Clinical Study Protocol

Title Page

Clinical Study Protocol 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 Number:	MS200095-0031
Amendment Number	2
Merck Compound Number:	MSC2156119J/EMD1214063
Merck Registered Compound Name in Japan:	TEPMETKO
Short Title:	Tepotinib plus osimertinib in osimertinib-relapsed MET amplified NSCLC
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	For all countries, except the US, Canada, and Japan: Merck Healthcare KGaA an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA In Japan: Merck Biopharma Co., Ltd. an affiliate of Merck KGaA, Darmstadt, Germany Arco Tower. 1-8-1 Shimomeguro Meguro-ku. Tokyo 153-8926, Japan

	Medical Responsible: Name: PPD Address: Merck Healthcare KGaA, Frankfurter Str. 250, Darmstadt, Germany Phone: + 49 6151 720 Fax: Not applicable
Regulatory Agency Identifying Numbers:	IND Number: 128073 ClinicalTrials.gov: NCT03940703 European Clinical Trials Database: 2019-001538-33
Protocol Version:	Version 3.0
Replaces Version:	09 April 2020 /Version 2.0
Approval Date:	04 May 2021
Medical Monitor Name and Contact Information:	PPD

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original protocol	20 Mar 2019
1.1 DEU	Local Amendment 1	04 Oct 2019
1.2 DEU	Local Amendment 2	06 Mar 2020
2.0	Global Amendment 1	09 Apr 2020
2.1 KOR	Local Amendment 1 for Republic of Korea only	03 Sep 2020
2.2 CHN	Local Amendment 2 for China only	21 Sep 2020
2.3 ITA	Local Amendment 3 for Italy only	17 Dec 2020
3.0	Global Amendment 2	04 May 2021

Protocol Version 3.0 (04 May 2021)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The purpose of this amendment is to provide a global protocol incorporating country-specific protocol amendments (local Amendment 2.1 KOR (03 September 2020), local Amendment 2.2 CHN (21 September 2020) and local Amendment 2.3 ITA (17 December 2020), in addition to administrative updates. Apart from these changes, safety part (e.g., new identified risks or similar, dose modification table) was updated in alignment with the most current Investigator's Brochure (IB).

Section # and Name	Description of Change	Brief Rationale
Title page	Clinical study protocol version updated and details of Coordinating Investigator Signature address.	Administrative update.
1.1 Synopsis 1.2 Schema, text, and Figure 1 4.1 Overall Design Text and Figure 3 6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding	A statement was added to clarify that participants in the Republic of Korea will not undergo randomization but will be assigned exclusively to the combination of tepotinib plus osimertinib, and therefore will not be treated with tepotinib monotherapy.	The exclusion of participants from the monotherapy arm was requested by the Republic of Korea Ministry of Food and Drug Safety (MFDS).
1.1 Synopsis 4.1 Overall Design 4.2 Scientific Rationale for Study Design 7.1 Discontinuation of Study Intervention 8.1 Efficacy Assessments and Procedures	A statement was added to clarify that during the randomized part of the study, verification of disease progression by Independent Review Committee (IRC) is required.	Updated to reflect the need for the verification of disease progression by IRC in the randomized part of the study.
1.1 Synopsis 4.1 Overall Design	A statement was added to clarify that End of Treatment (EoT) Visit will be conducted within 14 days since documented decision by the Investigator to permanently discontinue study intervention. In case EoT Visit and Safety Follow-up Visit end up falling within the same 7 days, only EoT Visit should be performed.	Updated to make clear the time window for EoT visit and Safety Follow-up Visit.
1.1 Synopsis 4.1 Overall Design 4.2 Scientific Rationale for Study Design 7.1 Discontinuation of Study Intervention	A statement was added to clarify that when progression by the IRC is verified, tepotinib monotherapy can be continued, if judged appropriate by the Investigator, until the switch over to the combination of tepotinib plus osimertinib.	Updated to clarify study treatment during tepotinib monotherapy.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	It is clarified that the EoT Visit should be ≤ 14 days since decision to interrupt IMP.	Clarification on the study procedures.
1.3 Schedule of Activities	The footnote “Time window from enrollment to administration of first dose: 72 hours” was moved to the notes.	Administrative update.
1.3 Schedule of Activities 8.8 Biomarkers	A statement has been added to clarify that circulating tumor DNA (ctDNA) blood sampling and exploratory biomarker blood sampling during treatment (including Cycle 1 Day 1 for exploratory biomarkers) and at the End of Treatment Visit is optional for participants in China. Clarification that for sites in China, collection of participant samples for biomarker research is either a mandatory or optional part of this study.	The leading Ethics Committee in China requested to move the “on treatment ctDNA testing” to the optional informed consent form (ICF) referring back to the Office of Human Genetic Resource Administration (OHGRA) application where the testing of ctDNA and blood exploratory biomarkers are part of the exploratory application form.
2.3 Benefit/Risk Assessment	Updated information on identified risks of tepotinib, including edema (mainly peripheral edema), creatinine increased, hypoalbuminemia, amylase and lipase increased, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased, diarrhea, and nausea and vomiting.	Updated to provide current guidance on tepotinib.
3 Objectives and Endpoints 9.4.1 Efficacy Analyses	The tertiary/exploratory endpoint on intracranial response has been updated to clarify that intracranial response (confirmed CR or PR) will be assessed by IRC.	Updated to clarify the requirement of IRC (and not by Investigator) assessment of intracranial response.
4.3 Justification for dose	The results of the safety run-in treatment part of the study until 11 August 2020, when the SMC meeting took place, are presented.	The Italian Medicines Agency (Agenzia italiana del farmaco, AIFA) requested that the results from the safety run-in part of the MS200095-0031 (INSIGHT-2) study, supporting the SMC recommendation to continue the enrollment in the expansion part of the study with tepotinib 500 mg daily combined regimen, to be included and discussed in the study protocol.
6.6 Dose Selection and Modification, Table 3	Adverse reaction on target organs including Body and Pancreas, with dose modification recommendations, have been added. The Other Adverse event has been changed to any other adverse reaction of Grade ≥ 3 and has been split into Grade 3 and Grade 4. Dose modification recommendations have been updated.	Updated to provide current guidance on tepotinib.
6.6 Dose Selection and Modification	The following have been added:	Updated with the approval of tepotinib in the US. Clarification on the amount of tepotinib free base administered.

Section # and Name	Description of Change	Brief Rationale
	• The dose of 500 mg tepotinib once daily is the labeled dose of tepotinib in US and Japan for patients with NSCLC with METex14 skipping alterations. • The proposed administered dose of 500 mg tepotinib corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (free base form). The 250 mg tepotinib corresponds to 250 mg tepotinib hydrochloride hydrate and is equivalent to 225 mg tepotinib (free base form).	
6.9 Management of Specific Adverse Events, Adverse Events of Special Interest or Adverse Drug Reactions	When referring to edema as a specific adverse event of tepotinib, cross-reference to Section 6.6 has been added for dose modification recommendations.	Updated to provide current guidance on tepotinib.
7.1 Discontinuation of Study Intervention	A statement was added to clarify that participants must be discontinued from study intervention if there is objective disease progression as per RECIST Version 1.1 as per Investigator.	Clarification on the study procedures.
8 Study Assessments and Procedures	A statement was added to clarify that submission of tumor tissue and blood sample obtained after progression on first-line osimertinib, is mandatory for all patients for MET amplification testing during Prescreening.	Added to make emphasis (as already in other sections) on the mandatory submission of tumor tissue and blood sample.
8 Study Assessments and Procedures	The word “previous” was added before local FISH testing for MET amplification.	Administrative update.
8.1 Efficacy Assessments and Procedures	A statement was added to clarify that tumor assessment according to RECIST Version 1.1 at EoT Visit is requested only if last tumor assessment was performed ≥ 6 weeks within the first 9 months, or ≥ 12 weeks after 9 months prior to EoT Visit.	Clarification on the study procedures.
8.2.4 Clinical safety Laboratory Assessments Appendix 5 Clinical Laboratory Tests	A statement has been made to clarify that in sites in China, laboratory assessments (e.g., lipase) can be performed in a local or a central laboratory, depending on the availability of the test in the local laboratory.	The reason of this change is the fact that some sites in China cannot perform some laboratory assessments locally (e.g., lipase).
8.8 Biomarkers	A statement was added to clarify that for a local FISH assay to be acceptable must evaluate both MET gene copy number and MET/CEP7 ratio.	Clarification on the requirements of a local FISH assay.
10 References	Added full title of reference stated in Appendix 7.	Administrative update.
Appendix 1	Abbreviations have been updated.	Administrative update.
Appendix 5 Clinical Laboratory Tests	It is clarified that for Calcium the following values must be reported: Total Calcium and Calculated [or Adjusted] and/or Ionized [or free] Calcium.	Updated to provide clarification on the Calcium measurement.
Appendix 5 Clinical Laboratory Tests	It is clarified that aPTT may be expressed directly in seconds or in ratio.	Updated to provide clarification on aPTT measurement.
Appendix 7 Response	Reference abbreviated to internal presentation convention.	Administrative update.

