Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS200095-0031
Title	A Phase II, two-arm study to investigate tepotinib combined with osimertinib in MET amplified, advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating EGFR mutations and having acquired resistance to prior osimertinib therapy (INSIGHT 2 Study)
Study Phase	Phase II
Investigational Medicinal Product(s)	Tepotinib in combination with osimertinib
Clinical Study Protocol Version	04 May 2021/Version 3.0
Integrated Analysis Plan Author	**Coordinating Author** PPD
Integrated Analysis Plan Date and Version	04 April 2023/Version 4.0
Integrated Analysis Plan Reviewers	PPD

Approval Page

Integrated Analysis Plan: MS200095-0031

A Phase II, two-arm study to investigate tepotinib combined with osimertinib in MET amplified, advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating EGFR mutations and having acquired resistance to prior osimertinib therapy
(INSIGHT 2 Study)

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within BREEZE via eSignature. With the approval, the Merck responsible for each of the analyses also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

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2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AIC	Akaike Information Criteria
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical classification
AUC_{0-t}	Area Under Concentration-time curve from time zero to the last quantifiable concentration
AUC_{0-12}	Area Under Concentration-time curve from time zero to 12 hours postdose
AUC_{0-24}	Area Under Concentration-time curve from time zero to 24 hours postdose
AUC_{τ}	Area under the concentration-time curve over the dosing interval
BLQ	Below the lower limit of quantification
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
CEP7	Centromere 7
CI	Confidence Interval
CDISC	Clinical Data Interchange Standards Consortium
CIPD	Clinically Important Protocol Deviation
C_{av}	Average concentration at steady state
$C_{L/f}$	Formation Clearance of a drug to a Metabolite
C_{max}	Maximum Concentration
C_{min}	Minimum observed concentration during a complete dosing interval
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
CR	Complete Response
eCRF	electronic Case Report Form
CSR	Clinical Study Report
CV	Coefficient of variation
DLT	Dose Limiting Toxicity

DC	Disease Control
DOR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal Growth Factor Receptor
EGFRm+	Epidermal Growth Factor Receptor mutation positive
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D-5L	EuroQol 5 Dimension 5 Level Scale
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FISH	Fluorescence In Situ Hybridization
FU	Follow-up
GCP	Good Clinical Practice
GeoCV	Geometric Coefficient of Variation
GeoMean	Geometric Mean
HGF	Hepatocyte Growth Factor
HRQOL	Health Related Quality of Life
IAP	Integrated Analysis Plan
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IPD	Important Protocol Deviation
IRC	Independent Review Committee
L+	Positive central MET Amplification test based on liquid biopsy
LBx	Liquid Biopsy
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
$MR_{(AUC)}$	Metabolite to Parent Ratio based on AUC_{τ}
$MR_{(Cmax)}$	Metabolite to Parent Ratio based on C_{max}
MW	Molecular weight
MET	Mesenchymal-Epithelial Transition factor
mFAS	Modified Full Analysis Set

MMRM	Mixed-effect Model Repeated Measurements
NA	Not Applicable
NCA	Noncompartmental
NE	Not Evaluable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease or Protocol Deviation or Pharmacodynamics
PFS	Progression Free Survival
P-gp	P-glycoprotein
PT	Preferred Term
PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PR	Partial Response
PRO	Patient-reported Outcome
PTF	Peak trough fluctuation ratio
Q1	25^{th} percentile
Q3	75^{th} percentile
QOL	Quality of Life
QTcF	Fridericia's formula for corrected QT interval
$R_{acc(AUC)}$	Accumulation Factor for AUC_{τ}
$R_{acc(Cmax)}$	Accumulation Factor for C_{max}
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAF	Safety population
SAQ	Symptom Assessment Questionnaire
SD	Stable Disease
SMC	Safety Monitoring Committee

SOC	System Organ Class
SRIAS	Safety Run-In Analysis Set
StDev	Standard Deviation
T+	Positive central MET amplification test based on tumor tissue biopsy (FISH)
TBILI	Total Bilirubin
TBx	Tumor Tissue Biopsy
TEAE	Treatment Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
t_{lag}	Time prior to the first quantifiable (non-zero) concentration
TLF	Tables, Listings, and Figures
t_{max}	Time of C_{max}
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
$V_{Z/f}$	Apparent volume of distribution during the terminal phase following extravascular administration
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	27 October 2020	PPD	This is the first version.
2.0	12 November 2021	PPD	• List of abbreviations updated. • Removed the “Investigator” from the intracranial response endpoint as per protocol. • Section 6.2 updated to indicate the possibility to have PK data for IDMCs. Some text added to explain additional outputs produced for IDMC1. • Section 7: Sentence about intracranial evaluation being performed only by IRC removed as per protocol. • Section 7.1: Part related to the tele-visits updated to follow the updated Date of Visit eCRF page. Listing and table for COVID-19 vaccinations added. • Section 8.1.2: Specification added that the tables presenting compliance and exposure will not present the overall total column. • Section 8.2: Labels and options for Japanese and Chinese status updated.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			• Section 9.6: Conversion factor for creatinine clearance calculation added. • Section 9.7: Electrocardiogram as assessment.added • Section 9.9: Clarification to AE imputation rules added. • Section 10.1: “Subjects active in screening” added. • Section 10.2: Analysis of the local TBx test updated. • Section 14: Efficacy analysis on subjects at least 90 days from first dose updated update to clarify that they may be produced or not and only while recruitment is still ongoing. Estimands table added. • Section 14.1.1: Listings added for histological/cytological assessments as well as for neurological assessments. • Section 14.2.5: Text for partial dates of subsequent therapy updated. • Section 15.2.1: Text added to better explain how AEs changing in grade are handled and presented. Text for the identification of the AE of Special Interest. • Section 15.4: Details added on how data will be summarized. Derivations added for creatinine clearance and corrected calcium. • Section 15.6.2: Details added on how data will be summarized. Derivation added for QTcF. • Section 16.1.2: Distinction in analysis for final and SMC/DMC meetings specified. • Appendix 1: updated tables for gradable and non-gradable parameters. • Appendix 3 and 4: added.
3.0	13 May 2022	PPD	• List of abbreviations updated. • Section 6.4: Final Analysis may be a rerun of the Primary Analysis. • Section 7 and 8.1: added clarification on the purpose of the mFAS. • Section 7.1: Updated derivation for participants potentially affected by COVID-19 pandemic. • Section 8.1.2: Biomarker analysis and CNS analysis based on RANO-BM criteria added in analysis set table. • Section 8.2: New subgroups added. • Section 9.9: New imputation rules for partial dates added. • Section 10.3.1: Rule of protocol deviation wording and mapping updated. • Section 11.5: New data to be presented added to the prior anti-cancer drug therapy • Section 11.6: Rule on rounding for the presentation of results for nicotine removed.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			• Section 12: Specified how to derive the order for the subsequent anti-cancer drug regimens. Analysis for the subsequent anti-cancer drug regimens duration added. • Section 14: removed sentences for the analyses based on participant who have started study treatment at least 90 days before the cut-off date. Only the general one in Section 14 is kept. Updated text for the intracranial response • Section 14.1.1: Removed "12 weeks" from the derivation of PD in the BOR derivation to keep only 90 days. More details added to describe the spider and waterfall plots. • Section 14.3: Analysis of data based on RANO-BM assessments expanded. • Section 16.3: Analysis for Mean Gene Copy Number and MET/CEP7 ratio added. • Section 17: Reference to the RANO group publication added.
4.0	04 April 2023	PPD	• Sections 6, 6.3, 6.4 (new section): Text added to mention potential additional analyses to support submission activities • Sections 7, 8.1 and 8.1.1: Updates made to indicate how participants enrolled after the completion of global enrollment (i.e., 8th July 2022) will be handled in the modified Full Analysis Set. • Sections 7 and 8.2: Removed analysis for C797X as data will not be available. • Sections 7.1, 8.1.2 and 14: Added supplementary efficacy analysis for treatment discontinuation due to COVID-19. • Section 8.2: Updated subgroup levels for mean gene copy number. • Section 10.1: added prescreened participants under protocol version 2 onwards. • Section 10.2: added analysis for participants enrolled from protocol version 2 onwards. • Section 10.3.1: Added explanation how to handle the new PD categories introduced in May 2022. • Section 11.3: Added "Earlier stage or unknown" as option to the clinical stage at initial diagnosis. • Section 14.1.1: Added spider plot for participants in the monotherapy arm who switched. • Section 14.2.7: Update made to present the change from baseline in the boxplots rather than the actual value. Added the calculation of Cohen's d and the bar chart. • Section 15.4 and Appendix 1: Added new coagulation parameter Activated PTT/Standard Ratio. • Section 16.3: Updates made to reflect data availability.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			• Appendix 5: Appendix added to provide more details for the analysis using mixed-effect model for repeated measurements.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for all the analyses of data collected for protocol MS200095-0031. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR) or in separate reports. Additionally, the planned analyses identified in this IAP may 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 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with International Conference on Harmonization (ICH) E9. It describes analyses planned in the protocol and protocol amendments, with the exception of the population PK analysis, analyses exploring the genetic variations of genes involved in the PK and safety of tepotinib, or that investigate the exposure-response relationship which will be described and reported separately. As analyses for the regular Independent Data Monitoring Committee (IDMC) meetings will be a subset of the full set of tables, listings and figures that will be prepared for the CSR, a separate IDMC IAP will not be produced.

Details on outputs used to support review of the study by a Safety Monitoring Committee (SMC) during the safety run-in period are available in the SMC Charter.

5 Objectives and Endpoints

Safety run-in only

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To confirm a safe and tolerable recommended Phase II dose (RP2D) of tepotinib when used in combination with osimertinib.	Occurrence of dose-limiting toxicities (DLTs) during the first treatment cycle.	15.1

Overall study including safety run-in:

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		

Objectives	Endpoints (Outcome Measures)	IAP section
To assess the efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and Mesenchymal-Epithelial Transition factor (MET) amplification, determined centrally by fluorescence in situ hybridization (FISH).	Objective response (confirmed complete response [CR] or partial response [PR]) determined according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as per Independent Review Committee (IRC).	14.1
Secondary		
To assess the efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification determined centrally by blood-based next generation sequencing.	Objective response (CR or PR) determined according to RECIST Version 1.1 as per IRC.	14.1
To assess the efficacy of tepotinib monotherapy in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification determined centrally by FISH.	Objective response (CR or PR) determined according to RECIST Version 1.1 as per IRC.	14.1
To assess tolerability and safety in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification treated with the combination of tepotinib plus osimertinib.	Occurrence of Adverse Events (AEs) and treatment related AEs. Occurrence of abnormalities (Grade ≥ 3) in laboratory test values (hematology and coagulation, biochemistry) and urinalysis. Occurrence of markedly abnormal vital sign measurements, change in body weight, and Eastern Cooperative Oncology Group (ECOG) performance status. Occurrence of clinically significantly abnormal electrocardiograms (ECGs).	15
To assess tolerability and safety in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification treated with tepotinib monotherapy.	Occurrence of AEs and treatment related AEs. Occurrence of abnormalities (Grade ≥ 3) in laboratory test values (hematology and coagulation, biochemistry) and urinalysis. Occurrence of markedly abnormal vital sign measurements, change in body weight, and ECOG performance status. Occurrence of clinically significantly abnormal ECGs.	15

Objectives	Endpoints (Outcome Measures)	IAP section
To further assess efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH.	Objective response according to RECIST Version 1.1 assessed by Investigator. Confirmed CR assessed by IRC and by Investigator. Duration of response assessed from CR or PR until progressive disease (PD), death, or last tumor assessment assessed by IRC and by Investigator. Disease control (confirmed CR + PR or stable disease [SD] lasting at least 12 weeks) as assessed by IRC and by Investigator. Progression free survival (PFS) according to RECIST Version 1.1 by IRC and by Investigator. Overall survival.	14.2
To further assess efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by blood-based next generation sequencing.	Objective response according to RECIST Version 1.1 assessed by Investigator. Confirmed CR assessed by IRC and by Investigator. Duration of response assessed from CR or PR until PD, death, or last tumor assessment assessed by IRC and by Investigator. Disease control (confirmed CR + PR or SD lasting at least 12 weeks) as assessed by IRC and by Investigator. PFS according to RECIST Version 1.1 by IRC and by Investigator. Overall survival.	14.2
To further assess efficacy of tepotinib monotherapy in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH.	Objective response according to RECIST Version 1.1 assessed by Investigator. Confirmed CR assessed by IRC and by Investigator. Duration of response assessed from CR or PR until PD, death, or last tumor assessment assessed by IRC and by Investigator. Disease control (confirmed CR + PR or SD lasting at least 12 weeks) as assessed by IRC and by Investigator. PFS according to RECIST Version 1.1 by IRC and by Investigator.	14.2
To assess health-related quality of life in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification treated with the combination of tepotinib plus osimertinib.	Patient-reported outcomes/health-related quality of life as reported using the following: • EuroQol Five Dimension Five Level Scale (EQ-5D-5L). • European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). • NSCLC Symptom Assessment Questionnaire (NSCLC-SAQ).	14.2.7

Objectives	Endpoints (Outcome Measures)	IAP section
To assess the pharmacokinetics (PK) of tepotinib and osimertinib and their metabolites.	Single- and multiple-dose PK profile of osimertinib, tepotinib, and their metabolites including but not limited to AUC_{0-t}, C_{max}, and t_{max} after first dose (Day 1) and after multiple study intervention dose administrations (Day 15) (safety run-in). --- Population PK profile of osimertinib, tepotinib, and their metabolites, including, but not limited to, $C_{L/f}$ and $V_{Z/f}$ based on sparse PK sampling on Day 1, Cycle 1 and 2 (all study participants).	16.1 --- Separate document
To assess resistance markers related to EGFR and other molecular pathways.	Mutation status in EGFR and other pathways assessed in circulating tumor deoxyribonucleic acid (ctDNA) at Baseline and progression (all study participants).	Separate document
Tertiary/Exploratory		
To explore efficacy in participants with known brain metastases, if applicable.	Intracranial response (confirmed CR or PR) by IRC.	14.3.1
To explore a possible link between biomarkers and the combined activity of tepotinib and osimertinib.	Antitumor activity and resistance of biomarkers including, but not limited to, markers of MET pathway activation (eg, Hepatocyte Growth Factor [HGF] levels and MET mutations), and other relevant oncogenic pathways.	8.2 and 16.3
To explore genetic variations of genes involved in the PK and safety of tepotinib.	Assessment of genes (eg, P-glycoprotein [P-gp], Breast Cancer Resistance Protein [BCRP]) involved in the PK of tepotinib.	Separate document
To investigate the exposure-response relationship.	Assessment of PK with other primary and secondary efficacy endpoints.	Separate document

6 Overview of Planned Analyses

This IAP covers the analyses for efficacy, safety, PK and biomarker data to be performed for IDMC meetings and for the primary and final analyses. The primary safety endpoint (i.e. the occurrence of DLTs during the first treatment cycle of the safety run-in period) will be evaluated during SMC meetings , based on participant profiles. More details about each specific analysis are provided in the subsections below.

Statistical analyses will be performed based on CDISC SDTM data. These SDTM data contain as clean as possible eCRF data as well as external data, including biomarker data, laboratory data and tumor assessment results by the IRC.

A data review meeting will be held prior to any database lock. In addition, no database can be locked until this IAP has been approved (except for emergency).

In addition to the analyses described below, further interim analyses at time points that are not specified in the protocol may be performed. These may include analyses needed to support

submission activities in countries like Japan and China. Any output produced in this study will be tracked in the "MS200095-0031_Output_Delivery_TOC_YYYYMMDD" document.

6.1 Analyses for SMC meetings

An initial subset of at least 6 participants, who are MET amplified with any of the methods (central/local tissue biopsy [TBx] test or central liquid biopsy [LBx] test) described in Section 4.1 of the protocol, will be enrolled in a safety run-in to confirm the safety of the combination dose of 500 mg once daily of tepotinib together with osimertinib 80 mg once daily. During this period, a dedicated SMC will meet after the first 3 participants have completed Cycle 1 for an interim assessment, and again after at least 6 participants of the respective cohort have completed Cycle 1.

The purpose of these meetings will be to assess the primary safety endpoint by reviewing safety, tolerability, and available PK data in order to confirm a safe and tolerable RP2D of tepotinib when used in combination with osimertinib. The safety run-in primary endpoint analysis is the occurrence of DLTs during the first treatment cycle (of 21 days). Once all participants of the respective cohort have completed the safety run-in period or discontinued from trial prematurely due to DLTs, a database snapshot will be taken for provision of SMC outputs (participant profiles). The SMC may recommend the tepotinib dose of 500 mg as the RP2D or reduce the tepotinib dose from 500 mg to 250 mg as part of the safety run-in and/or for the whole study.

The specific working procedures followed by the SMC can be found in the SMC Charter and will not be further described in the IAP.

