thirds of the subjects have died
- In addition to the analyses described above, further interim and follow-up analyses at time points that are not specified in the protocol may be performed.

Cohort A and Cohort C

In addition to the analysis of Cohort C, a pooled analysis of all subjects with METex14 skipping alterations enrolled in the global enrollment phase will be conducted, i.e., combining data from Cohort A and Cohort C.

Cut-off dates:

Statistical analyses will be performed using cleaned electronic Case Report Form (eCRF) data gained until the cut-off date for the respective analysis.

If the cut-off date is based on the number of deaths, due to cleaning activities, the final number of deaths might deviate from the planned number. The data cut-off date will not be adjusted retrospectively in this case.

Handling of data dated after a cut-off date is detailed in Section 9.

6.1 Interim Futility Analysis

The ORR (defined in Section 14.1.1) determined according to RECIST Version 1.1 based on independent review will be assessed.

Due to the non-comparative nature of the trial, the analysis outputs will be provided by IQVIA Biostatistics. These outputs will be distributed to the IDMC members in advance of the meeting. The IDMC members will recommend whether the trial should continue or be terminated due to futility and will disseminate this decision in line with IDMC charter.

The outputs required for the futility analysis will be a subset of the primary and final analysis outputs as defined in the Appendix 1. Any SAS outputs required in addition to the primary and final analysis are detailed in Section 14 of this IAP.

6.2 Periodic IDMC Safety Reviews

The first IDMC Safety Review will be conducted at the same meeting as the Interim Futility Analysis review. The outputs required for the safety reviews will be a subset of the primary and final analysis outputs as defined in the Appendix 1 and will cover topics defined in the IDMC Charter.

Recommendations and actions based on each IDMC Safety Review will be documented and followed up in line with the IDMC Charter.

Additional non-SAS safety related outputs (e.g. patient profiles from JReview) required for IDMC Safety Reviews are not detailed in this IAP.

6.3 18th February 2019 Cut-Off, 19th July 2019 Cut-off, Subsequent Follow-up Analyses, and Final Analysis

A data review meeting will be held to agree the final analysis sets and ensure that all data queries have been resolved prior to database lock.

The planned analyses of all endpoints in this IAP will be performed unless stated otherwise. Unplanned exploratory analyses may also be included.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods as mentioned in the protocol will be adopted. There are no changes to the planned analyses.

Based on a cut-off date of 18th February 2019 an unplanned interim analysis for the purpose of presentation of results at ASCO 2019 had been conducted. This analysis included a subset of the outputs defined in this analysis plan. Following an interaction with the Japanese Pharmaceuticals and Medical Devices Agency, an additional full analysis based on the 19th July 2019 cut-off analysis for a potential regulatory submission was done. It was based on all patients enrolled by 19th July 2019 and included all visits and events observed by that date.

The initially planned Per-protocol analysis sets have been omitted because of the limited value seen in results from analyses in the Per-protocol analysis sets conducted so far. The clinically important protocol deviations leading to exclusion of subjects from the Per-protocol analysis sets are heterogenous. It is not anticipated that analyses in the Per-protocol analysis sets will provide additional insights.

Efficacy analyses will be repeated on the SAF analysis set. These analyses have been introduced in accordance with feedback on the US prescribing information from the FDA.

A follow-up analysis after all subjects enrolled in Cohort C (global enrollment phase or China extension) have either been treated with tepotinib for at least 3 months, died or have prematurely discontinued trial treatment for any reason has been added for the initial China submission.

7.1 COVID-19 Impact

No changes to the planned analysis of the efficacy endpoints will be performed due to the impact of Coronavirus disease 2019 (COVID-19) outbreak.

Additional outputs (summary table and listing) will be generated for a description of the impact by COVID-19 in terms of the following:

- Potentially affected by COVID-19
- Adverse Events
- Protocol deviations (important and non-important)
- Missed Visits (including number of missed visits)
- Missed efficacy evaluations (including number of missed efficacy evaluations)
- Tele-Visits performed (including number of Tele-Visits)
- Drug Administration - missed doses
- Drug Administration – dose interruptions
- Laboratory testing performed by external laboratory unit (only if at least 10 subjects are affected)

- Treatment Discontinuation
- Study Discontinuation
- Death

Potentially affected subjects (either due to infection or due to circumstances of social distancing affecting the capabilities of sites/hospitals etc.) are defined as:

a) Patients who started treatment after start of the COVID-19 pandemic, or
b) Patients who started treatment prior to start of the COVID-19 pandemic and had tumor assessments planned after the start of the pandemic (i.e., did neither have progressive disease, died or withdrew from tumor assessments prior to start of the pandemic).

The start of COVID-19 pandemic will be defined by country as the earliest date of either the date of the first death from COVID-19 occurred in each country according to the published data by European Centre for Disease Prevention and Control on 26th June 2020 (https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide) or 11th March 2020 (when the WHO declared COVID-19 pandemic).

A frequency table will be produced for the SAF analysis set to present the number of subjects with important protocol deviations related to COVID-19 (categorized by frequency of subjects with an important protocol deviation overall as well as by category of protocol deviation and type of protocol deviation). A separate table for the non-important protocol deviations related to COVID-19 (categorized by frequency of subjects with a non-important protocol deviation overall as well as by category of protocol deviation) will also be produced.

A frequency table based on concomitant medication data will be produced on the SAF analysis set to present the number of subjects with COVID-19 vaccinations. COVID-19 vaccinations will be identified according to the Standardized Drug Groupings (SDGs) subgroup "Vaccines for COVID-19" and corresponding SDG subcategories of the latest version of the WHO-DD. The summary will include counts for vaccines that were given prior to first administration of any trial treatment as well as concomitant vaccines.

These frequency tables will also be presented by Chinese status.

In addition, separate listings (overall and on subjects enrolled in mainland China only) of COVID-19 specific adverse events, vaccinations and protocol deviations will also be produced.

Outputs related to disposition and exposure will be amended to present reason of treatment/study discontinuations due to COVID-19 and treatment delays due to COVID-19 (if possible).

Laboratory results performed by external laboratory units will be included in the summary statistics and shift analyses, provided that normal ranges are not missing; if they are missing, results will be listed and included in summary statistics outputs only.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations

Protocol deviations describe how close the trial has been conducted according to the protocol as expected per Good Clinical Practice (GCP). Important protocol deviations (IPDs) are those that might significantly affect the completeness, accuracy, and/or reliability of the trial data or that might significantly affect a subject's rights, safety, or well-being.

Important protocol deviations include:

- Subjects that are dosed on the study despite not satisfying the inclusion/exclusion criteria
- Subjects that develop withdrawal criteria whilst on the study but are not withdrawn
- Subjects that receive an incorrect dose and/or exposure to treatment (a dose outside of the protocol defined doses of 500 mg once daily, the dose reduction specified in the trial protocol and subsequent amendments or any other dose which has been agreed by the sponsor)
- Subjects that receive a prohibited medication
- Deviation from Good Clinical Practice (GCP) as determined by medical review (e.g. no written informed consent provided/collected)

Any of the above deviations will be identified and confirmed prior to or at each Data Review Meeting at the latest. Each deviation will be assessed for clinical importance, which is defined as a deviation potentially impacting efficacy (see Section 8.2).

The protocol deviations recorded in the Clinical Trial Management System (CTMS) may utilize different terminology. The table below displays how the terminology used in CTMS translates to the terminology used in the SAP, the SDTM and ADaM datasets, and ultimately the CSR:

CTMS	SAP	SDTM	ADaM
Minor	Non-important (only for protocol deviations related to COVID-19)	All protocol deviations are included	Only protocol deviations related to COVID-19 are included
Major	Important	Flagged with PDEVXXX code	Flagged with PDEVXXX code
Critical (subset of Major)	NA	Mapped to Important	Mapped to Important
NA	Clinically Important (potentially impacting efficacy)		Additional flag = Y/N in ADDV (may also include conditions not considered to be PD's)

8.2 Definition of Analysis Sets and Subgroups

Prescreened analysis set (PSCR)

The Prescreening analysis set will comprise all subjects who provided informed consent for prescreening or screening. This includes patients enrolled in Japan who could be enrolled without pre-screening.

Screened analysis set (SCR)

The Screening analysis set will comprise all subjects who provided informed consent for the main screening, regardless of the subject's treatment status in the trial.

Safety analysis sets (SAF)

The SAF analysis set will comprise all subjects who were administered at least 1 dose of tepotinib.

Intention-to-treat (ITT)

The ITT analysis sets will comprise all subjects who were administered at least 1 dose of tepotinib and had METex14 skipping alterations or MET amplification confirmed by a validated central laboratory assay in tissue (TBx) and/or liquid (LBx) samples.

Below details of the ITT and SAF analysis sets for each cohort:

Cohort A, Cohort C and pooled Cohort A + C

For efficacy analyses, the following analysis sets are defined taking into account for the assessment used to identify subjects with METex14 skipping alterations.

- TBx and/or LBx (combined) analysis set defined as:
    - ITT TBx and/or LBx (combined): all subjects enrolled in the global enrollment phase who were administered at least 1 dose of tepotinib and tested positive for METex14 skipping alterations in tumor tissue or plasma ctDNA by a validated central laboratory assay (including those tested positive for METex14 skipping alterations in both tumor tissue and plasma ctDNA).
    - SAF TBx and/or LBx (combined): all subjects enrolled in the global enrollment phase who were administered at least 1 dose of tepotinib, including subjects with METex14 skipping alterations not confirmed by a validated central laboratory assay
- ITT and SAF LBx analysis set defined as all subjects enrolled in the global enrollment phase who were administered at least 1 dose of tepotinib and tested positive for METex14 skipping alterations in plasma ctDNA by a validated central laboratory assay.
- ITT and SAF TBx analysis set defined as all subjects enrolled in the global enrollment phase who were administered at least 1 dose of tepotinib and tested positive for METex14 skipping alterations in tumor tissue by a validated central laboratory assay.

Subjects who are tested positive in tissue and in plasma will be assigned to both, the LBx and TBx analysis sets, respectively. For those subjects with samples for both, TBx and LBx, available

- ITT TBx+/LBx+ analysis set (ITT T+L+): will comprise all subjects enrolled in the global enrollment phase tested positive for METex14 skipping in both, tumor tissue and plasma ctDNA.
- ITT TBx+/LBx- analysis set (ITT T+L-): will comprise all subjects enrolled in the global enrollment phase tested positive for METex14 skipping in tumor tissue, but not in plasma ctDNA.
- ITT TBx-/LBx+ analysis set (ITT T-L+): will comprise all subjects enrolled in the global enrollment phase tested positive for METex14 skipping in plasma ctDNA, but not in tumor tissue.

Cohort B

For the efficacy analyses in the cohort of subjects tested positive for MET amplification and negative for METex14 skipping alterations, the primary analysis set will be:

- ITT LBx analysis set defined as all subjects tested positive for MET amplification in plasma ctDNA, irrespective of the TBx result.