Section # and Name	Description of Change	Brief Rationale
Evaluation Criteria in Solid Tumors (RECIST) Version 1.1		
Appendix 9	Reference to changes described in this table.	Administrative update.
Appendix 10 Sponsor Signature Page	Clinical study protocol version updated. ClinicalTrials.gov and European Clinical Trials Database numbers added for consistency.	Administrative update.
Appendix 11 Coordinating Investigator Signature Page	Clinical study protocol version updated and details of Coordinating Investigator address. ClinicalTrials.gov and European Clinical Trials Database numbers added for consistency.	Administrative update.
Appendix 12 Principal Investigator Signature Page	Clinical study protocol version updated. ClinicalTrials.gov and European Clinical Trials Database numbers added for consistency.	Administrative update.

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1 Protocol Summary

1.1 Synopsis

Protocol 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).

Short Title: Tepotinib plus osimertinib in osimertinib relapsed MET amplified NSCLC.

Rationale: Mesenchymal-epithelial Transition Factor (MET) amplification has been identified as a common resistance mechanism to all (ie, 1st to 3rd generation) epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). Tepotinib is a highly selective MET inhibitor, which showed clinical efficacy in patients with MET amplified, EGFR TKI-relapsed, T790M negative NSCLC, in combination with gefitinib. Osimertinib is a 3rd generation EGFR inhibitor which demonstrates efficacy in NSCLC patients with activating EGFR mutations. However, there is currently no personalized treatment option available for EGFR-mutant (EGFRm+) patients who had relapsed on previous first-line osimertinib treatment. The INSIGHT 2 study seeks to fill this current knowledge gap in this NSCLC population with high unmet medical need.

Objectives and Endpoints:

Safety run-in only:

Objectives	Endpoints (Outcome Measures)
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.

Overall study including safety run-in:

Objectives	Endpoints (Outcome Measures)
Primary	
To assess the efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by fluorescence in situ hybridization (FISH).	Objective response (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).
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.

Objectives	Endpoints (Outcome Measures)
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.
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).
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.
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 according to RECIST Version 1.1 by IRC and by Investigator. Overall survival.
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 stable disease [SD] lasting at least 12 weeks) as assessed by IRC and by Investigator. Progression free survival according to RECIST Version 1.1 by IRC and by Investigator. Overall survival.
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 stable disease [SD] lasting at least 12 weeks) as assessed by IRC and by Investigator. Progression free survival according to RECIST Version 1.1 by IRC and by Investigator.

Objectives	Endpoints (Outcome Measures)
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. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30. NSCLC Symptom Assessment Questionnaire.
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).
To assess resistance marker 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).

Overall Design: Phase II, two-arm, open-label study. This study will assess the antitumor activity, safety, tolerability, and pharmacokinetics of tepotinib combined with osimertinib and tepotinib monotherapy in participants with advanced or metastatic NSCLC harboring activating EGFR mutations and having relapsed on previous first-line osimertinib treatment due to MET amplification.

An initial subset of at least 6 participants will be enrolled in a safety run-in to confirm if the combination of 500 mg once daily tepotinib dose (as currently used in the Phase II single agent VISION study) together with osimertinib 80 mg once daily (approved dose for NSCLC) is appropriate or needs adjustment. A Safety Monitoring Committee (SMC) will monitor these participants and, based on the safety, tolerability, and available pharmacokinetic information, decide on the final tepotinib dose and regimen.

Number of Participants: It is anticipated that approximately 120 participants will be enrolled.

Study Intervention Groups and Duration: Study participation is composed of the following stages:

1. Prescreening (performed after progression on first-line osimertinib): After providing written Prescreening consent, MET amplification status will be assessed centrally by FISH or by reviewing pre-existing local FISH results using tumor tissue (TBx), and centrally by blood-based next generation sequencing (LBx).
2. Screening: After providing written consent at Screening, study eligibility will be assessed within -28 to -1 days prior to Day 1 of study intervention.
3. Treatment Period:
    a. For the safety run-in, an initial subset of at least 6 participants, who are detected to be MET amplified with any of the methods (central/local TBx or central LBx) described at Prescreening, will be enrolled to confirm the combination dose of tepotinib 500 mg once daily and osimertinib 80 mg once daily; the decision will be

made by the SMC based on predefined dose-limiting toxicity criteria and supported by a Bayesian Optimal Interval Design (BOIN).

b. For the main treatment, eligible participants who are detected to be MET amplification positive by central or local FISH (TBx) will be randomly assigned in a ratio of 2:1 to either the combination of tepotinib at a dose defined by the SMC and osimertinib at the recommended daily dose of 80 mg or tepotinib alone at the daily dose of 500 mg (as currently used in the Phase II single agent VISION study) in cycles of 21-day duration until disease progression (according to RECIST Version 1.1), death, adverse event (AE) leading to discontinuation, study withdrawal or consent withdrawal. The randomization to the two arms of the study will continue until 12 participants who are MET amplification positive by centrally confirmed FISH (TBx), are enrolled in the monotherapy arm. After this, all participants will be assigned to the combination of tepotinib plus osimertinib. For participants in the randomized part of the study, verification of disease progression by IRC is required. Participants who are randomized to the tepotinib monotherapy will have the opportunity to switch over to receive the combination of tepotinib plus osimertinib if they experience disease progression according to RECIST Version 1.1 reported by Investigator and verified by IRC. Until progression is verified by IRC and the switch over to the combination of tepotinib plus osimertinib takes place, tepotinib monotherapy can be continued, if judged appropriate by the Investigator. However, if disease progression is not verified by IRC, the participant must discontinue study intervention. Participants who permanently discontinue tepotinib monotherapy due to an AE, withdraw consent, or for any reason other than progressive disease, will not be eligible to switch over to receive the combination of tepotinib plus osimertinib. Participants in the Republic of Korea will not undergo randomization but will be assigned exclusively to the combination of tepotinib plus osimertinib, and therefore will not be treated with tepotinib monotherapy.

   Eligible participants who are detected to be MET amplified only by central blood-based next generation sequencing (LBx) will be assigned to the combination of tepotinib at a dose defined by the SMC and osimertinib at the recommended daily dose of 80 mg in cycles of 21-day duration until disease progression (according to RECIST Version 1.1), death, AE leading to discontinuation, study withdrawal or consent withdrawal. There will be no monotherapy arm for participants who are detected to be MET amplified only by central blood-based next generation sequencing (LBx).

4. Treatment follow-ups (for all participants): End of Treatment (EoT) Visit will be conducted within 14 days since documented decision by the Investigator to permanently discontinue study intervention.

5. Safety Follow-up Visit (for all participants): 30 ± 3 days after the last dose of study intervention for those who discontinue study intervention permanently. In case EoT Visit and Safety Follow-up Visit end up falling within the same 7 days, only EoT Visit should be performed.

6. Participants who discontinue study intervention for reasons other than PD or death will have additional visits for tumor assessments every 6 weeks until 9 months after first administration of study intervention and every 12 weeks thereafter until disease progression. Survival follow-up is to be performed every 3 months (± 2 weeks) at clinic visits or by telephone contact.