Note: On the 5th of May 2020 and on the 11th of August 2020, the first and second SMC meeting were held; the RP2D for tepotinib was confirmed to be 500 mg daily.

6.2 Analyses for IDMC meetings

After the safety run-in is completed and the RP2D has been selected, periodic IDMC meetings will take place. The IDMC will be responsible for periodic (as defined by the study protocol) evaluations of the clinical study to ensure continued participant safety as well as the validity and scientific merit of the study. The outputs required for the review will be a subset of the full set of tables, figures, and listings which will be prepared for the final analysis. IDMC outputs will be indicated in the "MS200095-0031_Output_Delivery_TOC_YYYYMMDD" document and they will include, but not limited to, participant disposition, demographics and baseline characteristics, key efficacy results, AEs, exposure, laboratory parameters, ECGs, vital signs, and withdrawals from study treatment. IDMC meetings may also include available PK data, if requested. IDMC meetings, as described in Section 9.4.4. of the protocol (refer to clinical study protocol MS200095-0031), will be triggered by the following criteria:

- 90 days after 12 participants who are MET amplification positive by centrally confirmed fluorescence in situ hybridization (FISH) (T+) have received the first dose of combination treatment
- 90 days after 24 T+ participants in the combination treatment arm and 12 T+ participants in the monotherapy arm have received the first dose of study treatment (i.e., enrollment into the monotherapy arm is completed)
- 90 days after 48 T+ participants have received their first combination dose

- 90 days after 72 T+ participants have received their first combination dose
- 90 days after complete global enrollment of T+ participants.

Other working procedures as well as documentation and follow-up of recommendations and actions based on each IDMC Safety Review can be found in the IDMC charter.

The study is an open-label study, nevertheless, during the randomized period it is handled as blinded as possible. No aggregated analyses by treatment arm are shared with the Sponsor, but only with IDMC members. From the second IDMC onwards, the Sponsor will receive the same outputs as the IDMC members.

Note: For a more detailed description of the participants who are T+, please see Section 8.1.1.

6.3 Primary Analysis

The primary analysis will be conducted once all participants enrolled during the global enrollment period in the primary analysis set (T+, see also Section 8.1 for the primary analysis set for efficacy) have either been treated with the RP2D of tepotinib in combination with osimertinib for at least 9 months, died or have prematurely discontinued study treatment for any reason, whichever comes first. Participants from the Chinese extension period will not be included into the primary efficacy analysis, but into all safety analyses.

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

The planned analyses of all endpoints in this IAP will be performed unless stated otherwise.

6.4 Analysis after Chinese extension period

An additional analysis is planned 9 months after start of treatment for the last enrolled participant including the Chinese extension period. This analysis will cover selected outputs from the primary analysis as well as dedicated analyses for Chinese and non-Chinese subjects. TLFs to be produced for this analysis will be indicated in the "MS200095-0031_Output_Delivery_TOC_YYYYMMDD" document. Efficacy data from participants enrolled after the global enrollment period will be included in this analysis.

6.5 Final Analysis

The final analysis will be done at the time point at which all participants have discontinued the study treatment and two-thirds of the participants have died, or 3 years after the last participant's first dose, whichever occurs first.

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

The final analysis may either be a replicate of the TLFs produced for the primary analysis or a reduced version of it, performed when the database is locked. TLFs to be produced for the final

analysis will be indicated in the "MS200095-0031_Output_Delivery_TOC_YYYYMMDD" document.

7 Changes to the Planned Analyses in the Clinical Study Protocol

The modified Full Analysis Set is introduced as an additional analysis set, which does not reflect new analyses, but enables easier entitling of multiple efficacy tables, please see Section 8.1. It excludes those participants enrolled under protocol version 1.0 who do not meet the eligibility criteria of protocol version 2.0 (refer to clinical study protocol MS200095-0031), those who were enrolled based on the local FISH test but were later found to be negative on both the central tests based on tissue biopsy and liquid biopsy and participants who did not receive osimertinib as only prior line. The majority of efficacy tables is based on this analysis set. Global enrollment was closed on the 8th July 2022. The last participant enrolled globally started treatment on 28th June 2022. Enrollment in China continued until 7th November 2022 (see Protocol Version 3.1 CHN - Local Amendment 1 for China only). The inclusion or exclusion of participants who started treatment after the 8th July 2022 into the modified Full Analysis Set (mFAS) depends on the purpose of the analysis to be performed.

Specific rules are added on how to present the data and calculate the endpoints for those participants in the monotherapy arm who switch to the combination treatment, see in particular Sections 9.3, 9.11, 13, 14, 15.

The efficacy considering the C797X status which is mentioned in Section 9.4.1 of the study protocol will be performed separately as data will be available at a later timepoint. The analysis will be described in a separate document.

The PK parameters $C_{L/F}$ (for single dose) and $V_{Z/F}$ (for single and multiple dose) cannot be determined because λ_z (for single and multiple dose) and $AUC_{0-\infty}$ (for single dose) are not estimable in this study.

7.1 COVID-19 Impact

No changes to the planned analysis of the efficacy or safety endpoints are planned due to the impact of Coronavirus disease 2019 (COVID-19) outbreak.

The following sensitivity analyses based on IRC assessment will be performed on participants in the combination arm from the mFAS:

- Best Overall Response (BOR) and related endpoints will be analyzed as described in Sections 14.1.1, 14.2.2 and 14.2.4 but considering only participants with no study treatment discontinuation due to COVID-19.
- Progression Free Survival (PFS) will be analyzed as described in Section 14.2.5; however, participants who discontinued study treatment due to COVID-19 and subsequently had an event (PD or death) will be censored at the date of the event.

Additional outputs (summary table and listing) will be generated for a description of the impact by COVID-19 on the study. The number and percentage of participants will be presented for the following findings due to COVID-19:

- 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 (remote audio video or telephone call) or emails replacing site visits (including number of tele-visits/emails)
- Drug administration - missed doses (of osimertinib and/or tepotinib)
- Drug administration - dose adjustments (of osimertinib and/or tepotinib)
- Laboratory testing performed by external laboratory unit
- Treatment discontinuation (of osimertinib and/or tepotinib)
- End of tumor assessment visits
- Study discontinuation
- Death

Potentially affected participants (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 were still ongoing in the study after the start of the pandemic (i.e., neither died or withdrew from study 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 participants with important protocol deviations related to COVID-19 (categorized by frequency of participants 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 participants 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 for the SAF analysis set to present the number of participants 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 study treatment as well as concomitant vaccines.

In addition, separate listings of COVID-19 related 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 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

Full Analysis Set (FAS) / Safety Analysis Population (SAF)

All participants who were administered any dose of any study treatment (regardless of the protocol version). Analyses will consider participants as treated and will be performed per treatment arm. As the definition of these analysis sets is identical, from now on the SAF Analysis Set will be referenced only.

Modified Full Analysis Set (mFAS)

The mFAS is defined as a subset of the FAS consisting of those participants who were tested MET amplification positive based on central TBx FISH testing (T+) or based on central LBx test (L+), or both, and who progressed on first-line osimertinib as the only prior line of therapy in the noncurative advanced or metastatic NSCLC setting (participants enrolled under any protocol version who meet the above criteria). The intent of introducing the mFAS is to enable easier entitling of respective efficacy tables and figures, there is no change of the analysis strategy as planned per study protocol.

For the fifth IDMC and for the primary analysis, participants from the Chinese extension period who started study treatment after the 8th July 2022 (i.e., date of completion of global enrollment) will be excluded from this analysis set due to insufficient length of follow-up, whereas they will be included in the mFAS for analysis of the Chinese extension period and for the final analysis.

Unless otherwise stated, all efficacy tables and figures will be based on the mFAS. The efficacy results for all the participants in the FAS will be listed.

Primary Analysis Set for Efficacy

The primary analysis set for efficacy will consist of all mFAS participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH (central TBx FISH testing [T+]). The primary analysis set for the combination treatment arm supports the primary objective of the study.

Secondary Analysis Sets for Efficacy

Two secondary analysis sets for efficacy will be defined:

- All mFAS participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by LBx test (L+)
- All mFAS participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by either TBx or LBx test (T+ and/or L+).

Safety Run-In Analysis Set (SRIAS)

The SRIAS will include all participants treated in the safety run-in who received at least 75% of the tepotinib and osimertinib planned dose and completed the DLT period (3 weeks after start of treatment with study treatment), or who experienced a DLT during the DLT period regardless of the received amount of each study treatment.

Planned tepotinib dose: 500 mg × 21 days = 10500 mg.

Planned osimertinib dose: 80 mg × 21 days = 1680 mg.

DLTs are identified as those AEs with answer “Yes” to the question “Is this adverse event a dose limiting toxicity”, which is collected on the “Adverse Event Details” eCRF page. The respective eCRF flag will reflect the decisions of the SMC regarding the assessment of an adverse event being a DLT.

Pharmacokinetic Analysis Set (PKAS)

All participants who receive at least one dose of study treatment, have no important events or protocol deviations affecting PK and provide at least one measurable post-dose concentration.

The PKAS will include all participants:

- Who have PK data without any relevant protocol deviations and factors likely to affect the validity of these data
- With adequate study treatment compliance (i.e., dosing and dosing regimen is as scheduled on the PK measurement day(s), as well as on prior days which have the potential to impact PK results).
- With evaluable PK data, i.e., non-missing values sufficient to derive PK endpoints.

If participants received prohibited concomitant therapy or medicines, as specified in Section 6.5 of the protocol (refer to clinical study protocol MS200095-0031), they will be excluded from the PKAS. Relevant decisions will be made before database lock.

Additionally, the following will be considered for inclusion in the PKAS: if a participant has a tepotinib dose change, the affected PK data (for both tepotinib and osimertinib treatment) will no longer be included in the PKAS from the time of the change.

If there is a change in scheduled osimertinib dose which can affect osimertinib PK (e.g., inadequate washout of prior osimertinib treatment or missed osimertinib doses), the affected osimertinib concentrations and/or PK parameters will be excluded from the PKAS.

All PK summaries will be based on the PKAS population.

8.1.1 Presentation of Analysis Results (PK analysis excluded)

Based on the results of the central TBx and LBx tests for MET amplification, the following groups of participants will be defined for each treatment arm (combination arm: tepotinib RP2D + osimertinib 80 mg daily, monotherapy arm: tepotinib 500 mg daily) and results presented accordingly:

- T+: participants in the mFAS with a positive central test based on TBx (FISH);
- L+: participants in the mFAS with a positive central test based on LBx;
- Combined (T+ and/or L+): all participants in the mFAS, i.e. with a positive central test based either on TBx or LBx or both tests;
- Other: participants who cannot be considered as T+ or L+ (e.g., participants whose central TBx and LBx test results are both negative or not determined, or participants enrolled under any protocol version who did not progress on first-line osimertinib as the only prior line of therapy).

According to the type of analysis, results may also be presented considering all the participants treated in the combination arm (Total Tepo+Osi), in the monotherapy arm (Total Tepo) and overall (Total).

8.1.2 Analyses per Analysis Set

The following table summarizes the use of the analysis sets and the groups specified above to present the results of the different analysis in tables and figures.

Table 1. Analysis Sets: presentation of the results in tables and figures

Analysis	Analysis set	Results to be presented by
Baseline Characteristics, Baseline Biomarkers, Protocol Deviations, Previous or Concomitant Medications/Procedures	SAF	Tepotinib RP2Dmg + Osimertinib 80mg: T+, L+, Combined (T+ and/or L+), Other, Total Tepo+Osi Tepotinib 500mg: T+, L+, Combined (T+ and/or L+), Other, Total Tepo Total

Analysis	Analysis set	Results to be presented by
Efficacy (excluding sensitivity analyses, subgroup analyses, overall survival and QoL): primary and secondary endpoints	mFAS	Tepotinib RP2Dmg + Osimertinib 80mg: T+, L+, Combined (T+ and/or L+) Tepotinib 500mg: T+, L+, Combined (T+ and/or L+)
Efficacy (sensitivity analysis: start of subsequent anti-cancer treatment, study treatment discontinuation due to COVID-19, subgroup analyses, overall survival and QoL only): primary and some secondary endpoints	mFAS	Tepotinib RP2Dmg + Osimertinib 80mg: T+, L+, Combined (T+ and/or L+)
Efficacy (sensitivity analysis: all participants in the FAS): primary endpoint and some secondary endpoints	FAS	Tepotinib RP2Dmg + Osimertinib 80mg Tepotinib 500mg
Efficacy (Central Nervous System Tumor Response based on RANO-BM criteria): tertiary/exploratory endpoints	FAS/mFAS	Tepotinib RP2Dmg + Osimertinib 80mg: T+, L+, Combined (T+ and/or L+), Other, Total Tepo+Osi (as applicable according to whether FAS or mFAS is presented)
Safety: primary endpoint for the safety run-in	SRIAS	Tepotinib 500mg + Osimertinib 80mg
Safety: all other safety endpoints; Compliance and Exposure	SAF	Tepotinib RP2Dmg + Osimertinib 80mg: T+, L+, Combined (T+ and/or L+), Other, Total Tepo+Osi Tepotinib 500mg: T+, L+, Combined (T+ and/or L+), Other, Total Tepo
Listings (excluding enrollment)	SAF or FAS	SAF for listings presenting baseline and safety data FAS for efficacy listings

8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed on primary and key secondary efficacy endpoints as defined in Table 2; due to the low sample size in the monotherapy arm, only results for the combination arm will be presented. All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed. Endpoints for which subgroup analyses will be performed can be found in Section 14. In case of low number of participants within a subgroup level (< 5 participants), levels will be pooled when meaningful.

For the definition of subgroup levels, data as documented in the electronic case report form (eCRF) or provided in the SDTM datasets (e.g. country) will be taken. The category “missing” will not be included in any subgroup analysis.

Table 2. Subgroups

Subgroup	Subgroup level	Definition/ Derivation
Age	• < 65 years • ≥ 65 years	Age calculated at the date the screening informed consent is signed. See Section 11.1 for more details.
Sex	• Male • Female	Collected on the "Demographics" eCRF page.
Race	• Caucasian / White • Black or African American • Asian • Other/More than one race	Collected on the "Demographics" eCRF page. If race is "Not collected at this site" then it will be handled as "missing" (only for the purpose of the subgroup analysis). In case, for example, the race indicated is both "White" and "Asian", the participant will be included in the "Other/More than one race" category.
Pooled Region	• Asia • Europe • North America	This is derived considering the country where each site is located. The variable "COUNTRY" will be provided in the SDTM demographic dataset.
Japanese Status	• Japanese • Not Japanese	Consider as "Japanese" participants enrolled in Japan with "Ethnicity 2" equal to "Japanese". Set to "Not Japanese" all the other participants for which both country and "Ethnicity 2" are available.
Chinese Status	• Chinese • Not Chinese	Consider as "Chinese" participants enrolled in China with race equal to Asian, not collected at this site or missing. Set to "Not Chinese" all the other participants.
ECOG PS	• 0 • 1	Refer to "ECOG Performance Status" eCRF page. Only participants with score 0 or 1 at Screening should enter the study.
Baseline brain metastases (IRC)	• Present • Absent	This subgroup classifies participants according to whether or not they have target or non-target lesions in the brain. This information comes from IRC assessment at baseline.
Baseline brain metastases (Investigator)	• Present • Absent	This subgroup classifies participants according to whether or not they have target or non-target lesions in the brain as per investigator assessment. This information is collected on the "Tumor Assessment (according to RECIST 1.1) – Target Lesions" and "Tumor Assessment (according to RECIST 1.1) – Non-target Lesions" eCRF pages at baseline.
Histopathological classification	• Adenocarcinoma • Squamous • Other	This information is collected in the "Histology" eCRF page.

Subgroup	Subgroup level	Definition/ Derivation
Clinical stage at study entry	• Advanced • Metastatic	This information is collected in the "Disease History" eCRF page. The TNM classification at study entry will be used to derive the subgroup levels. See details in Section 18.2.
Time from metastatic disease diagnosis to first dose	• < 6 months • ≥ 6 months	The date of documented metastatic disease diagnosis collected in the "Disease History" eCRF page will be used.
Duration of prior osimertinib	• < 12 months • ≥ 12 months	Duration of prior osimertinib therapy (months) as first and only prior anti-cancer therapy. See Section 11.5 for more details.
Time from disease progression on prior osimertinib to first dose	• < 2 months • ≥ 2 months	Time from disease progression on prior osimertinib therapy as first and only prior anti-cancer therapy to start of study treatment (months). See Section 11.5 for more details.
Mean Gene Copy Number	• < 10 • ≥ 10 • < 8 • ≥ 8	Mean Gene Copy Number resulting from the analysis of tumor tissue samples performed centrally with the FISH test.
MET/CEP7 ratio	• < 2 • ≥ 2 • 2 – < 4 • ≥ 4	MET/CEP7 (centromere 7) ratio resulting from the analysis of tumor tissue samples performed centrally with the FISH test.
Smoking Status	• Current Smoker • Former Smoker • Never Smoker	Smoking status derivation can be found in Section 11.6.