PK analysis set (PK)

The PK analysis set will comprise all subjects who have received tepotinib and who had at least one post-dose blood sample drawn that provides drug concentration data for PK evaluation.

Biomarker-Blood analysis set (BB)

The Biomarker-Blood population includes all subjects who receive at least one dose of tepotinib and provided at least one pre-dose blood sample for exploratory markers in plasma. Selected biomarker analyses will be performed on this population.

Biomarker-Tumor analysis set (BT)

The Biomarker-Tumor population includes all subjects who received at least one dose of tepotinib and provided a pre-dose tumor biopsy.

Pharmacogenetic analysis set (PGx analysis set)

The Pharmacogenetic population includes all subjects included in this trial who gave informed consent on a separate PGx ICF for the exploratory PGx analyses, received at least one dose of tepotinib and provided at least one PGx blood sample.

Subgroup definition and parameterization

Unless otherwise specified the analyses will be performed by Cohorts (Cohort A, Cohort B and, Cohort C). Additionally, Cohort A and Cohort C results will be pooled and presented.

In addition, within each cohort, subgroup analyses will be performed on subgroups as defined below. For the definition of subgroup class, data as documented in the eCRF will be taken. Endpoints for which subgroup analysis will be performed will be detailed in Section 14.

For including baseline variables into statistical models in SAS® the GLM parameterization method is to be used with the reference level set to that specified below. In case of low numbers of subjects within a category, categories may be pooled for statistical analysis purposes but for descriptive summaries, original groups will be preserved.

The following subgroups will be defined:

- Age 1 (based on derivation defined in Section 11.1)
  - < 65 years
  - ≥ 65 years
- Age 2 (based on derivation defined in Section 11.1)
  - < 75 years
  - ≥ 75 years
- Age 3 (based on derivation defined in Section 11.1)
  - < 80 years
  - ≥ 80 years
- Sex (based on data collected in the Demographics CRF page)
  - Male
  - Female
- Race (based on data collected in the Demographics CRF page)
  - Caucasian / White
  - Asian
  - Other
- Geographic region (based on country of enrolment)
  - North America
  - Europe
  - Asia
- Japanese status (based on country of enrolment)
  - Enrolled in Japan
  - Enrolled outside Japan
- Chinese status (based on country of enrolment)

- Enrolled in mainland China
- Enrolled outside mainland China

- Chinese race status (based on country of enrolment)
  - Enrolled in Greater China (mainland China or Taiwan)
  - Enrolled outside Greater China (mainland China or Taiwan)
- Eastern Co-operative Oncology Group (ECOG) Performance Status (PS) (based on data collected on the ECOG Performance Status CRF page)
  - ECOG PS 0
  - ECOG PS 1
- Any prior anti-cancer drug therapy (for non-metastatic or metastatic disease) (based on derivation defined on Section 12)
  - Yes
  - No
- Line of Therapy (based on derivation defined on Section 12)
  - First-line (no prior lines of therapy; reference level)
  - Second-line (one prior line of therapy)
  - Second or later line (one or more prior lines of therapy)
  - Third or later line (two or more prior lines of therapy)

    Of note, a selected set of outputs will be created using the following reduced line of therapy subgroups:
    - Treatment naïve (i.e. first-line; reference level)
    - Pretreated (i.e. second or later line)
- Line of Therapy nested within Chinese status and Chinese race status (as defined above). I.e., line of therapy categories separately for patients
    - Enrolled in mainland China
    - Enrolled outside mainland China
    - Enrolled in Greater China (mainland China or Taiwan)
    - Enrolled outside Greater China (mainland China or Taiwan)
- Line of Therapy for Metastatic Disease (i.e. subjects with stage IV at study entry) (based on derivation defined on Section 12)
  - First-line (no prior lines of therapy; reference level)
  - Second-line (one prior line of therapy)
  - Second or later line (one or more prior lines of therapy)

  - Third or later line (two or more prior lines of therapy)
- Prior Platinum-based Chemotherapy for Metastatic Disease (i.e. subjects with stage IV at study entry) (based on derivation defined on Section 12)
  - Yes
  - No
- Immunotherapy and Platinum-based Chemotherapy in Subjects with Prior Platinum-based Chemotherapy for Metastatic Disease (i.e. subjects who were stage IV at study entry and received platinum-based chemotherapy as prior anti-cancer drug therapy, based on derivation defined on Section 12):
  - Immunotherapy as monotherapy (i.e. the subject has at least one prior line of therapy where, among the types of therapies available in the eCRF page, only Immunotherapy is selected)
  - Platinum-based Chemotherapy alone (i.e. the subject has at least one prior line of therapy where platinum-based chemotherapy was administered and, among the types of therapies available in the eCRF page, only Cytotoxic Therapy and/or Monoclonal Antibodies therapy are selected)
  - Immunotherapy in combination with Platinum-based Chemotherapy (i.e. the subject has at least one prior line of therapy where platinum-based chemotherapy was administered and, among the types of therapies available in the eCRF page, Immunotherapy is also selected. Immunotherapy and platinum-based chemotherapy are considered to be in combination also in the case where their administration was sequential)
  - Immunotherapy as monotherapy or in combination with Platinum-based Chemotherapy
- Immunotherapy and Platinum-based Chemotherapy in Subjects in the Second or Later Line of Therapy (based on derivation defined on Section 12):
  - Immunotherapy as monotherapy (i.e. the subject has at least one prior line of therapy where, among the types of therapies available in the eCRF page, only Immunotherapy is selected)
  - Platinum-based Chemotherapy alone (i.e. the subject has at least one prior line of therapy where platinum-based chemotherapy was administered and, among the types of therapies available in the eCRF page, only Cytotoxic Therapy and/or Monoclonal Antibodies therapy are selected)
  - Immunotherapy in combination with Platinum-based Chemotherapy (i.e. the subject has at least one prior line of therapy where platinum-based chemotherapy was administered and, among the types of therapies available in the eCRF page, Immunotherapy is also selected. Immunotherapy and platinum-based chemotherapy are considered to be in combination also in the case where their administration was sequential)
  - Immunotherapy as monotherapy or in combination with Platinum-based Chemotherapy
- Baseline brain metastases (as per IRC assessment) (based on external data from IRC where both target and non-target lesions are considered)
  - Present

  - Absent
- Baseline brain metastases (as per investigator assessment) (based on data collected on the Target Lesions and Non-Target Lesions CRF pages)
  - Present
  - Absent
- Baseline brain metastases (as per IRC or per investigator assessment) (based on external data from IRC where both target and nontarget lesions are considered as well as on data collected on the Target Lesions and Non-Target Lesions CRF pages)
  - Present
  - Absent
- Histological classification (based on data collected on the Disease History CRF page)
  - Adenocarcinoma
  - Squamous
  - Other
- Clinical stage at diagnosis (based on data collected on the Disease History CRF page)
  - I, II
  - III
  - IV
- Clinical stage at study entry (based on data collected on the Disease History CRF page)
  - III b/c
  - IV
- Time from diagnosis to first dose (based on derivation defined in Section 11.4)
  - < 6 months
  - >= 6 months
- Smoking status (based on data collected on the Nicotine Consumption CRF page)
  - Smoker (former, occasional or regular use of nicotine)
  - Non-Smoker (never used nicotine)

9 General Specifications for Statistical Analyses

Data handling after a cut-off date:

Data after the cut-off date will not undergo the cleaning process and will not be used in the analyses.

However, for the final analysis, the database will be locked completely after all data has gone through the full data cleaning process.

Pooling of centers:

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

Significance level:

All statistical tests mentioned in this IAP are to be regarded as exploratory. All p-values presented are two-sided and confidence intervals have a confidence probability of 95%.

Presentation of continuous and qualitative variables:

Unless otherwise stated, all data will be summarized separately for:

1. Cohort A: LBx+, TBx+ and combined (LBx+ and/or TBx+)
2. Cohort C: LBx+, TBx+ and combined (LBx+ and/or TBx+)
3. Cohort A + Cohort C: LBx+, TBx+ and combined (LBx+ and/or TBx+)
4. Cohort B: LBx+
5. Cohort A + Cohort B + Cohort C: overall

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

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

Pharmacokinetic concentrations will be summarized using number of subjects, arithmetic mean, standard deviation (StD), standard error of the mean, median, minimum, maximum and coefficient of variation (CV in %). Qualitative variables will be summarized by counts and percentages.

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

For variables where a subject may have more than one category due to multiple responses per subject, the number of subjects included in each category will be summarized as a percentage from

all subjects. Therefore, the total frequency across categories may not equal the total number of all subjects in the population.

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 non-missing measurement prior to start of trial treatment will serve as the baseline measurement.

If the assessment time of any pre-dose baseline assessments (as planned per the protocol) and/or the time of initial dosing are unknown, but they are known to have been performed on the same day, it will be assumed that it was performed prior to dosing. Unscheduled assessments may be used in the determination of baseline, however, if the time is missing, it will be considered to have been obtained after study treatment administration.

On-treatment data:

Any data collected following the first dose and within 30 days of the final dose of trial treatment will be considered as on-treatment data.

Definition of duration:

Unless otherwise specified, duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of start of treatment + 1).

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

Conversion factors:

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

If height is recorded in inches, height (cm) = height (in) × 2.54.

If weight is recorded in pounds, weight (kg) = weight (lbs) ÷ 2.2046.

Handling of missing data:

Unless otherwise specified, missing data will not be replaced.

Imputation for missing dates is carried out for the following:

- Date of informed consent and date of birth for calculation of age (detailed in Section 11.1)
- Tumor assessment dates (Section 14.2)

- AE-related dates (Section 15.1)
- Nicotine Consumption (Section 11.3)
- Prior anti-cancer therapies dates (Section 11.2)
- Other baseline characteristics (Section 11.4)

In all subject data listings, imputed or censored values will be presented. In all listings, imputed or censored information will be flagged.

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

Non-missing observations will be summarized in tables presented over time related to laboratory values, ECGs and vital sign and percentages will be based on the analysis set of interest.

Scheduled and unscheduled visits

Data collected at both scheduled and unscheduled visits will be included in the derivation of safety and efficacy endpoints.

Unless specified otherwise, summaries by visit will be presented by the appropriate planned scheduled visit (i.e. Cycle 1 Day 1, Cycle 2 Day 1 … etc.) as indicated in the eCRF and only visits available for more than 10 patients will be considered. For laboratory measurement summaries by visit, the handling of unscheduled visits is detailed in Section 15.3.

End of Treatment (EOT) data will be presented in a separate record in those summaries by scheduled visit.

Time Windows:

For the purpose of PRO longitudinal analyses, time windows are defined as follows:

Analysis Cycle X Day 1 = Cycle X Day 1 target date +/- 21 days

In case of multiple PRO assessments in the analysis window, the one closest to the target date specified in the protocol will be used in the analysis.