The primary analysis will be conducted once all participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH (TBx), have either been treated with the recommended Phase II dose of tepotinib and osimertinib for at least 9 months, died or have prematurely discontinued study intervention for any reason, whichever comes first.

Participants assigned to tepotinib monotherapy and who are MET amplification positive by centrally confirmed FISH (TBx) will be evaluated for a secondary efficacy objective of the study. The efficacy outcomes of the participants in each of the two arms who are MET amplification positive only by local but not centrally confirmed FISH (TBx) will only be listed. Participants who are MET amplification positive by central blood-based next generation sequencing (LBx) will be evaluated for a secondary efficacy objective of the study.

The final analysis will be done 3 years after the last participant's first dose or when all participants have discontinued study intervention and two thirds of the participants have died, whichever comes first.

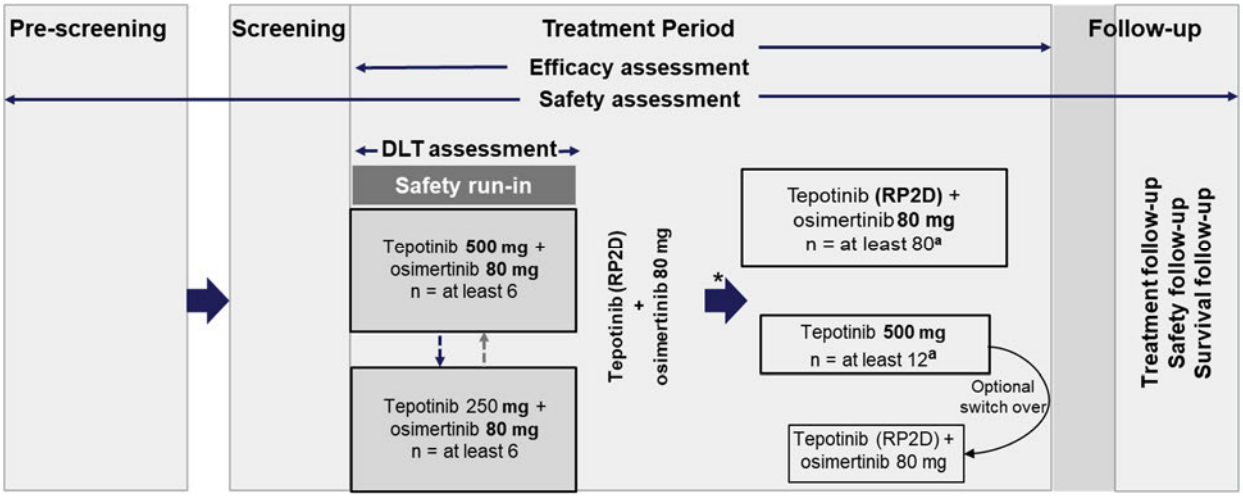
Involvement of Special Committee(s): Yes

1.2 Schema

This two-arm, open-label, Phase II study will assess the antitumor activity, safety, tolerability, and pharmacokinetics of the mesenchymal-epithelial transition factor (MET) inhibitor tepotinib alone and combined with the 3rd generation epidermal growth factor receptor (EGFR) inhibitor osimertinib (Tagrisso®), in participants with advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating EGFR mutations and having relapsed on prior first-line osimertinib due to MET amplification.

The study design is presented in Figure 1 below.

Figure 1 Study Schema



DLT: dose-limiting toxicity; RP2D: recommended Phase II dose.

* After the safety run-in part, there will be an initial assignment of participants with MET amplification based on FISH (TBx) into the combination and the monotherapy arm according to a 2:1 randomization. As soon as 12 participants (MET amplification centrally confirmed by FISH) are enrolled in the monotherapy arm, all further participants will receive combination treatment. Participants who are MET amplification positive only by central blood-based next generation sequencing (LBx) will be assigned directly to the combination arm. Participants in the Republic of Korea will not undergo randomization but will be assigned exclusively to the combination of tepotinib plus osimertinib, and therefore will not be treated with tepotinib monotherapy.

a: Approximately 120 participants in total are expected to achieve 80 in the primary analysis combination set and 12 for the secondary analysis of the monotherapy arm.

1.3 Schedule of Activities

The Schedule of Activities including all study assessments is provided in Table 1.

The eligibility of participants is checked at Screening by review of inclusion/exclusion criteria, considering the available information (including information gathered at Prescreening). The last measurement of an assessment prior to the first administration of the study intervention will serve as baseline value.

Prescreening must happen prior to Screening, and after participants have relapsed on previous first-line osimertinib treatment. Tumor and blood samples for MET amplification testing must be collected after progression on first-line osimertinib. Screening should only occur once results from Prescreening assessments have been received.

Table 1 Schedule of Activities

	Prescreening	Screening/ Baseline	Intervention Period (in cycles of 3 weeks)							EoT	Safety Follow-up	Additional Follow-up	Survival Follow-up	Notes
			Cycle 1					Cycle 2	Cycle 3, 5, 7, 9, 11, 13, etc.	Cycle 4, 6, 8, 10 and 12					
				For safety-run in only										
DAY		-28 to -1	1	2	8	15	16	1 ± 3 d	1 ± 3 d	1 ± 3 d	≤ 14 d since decision to stop IMP	30 d ± 3 d after last dose	Refer to Section 8.1.		
Written Informed Consent	X	X												
PGx Informed Consent (optional)		X												
Documentation of EGFR TKI relapse, EGFR alterations, age, gender, height, race, ethnicity, smoking status, tumor histology	X													
TBx for MET amplification status	X													Refer to Section 8.8.
LBx for MET amplification status	X													Refer to Section 8.8.
Tissue for central confirmation of local TBx results	←	→												Central confirmation is not mandated prior to treatment initiation. Refer to Section 8.8.

	Prescreening	Screening/ Baseline	Intervention Period (in cycles of 3 weeks)							EoT	Safety Follow-up	Additional Follow-up	Survival Follow-up	Notes
			Cycle 1					Cycle 2	Cycle 3, 5, 7, 9, 11, 13, etc.	Cycle 4, 6, 8, 10 and 12					
DAY		-28 to -1	1	For safety-run in only 2	8	15	16	1 ± 3 d	1 ± 3 d	1 ± 3 d	≤ 14 d since decision to stop IMP	30 d ± 3 d after last dose	Refer to Section 8.1.		
Tissue for NGS TBx testing, if available and allowed locally	←	→													Tissue for NGS TBx testing can be provided at Prescreening or at Screening if available and allowed locally. Refer to Section 8.8.
Full Medical and Disease History		X													Including assessment of life expectancy (> 12 weeks.
Demography		X													
Weight	X		X					X	X	X					Refer to Section 8.2.2.
ECOG PS		X	X					X	X	X	X	X			
Full Physical Examination		X													

	Prescreening	Screening/ Baseline	Intervention Period (in cycles of 3 weeks)							EoT	Safety Follow-up	Additional Follow-up	Survival Follow-up	Notes
			Cycle 1					Cycle 2	Cycle 3, 5, 7, 9, 11, 13, etc.	Cycle 4, 6, 8, 10 and 12					
DAY		-28 to -1	1	For safety-run in only: 2	8	15	16	1 ± 3 d	1 ± 3 d	1 ± 3 d	≤ 14 d since decision to stop IMP	30 d ± 3 d after last dose	Refer to Section 8.1.		
Brief Physical Examination			X						X						Can be repeated during study at Investigator discretion. Refer to Section 8.2.1 for Physical Examinations.
Ophthalmology examination		X									X				Refer to Section 8.2.1.
Tumor Assessment (RECIST Version 1.1)		X							X		X		X		Mandatory assessment to determine eligibility. For participants beyond Cycle 13, refer to Section 8.1.
Brain imaging		X							X		X		X		Mandatory follow-up in participants with confirmed by IRC brain metastases on the baseline brain scan. Refer to Section 8.1.