9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections.

Presentation of continuous and qualitative variables:

Continuous variables other than PK will be summarized using descriptive statistics, i.e., the number of participants with non-missing values (n), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum.

Mean, median, Q1, Q3, minimum, and maximum will have the same precision as collected in SDTM datasets for non-derived data. Standard deviation will be presented with one digit more than the mean. Percentage and percent change from baseline will be reported using one decimal

digit, if not specified otherwise. Derived data such as duration and "time since" variables (see Section 9.5) will be displayed with one decimal digit, unless stated otherwise.

Boxplots will be used as graphical representations of the distribution of continuous data (e.g., laboratory values by visit). The center line in the box will present the median whereas the bottom and top lines will present the Q1 and Q3, respectively. Whiskers will extend 1.5 times the interquartile range (i.e., Q3 – Q1) from the top and bottom of the box. If the data do not extend to the end of the whiskers, then the whiskers will extend to the minimum and maximum values. If there are values that fall above or below the end of the whiskers, they will be considered as outliers and plotted as dots.

Pharmacokinetic concentrations will be summarized using n, arithmetic mean, standard deviation (StDev), coefficient of variation (CV in %), median, minimum, and maximum. Summaries of PK parameters will additionally include the geometric mean (GeoMean), the geometric CV (GeoCV in %), and the 95% confidence interval (CI) for the geometric mean (except for t_{max} and t_{lag} which will be summarized using n, arithmetic mean, median, minimum, and maximum only). All data will be analyzed unrounded, but the following rounding conventions will be applied when reporting descriptive statistics for concentrations and PK parameter data, except for t_{max} and t_{lag} which will use the same level of decimal precision (instead of significant digits) as specified below:

Mean, Min, Median, Max, GeoMean, 95% CI:	3 significant digits
StDev:	4 significant digits
CV%:	1 decimal place

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the number of participants of 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 participant may have more than one category due to multiple responses per participant, the number of participants included in each category will be summarized as a percentage from all participants. Therefore, the total frequency across categories may not equal the total number of all participants in that analysis group.

Scheduled and unscheduled visits

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

Descriptive statistics by nominal visit or time point, e.g., for laboratory measurements, will include only data from scheduled visits. Unscheduled visits will be included in the derivation of baseline or worst on-treatment values.

Significance level:

All statistical tests mentioned in this IAP are to be regarded as exploratory. If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

Pooling of sites:

In order to provide overall estimates of treatment effects, data will be pooled across sites. The "site" factor will not be considered in statistical models or for subgroup analyses due to the high number of participating sites in contrast to the anticipated small number of participants treated at each site.

Statistical software:

All analyses will be performed using SAS® Software version 9.2 or higher.

9.1 Data Handling After Cut-off Date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations.

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

These rules will be applied to all analyses performed for the IDMC meetings as well for the primary analysis. For the final analysis no cut-off date will be applied: the analysis will be performed only after all the data have been collected, fully cleaned and the database has been locked.

9.2 Study Day / Study Treatment Day

In this IAP, "study treatment" comprises tepotinib and osimertinib in the combination arm and indicates tepotinib only in the monotherapy arm; "study treatment component" will be used to refer to each study drug separately.

Day 1 is the day of the start of study treatment, the day before is Day -1 (no Day 0 is defined). Study day / Study treatment day is defined relative to Day 1.

Study treatment start date:

For each participant, the study treatment start date is the date of first administration of the study treatment (for the combination arm, it will be the earliest date between the two study treatment components; for the monotherapy arm it will be the date of the first administration of tepotinib).

Study treatment end date:

For each participant in the combination arm, the study treatment end date is the date of the last administration of the study treatment (for the combination arm, it will be the latest date between

the two study components; for the monotherapy arm it will be the last date of administration of tepotinib as monotherapy).

9.3 Definition of On-treatment Periods

Participants in the monotherapy arm will be allowed to switch to the combination treatment once PD is confirmed. The following on-treatment periods are defined in order to indicate which data will be used for the analyses.

Table 3. On-treatment Periods

		Combination Arm	**Monotherapy Arm - No Switch**	**Monotherapy Arm – Switch[a]**
Period 1	Start	First dose of study treatment	First dose of study treatment	First dose of study treatment
	End	Last dose of study treatment + 30 days or the cut-off date or death, whichever occurs first	Last dose of study treatment + 30 days or the cut-off date or death, whichever occurs first	First dose of osimertinib[b]
Period 2	Start	NA	NA	First dose of osimertinib[b]
	End	NA	NA	Last dose of combination treatment[c] + 30 days or the cut-off date or death, whichever occurs first

a: Unless stated otherwise, data from Period 1 will contribute to tables, figures and listings whereas data from Period 2 to study discontinuation will only be listed.
b: Measurements collected on the day of the start of the combination treatment will be considered to belong to Period 1 unless clearly collected after the first administration of osimertinib. The same rule applies to adverse events.
c: The last dose of the combination treatment is considered as the last dose of tepotinib or osimertinib, whichever is later.

9.4 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to start of study treatment will serve as the baseline measurement for both periods (see Table 3).

If the assessment time of any pre-dose baseline assessments (as planned per 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 of either the assessment or initial dose is missing, the unscheduled assessment will be considered to have been obtained after study treatment administration.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be analyzed similar to an unscheduled post-dose measurement.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.5 Definition of Duration and 'time since' Variables

Durations in days will be calculated by the difference of start and stop date + 1, if not otherwise specified.

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

9.6 Conversion Factors

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

- 1 week = 7 days
- 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 (lb) ÷ 2.2046.

For the calculation of creatinine clearance: serum creatinine (mg/dL) = serum creatinine (umol/L) / 88.42.

9.7 Date of Last Contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date prior to or at the data cut-off date among the following:

- All participant assessment dates (blood draws (laboratory, PK, ctDNA, biomarker, PGx, etc.), vital signs, ECOG performance status, ECG, tumor assessments, quality of life assessments, pregnancy tests, echocardiogram);
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Concomitant medication/procedures start and end dates
- Last known to be alive date collected on the "Subject Status / Survival Follow-up" eCRF page
- Tepotinib and osimertinib administration start and end dates
- Date of discontinuation on disposition eCRF pages (do not use this date if the reason for discontinuation is lost to follow-up)

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date. This rule is to be applied to AE stop dates too: if an AE started before the cut-off date and ended after the cut-off date, only the complete start date will be used in the derivation of the last date of contact.

9.8 Time Window

For the purpose of Patient-reported Outcome (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; if two assessments are equally distanced from the target date, the earliest one will be selected. Both scheduled and unscheduled visits will be considered.

9.9 Imputation of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Imputed dates will be used for the calculation of durations.

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

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

Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment. If the end date or resolution date indicates that the AE has stopped before the start of treatment, this date will be used for imputation instead of the start of treatment date.

- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015. If the end date or resolution date indicates that the AE has stopped before the start of treatment, this date will be used for imputation instead of the start of treatment date.

- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014. If the end date or resolution date indicates that the AE has stopped before the start of treatment, this date will be used for imputation instead of the start of treatment date.

- In all other cases the missing onset day or missing onset month will be replaced by 1.

- Incomplete stop date 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 participant'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 cut-off this date will be kept.

Special cases: AEs may be split into multiple records if the toxicity grade changes (see Section 15.2.1 for more details). The end date of the previous record and the start date of the new record are expected to be the same. In the event that the month and year are indeed the same, but the day is missing, it will be imputed by 15. In case the imputed start date of the new record is after the end date of this same record, no imputation will be performed.

Prior osimertinib start and end dates

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.
- 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.
- For both start and stop dates, if the month is missing or the date is completely missing, no imputation will be done.

Documented progressive disease

Incomplete dates for documented progressive disease as collected in the "Prior EGFR-TKI Drug Therapies Details", "Prior Osimertinib Therapies Details" and "Prior Anti-Cancer Drug Therapies Details" eCRF pages will be imputed as follows:

- If the day is missing, it will be imputed to the first day of the month.
- If the month is missing or the date is completely missing, no imputation will be done.

Previous and concomitant medication/procedure

For identification of previous or concomitant medications/procedures by period, no formal imputation will be performed on missing or incomplete dates. Rules presented in Table 4 and Table 5 will be used to define if a medication/procedure is considered as a previous, concomitant or both previous and concomitant medication/procedure.

If a medication/procedure could be allocated to both Period 1 and Period 2 due to missing start/stop dates, it will be allocated to Period 1. If a medication/procedure starts in Period 1 and continues in Period 2 it will also be allocated to Period 1.

Table 4. Stopping rules for medication/procedure end dates

End date of medication/procedure			Stopping rule
Day	**Month**	**Year**	
UNK	UNK	UNK	After treatment start (ongoing)
UNK	UNK	< Treatment start (year)	Before treatment start
UNK	UNK	≥ Treatment start (year)	After treatment start
UNK	< Treatment start (month and year)		Before treatment start
UNK	≥ Treatment start (month and year)		After treatment start
< Treatment start (complete date)			Before treatment start
≥ Treatment start (complete date)			After treatment start

UNK = Unknown

Table 5. Rules to define previous and/or concomitant medication/procedure

Start date of medication/procedure			Stopping rule (see Table 4)	Medication/procedure
Day	**Month**	**Year**		
UNK	UNK	UNK	Before treatment start	Previous
UNK	UNK	UNK	After treatment start	Previous and concomitant
UNK	UNK	≤ Period 1 start (year)	Before treatment start	Previous
UNK	UNK	≤ Period 1 start (year)	After treatment start	Previous and concomitant
UNK	UNK	> Period 1 start (year) and ≤ latest of Period 1 or Period 2 end (year)	After treatment start	Concomitant
UNK	≤ Period 1 start (month and year)		Before treatment start	Previous
UNK	≤ Period 1 (month and year)		After treatment start	Previous and concomitant
UNK	> Period 1 (month and year) and ≤ latest of Period 1 or Period 2 end (month and year)		After treatment start	Concomitant
≤ Period 1 start (date)			Before treatment start	Previous
≤ Period 1 start (date)			After treatment start	Previous and concomitant

Start date of medication/procedure			Stopping rule (see Table 4)	Medication/procedure
Day	**Month**	**Year**		
> Period 1 start (date) and and ≤ latest of Period 1 or Period 2 end (date)			After treatment start	Concomitant

UNK = Unknown

Death date

In general, missing or partial death dates will not be imputed. However, for the purpose of survival analyses, partially missing death dates will be imputed as follows: if only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last contact (see Section 9.7) and the 15th day of the month.

Tumor assessments

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (e.g., X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

Dates of subsequent anti-cancer therapy

<u>For sensitivity analyses where the start of subsequent anti-cancer treatment is considered</u>

Incomplete dates for the start date of subsequent anti-cancer therapies (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy related sensitivity analyses:

- If only the day is missing, it will be imputed as the first day of the month unless it results in a date before the end date of study treatment. In that case, the incomplete anti-cancer therapy start date will be imputed as the end date of study treatment.

- If both the day and month are missing, the incomplete anti-cancer therapy start date will be imputed as the end date of study treatment if the subsequent therapy started on the same year as the end of study treatment; otherwise, day and month will be imputed as the 1st of January.

For duration of subsequent anti-cancer drug therapies

Incomplete dates of subsequent anti-cancer drug therapies will be imputed as follows:

- If only the day is missing in the start date, the same rule as for the sensitivity analysis described above will be applied.
- If only the day is missing in the end date, 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.

Nicotine consumption

Imputation will be used for the calculation of duration of consumption (years) only.

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

- Missing month of start date will be imputed as January
- Missing month of end date will be imputed as December

In case the start date is missing completely, the start date will not be imputed and duration will not be calculated.

In the case that the end date is missing completely (i.e. the participant is still using nicotine), in order to allow the calculation of duration, the end date will be imputed by the screening informed consent date.

As the day of the month is also needed to calculate the duration of consumption, the first day and last day of the month for the start date and end date will be used, respectively.

Disease history

Incomplete dates for disease history (e.g., initial diagnosis date, date of documented metastatic disease diagnosis) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month
- If both the day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as the 1st of July
- If both the day and month are missing and the year is the same as the year of the first study treatment, the month and day will be imputed as the 1st of January

If the date is completely missing, no imputation will be performed.

9.10 Scoring of HRQOL Data

Unless otherwise specified, HRQOL questionnaires will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual. See Section 14.2.7 for details.

9.11 Tumor Evaluation and Adjudication

Missing data from scheduled tumor assessments not performed will not be imputed. Evaluable tumor assessments are defined as those with an overall response of CR, PR, SD or PD. Data from non-evaluable (NE) tumor assessments will be used in the derivation of endpoints in accordance with Eisenhauer et al., 2009.

For IRC assessments, only the response assessments which are flagged as accepted after adjudication will be taken over to ADaM datasets and will be analyzed. In the case of a missing adjudication flag for a response assessment and the earliest image dates being equal, the assessment of reader 1 (the reader who completed baseline first) will be taken for analysis. Otherwise the assessment for the reviewer who reviewed the record with the earliest image date will be analyzed. Analyses of tumor sizes will be based only on assessments of the reader whose assessment was accepted at baseline.

For those participants in the monotherapy arm who switch to combination treatment, the latest available scan at the time of switch will be used to perform the baseline tumor assessment for the combination period. Only investigator assessments will continue after the switch and data will be collected in the usual eCRF pages dedicated to collection of tumor response. These evaluations will be called “Evaluation re-baseline”, “Evaluation after re-baseline visit 1”, etc. IRC assessments will stop at the first PD.

10 Study Participants

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

10.1 Disposition of Participants and Discontinuations

All participants who performed prescreening will be considered. Percentages will be presented with respect to the number of SAF Analysis Set participants. Results will be presented as indicated in Sections 8.1.1 and 8.1.2.

Participant disposition will be summarized as follows, as applicable:

- Number of participants prescreened
- Number of participants prescreened based on protocol version 2.0 onwards
- Number of participants screened

- Number of participants who discontinued from the study prior to first dose of study treatment, overall and grouped by the main reason (e.g., the failed specific inclusion or exclusion criteria, withdrawal of consent)
- Number of participants active in screening (for outputs while recruitment is still ongoing)

The end of treatment status will be summarized by:

- Number of participants who received at least one dose of study treatment
- Number and percentage of participants who have permanently discontinued study treatment
- Number and percentage of participants with study treatment ongoing
- Number and percentage of participants who did not receive tepotinib
- Number and percentage of participants with tepotinib treatment ongoing
- Number and percentage of participants who permanently discontinued tepotinib treatment (overall and by primary reason)
- Number and percentage of participants who did not receive osimertinib
- Number and percentage of participants with osimertinib treatment ongoing
- Number and percentage of participants who permanently discontinued osimertinib treatment (overall and by primary reason)
- Number and percentage of participants in the monotherapy arm who switched to the combination treatment
- Number and percentage of participants in the monotherapy arm who switched to the combination treatment and treatment is still ongoing
- Number and percentage of participants in the monotherapy arm who switched to the combination treatment and treatment is permanently discontinued

The end of study status will be summarized by:

- Number and percentage of participants with any study treatment ongoing
- Number and percentage of participants in the monotherapy arm who switched to the combination treatment and treatment is still ongoing
- Number and percentage of participants off-treatment and in safety or survival follow-up
- Number and percentage of participants who discontinued the study (overall and by primary reason)

For each participant in the SAF analysis set, the first and last dosing date for each study component (including reason for treatment discontinuation) and study discontinuation date (including reason for study discontinuation) will be listed. For participants in the monotherapy arm who switch treatment, the first and last dosing date of each study component (including reason for treatment discontinuation) will also be listed.

Additionally, the number of participants enrolled in each analysis population will be provided overall, by region, by country within region and by site. Results will be presented by treatment arm. This information will also be provided for each participant in the SAF analysis set in a listing.

10.2 MET Amplification Results in Blood and Tissue Samples

The MET amplification result according to the local and central TBx (FISH) as well as LBx tests for all prescreened participants as well as for participants prescreened based on protocol version 2.0 onwards will be summarized. Frequencies and percentages will be calculated for all the different combinations of results from both the blood and tissue samples. Each result from the central liquid and tissue sample will be classified as Positive, Negative, Not Evaluable, Not Analyzed or No Sample Taken whereas the result from the local tissue sample will be classified as Positive, Negative or No Sample Taken.

10.3 Protocol Deviations / Exclusion from Analysis Populations

10.3.1 Important Protocol Deviations

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

Important protocol deviations include, but are not limited to:

- Participants enrolled and dosed on the study who did not satisfy enrollment criteria
- Participants who are not compliant with treatment: overdose, dose modifications not as per protocol, incorrect dose, etc.
- Participants who receive a prohibited concomitant medication
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)
- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

All IPDs are documented in SDTM datasets whether identified for all participants by either medical review processes or programmed by IQVIA Data Management and confirmed prior to or at the Data Review Meeting at the latest.