Common calculations:

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

- Test Value at Visit X – Baseline Value

BMI (kg/m2) = weight (kg) / (height (cm)/100)^2

BSA (m^2) = ([height (cm) x weight (kg)] / 3600)$^{1/2}$

Tumor evaluation:

Only tumor assessments conducted prior to withdrawal of the subject from the trial will be evaluable for inclusion in the derivation of the primary and relevant secondary endpoints as detailed in Section 14. Missing data from scheduled tumor assessments not performed will not be imputed.

Evaluable tumor assessments are defined as those with outcome CR, PR, SD or PD. Data from non-evaluable (NE) tumor assessments will be used in the derivation of endpoints in accordance with RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 (Eisenhauer et al., 2009) and RANO (Response Assessment in Neuro-Oncology) (Lin et al., 2015).

The date of the tumor assessment of interest is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

Statistical software:

All analyses will be performed using SAS® (Statistical Analysis System, SAS Institute, Cary NC, USA, windows version 9.2 or higher).

10 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.

Unless otherwise stated, all analyses described will be conducted on the SAF population.

10.1 Disposition of Subjects and Discontinuations

All subjects who provide informed consent prior to prescreening will be accounted for in this study.

Subjects disposition will be summarized as follows:

- Total number of subjects prescreened
- Total number of subjects not prescreened (given that for subjects enrolled in Japan, pre-screening is not required)
- Total number of subjects screened (i.e. subjects who gave informed consent for the main screening period)
- Number of subjects who discontinued from the trial prior to treatment, overall and grouped by main reason (e.g. failed inclusion or exclusion criteria, withdrawal of consent)
- Number of subjects actively in screening
- Number of subjects treated with study drug

- Number of subjects with treatment ongoing
- Number of subjects with treatment permanently discontinued, overall and grouped by main reason
- Number of subjects in follow up (i.e. end of treatment CRF page completed, trial termination CRF page not completed and death page not present). Number of subjects within and above 3 months of follow up will be presented separately
- Number of subjects who discontinued from the study, overall and grouped by main reason

In addition, within each cohort summaries of subject disposition by line of therapy and Chinese status will be presented.

For each subject in the SCR analysis set the reason for discontinuation prior to trial treatment or date of first dose will be listed along with whether the subject is included in the SAF set.

For all cohorts, for each subject in the SAF analysis set, the first/last dosing date (including reason for treatment discontinuation) and completion/termination status (including reason for trial discontinuation) will be listed. The listing will also be produced for subjects enrolled in mainland China.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

A frequency table will be produced for the SAF analysis set to present the number of subjects with important protocol deviations (categorized by frequency of subjects with an important protocol deviation overall as well as by category of protocol deviation and type of protocol deviation). A table for the clinically important protocol deviations will also be produced.

Separate listings will also be provided showing inclusion/exclusion violations at screening and other important protocol deviations for the SAF analysis set. Clinically important protocol deviations will be flagged.

In addition, the frequency tables will be presented by Chinese status and the listings will be repeated on subjects enrolled in mainland China.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

The number of subjects included in each analysis set will be presented overall, by geographical region and country.

Additionally, inclusion/exclusion of each subject in all the analysis sets will be listed.

10.3 Results in tissue and blood

The result for all patients pre-screened/screened will be presented in two tables taking into account the assessment used to identify subjects with METex14 skipping alterations (Cohorts A and C) and MET amplification (Cohort B). Frequencies and percentages will be calculated for all the different combinations of results from both the tissue and blood sample. This will include the following categories for subjects with tissue or blood sample taken (Positive, Negative, Not Evaluable, Not Analyzed) and a category for No Sample Taken.

The table on METex14 Results will also be presented by Chinese status.

In addition, a table summarizing reasons for not analyzing a sample taken will be provided separately for METex14 skipping alterations and for MET amplification.

For each subject in the SCR analysis set, results in tissue and blood will be listed along with the reason for discontinuation prior to trial treatment.

11 Demographics and Other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the SAF analysis set.

Analyses will be conducted by cohort and overall using summary statistics for continuous variables and frequency tables for categorical variables.

Within each cohort, summary of demographics data and other baseline characteristics by line of therapy and prior platinum-based chemotherapy for metastatic disease, Chinese and Japanese status will also be presented.

11.1 Demographics

Demographic characteristics will be summarized using the following information from the Demographics eCRF pages as specified below:

- Sex: Male, Female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Collected at Site, Other
- Ethnicity:
  - Hispanic or Latino, Not Hispanic or Latino
  - Japanese, Not Japanese
- Age (years): Summary statistics
- Age categories:
  - < 65 years, ≥ 65 years
  - 65-74, 75-84, ≥ 85

  - Age = (Date of informed consent for screening - Date of Birth + 1) / 365.25
  - In the case when there is a missing day for at least one date, but the month and year are available for both dates, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
  - In the case when there is a missing month for at least one date, but year is available for both dates, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used
- Country
- Pooled Region: North America, Europe, Asia

Listings showing demographic data and other baseline characteristics will be presented for the SAF analysis set. These listings will be repeated on subjects enrolled in mainland China.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA (latest version at the time of database lock for each analysis; will be specified in outputs), with the MedDRA preferred term (PT) as event category and MedDRA system organ class (SOC) body term as Body System category, by cohort and overall.

Medical history will be displayed in terms of frequency tables ordered by primary SOC and PT in alphabetical order (including overall SOC category). Frequencies and percentages will reflect subjects with at least one condition within each SOC/PT category.

A listing of medical histories captured in the "Medical History" eCRF page will be provided with SOC term, PT term, NCI-CTCAE (Version 4.03) toxicity grade (only for ongoing observations) and whether related to the study condition.

In addition, the medical history table based on the SAF will be presented by Chinese status and the listing will be repeated for subjects enrolled in mainland China.

Information on prior anti-cancer drug therapy are collected on the "Prior Anti-Cancer Drug Therapies" eCRF page and coded using WHO-DD (latest version at the time of database lock for each analysis; will be specified in outputs).

Summaries and listings will be presented for the following:

- Any prior anti-cancer drug therapy (yes/ no)
- Number of prior anti-cancer drug therapy lines for metastatic (IV) disease
- Number of prior anti-cancer drug therapy lines for advanced (IIIb/IIIc) disease
- Prior anti-cancer drug therapies
- Prior anti-cancer drug combinations
- Type of prior anti-cancer drug therapies

- Intent of prior anti-cancer drug therapies
- Best Response for first prior anti-cancer drug therapy
- Criteria used for Best Response for first prior anti-cancer drug therapy
- Longest duration of response (DOR) in months for first prior anti-cancer drug therapy
- Longest progression free survival (PFS) in months for first prior anti-cancer drug therapy
- Best Response for second prior anti-cancer drug therapy
- Criteria used for Best Response for second prior anti-cancer drug therapy
- Longest DOR (months) for second anti-cancer drug therapy
- Longest PFS (months) for second anti-cancer drug therapy
- Best Response across all prior anti-cancer drug therapies
- Criteria used for Best Response for all prior anti-cancer drug therapy
- Longest DOR (months) across all prior anti-cancer drug therapies
- Longest PFS (months) across all prior anti-cancer drug therapies
- Best Response for most recent anti-cancer drug therapy prior to first administration of study treatment
- Criteria used for Best Response for most recent anti-cancer drug therapy prior to first administration of study treatment
- Longest DOR (months) for most recent anti-cancer drug therapy prior to first administration of study treatment
- Longest PFS (months) for most recent anti-cancer drug therapy prior to first administration of study treatment
- Best Response across all prior immunotherapies
- Criteria used for Best Response for prior immunotherapy
- Longest DOR (months) across all prior immunotherapies
- Longest PFS (months) across all prior immunotherapies
- Best Response across all prior platinum-based chemotherapy for metastatic disease
- Criteria used for Best Response for prior platinum-based chemotherapy for metastatic disease
- Longest DOR (months) across all prior platinum-based chemotherapy for metastatic disease
- Longest PFS (months) across all prior platinum-based chemotherapy for metastatic disease
- Duration of therapy across all different prior anti-cancer drug therapy regimens (months)
    - Duration for each prior anti-cancer drug therapy regimen recorded = (Date of end of prior anti-cancer therapy - Date of start of anti-cancer therapy + 1) / 30.4375

- In case of multiple drugs are given within the same regimen then the earliest start and the latest end dates will be considered, respectively. If for some drugs within a regimen the dates are missing, they are not taken into account in the calculation.
- The following rules will be adopted to impute missing start or end dates:
    1. In case of partial start date with missing day, it will be imputed as the first day of the month.
    2. In case of partial end date with missing day, it will be imputed as the last day of the month or the day before the first dose of study treatment, whichever comes first.
    3. For both start and stop dates, if the month is missing or the date is completely missing, then no imputation will be done and the duration will be considered missing.
- Duration is summarized by regimen number (i.e. first prior anti-cancer drug therapy second anti-cancer drug therapy and so on).

In the table presenting the information above, the focus will be on prior anti-cancer therapies for advanced/metastatic disease. Another table will be produced presenting only the number of subjects who received prior anti-cancer drug therapy for non-advanced disease as well as a summary for these drug therapies and drug combinations.

In addition, a table summarizing the details below across all prior cytotoxic therapies and specific prior anti-cancer therapies of interest (at least Pembrolizumab, Nivolumab and Atezolizumab) will be created:

- Best Response
- Criteria used for Best Response
- Longest DOR (months)
- Longest PFS (months)

An additional similar table will present the following prior anti-cancer therapies of interest:

- All prior Immunotherapy in combination with Platinum-based Chemotherapy for Metastatic Disease
- Prior Immunotherapy in combination with Platinum-based Chemotherapy for Metastatic Disease as first prior anti-cancer drug therapy
- Prior Immunotherapy in combination with Platinum-based Chemotherapy for Metastatic Disease as second prior anti-cancer drug therapy
- All prior Immunotherapies as Monotherapy
- Prior Immunotherapy as Monotherapy as first prior anti-cancer drug therapy
- Prior Immunotherapy as Monotherapy as second prior anti-cancer drug therapy

- All prior Platinum-based Chemotherapy for Metastatic Disease without Concurrent Immunotherapy
- Prior Platinum-based Chemotherapy for Metastatic Disease without Concurrent Immunotherapy as first prior anti-cancer drug therapy
- Prior Platinum-based Chemotherapy for Metastatic Disease without Concurrent Immunotherapy as second prior anti-cancer drug therapy

Information on prior anti-cancer radiotherapy collected on the "Prior Anti-Cancer Radiotherapy Details" eCRF page at the screening visit will be presented.