	Prescreening	Screening/ Baseline	Intervention Period (in cycles of 3 weeks)							EoT	Safety Follow-up	Additional Follow-up	Survival Follow-up	Notes
			Cycle 1					Cycle 2	Cycle 3, 5, 7, 9, 11, 13, etc.	Cycle 4, 6, 8, 10 and 12					
DAY		-28 to -1	1	For safety-run in only 2	8	15	16	1 ± 3 d	1 ± 3 d	1 ± 3 d	≤ 14 d since decision to stop IMP	30 d ± 3 d after last dose	Refer to Section 8.1.		
Independent confirmation of measurable disease		X													
Chest X-Ray		X													Can be repeated during study at Investigator discretion. Not necessary if thoracic CT is performed as part of the tumor assessment (RECIST Version 1.1) at Screening.
Echocardiogram		X									X				Can be repeated during study at Investigator discretion.
12-lead ECG		X	X	X	X	X	X	X	X	X	X	X			Refer to Section 8.2.3.
Vital signs		X	X	X	X	X	X	X	X	X	X	X			Refer to Section 8.2.2.

	Prescreening	Screening/ Baseline	Intervention Period (in cycles of 3 weeks)							EoT	Safety Follow-up	Additional Follow-up	Survival Follow-up	Notes
			Cycle 1					Cycle 2	Cycle 3, 5, 7, 9, 11, 13, etc.	Cycle 4, 6, 8, 10 and 12					
DAY		-28 to -1	1	For safety-run in only 2	8	15	16	1 ± 3 d	1 ± 3 d	1 ± 3 d	≤ 14 d since decision to stop IMP	30 d ± 3 d after last dose	Refer to Section 8.1.		
Serum Pregnancy Test for WOCBP		X													Can be repeated during study at Investigator discretion. Refer to Section 8.2.4.
Urine Pregnancy Test for WOCBP			X					X	X	X	X	X			Can be repeated during study at Investigator discretion. Refer to Section 8.2.4.
Hematology and Coagulation		X[a]	X	X	X	X		X	X	X	X	X			[a] A 3-day window is permitted for Day 1 Cycle 1. Refer to Section 8.2.4.
Biochemistry		X[a]	X	X	X	X		X	X	X	X	X			
Urinalysis		X[a]	X			X			X						
ctDNA Blood sampling									X		X				C3, 5, 9, 13 and EOT only. Optional for participants in China. Refer to Section 8.8.

	Prescreening	Screening/ Baseline	Intervention Period (in cycles of 3 weeks)							EoT	Safety Follow-up	Additional Follow-up	Survival Follow-up	Notes
			Cycle 1					Cycle 2	Cycle 3, 5, 7, 9, 11, 13, etc.	Cycle 4, 6, 8, 10 and 12					
DAY		-28 to -1	1	For safety-run in only: 2	8	15	16	1 ± 3 d	1 ± 3 d	1 ± 3 d	≤ 14 d since decision to stop IMP	30 d ± 3 d after last dose	Refer to Section 8.1.		
Exploratory Biomarker Blood sampling			X						X		X				Optional for participants in China. Refer to Section 8.8.
PGx Blood sampling		X													Optional. Refer to Section 8.7.
Sparse PK Sampling			X					X							Not applicable to safety run-in. Refer to Section 8.5.
Rich PK sampling			X	X		X	X								Safety run-in only.
Adverse Events Assessment	←	———	———	———	———	———	———	———	———	———	→				
Concomitant Medication/ Procedure		←	———	———	———	———	———	———	———	———	→				
PRO questionnaires		X							X		X	X			Refer to Section 8.1.
Drug Dispensation			X					X	X	X					Including diary cards; refer to Section 6.4

	Prescreening	Screening/ Baseline	Intervention Period (in cycles of 3 weeks)							EoT	Safety Follow-up	Additional Follow-up	Survival Follow-up	Notes
			Cycle 1					Cycle 2	Cycle 3, 5, 7, 9, 11, 13, etc.	Cycle 4, 6, 8, 10 and 12					
DAY		-28 to -1	1	For safety-run in only: 2	8	15	16	1 ± 3 d	1 ± 3 d	1 ± 3 d	≤ 14 d since decision to stop IMP	30 d ± 3 d after last dose	Refer to Section 8.1.		
Tepotinib Intake			←	—	—	—	—	—	—	→					Refer to Section 7.1. Time window from enrollment to administration of first dose: 72 hours
Osimertinib Intake (only for combination therapy)			←	—	—	—	—	—	—	→					Refer to Section 7.1 Time window from enrollment to administration of first dose: 72 hours
Survival and anticancer therapies													X	X	

CT: computed tomography; ctDNA: circulating tumor DNA; d: day; DNA: deoxyribonucleic acid; ECG: electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EoT: end of treatment; ICF: informed consent form; IMP: Investigational Medicinal Product; IRC: Independent Review Committee; LBx: liquid biopsy; MET: mesenchymal-epithelial transition factor; NGS: next generation sequencing; PGx: pharmacogenetics; PK: pharmacokinetics; PROs: patient reported outcomes; RECIST: Response Evaluation Criteria in Solid Tumors; TBx: tissue biopsy; TKI: tyrosine kinase inhibitor; WOCBP: women of childbearing potential.

2 Introduction

Tepotinib is a novel, highly selective, reversible adenosine triphosphate (ATP)-competitive, small molecule inhibitor of mesenchymal-epithelial transition factor (MET). Oncogenic activation of this tyrosine kinase receptor via mechanisms such as MET mutations or MET amplification has been identified not only to drive primary tumorigenesis but also to mediate resistance to cancer treatments including epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs). In both settings, tepotinib has shown activity in preclinical models and in clinical studies in patients with non-small cell lung cancer (NSCLC).

Complete information on the chemistry, pharmacology, efficacy, and safety of tepotinib is in the Investigator's Brochure (IB).

2.1 Study Rationale

MET amplification has been identified as a common resistance mechanism to all, ie, 1st to 3rd generation, EGFR TKIs in NSCLC (Shi. 2016). Tepotinib is a highly selective MET inhibitor, which has already shown signals of clinical efficacy in the previous INSIGHT study (NCT01982955) in patients with MET amplified, EGFR TKI-relapsed, T790M negative NSCLC in combination with the 1st generation EGFR TKI gefitinib (Wu. 2018). The 3rd generation EGFR TKI osimertinib has been propelled into first-line therapy for patients with advanced or metastatic NSCLC with activating EGFR mutations, regardless of their T790M status, based on the results of the FLAURA Phase III trial (Soria 2018). However, there is currently no personalized treatment option available for patients who have relapsed on previous osimertinib treatment when used as first-line EGFR TKI. This study seeks to fill this current knowledge gap in a NSCLC population with high unmet medical need.

2.2 Background

Lung cancer remains the leading cause of cancer death worldwide. Approximately 85% of patients have NSCLC and most present with advanced stage disease (not amenable to curative intent). Novel targeted therapies that interfere with specific molecular signaling pathways have emerged as a new standard option for selected patients with EGFR mutation, including the oral EGFR TKIs. EGFR TKIs inhibit the intracellular tyrosine kinase domain of the EGFR and therefore block the signal transduction pathways implicated in the proliferation and survival of cancer cells.

A secondary mutation in the EGFR gene (T790M mutation) has been identified as the main reason for resistance to 1st and 2nd generation EGFR TKIs in NSCLC. Osimertinib is a 3rd generation, T790M directed, EGFR TKI. This product showed benefit in patients with EGFR mutant (EGFRm+) NSCLC who relapsed on previous 1st and 2nd generation EGFR TKIs and received approval in this indication based on the results of the AURA 3 study (Mok 2017). Osimertinib was also recently approved as first-line treatment in NSCLC in patients whose tumors harbor activating EGFR mutations irrespective of the T790M status based on the results from the FLAURA study (Soria 2018). In addition to the United States (US) and European Union, osimertinib is also approved in Japan and in China. Osimertinib is the first EGFR TKI monotherapy to show a

statistically significant overall survival benefit versus another EGFR TKI. The final overall survival analysis of FLAURA study reinforces osimertinib as the standard of care for first-line treatment in patients with EGFRm+ advanced or metastatic NSCLC (Ramalingam 2020).