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 IAP, the SDTM and ADaM datasets, and ultimately the CSR:

CTMS	IAP	SDTM	ADaM

Minor	Non-important	Minor (all protocol deviations are included)	Minor (only protocol deviations related to COVID-19 are included)
Major	Important	Flagged with PDEVXXX code	Flagged with PDEVXXX code
Critical (subset of Major)	Important	Mapped to Important	Mapped to Important

Clinically important protocol deviations (CIPDs) are flagged in CTMS after medical review and this information will be available in the SDTM datasets.

A full list of potential IPDs including definition and categorization is maintained by IQVIA in a separate document, the Protocol Deviation Management Plan, which is updated as needed during the course of the study.

A frequency table for the IPDs and one for the CIPDs will be created based on the SAF analysis set; all IPDs will be listed and CIPDs will be flagged. All PDs will be tabulated, including those related to the period after the switch from monotherapy to combination treatment. PDs related to the period after the switch will be flagged in the listings.

A listing containing any violation of inclusion/exclusion criteria at screening will also be produced.

On the 16th May 2022, IQVIA implemented changes to the PD management process and IQVIA CTMS to allow a risk-based approach to protocol deviation and site non-compliance reporting, tracking, trending and oversight. Due to the status of this study when these enhancements were implemented, there are two sets of PD categories used. The old categories will be kept for analysis purposes. The mapping from the new to the old categories is performed via programming in the SDTM datasets DV/SUPPDV in accordance to Table 5 of the Protocol Deviation Management Plan from version 4.0 onwards.

10.3.2 Reasons Leading to the Exclusion from the Per Protocol Analysis Set

Not applicable.

11 Demographics and Other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for the SAF analysis set using summary statistics for continuous variables and frequency statistics (i.e., counts and percentages) for categorical variables. Results will be presented as indicated in Sections 8.1.1 and 8.1.2.

Listings showing demographic data and other baseline characteristics will be presented for the SAF analysis set.

11.1 Demographics

Demographic characteristics will be summarized descriptively using the following information from the Prescreening and Screening/Baseline Visit eCRF pages:

- Sex: male, female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected at this site, more than one race, other, missing
- Ethnicity:
    - Hispanic or Latino / Not Hispanic or Latino
    - Japanese / Not Japanese
- Age (years)
- Age categories:

  < 65 years

  ≥ 65 years

  65 < 75

  75 < 85

  ≥ 85 years
- Pooled Region: North America, Europe, Asia
- Geographic Region (e.g.: North America, Western Europe, Eastern Europe, Asia, …)
- Country (e.g.: Belgium, China, Germany, Malaysia, Spain, Turkey, USA, …)

Specifications for computation:

- Age [years]

  Age = (date of given informed consent for screening - date of birth + 1) / 365.25.

  In case of missing day for at least one date, but month and year 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 case of missing month for at least one date, but year 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.

  The integer part of the calculated age will be used for reporting purposes.
- Site codes will be used for the determination of the participant's pooled region, geographic region and country.

- Participants with more than one race will be summarized in the "more than one race" category.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, preferred term as event category and System Organ Class (SOC) body term as Body System category. Each participant will be counted only once within each Preferred Term (PT) or SOC.

Medical history will be displayed in terms of frequency tables ordered by primary SOC in alphabetic order and PT in descending frequency of the overall total column.

A listing will be provided with SOC term, PT term, toxicity grade (if ongoing) and whether related to the study condition and to EGFR-TKI treatment.

11.3 Disease History

Information on disease history is collected during the screening visit on the "Disease History" eCRF page and the histopathological classification is collected on the "Histology" eCRF page. Information on the EGFR mutation status is collected on the "EGFR Molecular Abnormalities" eCRF page. Data will be summarized and listed as follows:

- 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 start of study treatment – date of initial cancer diagnosis + 1) / 365.25
- Time since documented metastatic disease diagnosis (years) = (date of start of study treatment – date of documented metastatic disease diagnosis + 1) / 365.25
- Histopathological Classification: Adenocarcinoma / Squamous / Large cell / Adenosquamous / Other
- TNM classification at initial diagnosis
- TNM classification at study entry
- Clinical stage at initial diagnosis: Advanced / Metastatic / Earlier stage or unknown. See Appendix 2 for the classification into "Advanced" and "Metastatic". Any other clinical stage will be classified as "Earlier stage or unknown".
- Clinical stage at study entry: Advanced / Metastatic. See Appendix 2 for the classification into "Advanced" and "Metastatic".
- Life expectancy at study entry
- EGFR mutations

Incomplete dates for initial cancer diagnosis and documented metastatic disease diagnosis will be handled as specified in Section 9.9.

11.4 Baseline Tumor Assessment

The baseline tumor assessment as collected by the Investigator at the screening visit on the "Tumor Assessment (according to RECIST 1.1)" eCRF pages and "Sum of Diameters (according to RECIST 1.1)" eCRF page will be presented. The baseline tumor assessment will also be performed by the IRC - data will be provided by the vendor. Summaries will be presented for the following:

- Target lesions (both Investigator and IRC when data is available)
    - Number of target lesions
    - Sum of target lesion diameters (sum of longest diameters for non-nodal lesions, short axis for nodal lesions)
    - Type: Primary / Recurrence, Node, Metastasis
    - Site
- Non-target lesions (both Investigator and IRC when data is available)
    - Number of participants with at least one non-target lesion
    - Number of non-target lesions
    - Type: Primary / Recurrence, Node, Metastasis
    - Site

Tumor information based on Investigator and IRC assessments that is collected during the study will be listed.

For those participants in the monotherapy arm who switch to the combination treatment, a second baseline tumor assessment will be defined by the Investigator using the latest available scan at the time of switch and the data collected after that will only be listed (see also Section 9.11).

11.5 Prior Anti-Cancer Therapy

The prior anti-cancer therapies are collected under the "Prior EGFR-TKI Drug Therapies Details" (active only under protocol version 1.0), "Prior Osimertinib Therapies Details", "Prior Anti-Cancer Drug Therapies Details", "Prior Anti-Cancer Radiotherapy Details" and "Prior Anti-Cancer Surgeries Details" eCRF pages.

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

- Prior anti-cancer drug therapy for locally advanced or metastatic disease (EGFR-TKI as well as other prior drug therapy)
    - Any prior anti-cancer drug therapy: Yes / No
    - Number of prior anti-cancer drug therapy lines: 1 / 2 / 3 / 4 / ≥ 5

- Prior anti-cancer drug therapies
- Prior anti-cancer drug combinations
- Best response across all prior anti-cancer drug therapies: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD) / Not Evaluable / Unknown
- Received osimertinib as first and only prior line of therapy: Yes / No
- Duration of prior osimertinib therapy (months) as first and only prior anti-cancer therapy: summary statistics as well as into < 12 months and ≥ 12 months. To be calculated as (end of osimertinib therapy - start of osimertinib therapy + 1) / 30.4375. The start and end date of osimertinib therapy correspond to the "Start date" and "End date" of osimertinib, irrespective of possible other drugs administered in combination. See Section 9.9 in case of incomplete dates.
- Time from disease progression on prior osimertinib therapy as first and only prior anti-cancer therapy to first dose of study treatment (months): summary statistics as well as categorized into < 2 months and ≥ 2 months. To be calculated as (date of first dose of study treatment - date of documented progressive disease + 1) / 30.4375. See Section 9.9 in case of incomplete dates.
- Best response for osimertinib as first and only prior anti-cancer drug therapy: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD) / Not Evaluable / Unknown
- Duration of the best response (weeks) for osimertinib as first and only prior anti-cancer drug therapy: summary statistics

- Prior anti-cancer radiotherapy
  - Any prior anti-cancer radiotherapy: Yes / No
  - Number of prior anti-cancer radiotherapy regimen: 1 / 2 / 3 / ≥ 4
  - Best response across all prior anti-cancer radiotherapies: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD) / Not Evaluable / Unknown.
  - Intent of therapy
- Prior anti-cancer surgery
  - Any prior anti-cancer surgery: Yes / No
  - Number of prior anti-cancer surgeries: 1 / 2 / 3 / ≥ 4
  - Type of prior anti-cancer surgeries
  - The surgery was curative in intent: Yes / No

- Best outcome across all prior anti-cancer surgeries: No residual tumor after resection (R0) / Tumor/metastases not resected completely with microscopic residual lesions (R1) / Tumor/metastases not resected completely with macroscopic residual lesions (R2) / Metastases not resected (NR), Other

The listings of prior anti-cancer treatments and procedures will also be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of prior EGFR-TKI drug therapies
- Listing of prior anti-cancer drug therapies
- Listing of prior anti-cancer radiotherapy
- Listing of prior anti-cancer surgeries

11.6 Other baseline characteristics

Information on other characteristics collected at baseline will be summarized and listed. Summary statistics will be presented for:

- ECOG PS
- Height, weight, body surface area (BSA), and body mass index (BMI)

Specifications for computation:

- BSA [m^2] = $\sqrt{\frac{\text{height[cm]} \times \text{weight[kg]}}{3600}}$
- BMI [kg/m^2] = $\frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$
- In the formula above, values at baseline should be used for both weight and height.

ECOG PS, height, weight, BSA and BMI will be added to the listing presenting demographic data.

Other baseline characteristics such as vital signs, clinical laboratory evaluations and ECGs will be part of Section 15 (Safety Analyses).

Nicotine consumption

Information about nicotine use is collected at prescreening on the "Nicotine Usage" eCRF page. The nicotine source options specified in the eCRF page will be classified in:

- products that are smoked: cigarettes, cigars, pipes and e-cigarettes
- products that are smokeless: chewing tobacco and nicotine gum

The information collected about products that are smoked will be used to derive the smoking status for each participant:

- Current Smoker: a participant is a current smoker if at least one smoked product was answered "Current" (missing information about one or more smoked products is allowed);
- Former Smoker: a participant is a former smoker if he/she is not a current smoker and at least one smoked product was answered "Former" (missing information about one or more smoking options is allowed);
- Never Smoker: a participant is considered to have never smoked if all the smoking options were answered "Never".
- Unknown: in case the information is missing for one or more of these smoking options and the participant cannot be classified as current or former smoker, the smoking status should be "Unknown", even though all the remaining options were answered "Never".

In addition, for each product that is smoked, the following will be presented:

- Number of cigarettes/cigars/pipes/e-cigarettes smoked per week
- Duration of cigarettes/cigars/pipes/e-cigarettes consumption (years)

Incomplete start and end dates for each nicotine source option will be handled as specified in Section 9.9.

To convert days, months and years into weeks, please see the conversion factors in Section 9.6. For example, if it is needed to calculate the number of cigarettes smoked per week and it is known that the participant used to smoke 100 cigarettes per month, the following calculation will be performed: 100 / (30.4375/7) = 22.998.

A listing will be produced to present data collected on all the nicotine source options.

Chest X-Ray

A listing will be produced to present the results from chest X-rays performed at screening. The information is collected on the "Chest X-ray" eCRF page.

12 Previous or Concomitant Medications/Procedures

The following analyses will be performed based on the SAF analysis set and presented as indicated in Sections 8.1.1 and 8.1.2.

Concomitant medications are medications, other than study treatment, which are taken by participants any time during the on-treatment periods, see Section 9.3.

Previous medications are medications, other than study treatment, which started before first administration of any study treatment.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date. To derive these flags in case of missing or partial dates, see Section 9.9.

Concomitant medications from Period 1 and previous medications will be summarized by number and percentage of participants from the "Concomitant Medications Details" eCRF page. ATC-2nd level and PTs will be tabulated as given in the most current version of the WHO-DD dictionary at the time of analysis. If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by ATC-2nd level and PT in descending frequency of the overall total column. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have an ATC-2nd level coded term, it will be summarized under the "UNCODED" ATC classification category. Each participant will only be counted once, even if he/she received the same medication at different times.

Any medication recorded on the "Concomitant Medications Details" eCRF page will be listed with an indication of whether the medication was previous, concomitant or both. Concomitant medications will be distinguished according to whether they started in Period 1 or Period 2.

Procedures performed during the study will be collected on the "Concomitant Procedures Details" eCRF page. Concurrent procedures will be classified using the most recent MedDRA version at the time of analysis.

A listing with the relevant information about concurrent procedures will be produced. A flag will be added to indicate whether the procedure is:

- Prior: the procedure started before the first dose of study treatment
- Concurrent: the procedure started before the first dose of study treatment and was still ongoing when study treatment started or it started after the first dose but during the on-treatment periods.
- Post: the procedure started after the on-treatment periods, as applicable.

A procedure could therefore be prior and concurrent in Period 1.

The number and percentage of participants with concurrent procedures in Period 1 will be presented by SOC and PT in descending frequency of the total column.

Subsequent anti-cancer therapy

The subsequent anti-cancer therapies are collected under the "Anti-Cancer Treatment After Discontinuation Details", "Radiotherapy after Discontinuation Details" and "Surgery after Discontinuation Details" eCRF pages.

The number and percentage of participants in each of the following anti-cancer treatment categories will be tabulated:

- Number of participants with subsequent anti-cancer treatment
- Subsequent anti-cancer drug therapy after discontinuation of study treatment
    - Any subsequent anti-cancer drug therapy: Yes / No
    - Number of subsequent anti-cancer drug therapy regimens: 1 / 2 / 3 / ≥ 4. Regimens will be ordered based on the earliest start date within the regimen.
    - Type of anti-cancer drug therapy
    - Intent of anti-cancer drug therapy: Metastatic / Metastatic/Locally advanced / Neoadjuvant / Adjuvant
    - Subsequent anti-cancer drugs
    - Best response across all subsequent anti-cancer drug therapies: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD) / Not Evaluable / Unknown.
    - Duration of each regimen of therapy administered after discontinuation of study treatment (months) = (date of end of anti-cancer therapy - date of start of anti-cancer therapy + 1) / 30.4375. In case of multiple drugs administered within the same regimen, the earliest start among the start dates and the latest end among the end dates will be considered as regimen start and end dates, respectively. See Section 9.9 in case of incomplete dates. The duration of regimens that are still ongoing will not be calculated.
- Subsequent radiotherapy after discontinuation of study treatment
    - Any subsequent anti-cancer radiotherapy: Yes / No
- Surgery after discontinuation of study treatment
    - Any subsequent anti-cancer surgery: Yes / No

The listings of subsequent anti-cancer treatments will also be provided as follows. These will include the participant identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of subsequent anti-cancer drug therapies
- Listing of subsequent anti-cancer radiotherapy
- Listing of subsequent anti-cancer surgeries

13 Study Treatment: Compliance and Exposure

All summaries and listings related to study treatment compliance and exposure will be based on the SAF analysis set. Data will be presented as indicated in Sections 8.1.1 and 8.1.2.

All dosing calculations and summaries will be based on the “Tepotinib Administration Details” and “Osimertinib Administration Details” eCRF pages. The date of last drug administration will

be taken from the "Tepotinib Termination" and "Osimertinib Termination" eCRF pages for those participants who have discontinued treatment by the cut-off date; whereas, for those participants who are still on study treatment, the last dosing date before or at the cut-off date will be used.

For those participants in the monotherapy arm who switch to the combination treatment, the date of last drug administration of tepotinib for Period 1 (see Table 3) will be the last dose of tepotinib that is > 0 mg before the start of the combination treatment.

A dose of tepotinib will be regarded as being taken on a particular day if the actual dose of tepotinib taken is > 0 mg. Interruptions, compliance, and dose changes are not taken into account for the calculation of duration of therapy. These same rules apply to osimertinib.

The following parameters will be provided in summaries and listings for both tepotinib and osimertinib separately:

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

All participants in the SAF analysis set will have the above parameters calculated per period. For those participants in the monotherapy arm who switch to the combination treatment, results for Period 2 will only be listed.

For the combination arm only, duration of therapy will also be calculated in terms of study treatment by taking into account the date of first and last dose of study treatment.

Duration of therapy and number of 3-week cycles

The duration of therapy is defined as

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

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

Cumulative actual dose

The cumulative actual dose (mg) per participant is the sum of the total doses that the participant received while on-treatment per period (i.e. total dose administered [mg]).

Dose intensity and relative dose intensity

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

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

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) = RP2D mg × 21 days for tepotinib in the combination treatment
- Planned dose intensity (mg/3 weeks) = 500 mg × 21 days for tepotinib in the monotherapy treatment
- Planned dose intensity (mg/3 weeks) = 80 mg × 21 days for osimertinib

Dose reductions

In the combination arm, participants may have a dose reduction to 250 mg for tepotinib, which is also the minimum possible dose in this study.

The per protocol dose for osimertinib is 80 mg, which can be reduced to 40 mg if necessary.

The number of participants with and without any dose reduction will be summarized.