Summaries and listings will be presented for the following:

- Any prior anti-cancer drug radiotherapy (yes/ no)
- Number of prior anti-cancer radiotherapy lines
- Best Response across all prior anti-cancer radiotherapy lines
- Criteria used for Best Response of prior anti-cancer radiotherapy
- Longest DOR (months) across all prior anti-cancer radiotherapy lines
- Longest PFS (months) across all prior anti-cancer radiotherapy lines

Information on prior anti-cancer surgeries collected on the "Prior Anti-Cancer Surgeries Details" eCRF page at the screening visit will be presented.

Summaries and listings will be presented for the following:

- Any prior anti-cancer surgery (yes/ no)
- Number of anti-cancer surgeries
- Prior anti-cancer surgeries (MedDRA - latest version at the time of database lock for each analysis; will be specified in outputs)
- The surgery was curative in intent (yes/ no)
- Best outcome across all prior anti-cancer surgeries

In addition, except the anti-cancer drug therapies of interest, the summary tables based on the SAF analysis set will be presented by Chinese status and the listings will be repeated on subjects enrolled in mainland China.

11.3 Nicotine Consumption

Nicotine consumption will be summarized from the "Nicotine Consumption" eCRF page. Summary statistics will be presented for the following categories by cohort, overall, by line of therapy, by Chinese status and by prior platinum-based chemotherapy:

- Nicotine use status (Never used/Regular user/Occasional user/ Former user)
- For occasional, former and regular users:

- Number of cigarettes, cigars, pipes, chewing tobacco used (per week)
- Duration of consumption (years)

If number of cigarettes, cigars, pipes and chewing tobacco used is recorded in days, then to convert to weeks the result will be multiplied by 7.

Duration of consumption (years) will be calculated as follows: Month and year of ending – Month and year of starting.

In case of missing month, it will be imputed as follows:

- Missing month of starting will be imputed as January.
- Missing month of ending will be imputed as December.

In the case the end date is missing completely (they are still smoking), then end date will be imputed by the main informed consent date.

A subject data listing will also be provided for nicotine consumption. This listing will be provided both on the full SAF analysis set and on subjects enrolled in mainland China.

11.4 Other Baseline Characteristics

Information on disease history collected on the "Disease History" eCRF page at the screening visit will be presented. Summaries will be presented by cohort, overall, by line of therapy and by prior platinum-based chemotherapy, for the following:

- Site of Primary Tumor by International Classification of Diseases for Oncology (ICD-O) – codes will be translated into text for presentation in outputs
- Time since initial cancer diagnosis (years) = (date of informed consent for pre-screening/screening – date of initial cancer diagnosis+1) / 365.25.
- Histopathological Classification: Squamous, Adenocarcinoma, Large cell, Adenosquamous, Sarcomatoid, Other
- Grading: Well differentiated, Moderately differentiated, Poorly differentiated, Undifferentiated
- Stage at initial diagnosis
- Stage at study entry

The summary of disease history will be repeated by line of therapy and by Chinese status.

Incomplete dates for disease history (initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis) will be imputed as follows:

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Information on the baseline tumor assessment collected on the "Tumor assessment" eCRF page will be presented. Summaries and listings will be presented for the following:

- Target Lesions
  - Number of target lesions (both investigator and IRC)
  - Tumour load of target lesions, i.e. sum of longest diameters for non-nodal lesions, short axis for nodal lesions (both investigator and IRC)
  - Type (Primary / recurrence, Node, Metastasis) (investigator only)
  - Site (both investigator and IRC)
- Non-Target Lesions
  - Non-target lesions (Yes/No) (both investigator and IRC)
  - Number of non-target lesions (both investigator and IRC)
  - Type (Primary / recurrence, Node, Metastasis) (investigator only)
  - Site (both investigator and IRC)

The following baseline characteristics will be summarized by cohort and overall, for this study:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BSA (m^2) at Baseline (Screening)
- ECOG performance status at baseline (in addition, ECOG will be summarized by line of therapy, by prior platinum-based chemotherapy and by Chinese status as well).

Chest X-ray results at screening will only be listed for all subjects in the SAF analysis set and separately for subjects enrolled in mainland China.

Presentations of the following baseline characteristics are detailed as follows:

- Patient reported outcomes (Section 14.3.1)
- Biomarkers (Section 14.3.5)
- Laboratory parameters (hematology/biochemistry/coagulation/urinalysis) (Section 15.3)
- Other Vital Signs (Section 15.4)
- ECG (Section 15.5)

12 Previous or Concomitant Medications/Procedures

Analysis on previous and concomitant medications and procedures will be based on the SAF analysis set.

Analysis on anti-cancer treatments following study treatment discontinuation (i.e. drug therapies, radiotherapy and surgeries) will be based on the SAF analysis set.

Concomitant treatments are medications, other than trial treatment, which are taken by subjects any time whilst on-treatment.

Concomitant treatment will be summarized from the "Concomitant medications" eCRF. ATC-2nd level and preferred term from the WHO-DD dictionary (latest version at the time of database lock for each analysis; will be specified in outputs) will be tabulated. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.

Concomitant medications based on the SAF analysis set will also be reported by Chinese status.

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

Previous medications will be summarized from the "Concomitant medications" eCRF page. ATC-2nd level and preferred term from the most recent WHO-DD dictionary at the time of the relevant data cut-off will be tabulated and sorted by decreasing frequency. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting.

In the case the date values will not allow to unequivocally allocate a medication to either concomitant or previous medication the medication will be considered as both a concomitant medication and previous medication.

Previous medications based on the SAF analysis set will also be reported by Chinese status.

Any medication recorded on the "Concomitant medications" eCRF will be listed with an indication of whether the medication was previous or concomitant.

The corresponding listings will also be produced for subjects enrolled in mainland China.

All **concomitant procedures**, defined as those undertaken any time whilst on-treatment, will be summarized from the eCRF page "Concomitant Procedures". Concomitant procedures will be classified by medical review.

Anti-cancer post-treatment

Information on anti-cancer drug therapies following discontinuation of treatment collected on the "Anti-Cancer Treatment after Discontinuation" eCRF page will be presented. In addition, concomitant medication will be checked for post-therapies by medical review. Treatments will be categorized by means of coding and medical review as per the WHO-DD dictionary version (latest version at the time of database lock for each analysis; will be specified in outputs). Summaries and listings will be presented for the following:

- Any anti-cancer drug therapy after discontinuation of study treatment (yes/ no)

- Number of anti-cancer drug therapy lines after discontinuation of study treatment
- Anti-cancer drugs used after discontinuation of study treatment
- Anti-cancer drug combinations used after discontinuation of study treatment
- Type of systemic therapy after discontinuation of study treatment
- Intent of therapy after discontinuation of study treatment
- Best Response across all anti-cancer treatment lines after discontinuation of study treatment
- Criteria used for Best Response of anti-cancer treatment after discontinuation of study treatment
- Longest DOR (months) across all anti-cancer treatment lines after discontinuation of study treatment
- Longest PFS (months) across all anti-cancer treatment lines after discontinuation of study treatment
- Best Response for the first anti-cancer treatment after discontinuation of study treatment
- Criteria used for Best Response for the first anti-cancer treatment after discontinuation of study treatment
- Longest DOR (months) for the first anti-cancer treatment after discontinuation of study treatment
- Longest PFS (months) for the first anti-cancer treatment after discontinuation of study treatment
- Duration of therapy for all anti-cancer drug therapies after discontinuation of study treatment (months)
    - Duration for each regimen of therapy administered after discontinuation of study treatment = (Date of end of anti-cancer therapy - Date of start of anti-cancer therapy + 1) / 30.4375
    - The following rules will be adopted to impute missing start or end dates:
        1. In case of multiple drugs are given within the same regimen then the earliest start and the latest end dates will be considered, respectively. If for some drugs within a regimen the dates are missing, they are not taken into account in the calculation.
        2. The following rules will be adopted to impute missing start or end dates:
            - In case of partial start date with missing day, it will be imputed as the first day of the month or the day after the end of study treatment administration, whichever comes last.
            - In case of partial end date with missing day, it will be imputed as the last day of the month.
            - For both start and stop dates, if the month is missing or the date is completely missing, then no imputation will be done and the duration will be considered missing.

  - Duration is summarized by regimen number (i.e. first regimen after discontinuation of study treatment, second regimen after discontinuation of study treatment and so on).

- Anti-cancer drug therapies of interest after discontinuation of study treatment (for derivation please refer to details reported in Section 8.2):
  - All subsequent Immunotherapies
  - All subsequent Immunotherapies as Monotherapy
  - All subsequent Immunotherapy in combination with Platinum-based Chemotherapy
  - All subsequent Platinum-based Chemotherapy
  - All subsequent Platinum-based Chemotherapy without concurrent immunotherapy
- In addition, MET inhibitors will be summarized overall and separately for each drug, including at least:
    - Tepotinib
    - Capmatinib
    - Crizotinib
    - Cabozantinib
    - BOZITINIB
    - APL-101
    - TPX-0022

The list of MET inhibitors will be finalized before database lock.

In addition, Sankey plots will be presented to visualize flow of anti-cancer drug therapies prior to administration of tepotinib as well as after discontinuation of study treatment. Separate Sankey plots will be provided for

- All
- Treatment naïve (i.e. first-line)
- Pretreated (i.e. second or later line).

For definition of subgroups related to prior anti-cancer drug therapies, eCRF data are reviewed by the IQVIA medical team on an ongoing basis to make sure that the regimen number for all the prior anti-cancer drug therapies administered for non-advanced disease is zero. The following subgroups will be derived:

- Prior anti-cancer drug therapy (for non-metastatic or metastatic disease): subjects with at least one anti-cancer drug therapy either used for advanced/metastatic or non-advanced/non-metastatic disease (i.e. all regimen numbers will be considered);

Only the prior anti-cancer drug therapies with a regimen number greater than zero will be used for the derivation of the following subgroups:

- Line of therapy: number of prior anti-cancer drug therapies administered to each subject for advanced/metastatic disease;
- Line of therapy for metastatic disease: number of prior anti-cancer drug therapies administered for advanced/metastatic disease to each subject with metastatic disease at study entry;
- Prior platinum-based chemotherapy for metastatic disease: subjects with metastatic disease (i.e. stage IV at study entry) treated with "CARBOPLATIN" or "CISPLATIN" for advanced/metastatic disease;
- Immunotherapy and Platinum-based Chemotherapy in Subjects with Prior Platinum-based Chemotherapy for Metastatic Disease (i.e. subjects who were stage IV at study entry and received platinum-based chemotherapy as prior anti-cancer drug therapy);
- Immunotherapy and Platinum-based Chemotherapy in Subjects in the Second or Later Line of Therapy.

Information on anti-cancer radiotherapy after discontinuation of treatment collected on the "Anti-Cancer Radiotherapy after Discontinuation" eCRF page will be presented.