While most patients with EGFRm+ NSCLC suffer from resistance caused by mutations and genetic alterations within the EGFR pathway, a subset of patients also relapses on previous EGFR TKI treatment via activation of other oncogenic pathways, such as MET. Indeed, the combination of tepotinib and EGFR inhibitors has been shown to result in enhanced antitumor activity compared with either agent alone in NSCLC tumor models expressing EGFR wild-type or EGFR with activating kinase domain mutations, when these tumor cell lines also harbored MET activating alterations (Friese-Hamim 2017).

MET amplification was identified as a relevant resistance mechanism to 1st and 2nd generation EGFR TKIs, and several clinical studies have already shown the benefit of a combined administration of MET inhibitors with a 1st generation EGFR TKI after previous EGFR TKI resistance (Salgia 2017). Among these studies, the combination of tepotinib with gefitinib was investigated in the INSIGHT study (NCT01982955, Cheng 2018). The overall intention-to-treat population in the INSIGHT study, which consisted of patients with NSCLC with moderate to high MET overexpression or MET amplification, had similar progression-free survival (PFS) to the platinum doublet chemotherapy control arm. However, the predefined subset of MET amplified patients showed highly significant differences in PFS with a hazard ratio of 0.17 (90% confidence interval [CI]; 0.05, 0.57) with median PFS in the tepotinib/gefitinib arm of 16.6 months (90% CI 8.3, not estimable) compared with median PFS in the control arm of 4.2 months (90% CI 1.4, 7.0). Furthermore, an objective response rate (ORR) of 67% was observed in MET amplified patients. Safety and tolerability results from this study also showed that the combination of tepotinib with gefitinib was well tolerated.

However, MET amplification was not only identified to trigger resistance to 1st and 2nd generation EGFR TKIs but was also shown to cause resistance to osimertinib. Approximately 15% and 19% of patients with EGFRm+ NSCLC enrolled in first-line (FLAURA) and second-line (AURA 3) NSCLC studies were shown to harbor MET amplification by use of a liquid biopsy (LBx), next generation sequencing, testing methodology, respectively (Papadimitrakopoulou 2018; Ramalingam 2018). A first study (TATTON) indicated that the combination of the MET inhibitor savolitinib with osimertinib could overcome MET related osimertinib resistance (Sequist 2020).

Based on the available preclinical and clinical experience with tepotinib in combination with EGFR TKIs, the INSIGHT 2 study (MS200095-0031) will investigate the combination of osimertinib and tepotinib in patients who relapsed on previous first-line osimertinib due to MET amplification. The study introduces a single agent tepotinib arm to additionally assess the contribution of tepotinib to the osimertinib and tepotinib combination therapy. There is currently no personalized treatment option available for these selected NSCLC patients and therefore constitutes a clinical condition with high unmet medical need.

2.3 Benefit/Risk Assessment

Clinical efficacy and safety information for the use of MET inhibitors in combination with EGFR inhibitors is available from several studies. This includes information for tepotinib with the

1st generation EGFR TKI gefitinib, osimertinib with a selective MET inhibitor, savolitinib, and a head-to-head comparison between osimertinib and the 1st generation EGFR TKIs, gefitinib and erlotinib, which have been approved for decades (approved in the US in May 2003) and have been shown to be safe in patients with NSCLC.

The use of tepotinib in combination with gefitinib has already been investigated in patients with advanced NSCLC after failure of previous EGFR TKI treatment (NCT01982955, Cheng 2018). In particular, the subgroup of participants with MET amplified, T790M negative tumors, demonstrated positive efficacy signals including an ORR of 67% and a median PFS of 16.6 months were seen. Furthermore, 60 participants were exposed to tepotinib with the EGFR inhibitor. While all participants receiving this treatment experienced treatment-emergent adverse events (TEAEs), the majority of these TEAEs were mild or moderate. A comparison of tepotinib plus gefitinib versus chemotherapy showed 9.7% versus 4.3% having TEAEs leading to permanent discontinuation, 3.2% versus 0% of TEAEs leading to death (none of the TEAEs was related), 16.1% versus 30.4% had serious related TEAEs, 51.6% versus 52.2% had Grade ≥ 3 related TEAEs, and 12.9% versus 8.7% had lipase/amylase increase Grade ≥ 3 not accompanied by pancreatitis or respective symptoms. Overall, tepotinib in combination with gefitinib was considered safe and well tolerated (Cheng 2018).

Moreover, the 3rd generation EGFR TKI osimertinib was investigated in a clinical study in combination with the selective MET inhibitor savolitinib (TATTON, NCT02143466). The study results showed efficacy with ORRs of 30% in patients previously treated with a 3rd generation EGFR TKI, 67% in patients who had received no prior 3rd generation EGFR TKI (T790M positive) and 64% to 65% in patients who had received no prior 3rd generation EGFR TKI (T790M negative; Sequist 2020). Patients who received study treatment (n=138) were included in the safety analysis set, with 98% reporting an AE. Nausea (n=67 [49%]), fatigue (n=48 [35%]) and decreased appetite (n=47 [34%]) were the most commonly reported AEs. The incidence of Grade 3 or higher AEs was 57%. Serious adverse events (SAEs) were reported in 62 patients (45%) consisting mainly of pneumonia (4%), anaphylactic reactions (4%), pyrexia (4%) and dyspnea (4%). In the confirmatory expansion (Part D) part of the TATTON study 42 patients were included in the safety analysis set, with 93% experiencing any AE. The most common AEs were nausea (n=13 [31%]) and diarrhea, edema peripheral and rash (all n=8 [19%]). There were 16 patients with Grade 3 or greater AEs in this group. SAEs were reported in 11 (26%) patients consisting mainly of pneumonia (10%) and anaphylactic reactions (2%) (Sequist 2020).

In addition, osimertinib was investigated head-to-head in a randomized Phase III study in first-line NSCLC versus 1st generation EGFR TKIs, ie, gefitinib and erlotinib (FLAURA, Soria 2018). Osimertinib not only showed superior efficacy but also had a comparable safety profile to the two 1st generation EGFR TKIs, with a smaller number of severe TEAEs, but a slightly higher frequency of cardiovascular events and interstitial lung disease (ILD). As summarized by Mezquita 2018, 279 participants received osimertinib and 55 participants crossed over to osimertinib from the standard EGFR TKI arm. Fewer Grade ≥ 3 AEs (34%) were reported with osimertinib compared with the 1st generation EGFR TKIs (45%), with a similar overall toxicity profile and a lower SAE rate. The most common AEs were diarrhea (58%), rash (58%), and dry skin (36%). QTc prolongation was reported in 10% of participants (n = 29, one Grade ≥ 3) and ILD in 4% (n = 11, six Grade ≥ 3), with no fatal events. In the osimertinib group, 7 of 11 participants recovered from ILD, and the other 4 were recovering. The rate of permanent discontinuation was lower in the

osimertinib group than with the 1st generation EGFR TKIs (13% versus 18%); however, the rate of dose interruption (24% to 25%) and dose reduction (4% to 5%) due to AEs was similar in both groups.

ILD is considered an important identified risk for tepotinib in patients with advanced NSCLC due to the possible severity and mortality that can be associated with these events. This condition is known to occur in association with treatment with other TKIs or other MET inhibitors in the NSCLC setting. In the MS200095-0022 (VISION) study, 1 fatal case of acute respiratory failure secondary to an ILD-like event has been reported that was considered related to tepotinib by the Investigator. The causal relationship between ILD and tepotinib is confounded by the presence of other factors, such as the underlying NSCLC disease, smoking, prior anticancer treatments, the heterogeneity of manifestations, or the partly unconfirmed ILD diagnosis in some reported cases. However, due to the severity and mortality that can be often associated with this type of events, mitigation measures include careful monitoring in case of symptoms, withdrawal of treatment when ILD is suspected, treatment discontinuation and appropriate treatment for the event (eg, with steroids) upon ILD diagnosis. In summary, considering the severe implications of the condition, the risk can be well managed by the prompt diagnosis and permanent discontinuation of tepotinib treatment. For further details refer to the tepotinib IB.