Therapy delays

Delay will be defined as a number of days between two successive administrations greater than 1, i.e. date of current administration - date of previous administration >1.

Any delay of tepotinib treatment and any delay of osimertinib treatment greater than or equal to 1 day will be identified for each participant.

For Period 1, the following will be summarized for tepotinib and osimertinib:

- Number of participants with and without delays
- Number of participants with treatment delay, by the length of maximum delay: 1-2 days / 3-7 days / 8-14 days / 15-21 days / >21 days
- Number of participants by reason for treatment delay: Adverse Event / Missed Dose / Other / Missing

14 Efficacy Analyses and Estimands

The following analyses will be performed based on the mFAS and will be presented as described in Sections 8.1.1 and 8.1.2, except when otherwise stated. Details for additional analyses that may be performed are reported in the following sections.

Sensitivity efficacy analyses taking into consideration the treatment discontinuation due to COVID-19 related reasons are described in 7.1.

For those participants in the monotherapy arm who switch to the combination treatment, efficacy endpoints will be presented in tables and figures for Period 1 only (see Table 3). The same efficacy endpoints will also be derived using the data collected by the Investigators during Period 2. Results from both periods will be listed and those related to Period 2 will be flagged.

In general, efficacy endpoints will be calculated and listed for all the participants in the FAS.

In addition, while recruitment is still ongoing, a selection of efficacy outputs presenting a subset of participants in mFAS who have started study treatment at least 90 days before the cut-off date (cut-off date - start of study treatment ≥ 90 days) will also be provided. This analysis aims to present tumor response for participants who have spent enough time in the study to have had the two post-baseline tumor assessments required to identify a confirmed response.

Estimands

Endpoint	Estimand Attributes
Primary	
Objective Response	**Endpoint:** Objective Response according to RECIST 1.1 as assessed by IRC **Population:** Patients with MET amplification determined centrally by FISH (T+), with advanced or metastatic NSCLC harboring activating EGFR mutations and having acquired resistance to prior first-line osimertinib therapy **Treatment:** Tepotinib combined with osimertinib **Intercurrent Event Strategy:** • Discontinuation of treatment: ignoring the intercurrent event (treatment-policy strategy) • Start of subsequent anticancer treatment: ignoring the start of the intercurrent event (treatment-policy strategy) • Progression according to RECIST 1.1: assessment up to the intercurrent event (while not progressed strategy) **Population Level Summary:** Objective response rate (ORR) together with 2-sided exact Clopper-Pearson 95% confidence interval
	Sensitivity Analysis:

Endpoint	Estimand Attributes
	• As main estimand, but using Investigator assessment instead of IRC assessment. • As main estimand, but excluding subjects who discontinued treatment due to COVID-19.
	Supplementary Analyses: • As main estimand and sensitivity analysis, but based on different populations: FAS, L+, T+ and/or L+. • As main estimand, but based on a "while not treated with subsequent anticancer therapy strategy", to be performed also on populations L+, T+ and/or L+. • As main estimand and sensitivity analysis, but for tepotinib monotherapy as treatment and handling the additional intercurrent event "switch to combination treatment" with the "while not treated with the combination treatment strategy", to be performed also on populations L+, T+ and/or L+.
Secondary	
Complete Response	**Endpoint:** Complete Response according to RECIST 1.1 as assessed by IRC **Population:** as primary estimand **Treatment:** as primary estimand **Intercurrent Event Strategy:** as primary estimand **Population Level Summary:** Complete response rate together with 2-sided exact Clopper-Pearson 95% confidence interval
	Sensitivity Analysis: As main estimand, but using Investigator assessment instead of IRC assessment
	Supplementary Analyses: as supplementary analyses of the primary estimand but with the endpoint of the main estimand
Disease Control	**Endpoint:** Disease Control according to RECIST 1.1 as assessed by IRC **Population:** as primary estimand **Treatment:** as primary estimand **Intercurrent Event Strategy:** as primary estimand **Population Level Summary:** Complete response rate together with 2-sided exact Clopper-Pearson 95% confidence interval
	Sensitivity Analysis: As main estimand, but using Investigator assessment instead of IRC assessment

Endpoint	Estimand Attributes
	Supplementary Analyses: as supplementary analyses of the primary estimand but with the endpoint of the main estimand
Duration of Response	**Endpoint:** Duration of response according to RECIST 1.1 as assessed by IRC, measured by time from first documentation of objective response to PD or death, occurring within 126 days after last evaluable tumor assessment or first study intervention **Population:** Patients with MET amplification determined centrally by FISH (T+), with advanced or metastatic NSCLC harboring activating EGFR mutations and having acquired resistance to prior first-line osimertinib therapy with objective response according to RECIST 1.1 **Treatment:** as primary estimand **Intercurrent Event Strategy:** • Death within 126 days after last evaluable assessment: the intercurrent event will be considered as event of interest (composite strategy) • Discontinuation of treatment: ignoring the intercurrent event (treatment-policy strategy) • Start of subsequent anticancer treatment: ignoring the intercurrent event (treatment-policy strategy) **Population Level Summary:** • Median duration of response based on Kaplan-Meier estimates and 95% 2-sided CI • Kaplan-Meier estimates, including the Kaplan-Meier estimate at 6 months • Rate of participants by response duration categories
	Sensitivity Analyses: As main estimand, but using Investigator assessment instead of IRC assessment
	Supplementary Analyses: • As main estimand and sensitivity analysis, but based on different populations: L+, T+ and/or L+. • As main estimand and sensitivity analysis, but for tepotinib monotherapy as, to be repeated also on populations L+, T+ and/or L+.
PFS	**Endpoint:** Progression-free survival measured by time from first study intervention to PD according to RECIST 1.1 (by IRC) or death, occurring within 126 days after last evaluable assessment or first study intervention **Population:** as primary estimand **Treatment:** as primary estimand **Intercurrent Event Strategy:** • Death within 126 days after last evaluable assessment or first study intervention: the intercurrent event will be considered as event of interest (composite strategy) • Discontinuation of treatment: ignoring the intercurrent event (treatment-policy strategy)

Endpoint	Estimand Attributes
	• Start of subsequent anticancer treatment: ignoring the intercurrent event (treatment-policy strategy) **Population Level Summary:** • Median PFS time based on Kaplan-Meier estimates and 95% 2-sided CI • Kaplan-Meier estimates
	Sensitivity Analyses: • As main estimand, but using Investigator assessment instead of IRC assessment. • As main estimand but censoring participants who discontinued treatment due to COVID-19 before occurrence of an event at the time of event.
	Supplementary Analyses: • As main estimand and sensitivity analysis, but based on different populations: L+, T+ and/or L+. • As main estimand, but considering the start of subsequent anti-cancer therapy as PD (composite strategy), to be repeated also on populations L+, T+ and/or L+. • As main estimand and sensitivity analysis, based on tepotinib monotherapy as treatment., to be performed also on populations L+, T+ and/or L+.
OS	**Endpoint:** OS as measured by time from first study intervention to death **Population:** as primary estimand **Treatment:** Tepotinib combined with osimertinib, taking subsequent anti-cancer therapy into account **Intercurrent Event Strategy:** • Discontinuation of treatment: ignoring the intercurrent event (treatment-policy strategy) • Start of subsequent anticancer treatment: ignoring the intercurrent event (treatment-policy strategy) **Population Level Summary:** • Median OS time based on Kaplan-Meier estimates and 95% 2-sided CI • Kaplan-Meier estimates
	Supplementary Analyses: • As main estimand and sensitivity analysis, but based on different populations: L+, T+ and/or L+
HRQoL	**Endpoint:** Change from baseline in health state as measured by the Visual Analogue Scale (VAS) as a component of the EQ-5D-5L questionnaire; global health status, sub-dimensions of functional scales and symptoms scales as measured by EORTC QLQ-C30; cough, chest pain, dyspnea, fatigue, appetitive and overall severity of symptoms measured by NSCLC-SAQ. **Population:** as primary estimand

Endpoint	Estimand Attributes
	Treatment: as primary estimand **Intercurrent Event Strategy:** • Discontinuation of treatment: ignoring the intercurrent event (treatment-policy strategy) • Start of subsequent anticancer treatment: ignoring the intercurrent event (treatment-policy strategy) **Population Level Summary:** • LS Mean changes from baseline analysis for cough, pain and dyspnea (NSCLC-SAQ) • General descriptive statistics to summarize values and change from baseline by visit
	Supplementary analyses: • As main estimand but based on different populations: L+, T+ and/or L+
Tertiary / exploratory	
CNS (Intra-cranial) response	**Endpoint:** Objective Response according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria as assessed by IRC **Population:** Patients with MET amplification determined centrally by FISH (T+), with advanced or metastatic NSCLC harboring activating EGFR mutations and having acquired resistance to prior first-line osimertinib therapy with baseline lesions in the brain (CNS lesion) **Treatment:** as primary estimand **Intercurrent Event Strategy:** • Discontinuation of treatment: ignoring the intercurrent event (treatment-policy strategy) • Start of subsequent anticancer treatment: ignoring the start of the intercurrent event (treatment-policy strategy) • Progression according to RANO-BM criteria: assessment up to the intercurrent event (while not progressed strategy) **Population Level Summary:** Intracranial response rate together with 2-sided exact Clopper-Pearson 95% confidence interval
	Supplementary analyses: • As main estimand but based on different populations: L+, T+ and/or L+ • Additional population: subgroup of participants with target baseline CNS lesions

14.1 Primary Endpoint: Objective Response by IRC

14.1.1 Derivation and analysis

BOR will be assessed based on reported overall responses at different evaluation time points from the study treatment start date until documented disease progression in accordance with RECIST v1.1, taking requirements for confirmation into account as detailed below. Clinical deterioration will not be considered as documented disease progression. The date of the overall response assessment is the earliest date for imaging of target, non-target and new lesions of images taken at that response assessment.

BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks (28 days) apart (with no PD in between)
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks (28 days) apart (and not qualifying for a CR), with no PD in between
- SD = at least one SD assessment (or better) ≥ 12 weeks (84 days) after the start date of study treatment (and not qualifying for CR or PR)
- PD = PD ≤ 90 days after start date of study treatment (and not qualifying for CR, PR or SD)
- Not Evaluable (NE): all other cases.

There may be uncommon situations where the above rules might need further explanation. Some of these cases are listed below together with the BOR value that should be assigned:

- SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR-SD-SD-PD would be a best response of SD if the minimum duration for SD definition has been met.
- When an unconfirmed PR or CR is assessed at least 12 weeks after the start date of study treatment with no PD before, the best response would be SD.
- When there is an assessment of SD, PR or CR within 12 weeks from the start of study treatment followed by a PD after 90 days, the best response would be NE.

Participants are defined as having an Objective Response (OR) if they achieved either a confirmed BOR of CR or PR according to RECIST v1.1 from first administration of study treatment to first observation of PD.

The OR rate (ORR) is the proportion of participants with OR in the analysis set.

No formal statistical hypotheses will be tested.

The number and percentage of participants with BOR of confirmed CR, confirmed PR, SD, PD, and NE as well as the number of participants achieving objective response, the ORR and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.

BOR and ORR results will be presented for all participants in the mFAS.

Spider plots will show the percent change in the sum of target lesion diameters (sum of longest diameters for non-nodal lesions, short axis for nodal lesions) over time. Different line patterns will distinguish time on and off-treatment. For the participants in the monotherapy arm who switched to the combination treatment, an additional spider plot will be produced presenting the percent change in the sum of target lesion diameters after the switch.

In addition, waterfall plots will show the percent change in sum of target lesion diameters between baseline and the best post-baseline assessment for each participant. Different colors will illustrate the BOR.

The data collected in the "Cytological Assessment for IRC Details" and "Neurological Assessment" eCRF pages will be listed for the FAS.

14.1.2 Sensitivity Analyses

A sensitivity analysis will be conducted in which only tumor assessments performed before the start of any subsequent anti-cancer therapies (i.e., anti-cancer drug treatment, surgery or radiotherapy) will be considered in the assessment of BOR. If a tumor assessment was performed on the same day as start of new anti-cancer therapy, it will be assumed that the tumor assessment was performed prior to the start of the new anti-cancer therapy, therefore the tumor assessment will be included in the assessment of BOR. If only partial dates are known for the start of other anti-cancer treatment or procedures, the imputation rules described in Section 9.9 should be followed. This analysis will be performed for the combination arm only.

A further sensitivity analysis will be performed to display BOR and ORR for the FAS for both treatment arms overall (i.e., with no split by MET amplification test result).

14.1.3 Secondary Analyses

Tumor assessments by IRC vs Investigator assessment

A summary of the IRC assessment versus Investigator assessment in terms of OR will be provided including numbers of concordant and discordant assessments. Concordance is established if the same result in terms of OR (OR achieved: Yes/No) can be reached regardless of whether the IRC or the Investigator assessments are used; on the contrary, different OR results indicate discordance. For OR based on Investigator assessment, see Section 14.2.1.

14.1.4 Subgroup Analyses

Subgroup analyses will be performed on the primary endpoint for all the baseline subgroup levels defined in Section 8.2. Results will be presented for the combination arm only. All subgroup analyses are exploratory and no adjustment for multiplicity will be performed.

For each subgroup, the BOR, the number of participants achieving objective response, the ORR along with the two-sided exact Clopper-Pearson 95% CIs will be presented.

Forest plots will be created to graphically present ORRs and corresponding 95% CIs.

All subgroup analyses will be based on the mFAS.

14.2 Secondary Endpoints

14.2.1 Objective Response by Investigator assessment

BOR and OR based on Investigator assessment will be derived and analyzed as described for the primary endpoint based on IRC assessment (see Section 14.1.1).

The subgroup analysis as described in Section 14.1.1 as well as the sensitivity analysis based on FAS described in Section 14.1.2 will also be repeated based on Investigator assessments.

14.2.2 Confirmed CR by IRC and by Investigator

Participants are identified as having a confirmed CR if they achieve a confirmed CR from first administration of study treatment to first observation of PD, as described in Section 14.1.1.

Complete response rate (confirmed CR) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented by IRC and by Investigator. Complete response rate will also be presented by subgroup.

The sensitivity analyses described in Section 14.1.2 will also be performed.

14.2.3 Duration of Response by IRC and by Investigator

Duration of Response (DOR) will only be evaluated for participants with 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 126 days of the last evaluable tumor assessment, whichever occurs first (see Eisenhauer EA, et all 2009) (i.e., date of PD/death - date of last evaluable tumor assessment $\leq$ 126).

DOR data will be censored on the date of the last evaluable tumor assessment for participants who do not have an event (PD or death) or for participants with an event more than 126 days after the last evaluable tumor assessment (i.e. date of PD/death - date of last evaluable tumor assessment > 126).

The last evaluable tumor assessment is defined as the last tumor assessment result that is not "NE".

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics for duration of response: median and corresponding two-sided 95% confidence interval (CI), Q1 and Q3, minimum and maximum. Progression-free rate estimates at 3, 6, 9, 12, 15, 18 months and for every 3 months thereafter as applicable including the corresponding two-sided 95% CIs will also be reported. The CI for the median will be calculated according to Brookmeyer and Crowley (1982) and CIs 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:

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

Results for DOR as described above will be presented by IRC and Investigator assessments.

Time to and duration of response for every participant will be plotted using a swimmer plot; results will be presented by IRC and by Investigator. Color coded symbols will be used to show the time of the following events: CR, PR, PD, death, ongoing response and end of treatment.

Sensitivitiy analyses

DOR and summary of DOR tables by IRC and Investigator will also be presented for the FAS for both treatment arms overall (i.e., with no split by MET amplification test result).

Subgroup analyses

The Kaplan-Meier based analysis described above will be repeated for all the baseline subgroups identified in Section 8.2. Tables and Kaplan-Meier plots of DOR stratified by these subgroups will be provided. Results will be presented for the combination arm only. The same rules described in the first paragraph of Section 14.1.4 will apply.

Follow-up for duration of response

In order to assess the follow-up for DOR, Kaplan Meier estimates will be calculated reversing the DOR censoring and event indicators.

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for DOR for both IRC and Investigator assessments.

14.2.4 Disease control (confirmed CR + PR or SD lasting at least 12 weeks) by IRC and by Investigator

Participants are identified as having objective disease control (DC) if they achieve either a confirmed CR or PR (as defined in Section 14.1.1), or SD lasting at least 12 weeks (84 days).

DC rate, which is the proportion of participants with DC, and the corresponding two-sided exact Clopper-Pearson 95% CI will be presented by IRC and by Investigator. DC rate will also be presented by subgroup.

The sensitivity analyses described in Section 14.1.2 will also be performed.

14.2.5 Progression Free Survival by IRC and by Investigator

PFS time is defined as the time (in months) from first administration of study treatment to the date of the first documentation of PD or death due to any cause within 126 days of the last tumor assessment, whichever occurs first (i.e., date of PD/death - date of last evaluable tumor assessment ≤ 126).