Summaries and listings will be presented for the following:

- Any anti-cancer drug radiotherapy after discontinuation of study treatment (yes/ no)
- Number of anti-cancer radiotherapy lines after discontinuation of study treatment
- Best Response across all anti-cancer radiotherapy lines after discontinuation of study treatment
- Criteria used for Best Response of anti-cancer radiotherapy after discontinuation of study treatment
- Longest DOR (months) across all anti-cancer radiotherapy lines after discontinuation of study treatment
- Longest PFS (months) across all anti-cancer radiotherapy lines after discontinuation of study treatment

Information on anti-cancer surgeries after discontinuation of treatment collected on the "Anti-Cancer Surgeries after Discontinuation" eCRF page will be presented.

Summaries and listings will be presented for the following:

- Any anti-cancer surgery after discontinuation of study treatment (yes/ no)
- Number of anti-cancer surgeries after discontinuation of study treatment

- Anti-cancer surgeries after discontinuation of study treatment (MedDRA - latest version at the time of database lock for each analysis; will be specified in outputs)
- The surgery after discontinuation of study treatment was curative in intent (yes/ no)
- Best outcome of surgery after discontinuation of study treatment
- In addition, the summary tables based on the SAF analysis set will be presented by Chinese status and the listings will be repeated on subjects enrolled in mainland China.

13 Treatment Compliance and Exposure

All dosing calculations and summaries will be based on the "Tepotinib Administration" eCRF form. The date of last drug administration will be taken from the "Tepotinib Termination" eCRF form.

All summaries and listings related to treatment compliance and exposure will be presented by cohort and based on the SAF analysis set.

In addition, within each cohort summaries of treatment compliance and exposure by line of therapy and Chinese status will be presented based on the SAF analysis set. A dose of tepotinib will be regarded as being taken on a particular day if the actual dose of tepotinib *taken* is > 0 mg. Therefore, interruptions, compliance, and dose changes are not taken into account for the calculation of duration of therapy.

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

$$\text{Duration of therapy} = \left(\frac{\text{Date of last dosing day - Date of first dosing day + 1}}{30.4375}\right)$$

The total number of 3-week cycles is defined as the duration of therapy (in weeks) / 3.

The cumulative dose (mg) per subject is the sum of the total doses that the subject received within that period (i.e. total dose administered (mg)).

The dose intensity and the relative dose intensity will be calculated for a 3-week cycle. The dose intensity (mg/3 weeks) is defined as

$$\text{Actual dose intensity (mg/3 weeks)} = \left(\frac{\text{Cumulative dose (mg)}}{\text{Total number of 3 week cycles}}\right)$$

The relative dose intensity is defined as

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{Actual dose intensity}}{\text{Planned dose intensity}}\right) \times 100$$

Where planned dose intensity (mg/3 weeks) = 500 mg * 21 days = 10500 mg

The following will be provided in summaries and listings:

- Duration of therapy (months)
- Total number of 3-week cycles
- Cumulative dose (mg)
- Dose intensity (mg/3 weeks)
- Relative dose intensity (%)

Batch and kit numbers used during the trial by each subject will be listed.

Dose reductions

The minimum dose of the trial treatment taken by a subject will be derived and categorized according to 100mg (20%), 200mg (40%), 250mg (50%), 300mg (60%), 400mg (80%) and 500mg (100%) with percentages compared to the planned 500mg dose. 100mg and 400mg are theoretically possible, but not foreseen according to the protocol and therefore will be presented only if they appear in the data. Dose omissions will not be considered as dose reductions.

The minimum dose level will be summarized with frequency tables as per the categories defined above. The minimum dose level overall will be listed.

The overall number of days on each reduced dose level will be summarized reporting the number of subjects with treatment on that dose level, by overall number of days on that dose level (1-2 days, 3-7 days, 8-14 days, 15-21 days, 22-42 days, 43-63 days, 64-84 days, >84 days).

Treatment delays

Any delay of tepotinib treatment where the number of days between successive administrations is greater than or equal to 2 days will be identified for each subject. Delays will only be calculated for subjects with at least 2 administrations of tepotinib.

The following will be summarized:

- The number of subjects with treatment delay of tepotinib, by the length of maximum consecutive delay (1-2 days, 3-7 days, 8-14 days, 15-21 days, >21 days).
- The number of subjects with each reason for treatment delay (toxicity and/or other reasons as recorded)

14 Endpoint Evaluation

14.1 Primary Endpoint Analyses

14.1.1 Primary analyses of objective response (based on independent review)

The primary endpoint is objective response (confirmed complete response [CR] or partial response [PR]) determined according to RECIST Version 1.1, based on independent review (IRC).

Subjects are identified as having an objective response if they achieve either a confirmed CR or PR from first administration of trial treatment to first observation of progressive disease (PD). Confirmation needs to take place by a tumor assessment at least 4 weeks (28 days) after the tumor assessments initially indicating CR or PR, as follows:

First post-baseline tumor assessment of CR or PR	Best subsequent tumor assessment at least 4 weeks after the first post-baseline tumor assessment of CR or PR	Objective response
CR	CR	Yes
PR	CR or PR*	Yes
CR or PR	PD	No
None	N/A	No

*After the first post-baseline assessment of CR/PR, a subject may have fluctuations in target lesion assessment, but as long as they have a subsequent assessment showing response at least 4 weeks after the initial assessment without an assessment of progressive disease, this would qualify as an objective response. For instance, if a subject has PR-SD-PR or PR-NE-PR at consecutive tumor assessments, the objective response would qualify for PR.

For all cohorts the primary analysis of the primary endpoint will be based on the SAF analysis set.

While enrolment into the study is ongoing, analysis of objective response will be conducted based on all subjects enrolled, as well as all subjects having at least 2 post-baseline assessments or who discontinued treatment for any reason. The latter analysis has been introduced for evaluation while the trial is ongoing, since 2 post-baseline assessments are required to identify a confirmed response.

For an analysis based on the cut-off 01 February 2021, efficacy outputs including all subjects with first dose before 1st November 2020 will be provided.

No formal statistical hypotheses will be tested. The number of subjects achieving objective response and the ORR (based on independent review) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.

For the purpose of evaluating futility (see Section 6.1), the results from ITT population will be used.

A spider plot will show the subject profiles of the tumor load of target lesions (sum of longest diameters for non-nodal lesions, short axis for nodal lesions) over time (presenting all subjects on the same graph). Different line patterns will distinguish time on and off-treatment. This plot will also be presented by Chinese status.

Finally, a waterfall plot will show the change in sum of target lesion diameters between baseline and the best post-baseline assessment for each subject. Different colours will illustrate the Best Overall Response (BOR). This plot will also be presented by Chinese status.

Listings of cytological or histological assessments for IRC and neurological assessments will be produced on the SAF analysis set and for subjects enrolled in mainland China.

14.1.2 Sensitivity Analyses of Objective Response

In order to explore the impact of the method for determining MetEx14 status on objective response, the primary endpoint analysis will be repeated on the different ITT analysis sets listed in section 8.2 as a sensitivity analysis.

A further sensitivity analysis will be conducted both on the SAF analysis set in which the start of any other anti-cancer drug treatment, surgery or radiotherapy prior to study discontinuation will be considered as PD, and any subsequent tumor assessments will not be considered in the objective response assessment. If only partial dates are known for the start of other anti-cancer treatment or procedures, then the earliest possible date (based on partial date entered) up to the date of last dose of trial treatment will be used.

14.1.3 Subgroup Analyses of Objective Response

BOR details and ORRs (based on independent review and investigator assessment) and corresponding 2-sided exact Clopper-Pearson 95% CIs will be presented within each of the identified subgroups as defined in Section 8.2.

In addition to the presentation in summary tables, forest plots will be created to graphically present ORR and corresponding 95% CIs. A forest plot of objective response based on IRC will also be presented based on SAF analysis set by Chinese status.

14.2 Secondary Endpoint Analyses

Unless otherwise stated, all secondary endpoints analyses will be performed by cohort using the primary analysis set as defined in Section 8.2.

Within each cohort, secondary endpoint analyses by line of therapy, prior platinum-based chemotherapy for metastatic disease, Chinese and Japanese status will also be presented.

For imputing missing parts of tumor assessment dates, the missing day in a date will be imputed as the 15th of the month, if month and year is documented. If the imputation is earlier than the date of start of treatment, the day of start of treatment will be taken. In all other cases missing or incomplete dates will not be imputed.

For imputing missing day of death date, if month and year is available, the day will be imputed by 15th, unless this results in a date earlier than the last date the subject is known to be alive. In that case the date of death will be imputed by the last date known to be alive + 1 day.

Listings of tumor imaging and tumor assessments will be provided. In addition, all the information to define the following endpoints, according to IRC and investigator (when applicable), will be listed:

- Duration of response (DOR)
- Progression free survival (PFS)

- Overall survival (OS)

14.2.1 Objective response (based on investigator assessment)

Objective response (based on Investigator assessment) will be derived and analyzed identically to the primary endpoint apart from the use of the investigator's evaluation rather than that of the IRC.

The independent review and investigator assessments of best overall response will be presented as cross-tabulations to show concordance between evaluations by cohort and for each analysis set as defined in Section 8.2.

14.2.2 Duration of response

This endpoint will be assessed using both the IRC results and the investigator assessment.

The DOR will only be evaluated in subjects that have an objective response (as defined in Section 14.1.1).

DOR is the time from when the CR/PR (whichever is first) criteria are first met until PD or death due to any cause within 84 days of the last evaluable tumor assessment, whichever occurs first (see Eisenhauer et al., 2009).

DOR data will be censored on the date of the last evaluable tumor assessment for subjects who do not have an event (PD or death) or for subjects with an event more than 84 days after the last evaluable tumor assessment.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics (median duration of response and 3-, 6-, 9-, 12-, 15-, 18-month disease progression rate estimates and estimates for every 3 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 the 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.

Categorical summaries of DOR features will be presented for the following items:

- Duration of response (≥ 6 months, ≥ 9 months, ≥ 12 months)
- Follow up among responders (≥ 6 months follow-up from onset of response/event or discontinued treatment < 6 months after onset of response, ongoing response with < 6 months duration)
- Follow up among responders (≥ 12 months follow-up from onset of response/event or discontinued treatment < 12 months after onset of response, ongoing response with < 12 months duration)

These summaries based on IRC and the SAF analysis set will be presented by Chinese status as well.

In addition, onset of response will be summarized on the overall population and on selected subgroups of interest, based on the following categories:

- At first tumor assessment
- At second tumor assessment
- After second tumor assessment

Time to and duration of response will be plotted using a swimmer plot for every subject by line of therapy, by use of prior platinum-based chemotherapy for metastatic disease, by Chinese and by Japanese status.

Additional Kaplan-Meier plots of DOR stratified by baseline subgroups identified in Section 8.2 will be provided. Also, the Kaplan-Meier estimates analysis described above will be repeated for all subgroups.

Every duration of response tables, including the DOR stratified by baseline subgroups, will be repeated using the results based on investigator assessments.