Edema (mainly peripheral edema), creatinine increased, hypoalbuminemia, amylase and lipase increased, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased, diarrhea, and nausea and vomiting are the risks that are considered adverse reactions to tepotinib. More detailed safety information on classification of risks is provided in the tepotinib IB.

Based on current knowledge, the risk for mutual drug interactions between osimertinib and tepotinib is considered low. Osimertinib is mainly metabolized via cytochrome P450 3A4 (CYP3A4), while tepotinib had no relevant effect on the exposure of the sensitive CYP3A4 substrate midazolam based on results from a clinical study (MS200095-0030), ie, is lacking a relevant influence on this drug metabolizing enzymes. However, both tepotinib and osimertinib have the potential to inhibit P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Tepotinib is a P-gp substrate and may therefore be susceptible to a drug transporter-mediated interaction with osimertinib. However, in the human mass balance study (EMR200095-007), 77.9% of the total radioactivity was recovered in feces including a high fraction (45%) of the administered tepotinib dose as parent compound. Since its absorption is high, resulting in an oral bioavailability of 72%, the fecal parent recovery is assumed to partly stem from systemic clearance via biliary secretion that may be in part dependent on active, P-gp-mediated efflux. Worst-case estimation suggests that full inhibition of this mechanism may increase tepotinib exposure by 43%. In addition, there could be enhanced absorption when intestinal P-gp is inhibited, leading to a 40% increase in exposure at most. However, given the favorable safety profile of tepotinib at doses up to 1400 mg, this is not considered clinically relevant. Similarly, osimertinib may not be prone to clinically relevant drug-drug interactions inhibiting its elimination because dose escalations up to 240 mg were performed in monotherapy without defining a maximum tolerated dose and a dedicated study with the CYP3A inhibitor itraconazole did not show a relevant effect on osimertinib (osimertinib Summary of Product Characteristics [SmPC]).

Nevertheless, to monitor any potential influence on the pharmacokinetics (PK) of each drug in the present study, rich PK sampling after the first and after multiple doses is planned for the safety run-in to evaluate tepotinib exposure under osimertinib co-administration and vice versa. In

addition, dedicated exclusion criteria related to available safety and tolerability information for tepotinib and osimertinib have been introduced in the protocol. Due to the sensitivity of osimertinib to an increase in CYP3A4 activity, strong inducers of CYP3A4 are prohibited. Furthermore, patients with a history of ILD or interstitial pneumonitis, including radiation pneumonitis that require steroid treatment, are excluded.

Osimertinib may prolong the QTc interval. Participants with abnormalities related to cardiac rhythm, conduction, or electrocardiogram (ECG) morphology, or pre-existing QTc risks will therefore be excluded, and the ECG and plasma electrolyte concentrations will be monitored periodically throughout the study. In addition, conditions that can affect left ventricular ejection fraction will be excluded, and echocardiography will be performed at enrollment, end of treatment (EoT), and any time in case of related symptoms in the discretion of the Investigator.

Promising signals for the clinical activity of combinations of EGFR TKIs and MET inhibitors in NSCLC have been observed in clinical studies. In addition, both tepotinib in combination with the EGFR inhibitor gefitinib and osimertinib in combination with the selective MET inhibitor savolitinib have been shown to be safe and well tolerated in clinical studies. Furthermore, the 2 approved EGFR TKIs, ie, gefitinib and osimertinib, have comparable clinical safety profiles. Tepotinib and osimertinib appear not to be prone to drug-drug interactions, and specific exclusion criteria have been defined to reduce the risk for this drug combination. Overall, the available clinical data generated to date indicate a positive benefit risk profile for this new combination and therefore it is considered justifiable to conduct the study, as specified in this protocol.

The study introduces a single agent tepotinib arm to additionally assess the contribution of tepotinib to the osimertinib and tepotinib combination therapy. The 500 mg once daily dose of tepotinib (as used in the ongoing Phase II single agent VISION study) is considered to be safe and in the biologically active range.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tepotinib and osimertinib may be found in Section 4.2 (Scientific Rationale for Study Design) and the tepotinib IB, as well as the osimertinib prescribing information.

Based on the available clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable, as these data indicate a positive benefit risk profile for this new combination.

3 Objectives and Endpoints

Safety run-in only:

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

Overall study including safety run-in:

Objectives	Endpoints (Outcome Measures)
Primary	
To assess the efficacy of tepotinib combined with osimertinib in participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by 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).
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.
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.
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).
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.
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 according to RECIST Version 1.1 by IRC and by Investigator. Overall survival

Objectives	Endpoints (Outcome Measures)
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 stable disease [SD] lasting at least 12 weeks) as assessed by IRC and by Investigator. Progression free survival according to RECIST Version 1.1 by IRC and by Investigator. Overall survival
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 stable disease [SD] lasting at least 12 weeks) as assessed by IRC and by Investigator. Progression free survival according to RECIST Version 1.1 by IRC and by Investigator.
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 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 Non–small Cell Lung Cancer Symptom Assessment Questionnaire.
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 $AUC_{0\text{-}t}$, 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, CL/f and Vz/f based on sparse PK sampling on Day 1, Cycle 1 and 2 (all study participants).
To assess resistance marker 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.
Tertiary/Exploratory	
To explore efficacy in participants with known brain metastasis, if applicable.	Intracranial response (confirmed CR or PR) by IRC
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, HGF levels and MET mutations), and other relevant oncogenic pathways.
To explore genetic variations of genes involved in the PK and safety of tepotinib.	Assessment of genes (eg, P-gp, BCRP) involved in the PK of tepotinib.
To investigate the exposure-response relationship.	Assessment of PK with other primary and secondary efficacy endpoints.

4 Study Design

4.1 Overall Design

This Phase II, two-arm, open-label study will assess the antitumor activity, safety, tolerability, and PK of the MET inhibitor tepotinib alone and combined with the 3rd generation EGFR inhibitor osimertinib in participants with advanced or metastatic NSCLC harboring activating EGFR mutations and having relapsed on prior first-line osimertinib due to MET amplification.

Prescreening

After written informed consent for Prescreening procedures has been obtained, MET amplification status will be centrally assessed by fluorescence in situ hybridization (FISH) or by reviewing pre-existing local FISH results using tumor tissue (TBx), and centrally by blood-based next generation sequencing (LBx). Biospecimens for TBx (central and local) and LBx prescreening must be collected after documented relapse of participants with EGFRm+ NSCLC on previous first-line osimertinib treatment.

Participants with MET amplification detected locally by FISH are required to sign the Prescreening informed consent form (ICF) and provide the information on the results and the local FISH assay used. Those participants must also provide blood for the central LBx testing after signing prescreening ICF (Section 8.8).

In case of administrative, operational or logistical errors, insufficient TBx material available/provided from previous local FISH testing or if the provided TBx or LBx sample could not be evaluated at the testing laboratory, repeat collections of TBx and/or LBx may be performed without the need to obtain a new written informed consent for Prescreening.

Participants who were identified MET amplification positive and who had progressed on previous first-line osimertinib are recommended to continue treatment with osimertinib beyond progression, at the discretion of the Investigators, also in line with current clinical guidelines (NCCN Version 3, 2019) and criteria as defined by Jackman 2010, until they either receive the experimental treatment as defined in this study, or in the case of ineligibility, a follow-up treatment as discussed with their physician.

Screening Period

After MET amplification positive participants (by central or local TBx, or by central LBx) have given written informed consent for screening procedures, study eligibility will be assessed within -28 to -1 days prior to Day 1 of study intervention. If, at Screening, the participant meets all the protocol-defined inclusion criteria and none of the exclusion criteria, the participant will be considered eligible and will be enrolled into the study. The screening period will include a baseline tumor RECIST Version 1.1 assessment and the confirmation of measurable tumor disease by two independent radiologists. Participants with MET amplification detected locally by FISH must provide tumor tissue at Screening (or at Prescreening) for central confirmation of the result. Central confirmation is not mandated prior to the start of study treatment. Participants who fail to meet the protocol-specified criteria or who discontinue the study before enrollment will be considered screening failures.