PFS data will be censored on the date of the last evaluable tumor assessment for participants who do not have an event (PD or death) or for participants with an event more than 126 days after the last tumor assessment (i.e. date of PD/death - date of last evaluable tumor assessment > 126).

The last evaluable tumor assessment is defined as the last tumor assessment result that is not "NE".

Participants who do not have an evaluable post-baseline tumor assessment will be censored at the date of the start of study treatment unless death occurred within 126 days of the first dose of study treatment in which case the death will be considered an event.

If a participant has only not evaluable tumor assessments prior to a PD which is within 126 days of the first dose of study treatment, the PD will be considered an event; if the PD is after the 126 days, the PFS will be censored at the date of first dose.

The censoring and event date options to be considered for the PFS are presented in Table 6.

Table 6. Date of event / censoring definition for PFS analysis

Status		Censoring	Date of event / censoring
Progressed or died	Within 126 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 the 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 the start of treatment, whatever is later

Kaplan-Meier product-limit estimates will be presented together with a summary of associated statistics for PFS: median and corresponding two-sided 95% confidence interval (CI), Q1 and Q3, minimum and maximum. Progression-free rate estimates at 3, 6, 9, 12, 15, 18 months and for every 3 months thereafter as applicable including the corresponding two-sided 95% CIs will also be reported. The CI for the median will be calculated according to Brookmeyer and Crowley (1982) and CIs 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.

Results for PFS as described above will be presented by IRC and Investigator assessments.

The above analyses for PFS will be repeated considering the start of any other anti-cancer treatment as PD (see Section 14.1.2). This sensitivity analysis will be based on IRC assessments.

The censoring and event status with respect to PFS and based on IRC assessments will be summarized.

Subgroup analyses

Subgroup analyses as described for DOR in Section 14.2.3 will be repeated for PFS.

PFS event: IRC versus Investigator

A summary of the IRC assessment versus Investigator assessment in terms of PFS will be provided including numbers of concordant and discordant assessments.

Follow-Up Duration of PFS

In order to assess the follow-up duration of PFS, Kaplan Meier estimates will be calculated reversing the PFS censoring and event indicators.

Kaplan-Meier estimates (product-limit estimates) will be presented in the same way as in the analysis described above for PFS for both IRC and Investigator assessments.

14.2.6 Overall Survival

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

For participants not known to be deceased at time of analysis or who died after the cut-off date, OS time will be censored at the date of last contact before data cut-off date as defined in Section 9.7.

The Kaplan-Meier based analysis described in Section 14.2.5 for the derivation of progression-free related estimates will be repeated for the survival related estimates.

The censoring and event status with respect to OS will be summarized.

OS analysis will be performed on the combination arm only.

Subgroup analyses

Subgroup analyses as described for DOR in Section 14.2.3 will be repeated for OS.

Follow-Up Duration of OS

In order to assess the follow-up duration of OS, Kaplan Meier estimates will be calculated reversing the OS censoring and event indicators.

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

This analysis will be performed on the combination arm only.

14.2.7 Patient Reported Outcomes

There are three PRO questionnaires expected to be filled in by the participants at each of the scheduled assessments: EQ-5D-5L, EORTC QLQ-C30 and NSCLC-SAQ. Results will be presented as described in Sections 8.1.1 and 8.1.2, but only for the combination arm. Data collected will be listed for both treatment arms.

For the definition of baseline, the same rules specified in Section 9.4 will be applied.

Questionnaires collected at the end of treatment (EOT) visit or at the safety follow-up (Safety FU) visit will be pooled together because, 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 as well as for the longitudinal analysis.

For each questionnaire, the change from baseline of dimension/domain scores as well as total scores will be presented using box and whiskers plots.

Only visits available for more than 10 participants will be included in tables and plots; on the other hand, the EOT/Safety FU visit will always be presented.

Questionnaire Completion

For each questionnaire and scheduled visit (i.e. Baseline, Cycle 3 Day 1, Cycle 5 Day 1, etc, EOT/Safety FU), the following will be summarized:

- Number and percentage of participants with an expected questionnaire
- Questionnaire completion: Number and percentage of participants who completed the questionnaire. Percentages will be calculated twice, as:

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

and

$$\%\ Questionnaire\ Completion = 100 \times \frac{number\ of\ subjects\ with\ all\ questionnaire\ items\ available}{number\ of\ subjects\ in\ the\ respective\ analysis\ set}$$

Number and percentage of participants who did not complete the questionnaire, by reason for non completion.

- Questionnaire compliance: Number and percentage of participants with an evaluable questionnaire, i.e., scores for each dimension/domain can be calculated.

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

and

$$\%\ Compliance = 100 \times \frac{number\ of\ subjects\ with\ evaluable\ questionnaire}{number\ of\ subjects\ in\ the\ respective\ analysis\ set}$$

Of note, the number of participants with an expected questionnaire, according to the protocol schedule of assessments, will be used as denominator for percentages. A questionnaire is expected in the following cases:

- the participant attended a scheduled visit where the questionnaire was required to be completed;
- the participant missed a visit where the questionnaire was required to be completed but he/she attended the following visit.

EQ-5D-5L

The EQ-5D-5L consists of 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression) and each dimension has 5 levels: no problems (1 = best), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5 = worst). In addition, participants will provide a global assessment of their health through the EQ VAS score: it goes from 100 (best imaginable heath) to 0 (worst imaginable health).

Baseline, post-baseline and change from baseline values of the EQ VAS score will be summarized at each time point. The number and percentage of participants whose score has improved, not changed or worsened will also be presented.

For each participant, EQ-5D-5L dimension scores and the EQ VAS score over time will be listed.

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 for that component will be set to missing, otherwise the mean of non-missing items will be calculated. Table 7 contains the instructions to be followed to calculate the scores.

Baseline, post-baseline and change from baseline values in each sub-dimension will be summarized at each time point. The number and percentage of participants whose scores have improved, not changed or worsened will also be presented.

Listings of each item and sub-dimension scores over time will be provided for each participant.

Table 7. Scoring the QLQ-C30 (version 3.0)

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

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

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

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

Then for **Functional scales**:

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

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

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

A higher score for a functional scale or for the Global Health Status indicates a more healthy level of functioning or higher quality of life, respectively; on the contrary, a high score for a symptom scale represents a high level of symptomatology.

NSCLC-SAQ (version 1.0)

The NSCLC-SAQ consists of seven items covering five domains: Cough, Pain, Dyspnea, Fatigue, and Appetite. All five of these domains must be non-missing to compute a total score. Pain and Fatigue domains each contain two items.

Table 8 contains the instructions to be followed to calculate the score for each of the 5 domains as well as the total score. Higher scores indicate more severe NSCLC-related symptomatology.

Table 8. Scoring the NSCLC-SAQ

Domain	Item		Response
Cough	1. How would you rate your coughing at its worst…?		0, 1, 2, 3, 4
Pain	2. How would you rate the worst pain in your chest…? 3. How would you rate the worst pain in areas other than your chest…?	*Create a single score by selecting the highest severity (i.e., value) on either item*	0, 1, 2, 3, 4
Dyspnea	4. How often did you feel short of breath during usual activities…?		0, 1, 2, 3, 4
Fatigue	5. How often did you have low energy…? 6. How often did you tire easily…?	*Create a single score by calculating the mean of these 2 items*	0, 1, 2, 3, 4
Appetite	7. How often did you have a poor appetite over the last 7 days?		0, 1, 2, 3, 4
NSCLC-SAQ Total Score (Sum the 5 domains)			**Range 0 to 20**

If a respondent is missing any of the five domain scores, his or her NSCLC-SAQ total score will not be computed. If one of the Pain or Fatigue items is missing, the available item will be used as domain score; if both items are missing, the domain score will be set to missing.

Baseline, post-baseline and change from baseline values for each domain and for the total score will be summarized at each time point. The number and percentage of participants whose scores have improved, not changed or worsened will also be presented.

Listings of single items and sub-dimension scores over time will be provided.

Longitudinal analysis of change from baseline

A mixed-effect model repeated measures (MMRM) analysis will evaluate longitudinal change from baseline. This analysis will be performed on the combination arm (mFAS) only. The following PRO scores will be analyzed:

- Cough (NSCLC-SAQ; item 1)
- Pain (NSCLC-SAQ; items 2 and 3)
- Dyspnea (NSCLC-SAQ; item 4).

A distinct MMRM will be run for the T+, L+ and Combined (T+ and/or L+) participants in the combination arm. The model will include change from baseline as a dependent variable and analysis visit (as defined in Section 9.8) and baseline PRO score as covariates and baseline PRO score by analysis visit interaction to account for a non-constant baseline effect across visits.

An unstructured covariance matrix will be used to model the within-subject error. In case the fit fails to converge or if convergence is unreliable (e.g. problems to make hessian matrix positive definite), the best variance-covariance pattern will be chosen based on the model fit using the Akaike's Information Criterion among Toeplitz, first-order autoregressive and variance components. 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. No subgroup analysis planned.

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 85 (Week 12, i.e. Cycle 5 Day 1), Day 169 (Week 24, i.e. Cycle 9 Day 1), Day 253 (Week 36, i.e. Cycle 13 Day 1), Day 337 (Week 48, i.e. Cycle 17 Day 1), Day 421 (Week 60, i.e. Cycle 21 Day 1) and every 12 weeks thereafter. Additionally, a line plot will be produced.

Technical details on the analysis described above are available in Appendix 5.

The week 12 assessment collected at Cycle 5 Day 1 is considered a key timepoint for comparative PRO evaluations. This time point would minimize loss of data due to deaths and disease progression and most participants are expected to be still exposed to treatment. Changes in symptoms as reported by the participants may manifest or likely occur at that time-point.

It is anticipated that the key symptoms pain, cough and dyspnea might remain stable or improve within the first 12 weeks after treatment initiation. The threshold for maintenance should ideally correspond to the anchor based on published and validated Minimum Important Difference. If not available, Cohen's d will be calculated and an absolute threshold of 0.2 used as non-relevance threshold.

In order to calculate the Cohen's d, the following formula will be applied:

$$\mathrm{d} = \frac{mean_{CHG}}{SD_{CHG}}$$

where

- $mean_{CHG}$ is the arithmetic mean of the change from baseline at Cycle 5 Day 1
- SD_{CHG} is the sample standard deviation of the change from baseline at Cycle 5 Day 1 calculated as follows

$$SD_{CHG} = \frac{1}{n-1}\sqrt{\sum_{i=1}^{n}(d_i - mean_{CHG})^2}$$

where n is the number of participants for which the change from baseline is not missing (i.e., both baseline and Cycle 5 Day 1 scores are available).

In addition, a bar chart presenting the change from baseline over time categorized as "Improved", "No change" "Worsened" will also be produced.

14.3 Tertiary/Exploratory Analysis

14.3.1 Central Nervous System (CNS) Tumor Response

Data used to perform the analyses described in the following sections will be provided by the vendor who performs the overall IRC tumor assessment and will be based on Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (Lin et al., 2015). This evaluation will not continue beyond the switch from monotherapy to combination treatment.

Unless stated otherwise, results from these analyses will be presented in tables and figures for all the participants in the combination arm from the FAS with baseline CNS metastases as defined below. Results from all the participants with baseline brain metastases will be listed.

CNS response may also be cited as "intracranial response".

14.3.1.1 Best Overall Response, Objective Response and Disease Control

Best Overall response (BOR) will be derived for all participants who undergo the brain evaluation perfomed by IRC following the RANO-BM criteria and for whom baseline CNS metastases were detected. Baseline CNS metastases are defined as metastases with "BRAIN" as location, either of target, enhancing non-target or non-enhancing non-target lesion. BOR will be derived based on IRC reported overall response assessments from the study treatment start date until documented disease progression, taking requirements for confirmation into account as detailed below.

BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks (28 days) apart (with no prior PD or PD in between)
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks (28 days) apart (and not qualifying for a CR), with no prior PD or PD in between
- SD = at least one SD assessment (or better) after the start date of study treatment with no prior PD (and not qualifying for CR or PR)
- Non-CR/non-PD (applicable only to participants without any target lesion at baseline) = at least one non-CR/non-PD assessment (or better) after start date without prior PD (and not qualifying for CR)
- PD = PD ≤ 90 days after start date of study treatment (and not qualifying for CR, PR, SD or Non-CR/non-PD as applicable)

- Not Evaluable (NE): all other cases

OR

Participants are defined as having an OR if they achieved either a confirmed BOR of CR or PR from first administration of study treatment to first observation of PD.

DC

Participants are identified as having objective DC if:

- They had a CNS target lesion at baseline and achieve a BOR of confirmed CR, PR or SD without prior PD
- They had only CNS non-target lesions at baseline and achieve a BOR of confirmed CR or non-CR/non-PD without prior PD

The number and proportion of participants with BOR of confirmed CR, confirmed PR, SD, Non-CR/non-PD, PD, and NE as well as the number and proportion of participants achieving OR and DC and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented. The number of participants with CNS baseline metastases (measurable and non-measurable disease) will be the denominator to derive percentages in this analysis.

Additionally, the number and proportion of participants with BOR of confirmed CR, confirmed PR, SD, PD, and NE as well as the number and proportion of participants achieving OR and the corresponding 2-sided exact Clopper-Pearson 95% CI will be tabulated for the subset of participants with target CNS baseline metastases (measurable disease). The number of participants with target CNS baseline metastases will be the denominator to derive percentages in this analysis.

A Spider plot will show the percent change in the sum of CNS target lesion diameters over time for each participant in the combination arm with target CNS baseline metastases who belongs to the mFAS. Different line patterns will distinguish time on and off-treatment.

In addition, a waterfall plot will show the percent change in sum of target lesion longest diameters between baseline and the best post-baseline assessment for each participant in the combination arm with target CNS baseline metastases who belongs to the mFAS. Different colours will illustrate the intracranial BOR.

For all the participants in the FAS who underwent this brain evaluation, data collected from the evaluation of the brain imaging and related response will be listed.

14.3.1.2 Duration of Response

The DOR will only be evaluated in participants with an OR (as defined in Section 14.3.1.1).

DOR is the time from when the CR/PR (whichever is first) criteria are first met until CNS PD or death due to any cause, within 126 days of the last evaluable tumor assessment, whichever occurs first (see Eisenhauer EA, et all 2009) (i.e., date of PD/death - date of last evaluable tumor assessment ≤ 126).

DOR data will be censored on the date of the last evaluable tumor assessment for participants who do not have an event (PD or death) or for participants with an event more than 126 days after the last evaluable tumor assessment (i.e. date of PD/death - date of last evaluable tumor assessment > 126).

The last evaluable tumor assessment is defined as the last CNS tumor assessment result that is not "NE".

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics. In addition, a swimmer plot will be produced to present the time and duration of response. See Section 14.2.3 for more details.

14.3.1.3 Progression Free Survival

PFS time is defined as the time (in months) from first administration of study treatment to the date of the first documentation of CNS PD or death due to any cause within 126 days of the last evaluable CNS tumor assessment, whichever occurs first (i.e., date of PD/death - date of last evaluable tumor assessment ≤ 126).

The PFS data will be censored on the date of the last evaluable CNS tumor assessment for participants who do not have an event (PD or death) or for participants with an event more than 126 days after the last evaluable CNS tumor assessment (i.e. date of PD/death - date of last evaluable tumor assessment > 126).

The last evaluable tumor assessment is defined as the last CNS tumor assessment result that is not "NE".

Participants who do not have an evaluable post-baseline CNS tumor assessment will be censored at the date of the start of study treatment unless death occurred within 126 days of the first dose of study treatment in which case the death will be considered an event.

If a participant has only not evaluable CNS tumor assessments prior to a PD which is within 126 days of the first dose of study treatment, the PD will be considered an event; if the PD is after the 126 days, the PFS will be censored at the date of first dose.

The censoring and event date options to be considered for the PFS are presented in **Error! Reference source not found.**.

Table 9. Date of event / censoring definition for PFS analysis

Status		Censoring	Date of event / censoring
Progressed or died	Within 126 days after last response assessment of CR, PR, SD, 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, non-CR/non-PD or date of the start of treatment, whatever is later

Neither progressed nor died	Censored	Date of last tumor assessment with outcome CR, PR, SD, non-CR/non-PD or date of the start of treatment, whatever is later

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics as described in Section 14.2.5.

15 Safety Analyses

The primary safety endpoint analysis will be performed on the SRIAS analysis set whereas the secondary safety endpoint analyses will be performed on the SAF analysis set. Results will be presented as described in Sections 8.1.1 and 8.1.2, unless stated otherwise.

Unless stated otherwise, for those participants in the monotherapy arm who switch to the combination treatment, any safety assessment such as laboratory test, vital signs, ECOG Performance Status, ECG collected after Period 1 (see Table 3) will not be presented in tables (either summary or shift tables) or figures but only listed. Any change from baseline or percent change from baseline will be calculated using the baseline of Period 1.