Time of Follow-Up (Duration of response)

In order to assess duration of follow-up for duration of response, 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
Neither progressed nor died		Event	Date of last tumor assessment with outcome CR, PR or SD
Progressed or died	Within 84 days after last response assessment of CR, PR or SD	Censored	Minimum (Date of PD, Date of death)
	Otherwise	Event	Date of last tumor assessment with outcome CR, PR or SD

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for duration of response (for both IRC and investigator results, by cohort, by Chinese status on the SAF analysis set and using the different ITT analysis sets as described in Section 8.2).

14.2.3 Objective disease control and best overall response

This endpoint will be assessed using both the IRC results and the Investigator assessment.

Subjects are identified as having objective disease control if they achieve either a confirmed CR or PR (as defined in Section 14.1.1), or stable disease (SD) lasting at least 12 weeks (84 days) without prior progressive disease.

The objective disease control rate and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.

The frequency and percentages of subjects achieving each level of BOR across the study will be presented. BOR will be derived in accordance with Eisenhauer et al., 2009 when confirmation of CR/PR is required. Each subject will be assessed down the list of scenarios of BOR until one is met and will be assigned that BOR. The table below shows the possible scenarios and their resulting objective response and best overall response:

Overall response First time point	Overall response Subsequent time point (4 weeks after first time point)	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE[b]	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD provided minimum criteria for SD duration met, otherwise NE
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE[b]	SD provided minimum criteria for SD duration met, otherwise NE
SD	PD	SD provided minimum criteria for SD duration met, otherwise PD
SD	NE[b]	SD provided minimum criteria for SD duration met, otherwise NE
PD	Any	PD
NE[b]	NE[b]	NE

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

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

[b] NE refers to a tumor assessment overall response of NE or where a tumor assessment is not available

The analyses will be repeated using the different ITT analysis sets listed in Section 8.2.

14.2.4 Progression free Survival

This endpoint will be assessed using both the IRC results and the Investigator assessment, by cohort.

PFS time is defined as the time (in months) from the first administration of trial treatment to the date of the first documentation of PD or death due to any cause within 84 days of the last evaluable tumor assessment, whichever occurs first. The PFS data will be censored on the date of the last evaluable tumor assessment for subjects who do not have an event (PD or death) or for subjects with an event more than 84 days after the last evaluable tumor assessment. Subjects who do not have an evaluable post-baseline tumor assessment will be censored at the date of the start of trial treatment unless death occurred within 84 days of the first dose of trial treatment in which case the death will be considered an event.

The date of event/censoring for PFS is defined as follows:

Status		Censoring	Date of event / censoring
Progressed or died	Within 84 days after last response assessment of CR, PR or SD or start of treatment	Event	Minimum (Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of start of treatment, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD or date of start of treatment, whatever is later

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics (median progression free survival time, 3, 6, 9, 12, 15 and 18-month progression free survival rate estimates and estimates for every 3 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.

Additional Kaplan-Meier plots of PFS stratified by baseline subgroups identified in Section 8.2 will be provided. Also, the Kaplan-Meier estimates analysis described above will be repeated for all subgroups.

The above analyses for PFS will be repeated for the different ITT analysis sets (for IRC results only) listed in Section 8.2.

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

The independent review and investigator assessments of PFS will be presented as cross-tabulations to show concordance between evaluations by cohort.

In addition, a sensitivity analysis considering the start of any other anti-cancer treatment as PD will be presented (see Section 14.1.2) on the SAF analysis set. For subjects treated with prior immunotherapy, in order to visually present PFS reached under this treatment and PFS reached under tepotinib treatment, a tornado plot will be created. For both treatments, the relevant line of therapy and BOR will be reported on the plot. In addition, tepotinib treatment ongoing at time of the analysis will be visually identified using an arrow.

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
Neither progressed nor died		Event	Date of last tumor assessment with outcome CR, PR or SD or date of start of treatment, whatever is later
Progressed or died	Within 84 days after last response assessment of CR, PR or SD or start of treatment	Censored	Minimum (Date of PD, Date of death)
	Otherwise	Event	Date of last tumor assessment with outcome CR, PR or SD or date of start of treatment, whatever is later

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for progression-free survival (for both IRC and investigator results, by cohort, by Chinese status on SAF analysis set and using the different ITT analysis sets as described in Section 8.2).

14.2.5 Overall Survival

Overall survival (OS) time will be measured as the time (in months) from first trial treatment administration to the date of death. For subjects not known to be deceased at time of analysis, OS time will be censored at the last date the subject was known to be alive.

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

Survival Status	Source	Censoring	Date of event/censoring
Died	Death eCRF	Event	Date of death
Alive (no date of death)	See below	Censored	Last date known to be alive

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

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of procedures and therapies administered during and after study treatment discontinuation.
- AE start and end dates
- Last known alive date collected on the 'Subject status/Survival follow-up' eCRF
- Study drug start and end dates

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics (median survival time, 3, 6, 9, 12, 15 and 18-month survival rate estimates and estimates for every 3 months thereafter as applicable) including the corresponding two-sided 95% confidence intervals, by cohorts. 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.

Additional Kaplan-Meier plots of OS stratified by baseline subgroups identified in Section 8.2 will be provided. Also, the Kaplan-Meier estimates analysis described above will be repeated for all subgroups.

The above analyses for OS (excluding subgroup analyses) will be repeated for the different ITT analysis sets defined in Section 8.2.

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 is defined as follows:

Survival Status	Source	Censoring	Date of event/censoring
Died	Death eCRF	Censored	Date of death
Alive (no date of death)	See above for 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, as well as by Chinese status on SAF analysis set.

14.3 Other Endpoint Analyses

14.3.1 Analysis of Patient Reported Outcomes

All PRO analyses will be performed using the SAF analysis set, by cohort using the primary analysis sets as defined in Section 8.2.

In case no time of collection is available, questionnaires collected on Cycle 1 Day 1 will be considered Predose for baseline definition. Additionally, questionnaires collected at EOT visit or at 30-day safety follow up visit will be pooled together, since in clinical practice only one out of two is usually completed. In the event both are completed, the earlier will be considered for descriptive summaries.

Questionnaire Completion and Compliance

For each questionnaire and scheduled visit, the following will be summarized:

- Number and percentage of subjects with expected questionnaire.
- Questionnaire completion: Number and percentage of subjects who completed the questionnaire, i.e. answered all the items of the questionnaire. Percentages will be calculated as:

$$\%\ Questionnaire\ Completion = 100 \times \frac{number\ of\ subjects\ with\ all\ questionnaire\ items\ available}{number\ of\ subjects\ for\ whom\ the\ questionnaire\ is\ expected}$$

- Number and percentage of subjects who did not complete the questionnaire, by reason for not non-completion.
- Questionnaire compliance: Number and percentage of subjects with an evaluable questionnaire, i.e. scores for each dimension/domain in the questionnaire can be calculated.

$$\%\ Compliance = 100 \times \frac{number\ of\ subjects\ with\ \ evaluable\ questionnaire}{number\ of\ subjects\ for\ whom\ the\ questionnaire\ is\ expected}$$

Of note, the number of subjects with expected questionnaire (i.e. who would have been expected to complete the questionnaire), according to the protocol schedule of assessments, will be used as denominator for all percentages.

EQ-5D-5L

The EQ-5D-5L consists of 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression), scored from 1 = best to 5 = worst. The health state will consist of a 5 digit reference constructed using the five respective scores ordered as above. Missing data will be classed as 9 in the health state. Each health state will be mapped to a country-specific index value and will be part of the health economic evaluation, and not reported as part of the CSR.

Baseline, post-baseline and change from baseline values of the overall health status (EQ VAS score) will be summarized at each time point and visually presented using box and whiskers plot. Only visits available for more than 10 patients will be included in tables and plots.

For each participant, EQ-5D-5L dimension scores, health state index value and overall health status over time will be listed. The listing will also be produced for subjects enrolled in mainland China.

EORTC QLQ-C30 (Version 3.0)

Each of the 15 component scores will be derived as the mean of all items within that component standardized to a 0 to 100 scale as described below for the specific sub-dimension that the component belongs to. If more than 50% of the items within a component are missing then the score will be set to missing, otherwise the mean of non-missing items will be calculated.

	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:

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

Then for **Functional scales**:

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

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

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

Baseline, post-baseline and change from baseline values in global health status, functioning and symptom scores will be summarized at each time point and visually presented using box and whiskers plot. Only visits available for more than 10 patients will be included in tables and plots.

Listings of each subject's sub-dimension scores over time will be provided. The listing will also be produced for subjects enrolled in mainland China.

EORTC QLQ-LC13

The dyspnea sub-dimension (items 3, 4 and 5) score, the cough sub-dimension (item 1) score and the chest pain sub-dimension (item 10) score will be calculated using the same methodology as for sub-dimensions in the EORTC QLQ-C30, however, if any single item is missing, the sub-dimension score will be set to missing.

Scale name	Scale	Number of items	Item range*	QLQ-LC13 Item numbers	†
Symptom scales / items					
Dyspnoea†	LCDY	3†	3	3,4,5	X
Coughing	LCCO	1	3	1	
Haemoptysis	LCHA	1	3	2	
Sore mouth	LCSM	1	3	6	
Dysphagia	LCDS	1	3	7	
Peripheral neuropathy	LCPN	1	3	8	
Alopecia	LCHR	1	3	9	
Pain in chest	LCPC	1	3	10	
Pain in arm or shoulder	LCPA	1	3	11	
Pain in other parts	LCPO	1	3	12	

* "Item range" is the difference between the possible maximum and the minimum response to individual items.

† The dyspnoea scale should only be used if all three items have been answered. Some respondents ignore question 5 because they never climb stairs; in this case, the score for the dyspnoea scale would be biased if it were based upon the other two items. Hence if item 5 is missing then items 3 and 4 should be used as single-item measures.

Baseline, post-baseline and change from baseline values in each sub-dimension will be summarized at each time point and visually presented using box and whiskers plot. Only visits available for more than 10 patients will be included in tables and plots.

Listings of each subject's dyspnea and cough sub-dimension scores over time will be provided. The listing will also be produced for subjects enrolled in mainland China.

Longitudinal analysis of change from baseline

A mixed-effect model repeated measures (MMRM) analysis will evaluate longitudinal change from baseline for the SAF analysis set, by cohort using the primary analysis sets as defined in Section 8.2. The following PRO scores will be analyzed:

- Dyspnea (EORTC QLQ-LC13; item 3, 4 and 5),
- Cough (EORTC QLQ-LC 13; item 1)
- Chest Pain (EORTC QLQ-LC 13; item 10)

A distinct MMRM model for each analysis set (LBx+, TBx+ and combined LBx and/or TBx) will be run for each Cohort. It will include change from baseline as dependent variable and patient, analysis visit (as defined in Section 9), baseline PRO score as a covariate and baseline PRO score

by analysis visit interaction to account for a non-constant baseline effect across visits. Following an ITT approach off-treatment assessments will be included in the analysis. To investigate the effect of treatment on PRO values while on-treatment, a separate sensitivity analysis including only on-treatment results will be conducted.