Treatment Period

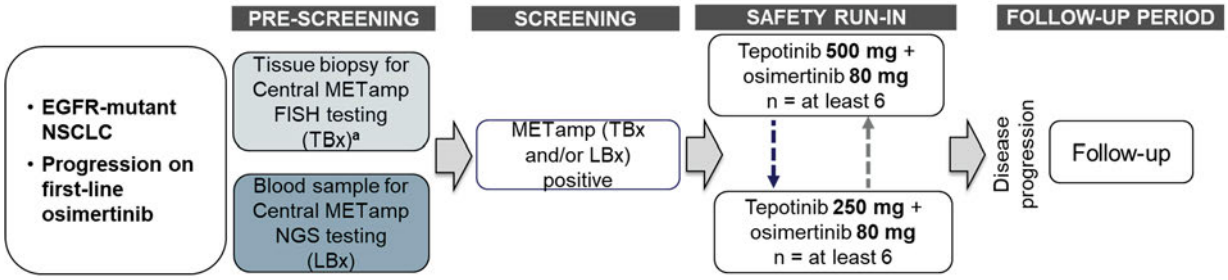
During the treatment period of the INSIGHT 2 study, an initial subset of at least 6 participants will be enrolled in a safety run-in treatment part for their first treatment cycle and the rest of the participants will be enrolled directly in the main treatment part as shown in Figure 2 and

Figure 3.

a. SAFETY RUN-IN

An initial subset of at least 6 participants, who are detected to be MET amplified with any of the methods (central/local TBx or central LBx) described at Prescreening, will be enrolled in a safety run-in to confirm the safety of the combination dose of 500 mg once daily of tepotinib as currently used in the Phase II single agent VISION study together with osimertinib 80 mg once daily (Figure 2).

Figure 2 Safety Run-In



EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-Small Cell Lung Cancer; TKI: Tyrosine Kinase Inh bitor; MET: Mesenchymal-epithelial Transition Factor; amp: amplification; FISH: fluorescence in situ hybridization; NGS: Next Generation Sequencing; TBx: Tissue Biopsy; LBx: Liquid Biopsy.

a Enrollment will be allowed based on positive local FISH testing; tumor tissue must be provided for central confirmation of result by FISH during Prescreening or Screening but central confirmation is not mandated prior to the start of study treatment; if available and allowed locally: additional tissue material to be provided for central TBx NGS.

For this part of the study, there will be a dedicated Safety Monitoring Committee (SMC) consisting of Sponsor representatives (including, but not limited to the Patient Safety Strategy Lead (chair), the Medical Responsible, and the Biostatistician), the coordinating and enrolling Investigators, or their deputies. The SMC will review safety, tolerability, and available PK data. The SMC will meet after 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, to decide on the final tepotinib dose and regimen to be used in the study.

The first participant of the initial dose cohort will be observed for at least 2 days by the enrolling Investigator before the second participant can be treated. The observation does not require hospitalization and includes vital signs, labs, and ECG, on Cycle 1 Day 2. Thereafter, enrollment will not be interrupted until a final decision for the combination is made. However, interruption of

enrollment and a related SMC meeting may be requested at any time by SMC member(s) if a safety or tolerability signal requires expedited discussions.

The SMC will recommend the Phase II dose (RP2D) of tepotinib to be used in the whole study in combination with osimertinib. The SMC may also recommend reducing the tepotinib dose to 250 mg in combination with osimertinib as part of the safety run-in and/or for the whole study. The SMC will be guided by the results of Bayesian Optimal Interval design (BOIN). The recommendation of the BOIN design is not binding (ie, the SMC may choose a different dose level other than suggested by the BOIN design; re-escalation is allowed). The RP2D for the whole study will be based on SMC recommendation and Sponsor decision (Medical Safety and Ethics Board [MSEB] decision).

Dose-limiting toxicities

Dose-limiting toxicities (DLT) will be evaluated using the NCI-CTCAE v5.0. Limits for dose escalations will be considered in accordance to Bayesian Optimal Interval design (BOIN) based on a maximum target toxicity rate of 30% and a maximum number of 12 participants (Yuan 2016). Tepotinib dose changes based on the number of DLTs observed in the total number of participants treated with the respective dose will be considered by the SMC according to Table 2.

Table 2 Bayesian Optimal Interval Design Decision Criteria for Tepotinib Dose Changes

Action	Number of participants treated at the current dose											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
De-escalate from 500 mg to 250 mg in case the number of DLTs is ≥	1	1	2	2	2	3	3	3	4	4	4	5
Escalate back from 250 mg to 500 mg in case the number of DLTs is ≤	0	0	0	0	1	1	1	1	2	2	2	2

DLT: Dose limiting toxicity

At least 6 participants on a dose level are regarded as necessary to select a dose for the Phase II part of the study. In the safety run-in part of the study, DLTs are defined as any of the following toxicities and judged by the Investigator and/or the Sponsor to be not attributable to the disease or disease-related processes under investigation:

- Grade 4 neutropenia for more than 7 days
- Grade ≥ 3 febrile neutropenia
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with non-traumatic bleeding
- Grade ≥ 3 nausea/vomiting and/or diarrhea that has not improved within 72 hours despite adequate and optimal treatment
- Any other Grade ≥ 3 non-hematological AE, except alopecia or Grade 3 nauseas/vomiting and/or diarrhea that has improved within 72 hours with optimal treatment.

A DLT is also defined specifically in case of:

- Occurrence of Hy's law cases (defined as aminotransferases > 3 × upper limit of normal (ULN), total bilirubin ≥ 2 × ULN, and alkaline phosphatase (ALP) < 2 × ULN, with no other reason to account for these abnormalities)
- Grade ≥ 3 lipase and/or amylase elevation with signs and symptoms suggestive of pancreatitis or if confirmation of pancreatitis, either based on clinical or radiological signs. An isolated lipase and/or amylase elevation of Grade ≥ 3 without clinical or radiological evidence of pancreatitis will not be defined as DLT
- Any QTcF increase associated with signs and symptoms of serious arrhythmia (Grade 4)
- Interstitial lung disease/pneumonitis

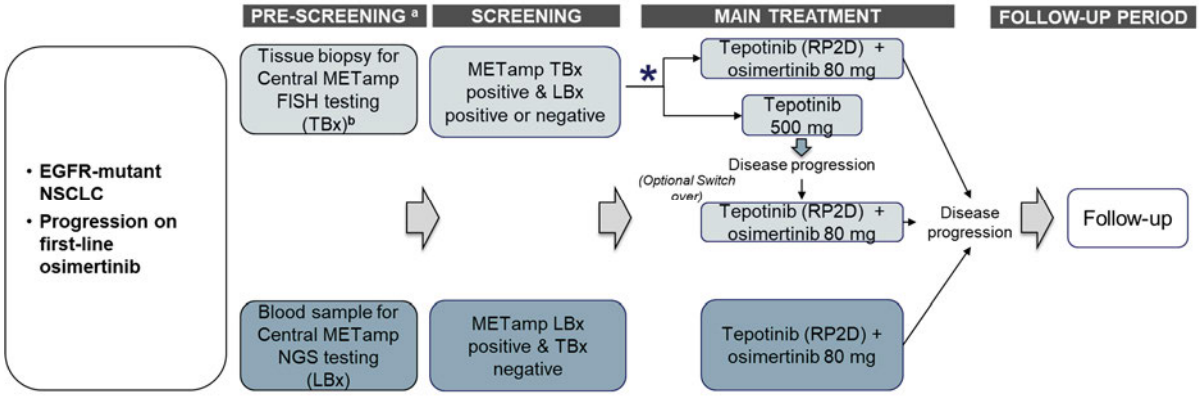
All participants enrolled in safety run-in who miss > 25% of the planned doses within Cycle 1 will be replaced if the dose reduction/interruption was not caused by any safety reasons/DLTs.

b. MAIN TREATMENT

The main treatment part overview is provided in

Figure 3.