The safety analyses will be done purely descriptively.

15.1 Primary Endpoint: Occurrence of DLTs during Cycle 1 of the Safety Run-In Period

The number and percentage of participants in the SRIAS analysis set with no DLT, 1 DLT or 2 or more DLTs observed during the DLT observation period (21 days after start of study treatment) will be tabulated together with the respective SOCs and PTs as well as the number of participants with any treatment emergent adverse event (TEAE) during Cycle 1. See Section 8.1 for the definition of DLT.

All relevant data for DLTs will also be listed.

15.2 Secondary Endpoints

15.2.1 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 5.0) toxicity grades.

Relationship with the study treatment components are collected in the “Adverse Events Details” eCRF page. Adverse Events can be related to tepotinib, osimertinib or both, depending on the treatment arm and period (see Table 3). As a general rule, if the relationship information is missing for a study treatment component, the AE will be considered as related to that component. On the other hand, if for a participant that belongs to the monotherapy arm and has switched, the AE

started or changed in toxicity grade in Period 1 and the relationship is missing for osimertinib, the AE will be considered as unrelated to osimertinib.

Incomplete AE-related dates will be handled as specified in Section 9.9.

TEAEs are those events that started during the on-treatment periods (see Section 9.3), or before Period 1 and worsened during the on-treatment periods. This includes also AEs ongoing at baseline, which first improve under study treatment and then worsen irrespective of baseline. The rules defined in Table 10 will be used to assign TEAEs to the on-treatment periods. Any AE occurring before Period 1 and resolved before Period 1 or not worsening during the on-treatment periods will be included in the AE listings, but will not be included in the TEAE summary tables (unless otherwise stated). Adverse events with changes in toxicity grade are recorded as separate entries in the eCRF with associated end and start dates (start date equals end date of previous entry, supported in eCRF by 'AENEWID' in SUPPAE). Records of the same AE will be considered as one event in the analysis. These events will be kept as separate records in the database in order to maintain the full detailed history of the events. In AE listings, records that are part of the same AE will be grouped together and presented in chronological order. If the severity of the reported event worsens after start of treatment, the TEAE flag will be re-evaluated for the worse and the subsequent records as per the TEAE definition: once one record is considered treatment emergent, all the subsequent records will be considered treatment emergent too, even if starting after the on-treatment periods.

All analyses described in Sections 15.2.2 and 15.2.3 will be based on TEAEs belonging to Period 1, if not otherwise specified. The AE listings will include all AEs (whether treatment emergent or not). A flag will be added to indicate if the AE is treatment emergent and in which period.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest and sorted by primary SOC and PT in alphabetic order.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within an SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

Table 10. Assignment of TEAEs to the on-treatment periods

	TEAE in Period 1	TEAE in Period 2
Starts before Period 1 and worsens during Period 1	X	
Starts before Period 1 and worsens during Period 2		X
Starts in Period 1 (regardless of worsening in Period 2)	X	
Starts in Period 2		X

15.2.2 All Adverse Events

Adverse Event information is collected on the "Adverse Events Details" eCRF page.

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using the latest version of MedDRA PT as event category and MedDRA primary SOC body term as Body System category.

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

The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following:

- TEAEs
- Study treatment related TEAEs (any study treatment and by study treatment components)
- Serious TEAEs
- Study treatment related serious TEAEs (any study treatment and by study treatment components)
- TEAEs with NCI-CTCAE Grade ≥ 3 and ≥ 4
- Study treatment related TEAEs with NCI-CTCAE Grade ≥ 3 and ≥ 4 (any study treatment and by study treatment components)
- TEAEs leading to death
- Study treatment related TEAEs leading to death (any study treatment and by study treatment components)
- Adverse Events of Special Interest (AESIs)

Adverse events of special interest are defined as events suggestive of drug-induced liver injury including hepatic / liver failure and hepatitis (non-infectious). Adverse Events of Special Interest (AESI) will be identified according to a pre-specified search list provided by the Sponsor Safety Lead using the last available version of MedDRA Preferred Terms at the time of each analysis.

In addition, the following tables summarizing the frequency of participants with TEAEs by SOC and PT will be produced:

- TEAEs
- Study treatment related TEAEs (any study treatment and by study treatment components)
- Serious TEAEs
- Non-serious TEAEs applying a frequency threshold of 5%
- Study treatment related serious TEAEs (any study treatment and by study treatment components)
- TEAEs by worst NCI-CTCAE Grade (Any, ≥ 3, ≥ 4 and 5)
- Study treatment related TEAEs by worst NCI-CTCAE Grade (Any, ≥ 3, ≥ 4 and 5) (any study treatment and by study treatment components)

- TEAEs leading to death
- Study treatment related TEAEs leading to death (any study treatment and by study treatment components)
- Adverse Events of Special Interest (AESIs)

Participant listings of AE details collected on the "Adverse Events Details" eCRF page will also be provided:

- AEs
- AESIs
- Serious TEAEs

The overall AE summary table as well as the TEAEs by SOC and PT table will be repeated if there are at least 6 participants in the monotherapy arm who switch to the combination treatment. For these tables, all TEAEs from both Period 1 and Period 2 (see Table 10) will be considered. Results will be presented overall, i.e. there will be no split by MET amplification test result.

15.2.3 Adverse Events Leading to Discontinuation / Dose Reduction of Study Treatment

The frequency (number and percentage) of participants with each of the following will be presented in a summary table:

- TEAEs leading to temporary discontinuation of study treatment (any study treatment and by study treatment components)
- Study treatment related TEAEs leading to temporary discontinuation of study treatment (any study treatment and by study treatment components)
- TEAEs leading to permanent discontinuation of study treatment (any study treatment and by study treatment components)
- Study treatment related TEAEs leading to permanent discontinuation of study treatment (any study treatment and by study treatment components)
- TEAEs leading to dose reduction of study treatment (any study treatment and by study treatment components)
- Study treatment related TEAEs leading to dose reduction of study treatment (any study treatment and by study treatment components)

In addition, tables summarizing the frequency of participants with AEs, presented by SOC and PT, in the above categories will be prepared. Tables summarizing TEAEs related to study treatment will be created to summarize TEAEs related to any study treatment and will be repeated to summarize TEAEs related to specific study treatment components (i.e. tepotinib and osimertinib).

Actions that can be taken by the Investigator to address an Adverse Event are collected by sections "Action(s) taken with Tepotinib" and "Action(s) taken with Osimertinib" on the "Adverse Events

Details" eCRF page. It is possible that a TEAE leads to more than one action: for example, a drug interruption followed by drug withdrawal. In this case, the TEAE will be counted among the TEAEs leading to temporary discontinuation as well as among the TEAEs leading to permanent discontinuation.

Participant listings showing the relevant information will also be provided:

- AEs leading to permanent discontinuation of study treatment
- AE leading to temporary discontinuation of study treatment

In case the AE leading to temporary or permanent discontinuation of study treatment is composed of several episodes with different toxicity grades or other characteristics, all the occurencies of this AE will be listed.

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

15.3.1 Deaths

Deaths from both Period 1 and Period 2 (see Table 3), deaths within 30 days after last dose of study treatment, deaths within 60 days after the first dose of study treatment, as well as reason for death, will be tabulated based on information from the "Death" eCRF page.

- Number of deaths overall and by primary reason
- Number of deaths within 30 days after the last dose of study treatment overall and by primary reason
- Number of deaths within 60 days after the first dose of study treatment overall and by primary reason

Primary reasons for death can be:

- Progressive disease and/or disease related condition
- Event unrelated to tepotinib and osimertinib
- Event related to tepotinib
- Event related to osimertinib
- Event related to tepotinib and osimertinib
- Unknown
- Missing

In addition, the date and cause of death will be provided in an individual participant data listing together with selected dosing information (date of first / last administration). This listing will also include:

- AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)

- Flag for death within 30 days of last study treatment
- Flag for death within 60 days of first study treatment

Deaths that occured during Period 2 will be flagged.

15.3.2 Serious Adverse Events

Please see Section 15.2.2 for the analysis of serious TEAEs.

A listing of serious TEAEs will also be provided.

15.3.3 Other Significant Adverse Events

Please see Section 15.2.2 for the analysis of AEs of special interest.

15.4 Clinical Laboratory Evaluation

Laboratory assessments such as hematology and coagulation, biochemistry, urinalysis and other screening tests (e.g., pregnancy tests) will be performed by local laboratories.

Laboratory results will be classified according to the NCI-CTCAE criteria version 5.0. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Baseline and change from baseline definitions are in Section 9.4.

Values below the detection limit will be imputed by half of the detection limit.

If a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g., "> 7.2 mmol" will be analyzed as 7.3.

Quantitative data will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and absolute changes from baseline to each scheduled visit over time. Only baseline and on-treatment values will be summarized. In addition, with the exception of the baseline, end of treatment and safety follow-up visits, all the other visits will be presented if the data are available for at least 6 participants overall.

Qualitative data based on reference ranges will be described according to the categories Low, Normal, and High (Hematology, Biochemistry and Coagulation). For qualitative data of urinalysis measurements, the raw classifications Normal, Trace/+, ++, +++, ++++ will be used instead. Results from the urinalysis microscopic examination (Erythrocytes, Leukocytes, Epithelial cells, Bacteria, Crystals and Casts) will only be listed.

Abnormalities classified according to NCI-CTCAE toxicity grading version will be described using the worst on-treatment grade. Measurements from both scheduled and unscheduled visits performed during Period 1 (see Table 3) will be considered for the worst on-treatment grade derivation. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa. For the biochemistry parameters alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, gamma glutamyl transferase and creatinine, the on-treatment grading is dependent upon the normality or abnormality of the baseline value; in such cases, the worst on-treatment grading will also be displayed according to the baseline grading (normal vs abnormal).

Derived Biochemistry Parameters

Creatinine clearance

24-hour creatinine clearance and/or creatinine clearance (Cockcroft-Gault) measurements are only collected at screening. Therefore, in order to monitor the renal impairment during the study, creatinine clearance (mL/min) will be calculated by the Cockcroft-Gault formula as

$$\frac{\{[140 - age(year)] \times weight(kg)\}}{72 \times serum\ creatinine\left(^{mg}/_{dL}\right)} \times [0.85\ for\ females]$$

Age at the date of the creatinine collection (only the integer part should be considered) and the closest measurement of weight to the date of creatinine collection will be used. See Section 9.6 for the conversion of serum creatinine from umol/L to mg/dL.

For the reference ranges, the following rules will be applied for each participant:

- if creatinine clearance (Cockcroft-Gault) is measured at screening and the reference ranges are available, these reference ranges will be used for all the collected or derived values;

- if creatinine clearance (Cockcroft-Gault) is not measured at screening and/or the reference ranges are not available, the reference ranges reported in Section 18.3 will be used for all the collected or derived values.

The derived creatinine clearance will be analysed and presented as a non-gradable parameter in tables and listings. The creatinine clearance values collected only at the screening visit and reported in the eCRF will only be listed.

Calcium

Total calcium, corrected calcium and ionized calcium will be collected in the eCRF when available. In case the corrected calcium is not provided but both the total calcium and the serum albumin are available, the corrected calcium will be calculated as

corrected calcium (mmol/L) = total calcium (mmol/L) + 0.02 × [40 - serum albumin (g/L)]

Therefore, the derived corrected calcium parameter will consider the values collected in the eCRF for corrected calcium if available, otherwise the values will be derived using the formula above when possible.

For the reference ranges of the derived corrected calcium, the following rules will be applied for each participant:

- if corrected calcium is measured at least once and the reference ranges are available, the reference ranges from the first measurement will be used for all the collected or derived values;
- if corrected calcium is never measured and/or the reference ranges are not available, the reference ranges reported in Section 18.3 will be used for all the collected or derived values.

All the calcium parameters collected in the eCRF as well as the derived corrected calcium will be listed. Only the total calcium and the derived corrected calcium will be tabulated as appropriate.

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of the test result over the upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment periods.

The summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment periods will be summarized by treatment group:

- ALT < 3×ULN, ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST < 3×ULN, AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT and AST) < 3×ULN, (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI < 2×ULN, TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and Alkaline Phosphatase (ALP) > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing.

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥ 10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN.

Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage. An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created by graphically displaying:

- Peak serum ALT(/ULN) versus peak total bilirubin (/ULN) including reference lines at ALT = 3×ULN and total bilirubin = 2×ULN
- Peak serum AST(/ULN) versus peak total bilirubin (/ULN) including reference lines at AST = 3×ULN and total bilirubin = 2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a post-baseline TBILI ≥ 2×ULN, ALT ≥ 3×ULN or AST ≥ 3×ULN will be provided.

Parameters with NCI-CTC grades available:

Laboratory toxicities will be tabulated (count and percentage) for each gradable parameter by the worst on-treatment CTCAE grade. Shifts from baseline to worst CTCAE grade during the on-treatment period will also be tabulated. The denominator to calculate percentages for each laboratory parameter is the number of participants in each analyzed group. Participants without baseline or on-treatment post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

Please see Section 18.1 for a list of the CTCAE-gradable parameters.

Parameters with NCI-CTC grades not available:

Laboratory abnormalities will be tabulated (count and percentage) for each non-gradable parameter by the worst on-treatment abnormality. For each parameter, shift tables from baseline to the maximum post-baseline as well as the minimum post-baseline on-treatment value will be presented. The denominator to calculate percentages for each laboratory parameter is the number of participants in each analyzed group. Participants without baseline or post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

The following figures will be provided for each above-mentioned test:

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

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, bilirubin, creatinine.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameter and assessment dates or visits for each participant. Laboratory values that are outside the normal range will be flagged in the data listings, along with corresponding normal ranges and CTCAE grades. The coagulation parameter Activated Partial Thromboplastin Time/Standard Ratio will only be listed as it is only reported for a restricted number of sites.

Results from pregnancy tests, both serum and urine, collected on the "Pregnancy Test" eCRF page will be listed together with Follicle-stimulating Hormone and Estradiol values collected at the screening visit.

15.5 Vital Signs

The maximum change (increase and decrease) in each vital sign measurement from baseline (where baseline is defined in Section 9.4) across on-treatment scheduled and unscheduled visits performed during Period 1 will be derived, as shown below for each participant. See Section 9.3 for the definition of on-treatment periods.

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 participants in each category will be presented as a shift table showing baseline category versus the maximum change. The denominator to calculate percentages for each vital sign parameter is the number of participants in each analyzed group. Participants without baseline or post-baseline results for a given parameter will be presented in the "Missing" category and will contribute to the denominator.

For body weight, the number and percentage of participants with a maximum on-treatment percent change from baseline increase and decrease will be presented. Categories will be: < 10%, ≥ 10% and missing. Those participants with no baseline and/or post-baseline measurement will be presented in the "Missing" category.

A participant data listing will present the baseline and maximum changes (increases and decreases) in each vital sign measurement. A listing presenting all vital sign measurements will also be produced. A flag will be used to indicate which measurements belong to the on-treatment periods.

15.6 Other Safety or Tolerability Evaluations

15.6.1 ECOG Performance Status

ECOG Performance Status information is collected on the "ECOG Performance Status" eCRF page.

ECOG Performance Status will be summarized using shift tables showing baseline versus minimum and maximum on-treatment values. Participants without baseline or on-treatment results from Period 1 will be presented in the "Missing" category and will contribute to the denominator. See Section 9.3 for the definition of on-treatment periods.

Listings of each participant's ECOG Performance Status over time will be provided. A flag will be used to indicate which measurements belong to the on-treatment periods.

15.6.2 Electrocardiogram (ECG)

Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTcF intervals. Electrocardiogram (ECG) results will be read locally and only one reading per visit will be performed.

For each of the ECG parameters (HR and QT, derived QTcF, QRS, PR intervals), descriptive statistics at baseline, at each on-treatment time point and changes from baseline at each on-treatment time point for scheduled visits will be presented. In addition, with the exception of the baseline, end of treatment and safety follow-up visits, all the other visits will be presented if the data are available for at least 6 participants overall.

The ECG assessment [Normal, Abnormal (not clinically significant), Abnormal (clinically significant)] will be presented as a shift table showing baseline versus the worst on-treatment result measured during Period 1. See Section 9.3 for the definition of on-treatment periods.

The change in QT interval corrected for the heart rate by the Fridericia's formula (i.e., QTcF) between baseline and the worst (maximum) 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)	≤ 450 ms > 450 ms > 480 ms > 500 ms	≤ 450 ms > 450 ms > 480 ms > 500 ms

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

Parameter	Baseline category	Worst change from baseline
QTc (Fridericia)	≤ 450 ms > 450 ms > 480 ms > 500 ms	≤ 30 ms > 30 ms > 60 ms

The QTcF will be collected in the eCRF page; if the ECG machine only provides the QT interval corrected with the Bazett formula (QTcB), the eCRF will automatically calculate the QTcF. If both QTcF and QTcB values are reported in the eCRF, two QTcF values will be available. In this case, only the QTcF and QTcB values reported by the Investigator in the eCRF will be listed.