An unstructured covariance matrix will be used to model the within-subject error. In case the fit fails to converge, an alternative, simpler covariance structure (i.e. variance components) will be employed to meet convergence criteria. The model will use restricted maximum likelihood (REML) to provide an overall adjusted mean estimate that will estimate the average treatment effect over visits giving each visit equal weight. The Kenward-Roger approximation will be used to estimate the degrees of freedom. No p-values will be presented.

Least square (LS) means estimates and corresponding 95% CIs will be presented overall, to provide an estimate of the treatment effect across visits, and at day 84 (week 12 i.e. Cycle 5 Day 1), day 168 (week 24 i.e. Cycle 9 Day 1), day 252 (week 36 i.e. Cycle 13 Day 1), day 336 (week 48 i.e. Cycle 17 Day 1), day 420 (week 60 i.e. Cycle 21 Day 1) and every 12 weeks thereafter. Additionally, a linear plot presenting LS means estimated by the model will be produced.

Time to deterioration (TTD) analysis

TTD analysis will be performed for the Dyspnea, Cough and Chest Pain QLQ-LC13 scores, QLQ-C30 global health state and EQ-5D-5L VAS.

The data collected at both scheduled and unscheduled visits will be included in the TTD analysis.

TTD is defined as the time between first dose and the first occurrence of a meaningful deterioration compared to the baseline score. For each PRO score a meaningful deterioration is defined as a change equivalent to or greater than the Minimum Important Difference (MID):

- QLQ-C30 global health score (GHS): decrease of 10 normalized score points (i.e. change from baseline < -10)
- EQ-5D-5L VAS: decrease of 10 score points (i.e. change from baseline < -10)
- QLQ-LC13 Composite endpoints - QLQ-LC13 symptom scales cough, chest pain, and dyspnea: increase of 10 score points (i.e. change from baseline > 10)

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics (median deterioration free survival time, 3, 6, 9, and 12-month deterioration free survival rate estimates and estimates for every 3 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 below table will be summarized, by cohort.

The date of event / censoring for PRO deterioration events is defined as follows:

Status	Censoring	Date of event / censoring
Deterioration in PRO score	Event	First Date of PRO deterioration
Death or no PRO deterioration	Censored	Date of last PRO assessment or date of start of treatment, whatever is later

14.3.2 Analysis on ECOG Performance Status

ECOG Performance Status will be summarized using shift tables showing baseline versus post-treatment values at each time point, by cohort on the SAF analysis set

Listings of each subject's ECOG Performance Status over time will be provided. The listing will also be produced for subjects enrolled in mainland China.

14.3.3 Analysis of Pharmacokinetic Endpoints

Tepotinib and metabolites (MSC2571109A and MSC2571107A) concentrations in plasma will be listed and presented in tables, and descriptively summarized by cohort, cycle/day, and scheduled time point. For descriptive statistics of concentration data, values below the lower limit of quantification (LLOQ) will be assigned a concentration of zero.

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

PK as well as corresponding exposure and clinical data will be reviewed prior to the analysis. Important events that might have an effect on the PK evaluation may lead to exclusion of individual concentration assessments from the analysis. Such events include, but may not be limited to, the following:

- Adverse events, diarrhea etc. (these instances will be discussed on a case-by case basis)
- Vomiting that occurs soon after oral dosing (these instances will be discussed in alignment with applicable regulatory guidelines on a case-by case basis)
- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g. dose administration delayed, dose change or missed doses)
- Pre-dose sample collected after the actual start of dosing
- Incomplete meal consumption prior to dosing

- Concomitant medication violations

Should one or more of these events be identified its implication for PK evaluation will be discussed with the sponsor. This may lead to exclusion of individual concentration assessments from the analysis. Such decisions need to be agreed amongst relevant trial team members and documented accordingly. A flag indicating the respective observations will be included in the corresponding listing.

14.3.4 Population Pharmacokinetic Analysis

Sparse sampled PK of tepotinib from study EMR 200095-022 will be analyzed jointly with data from study 001, 002, 003, 006 (phase Ib), 007 and other emergent studies with evaluable PK data by non-linear mixed effect approach. The plasma concentration time profiles after single or multiple dose administration of tepotinib 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 will be given in a separate Data Analysis Plan for Population Pharmacokinetic Analysis. The results will be reported separately.

14.3.5 Analysis of Molecular Marker

Tumor samples

Categorical biomarkers collected from the pre-screening Tumor biopsy will be summarized for the biomarker-tumor analysis set. Note that all analyses involving the Tumor biopsy will dependent on the availability.

The categorical Tumor biomarkers to be analyzed are:

- MET and oncogene mutations by NGS (+, -)

For each biomarker above, the following will be presented within each category:

- Number and percentage of subjects with objective response (as defined in Section 14.1.1)
- Kaplan Meier Plot of DOR, OS and PFS (as defined in Section 14.2.4)

A box-plot of the biomarker values will be provided for those subjects that did and did not achieve Objective Response.

A scatter plot showing the PFS time against the biomarker value will be presented with censored observations flagged appropriately. This will be repeated for overall survival time.

If there are less than 10 patients in any category, then the results will be presented in listings rather than performing the analyses described above.

Plasma samples

Summary statistics will be presented for continuous plasma biomarkers at each time point. In addition, the mean change from baseline in continuous plasma biomarkers will be plotted over time for the biomarker-blood population. A separate profile will be provided such that at each time point the mean is calculated on specific subjects that a) had a response of PD, b) did not have a response of PD and c) overall. Finally, the same analyses described above for the continuous Tumor biomarkers will be performed for the continuous plasma biomarkers at baseline. The continuous plasma biomarkers to be analyzed are:

- HGF by ELISA
- Shredded C-Met by ELISA

The same analyses as described above for the categorical Tumor biomarkers will be performed for MET and oncogene mutations.

In addition to the above, the relationship between the Tumor and plasma biomarkers will be explored as follows:

- MET and oncogene mutations (+, -) in Tumor vs. in plasma at each time point

All biomarker data from both Tumor and blood will be listed.

14.3.6 Pharmacogenetics

Pharmacogenetic data will be listed only (if generated).

14.3.7 Central Nervous System Tumor Response

For all cohorts the analyses of the CNS tumor response will be based on the SAF population.

14.3.7.1 Objective Response

CNS objective response is determined according to Response Assessment in Neuro-Oncology (RANO) criteria (Lin et al., 2015), based on independent review (IRC), only on subjects with baseline CNS metastases, defined as any subject with "BRAIN" as location of target, enhancing non-target or non-enhancing non-target lesion.

Subjects are identified as having an objective response if they achieve either a CR or PR after first administration of trial treatment and before first observation of PD.

The number of subjects achieving objective response and the ORR (based on independent review) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.

A spider plot will show the subject profiles of the sum of longest diameters of target lesions over time (presenting all subjects on the same graph). Different line patterns will distinguish time on and off-treatment.

Finally, a waterfall plot will show the change in sum of target lesion longest diameters between baseline and the best post-baseline assessment for each subject. Different colours will illustrate the Best Overall Response (BOR).

Both plots will also be presented by line of therapy.

BOR details and ORRs (based on IRC) and corresponding 2-sided exact Clopper-Pearson 95% CIs will be presented within each of the identified subgroups as defined in Section 8.2.

14.3.7.2 Objective disease control and best overall response

Subjects are identified as having objective disease control if:

- They had a CNS target lesion at baseline and achieve either a CR, PR or SD without prior PD;
- They had only CNS non-target lesions at baseline and achieve a non-CR/non-PD without prior PD.

The objective disease control rate and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.

The frequency and percentages of subjects achieving each level of BOR across the study will be presented. BOR will be derived in accordance with Lin et al., 2015.

14.3.7.3 Duration of response

The DOR will only be evaluated in subjects that have an objective response (as defined in Section 14.3.7.1).

DOR is the time from when the CR/PR (whichever is first) criteria are first met until PD or death due to any cause within 84 days of the last evaluable tumor assessment, whichever occurs first (see Eisenhauer et al., 2009).

DOR data will be censored on the date of the last evaluable tumor assessment for subjects who do not have an event (PD or death) or for subjects with an event more than 84 days after the last evaluable tumor assessment.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics, as described in Section 14.2.2.

Time to and duration of response will be plotted using a swimmer plot for every subject by line of therapy.

Additional Kaplan-Meier plots of DOR stratified by baseline subgroups identified in Section 8.2 will be provided. Also, the Kaplan-Meier estimates analysis described above will be repeated for all subgroups.

14.3.7.4 Progression free Survival

PFS time is defined as the time (in months) from the first administration of trial treatment to the date of the first documentation of CNS PD or death due to any cause within 84 days of the last evaluable CNS tumor assessment, whichever occurs first. The PFS data will be censored on the date of the last evaluable CNS tumor assessment for subjects who do not have an event (PD or death) or for subjects with an event more than 84 days after the last evaluable CNS tumor assessment. Subjects who do not have an evaluable post-baseline CNS tumor assessment will be censored at the date of the start of trial treatment unless death occurred within 84 days of the first dose of trial treatment in which case the death will be considered an event.

The date of event/censoring for PFS is defined as follows:

Status		Censoring	Date of event / censoring
Progressed or died	Within 84 days after last response assessment of CR, PR, SD or non-CR/non-PD or start of treatment	Event	Minimum (Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR, SD or non-CR/non-PD or date of start of treatment, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR, SD or non-CR/non-PD or date of start of treatment, whatever is later

Kaplan-Meier estimates (product-limit estimates) will be presented as described in Section 14.2.4.

Additional Kaplan-Meier plots of PFS stratified by baseline subgroups identified in Section 8.2 will be provided. Also, the Kaplan-Meier estimates analysis described above will be repeated for all subgroups.

15 Safety Evaluation

All safety analyses will be conducted on the SAF population, by cohort (including pooled Cohort A and Cohort C and overall) using the primary analysis sets as defined in Section 8.2, unless specified otherwise.

15.1 Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version (latest version at the time of database lock for each analysis; will be specified in outputs). Severity of AEs will be graded using the NCI-CTCAE (Version 4.03) toxicity grades. Adverse events related to trial treatment will be defined as any AE considered as related to tepotinib. Missing classifications concerning relationship to trial treatment will be considered related to the trial treatment.

Any treatment emergent AEs (TEAE) will be summarized, i.e., those events that are emergent during treatment having been absent pretreatment or worsen relative to the pretreatment state and with onset dates occurring within the first dosing day of trial treatment until 30 days after the last dose of trial treatment.