For analysis purposes, the QTcF value will be derived as:

$$QTcF\ (msec) = \frac{QT\ (msec)}{\sqrt[3]{\frac{60}{HR\ (beats/min)}}}$$

The derived QTcF will be presented in the summary table, listed and used for the shift tables described above.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the derivation of worst on-treatment values.

Listings of all participants ECG results will be presented. A flag will be used to indicate which measurements belong to the on-treatment periods.

Echocardiogram results from measurements performed at screening and at the end of treatment visit will also be listed.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

16.1.1 Concentration Data

Tepotinib and metabolite (MSC2571109A and MSC2571107A), and osimertinib and metabolite (AZD5104) concentrations in plasma will be listed and presented in tables, and descriptively summarized by treatment,day, and scheduled time point. For calculation of descriptive statistics of concentration data, values that are below the limit of quantification (i.e., BLQ; values that are below the lower limit of quantification [LLOQ]) will be set to zero. Descriptive summary tables and data listings will be prepared separately for the Rich PK Sampling subjects (i.e., Safety Run-in subjects) and the Sparse PK Sampling subjects. Pharmacokinetic concentrations will be

summarized by PK analyte, treatment arm (for Sparse PK Sampling subjects only), cycle/day, and nominal time, as described in Section 8.

The following plots will be prepared for the Rich PK Sampling Subject group:

- By-participant plots: Individual (i.e., by- participant) plasma concentration-time plots (one plot per participant, with both days overlaid) will be plotted separately by analyte (i.e., tepotinib, MSC2571109A, MSC2571107A, osimertinib, and AZD5104) on linear and semi-logarithmic scales using actual time points.
- Spaghetti plots: Spaghetti plots overlaying all participants' concentration-time profiles (linear and semi-logarithmic scales) will be plotted by day for each of the 5 analytes separately (i.e., tepotinib, MSC2571109A, MSC2571107A, osimertinib, and AZD5104) using actual time points.
- Mean plots: Mean plasma concentration time plots with both days overlaid will be plotted separately by analyte (i.e., tepotinib, MSC2571109A, MSC2571107A, osimertinib, and AZD5104) on linear (±StDev) and semi-logarithmic scales using scheduled time points.

A listing of PK blood sample collection times by individual as well as derived sampling deviations will be provided for all subjects with collected PK data. Data excluded from the PK analysis set will be flagged, along with the reason for exclusion.

The PK data from this study will also be analyzed jointly with data from other tepotinib studies using a non-linear mixed effect approach. The details of this population PK analysis will be described in a separate Data Analysis Plan, and results will be reported separately.

16.1.2 Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA) will be used to derive PK parameters applying Non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.4 or higher) may be used to generate additional PK parameters, produce tables, listings and figures.

For participants in the Rich PK Sampling group (i.e., Safety Run-in subjects), PK parameters will be calculated using standard non-compartmental methods. Actual elapsed sampling times and the actual administered dose will be used for calculation of parameters for the final analysis (after database lock). For SMC meetings or IDMC meetings, nominal times and doses will be used for calculation.. The PK parameters listed below will be calculated for tepotinib and metabolites (MSC2571109A and MSC2571107A) and for osimertinib and its metabolite (AZD5104) in plasma, when applicable.

C_{max}	Maximum observed concentration

t_{max}	Time of C_{max}
AUC_{0-t}	Area under the concentration-time curve from time zero to the last quantifiable concentration
AUC_{0-12}	Area under the concentration-time curve over the dosing interval from T_1=0 h (predose) to T_2=12 h. Calculated using the mixed log linear trapezoidal rule (linear up, log down). AUC_{0-12} on both Day 1 and Day 15 of Cycle 1 will be calculated as a partial area within the defined time range. If there is a time deviation at the 12-hour time point or the concentration is missing, the AUC will be interpolated to 12 hours.
t_{lag}	Time prior to the first quantifiable (non-zero) concentration (for Cycle 1 Day 1 only)
C_{av}	Average concentration at steady state, calculated on Cycle 1 Day 15 only. $C_{av} = AUC_\tau / \tau$ (AUC_{0-t} if necessary).
C_{min}	Minimum observed concentration during a complete dosing interval, calculated on Cycle 1 Day 15 only.
AUC_τ	Area under the concentration-time curve over the dosing interval from T_1=0 h (predose) to T_2=τ h. Since the dosing interval τ is equal to 24 hours in this study, this parameter is equivalent to AUC_{0-24} (area under the concentration-time curve from T_1=0 h [predose] to T_2=24 h) on both Day 1 and Day 15 of Cycle 1. Calculated using the mixed log linear trapezoidal rule (linear up, log down). For Cycle 1 Day 1, AUC_τ will be calculated as a partial area within the defined time range. For Cycle 1 Day 15, AUC_τ will be calculated at steady state from the pre-dose time point to the dosing interval time. AUC_τ will be calculated based on the observed concentration at the actual observation time, as long as actual time deviation is less than +/-10% at τ. If actual time deviation is equal to or greater than 10%, AUC_τ will be reported as missing.
CL/F	Apparent systemic clearance (calculated for tepotinib and osimertinib only), as Dose/AUC_τ. Calculated on Cycle 1 Day 15 only. For tepotinib, Dose is the tepotinib free base dose (i.e., adjusted for salt form). The tepotinib free base dose is calculated as: Actual dose × MW(free base)/MW(salt), where MW(free base) is the molecular weight (MW) of free base (i.e., 492.57), and MW(salt) is the MW of the

	hydrochloride hydrate salt (i.e., 547.05). For osimertinib, the dose administered is the free base form, so no dose adjustment is required.
AUC_{0-t}/Dose	Dose-Normalized AUC_{0-t} (calculated for tepotinib only). Normalized using actual dose (i.e., unadjusted for salt form).
AUC_{0-12}/Dose	Dose-Normalized AUC_{0-12} (calculated for tepotinib only). Normalized using actual dose (i.e., unadjusted for salt form).
AUC_{τ}/Dose	Dose-Normalized AUC_{τ} (calculated for tepotinib only). This parameter is equivalent to AUC_{0-24}/Dose. Normalized using actual dose (i.e., unadjusted for salt form).
C_{max}/Dose	Dose-Normalized C_{max} (calculated for tepotinib only). Normalized using actual dose (i.e., unadjusted for salt form).
PTF	Peak trough fluctuation ratio within a complete dosing interval at steady state in %, calculated on Cycle 1 Day 15 only. PTF = $100*(C_{max}-C_{min})/C_{av}$

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

Individual metabolite to parent ratios for AUC_{τ} and C_{max} ($MR_{(AUC)}$ and $MR_{(Cmax)}$, respectively), will be calculated for tepotinib and its metabolites by dividing the value obtained for each metabolite by the value obtained for the parent (i.e., MSC2571107A/tepotinib and MSC2571109A/tepotinib) after correction for MW differences between parent and metabolite (MW of tepotinib free base is 492.57, MW of MSC2571107A is 506.56, and MW of MSC2571109A is 506.56), separately for single dose (i.e., Cycle 1 Day 1) and multiple dose (i.e., Cycle 1 Day 15), and summarized descriptively for each dose level and day. Similarly, metabolite to parent ratios for AUC_{τ} and C_{max} will be calculated for osimertinib and its metabolite by dividing the value obtained for the metabolite by the value obtained for the parent (i.e., AZD5104/osimertinib) after correction for MW differences between parent and metabolite (MW of osimertinib free base is 499.6 and MW of AZD5104 is 485.6).

The dosing and sampling scheme in this study does not allow the reliable estimation of λ_z, considering the apparent terminal half-life of tepotinib and its metabolites, and osimertinib and its metabolite. Therefore, any PK parameters dependent on λ_z will not be determined, i.e., $AUC_{0-\infty}$ (single dose), CL/F (single dose), and V_Z/F (single and multiple dose).

Other parameters may be added as appropriate.

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

PK parameters will be evaluated and listed for all participants who provide sufficient concentration-time data. Data excluded from the PK analysis set will be flagged, along with the reason for exclusion. Pharmacokinetic parameters will be rounded for reporting as appropriate. In export datasets, PK parameters will be provided with full precision, and will not be rounded. PK parameters will be summarized by PK analyte, and cycle/day, as described in Section 0.

Formal statistical hypotheses have not been planned for PK parameters. Any statistical tests that might be performed will be considered exploratory.

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

16.2 Pharmacodynamics

No specific pharmacodynamic analysis will be performed.

16.3 Analysis of Molecular Marker (Biomarker)

Blood and tumor tissue samples for biomarker research are collected from the participants at prescreening as well as during the study. Some samples are mandatory whereas others are optional.

Biomarker results from blood and tissue samples will be tabulated. For continuous biomarkers, summary statistics (mean and standard deviation, median, Q1, Q3, minimum and maximum) will be presented; for categorical biomarkers, the number and percentage of participants in each category will be calculated. Results will be performed on the SAF analysis set and presented as indicated in Sections 8.1.1 and 8.1.2 for the baseline characteristics.

In particular, the following biomarkers at baseline (i.e., prescreening) will be summarized:

- Mean MET gene copy number as per central TBx FISH test: summary statistics as well as categorized into < 10, ≥ 10, < 8 and ≥ 8.
- MET/CEP7 ratio as per central TBx FISH test: summary statistics as well as categorized into < 2, ≥ 2, ≥ 2 - < 4, and ≥ 4

Details from the analysis of both, central tumor and blood samples, to evaluate MET amplification will be listed. Data collected on the "Tumor Biopsy Local FISH" eCRF page will also be listed.

No data from the NGS profiles at baseline (including EGFR kinase domain mutations such as C797S) and on-treatment were available at the time of database lock for the primary analysis. These data will be analyzed separately and reported in separate documents.

17 References

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18 Appendices

18.1 Appendix 1 - NCI-CTC Gradable and Non-Gradable Safety Laboratory Test Parameters and Direction(s) of Abnormality

NCI-CTC gradable parameters

Laboratory Assessment	Parameters	Name in NCI-CTC	Direction(s) of abnormality
Hematology	Hemoglobin	Anemia / Hemoglobin increased	Low/High
	Eosinophils	Eosinophilia	High
	Leukocytes (WBC)	White blood cell decreased / Leukocytosis	Low/High
	Neutrophils	Neutrophil count decreased	Low
	Lymphocytes	Lymphocyte count decreased / increased	Low/High
	Platelets	Platelet count decreased	Low
Biochemistry	Albumin	Hypoalbuminemia	Low
	Alanine Aminotransferase (ALT)	Alanine Aminotransferase increased	High
	Aspartate Aminotransferase (AST)	Aspartate Aminotransferase increased	High
	Alkaline Phosphatase	Alkaline Phosphatase increased	High
	Gamma Glutamyl Transferase (GGT)	GGT increased	High
	Total Bilirubin	Blood bilirubin increased	High
	Amylase	Serum amylase increased	High
	Lipase	Lipase increased	High
	Creatinine	Creatinine increased	High
	Sodium	Hyponatremia / Hypernatremia	Low / High
	Potassium	Hypokalemia / Hyperkalemia	Low / High
	Calcium Corrected/Ionized	Hypocalcemia / Hypercalcemia	Low / High
	Glucose	Hypoglycemia	Low
Coagulation	Activated Partial Thromboplastin Time	Activated Partial Thromboplastin Time prolonged	High
	Prothrombin Intl. Normalized Ration (INR)	INR increased	High

Note: parameters with both Low and High directions of abnormality are going to be split. For example, Calcium Corrected is going to be split in Calcium Corrected Low and Calcium Corrected High.

NCI-CTC non-gradable parameters

Laboratory Assessment	Parameters
Hematology	Hematocrit
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Reticulocytes
	Reticulocytes/Erythrocytes
	Neutrophils/Leukocytes (%)
	Lymphocytes/Leukocytes (%)
	Basophils
	Basophils/Leukocytes (%)
	Eosinophils/Leukocytes (%)
	Monocytes
	Monocytes/Leukocytes (%)
Biochemistry	Total Protein
	Urea Nitrogen (BUN)
	Calcium (Total)
	Creatinine Clearance
	Cystatin C
Coagulation	Prothrombin Time
	Prothrombin Time/Standard
	Activated Partial Thromboplastin Time/Standard Ratio
Urinalysis	Blood
	Bacteria (Microscopic analysis)
	Casts (Microscopic analysis)
	Crystals (Microscopic analysis)
	Epithelial Cells (Microscopic analysis)
	Bilirubin
	Glucose in Urine
	Urobilinogen
	Ketones
	Nitrite
	pH
	Proteins in Urine

Laboratory Assessment	Parameters
	Erythrocytes in Urine (Microscopic analysis)
	Leukocytes esterase
	Leukocytes in Urine (Microscopic analysis)
	Specific gravity

18.2 Appendix 2 - Correspondence between TNM classification, clinical stage and subgroup level

TNM Classification Version 8

Subgroup Level	Stage	T	N	M
Advanced	IIIB	T1/T2	N3	M0
		T3/T4	N2	M0
	IIIC	T3/T4	N3	M0
Metastatic	IVA	Any T	Any N	M1a
		Any T	Any N	M1b
	IVB	Any T	Any N	M1c

TNM Classification Version 7

Subgroup Level	Stage	T	N	M
Advanced	IIIB	T1/T2/T3	N3	M0
		T4	N2/N3	M0
Metastatic	IV	Any T	Any N	M1

Note: the use of either TNM version 8 or version 7 does not affect the categorization of participants in “Advanced” or “Metastatic”.

18.3 Appendix 3 - Standard Reference Ranges for creatinine clearance and corrected calcium

Laboratory Assessment	Gender	Age low (years)	Age high (years)	Low Range	High Range
Creatinine clearance (mL/min)	male	18	40	107	139
		41	50	100.5	132.5
		51	60	94	126
		61	70	87.5	119.5
		71	80	81	113
		81	90	74.5	106.5
		91	100	68	100
	female	18	40	87	107
		41	50	80.5	100.5
		51	60	74	94
		61	70	67.5	87.5
		71	80	61	81
		81	90	54.5	74.5
		90	100	48	68
Corrected calcium (mmol/L)	both	18	49	2.17	2.47
		50	999	2.17	2.53

Reference ranges for the creatinine clearance have as source the Sponsor document “Merck Standard Lab Units and Normal Ranges” version 2.2. Reference ranges for the corrected calcium are based on the following source: Gøransson LG, Skadberg Ø, Bergrem H. Albumin-corrected or ionized calcium in renal failure? What to measure? Nephrol Dial Transplant. 2005 Oct;20(10):2126-9. doi: 10.1093/ndt/gfh988. Epub 2005 Jul 19. PMID: 16030044.

18.4 Appendix 4 - List of outputs for each analysis

The outputs that are to be presented for each analysis (including analyses for IDMC meetings and possible additional analyses) are listed in a separate Excel tracker named "MS200095-0031_Output_Delivery_TOC_YYYYMMDD".

18.5 Appendix 5 - SAS code for Longitudinal Analysis

Mixed Model for Repeated Measurements

The following example will be used a basis for the analysis:

```
proc mixed data=adqs_dataset method=reml;
      class usubjid avisitn;
      model chg = base avisitn avisitn*base /
                  ddfm=kenwardroger cl intercept solution;
      repeated avisitn /
               subject=usjbjid type=variance_covariance_matrix;
      lsmeans avisitn/ at means cl;
      estimate "overall mean"
            intercept 1
            avisitn 1/number_levels_avisitn
            avisitn*base 1/number_levels_avisitn*mean_base
            base mean_base/cl;
run;
```

To derive `mean_base` the same approach used by SAS to derive standard least square (LS) means should be used, i.e. the average of BASE variable across all records included in the analysis (i.e., more than one record per subject). Of note, this is different from deriving the average of baseline values across subjects (i.e., only one record per subject). As an example, assuming there are analysis visits 1, 2 and 3 in the model and the average value of BASE across all records included in the analysis is 10.31, the following estimate statement should be used:

```
      estimate "overall mean"
            intercept 1
            avisitn 0.333333 0.333333 0.333333
            avisitn*base 3.436663 3.436663 3.436663
            base 10.31/cl;
```

The first variance-covariance matrix that will be considered is the unstructured (`type=un`). If it fails to converge or the convergence is not reliable, the Toeplitz (`type=toep`), first-order autoregressive (`type=ar(1)`) and variance components (`type=vc`) will be tested. The matrix that provides a reliable convergence and has the smallest Akaike's criterion (AIC) provided by default by proc mixed will be selected.

Additionally, analysis visits with less than three participants will not be included in the analysis to avoid non convergence and non-estimability of LS means. This threshold may be increased if needed.

Signature Page for VV-CLIN-313940 v2.0

Approval Task	PPD	

Signature Page for VV-CLIN-313940 v2.0