Pre-existing conditions continuing on treatment with grade equal or lower than the baseline grade will not be considered treatment emergent adverse events.

Incomplete AE-related dates will be handled as follows:

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

15.1.1 All Adverse Events

Overview of TEAEs will be presented in the SAF analysis set and by Chinese status.

Adverse events will be summarized by worst toxicity grade per subject, for the preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

Unless otherwise stated adverse events will be displayed in terms of frequency tables sorted by primary SOC in alphabetical order and within SOC by PT in decreasing incidence.

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

In case a subject had events with missing and non-missing toxicity grades, the maximum of the non-missing grades will be displayed.

The following overall frequency tables will be prepared. Those marked with a * will also be presented by Chinese status. The tables will be sorted by primary SOC in alphabetical order and within SOC by PT in decreasing order:

- Any TEAEs *
- Any serious TEAEs *

- Any TEAEs related to trial treatment *
- Any serious TEAEs related to trial treatment *
- Any non-serious TEAEs
- Any AE by NCI-CTCAE severity grade (Any, ≥3, ≥4, 5) *
- Any AE related to trial treatment by NCI-CTCAE severity grade (Any, ≥3, ≥4, 5) *
- TEAEs leading to death *
- TEAEs related to trial treatment leading to death *
- TEAEs by baseline subgroups, as identified in Section 8.2

Subject listings of AE details captured on the "Adverse Events" eCRF will be provided with SOC and PT. A listing of AEs will also be produced for subjects enrolled in mainland China.

15.1.2 Adverse Events Leading to Treatment Discontinuation

Overview of TEAEs leading to treatment discontinuation/dose reduction will be presented in the SAF analysis set and by Chinese status.

The following frequency tables, presented by PT and primary SOC in alphabetical order, will be provided overall and by Chinese status:

- TEAEs leading to dose reduction
- Treatment related TEAEs leading to dose reduction
- TEAEs leading to treatment interruptions
- Treatment related TEAEs leading to treatment interruptions
- TEAEs leading to permanent treatment discontinuation
- Treatment related TEAEs leading to permanent treatment discontinuation

TEAEs leading to temporary and permanent discontinuation will be listed separately, on the SAF analysis set and for subjects enrolled in mainland China.

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

15.2.1 Deaths

All deaths, deaths within 30 days after last dose of treatment (i.e. on-treatment), deaths within 60 days after first dose as well as reason for death, will be tabulated based on information from the "Death" eCRF form, overall and by Chinese status.

Any deaths will be provided in individual subject data listings together with selected dosing information (date of first / last administration, days between first dose and death, dose and number

of each dose), flags for death within 30 days of last trial treatment and death within 60 days of first trial treatment, primary reason of death and details of any fatal AEs. The listing will be produced also for subjects enrolled in mainland China.

15.2.2 Serious Adverse Events

Please refer to Section 15.1.1. in addition, for these serious TEAEs; summary tables, related SAEs by worst grade and subject listings will be provided.

The listing on serious TEAEs will also be provided based on subjects enrolled in mainland China.

15.2.3 Other Significant Adverse Event

Adverse events of special interest will be defined as any elevation of serum lipase/amylase ≥ grade 3 and are collected in an expedited manner in the Global Drug Safety database for close monitoring.

The number of subjects with elevation of serum lipase/amylase ≥ grade 3 will be summarized by SOC in alphabetical order and within SOC by PT in decreasing order and reported in a separate listing.

15.3 Clinical Laboratory Evaluation

Treatment emergent laboratory assessments are any sample collected on-treatment, i.e., from the first dosing day of trial treatment until 30 days after the last dose of trial treatment. All laboratory data will be summarized by cohort.

In addition, within each cohort shift tables by Chinese status will be presented.

Laboratory values (including corresponding normal ranges) from the local laboratories will be used for summary statistics and shift tables. Laboratory results will be classified according to the NCI-CTC Version 4.03 by IQVIA Biostatistics. 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 respective local laboratory normal ranges) with the exception of the following parameters:

- Eosinophils and basophils absolute counts: presented as above normal limits and within normal limits only
- Creatinine clearance and blood urea nitrogen: presented as below normal limits and within normal limits only

Derivations for Hematology Parameters

In case only relative differential counts are collected, absolute counts (Basophils, Neutrophils, Eosinophils, Monocytes, Lymphocytes) will be derived as follows:

$$\left(\frac{Relative\ differential\ count}{100}\right) * Absolute\ White\ Blood\ Cells\ count$$

Derivations for Biochemistry Parameters

- Creatinine Clearance (mL/min) will be derived using the Cockcroft-Gault formula and used for summaries as:
  - $\frac{\{[140-age(year)]*weight(kg)\}}{72*serum\ creatinine\ (^{mg}/_{dL})} * [0.85\ for\ female\ subjects]$

    Age at time of the creatinine sample collection will be used. Creatinine clearance values collected in the CRF will only be listed.
- In case only Urea or only Blood Urea Nitrogen is collected for a subject at a specific visit, conversion factors will be programmatically applied. Urea results will only be presented in listings.

The worst on-trial grade (i.e. on or after first trial treatment administration and within 30 days after last trial treatment administration) will be summarized considering only subjects with post baseline laboratory samples, using the following grades: ≥ 0, ≥ 3, ≥ 4.

For summaries by time point the protocol defined visits will be used.

Quantitative data (where applicable) will be examined for trends using actual values and changes from baseline (as defined in Section 9) to each visit over time.

Qualitative data based on reference ranges will be described according to the categories Low, Normal and High (hematology, biochemistry, coagulation and urine pH). For qualitative assessment of additional urinalysis endpoints, the same shift table will be presented using the raw classifications (i.e. Normal, Trace +, ++, +++, ++++). The number of subjects with clinical laboratory values below, within, or above normal ranges at baseline compared to each time point will be tabulated for each test. Shift tables of baseline versus each time point (as well as the worst value at any post-baseline visit) will be presented.

Abnormalities classified according to NCI-CTCAE toxicity grading version 4.03 will be described using the worst grade.

So, summarizing NCI-CTC grades available:

- Number and percentage of subjects with any, NCI-CTC grades ≥ 0, ≥ 3, ≥ 4 laboratory abnormalities under treatment – (worst case)
- Shifts in toxicity grading baseline to highest on-trial

NCI-CTC grades not available:

- Number of subjects with shifts baseline normal to at least one result above normal on-treatment

- Number of subjects with shifts baseline normal to at least one result below normal on-treatment

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

Listings on laboratory data will also be produced for subjects enrolled in mainland China.

Boxplots of the laboratory values by visit and the change from baseline by visit will presented for the laboratory values.

Boxplots for laboratory parameters where toxicity grades are defined based on the ratio of the parameter values and the upper limit of normal (ULN) will not be displayed using the unit of measurement but instead using the ratio of the measured value over ULN. This comprises ALP, ALT, AST, total bilirubin and creatinine.

A plot of peak ALT versus peak total bilirubin, both relative to the upper limit of normal (ULN) will be provided. This eDISH plot (evaluation of drug-induced serious hepatotoxicity) will have reference lines at 3×ULN for ALT and at 2×ULN for total bilirubin.

For all tests not mentioned above but present in the clinical data, a listing with the number of subjects with at least one result for the according test will be provided. Pregnancy test results will only be listed for all subjects in the SAF analysis set and separately for subjects enrolled in mainland China.

15.4 Vital Signs

The maximum change (increase and decrease) in each vital sign measurement from baseline (where baseline is defined in Section 9) across on-treatment visits will be categorized as shown below for each subject.

Body temperature increase <37° C, 37 - <38° C, 38 - <39° C, 39 - <40° C, >=40 ° C,	< 1°C , 1-<2°C , 2-<3°C, ≥ 3 °C
Pulse increase from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Pulse 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

The number and percentage of subjects in each category will be presented as a shift table showing baseline category versus the maximum change. Subjects with missing values for a vital sign at baseline or across all post-treatment visits will be classed as missing in a separate category.

In addition, within each cohort shift tables by Chinese status will be presented.

A subject data listing will present the baseline and maximum changes (increases and decreases) in each vital sign measurement.

Listings of vital signs results will be produced for all subjects, and, separately, for subjects enrolled in mainland China.

15.5 Electrocardiogram (ECG)

Electrocardiogram (ECG) results will be read both centrally (Cycles 1 and 2 by IQVIA Cardiac Services) or locally as per the protocol with no differentiation made in the described analyses below.

Locally read ECG readings will only have one reading. Centrally read ECG readings will be recorded as 12-lead resting ECGs in triplicates. For quantitative parameters and their categorization according to worst result, the average of these 3 results will be taken and used in the summaries/outputs. If any of the 3 results are missing, the average of available results will be used.

QTcF (msec) from local assessments will be derived and used for summaries as:

$$QT \Big/ \sqrt[3]{RR}$$

RR will be converted in sec for QTcF derivation.

ECG will be summarized in two ways; comparing both change in pre-dose ECG over the trial and the change between pre and 4-hours post dose on the same day. The below summaries will be presented for each with baseline defined either as pre first dose of any trial treatment or pre-dose of trial treatment on a particular day as appropriate.

Quantitative ECG assessments and change from baseline at each visit will be summarized for pre and 4-hours post dose on the same day only.

The ECG interpretation (Normal, Abnormal (not clinically significant), Abnormal (clinically significant)) will be presented as a shift table showing baseline versus the worst on-treatment result.

In addition, within each cohort shift tables by Chinese status will be presented.

The change in QTc interval between baseline and the worst (longest) on-treatment result will be summarized in shift tables as follows:

- Categorical shift from baseline to worst on-treatment value for the QTcF:

Parameter	Baseline category	Worst on-treatment value
QTc (Fridericia)	<= 450ms > 450 - <= 480ms > 480 - <= 500ms > 500ms	<=450ms >450 - <=480ms >480 - <=500ms >500ms

- Categorical shift from baseline to worst on-treatment change from baseline for the QTcF:

Parameter	Baseline category	Worst change from baseline
QTc (Fridericia)	<= 450ms > 450 - <= 480ms > 480 - <= 500ms > 500ms	<=0 ms >0 - <=30ms >30 - <=60ms >60ms

Listings of ECG results for all subjects, and, separately, for subjects enrolled in mainland China, will be presented separately with 1) pre-dose values across the trial and 2) pre and 4-hour post dose values at Cycle 1 and 2, day 1 assessments.

Analyses to assess the relationship of tepotinib exposure with QTc interval will be defined in a separate Analysis Plan. The results will be reported separately.

16 References

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17 Appendices

Appendix 1: IDMC Outputs

The outputs that are to be presented for each delivery (including Interim Analysis, IDMC meetings and regulatory deliveries are listed in a separate Excel tracker named "MS200095_0022_List_of_outputs_YYYYMMMDD.

Signature Page for VV-CLIN-280001 v3.0

Approval	PPD PPD -2022 10:20:05 GMT+0000

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