Figure 3 Main Treatment



* The randomization (2:1 ratio) in the main treatment part will continue until 12 MET amplification positive by centrally confirmed FISH (TBx) participants are enrolled in the monotherapy arm. After this all participants will be assigned to the combination of tepotinib plus osimertin b. Participants in the Republic of Korea will not undergo randomization but will be assigned exclusively to the combination of tepotinib plus osimertin b, and therefore will not be treated with tepotin b monotherapy.
EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-Small Cell Lung Cancer; TKI: Tyrosine Kinase Inhibitor; MET: Mesenchymal-epithelial Transition Factor; amp: amplification; FISH: fluorescence in situ hybridization; NGS: Next Generation Sequencing; TBx: Tissue Biopsy; LBx: Liquid Biopsy; RP2D: recommended Phase II dose.
[a] Submission of tumor tissue and blood sample obtained after progression on first-line osimertinib, is mandatory for all patients for MET amplification testing at Prescreening.
[b] Enrollment will be allowed based on positive local FISH testing; tumor tissue must be provided for central confirmation of result by FISH during Prescreening or Screening but central confirmation is not mandated prior to the start of study treatment; if available and allowed locally: additional tissue material to be provided for central TBx NGS.

During the main treatment part, participants with EGFRm+ NSCLC who have relapsed on previous first-line osimertinib due to MET amplification will be treated as follows (Figure 3):

- Eligible participants with MET amplification identified by FISH (TBx) (central or local) and independent of the MET status by LBx, will be randomly assigned in a ratio of 2:1 to either the combination of tepotinib at a dose defined by the SMC and osimertinib at the recommended daily dose of 80 mg or tepotinib alone at the daily dose of 500 mg (as currently used in the Phase II single agent study) in cycles of 21-day duration (two-arm study). Participants will continue to receive study treatment until disease progression (according to RECIST Version 1.1), death, AE leading to discontinuation, study withdrawal, or consent withdrawal. The randomization to the two arms of the study will continue until 12 participants who are MET amplification positive by centrally confirmed FISH (TBx) are enrolled in the monotherapy arm. After this, all participants will be assigned to the combination of tepotinib plus osimertinib. For participants in the randomized part of the study, verification of disease progression by IRC is required. Participants who are randomized to the tepotinib monotherapy will have the opportunity to switch over to the combination of tepotinib plus osimertinib if they experience disease progression according to RECIST Version 1.1 reported by investigator and verified by IRC. Until progression is verified by IRC and the switch over to the combination of tepotinib plus osimertinib takes place, tepotinib monotherapy can be continued, if judged appropriate by the Investigator. However, if disease progression is not verified by IRC, the participant must discontinue study intervention. Participants who permanently discontinue tepotinib monotherapy due to an AE, withdraw consent, or for any reason other than progressive disease, will not be eligible to switch over to the combination of tepotinib plus osimertinib.

Note that only participants assigned to the combination of tepotinib plus osimertinib and who are MET amplification positive by centrally confirmed FISH (TBx) will be evaluated for the primary objective of the study. Participants assigned to tepotinib monotherapy and who are MET amplification positive by centrally confirmed FISH (TBx) will be evaluated for a secondary efficacy objective of the study. Participants in the Republic of Korea will not undergo randomization but will be assigned exclusively to the combination of tepotinib plus osimertinib, and therefore will not be treated with tepotinib monotherapy. The efficacy outcomes of participants in each of the two arms who are MET amplification positive only by local but not centrally confirmed FISH (TBx) will only be listed (See Section 9.4.1).

- Eligible participants with MET amplification identified centrally by blood-based next generation sequencing (LBx) only, will receive the combination of tepotinib at a dose defined by the SMC and osimertinib at the recommended daily dose of 80 mg in cycles of 21-day duration. There will be no monotherapy arm for participants who are detected to be MET amplified by central blood-based next generation sequencing (LBx) only. Participants will continue to receive study treatment until disease progression (according to RECIST Version 1.1), death, AE leading to discontinuation, study withdrawal, or consent withdrawal. Approximately 20 participants with MET amplification identified by central blood-based next generation sequencing (LBx) only are expected to be assigned to the combination of tepotinib plus osimertinib.

Note that participants who are MET amplification positive by central blood-based next generation sequencing (LBx) will be evaluated for a secondary efficacy objective of the study and will not be part of the primary analysis set.

In addition to the SMC, which will monitor and guide the safety run-in, an Independent Data Monitoring Committee (IDMC) will be formed from a group of experts including one statistician and at least one oncologist who will not be participants in this conduct of this study. An IDMC charter and the integrated statistical analysis plan (IAP) will provide the details about the conduct of the IDMC meeting and frequency. The IDMC will be responsible for periodic (as defined by the IDMC charter) evaluations of the clinical study to ensure continued participant safety as well as the validity and scientific merit of the study.

Safety and efficacy data outputs for any interim analyses (Refer to Section 9) will be provided to the IDMC. The IDMC will give a recommendation regarding further conduct of the study. The Sponsor management will take the final decision if the IDMC recommends stopping the study. After the enrolment halt the requirements for an IDMC do no longer exist and no further IDMC meetings will be conducted.

Follow-up Period

All participants are to be followed up after stop of study intervention, including an EoT visit within 14 days since documented decision by the Investigator to permanently discontinue study intervention. A Safety Follow-up Visit will occur 30 ± 3 days after the last dose of study treatment for all participants who discontinue study intervention permanently. In case EoT Visit and Safety Follow-up Visit end up falling within the same 7 days, only EoT Visit should be performed. Participants who withdraw from the treatment for reasons other than progressive disease (PD) or death have additional visits for tumor assessments every 6 weeks until 9 months after first administration of study intervention and every 12 weeks thereafter until disease progression. Survival follow-up is to be performed every 3 months (± 2 weeks) at clinic visit or by telephone contact. Participants' survival information will be collected. Any subsequent anticancer therapy given to the participant until death should be recorded.

4.2 Scientific Rationale for Study Design

The Phase II, two-arm, open-label, INSIGHT 2 study has been designed to assess the efficacy and safety of tepotinib in combination with osimertinib in patients with EGFRm+ and MET amplified, locally advanced or metastatic NSCLC who have progressed on first-line osimertinib. It will also assess the contribution of tepotinib to the osimertinib and tepotinib combination therapy by assessing tepotinib monotherapy in the same population. No formal statistical comparison between the combination arm and the monotherapy arm is planned.

Somatic activating mutations in the tyrosine kinase domain of EGFR are present in approximately 10% of Caucasian (Europe and US) and nearly 30% of Asian patients with advanced or metastatic NSCLC. Almost 90% of these mutations consist of deletions in exon 19 or L858R point mutations within exon 21 (Carbonnaux 2016).

Several large-scale Phase III clinical trials have consistently demonstrated the superior efficacy of 1st and 2nd generation EGFR TKIs in comparison with standard first-line platinum-based chemotherapy for the treatment of patients with advanced EGFRm+ NSCLC (Sullivan 2017, NCCN version 3, 2019). Unfortunately, most patients ultimately progress on EGFR TKI treatment via a resistance mechanism most commonly related to EGFR such as the T790M mutation (Sullivan 2017). This limitation has been overcome by the introduction of 3rd generation TKIs, particularly osimertinib. Currently, osimertinib is the only 3rd generation EGFR TKI approved for the treatment of T790M positive patients who have progressed on 1st or 2nd generation EGFR TKIs. Osimertinib is also approved as first-line therapy for advanced EGFRm+ NSCLC, regardless of T790M mutation status. However, despite the robust clinical activity exerted by osimertinib, patients inevitably develop secondary resistance to this treatment, which poses a significant challenge due to the paucity of post-osimertinib pharmacological options available to date (Leonetti 2019).

Next to EGFR-related resistance, MET gene amplification constitutes the most frequent cause of bypass pathway activation as an acquired resistance mechanism to EGFR TKIs (Wu 2017; Papadimitrakopoulou 2018; Ramalingam 2018). When osimertinib was given as a first-line therapy, MET amplification was the most common resistance mechanism, encountered in 15% of patients by next generation sequence circulating tumor DNA (ctDNA) analysis. Moreover, this percentage is expected to be higher in tissue, due to the underestimation of gene amplification in plasma (Leonetti 2019; Ramalingam 2018).

Activated MET thereby acts as a secondary oncogenic driver in EGFRm+ NSCLC, requiring the concurrent inhibition of both MET and EGFR (Engelman 2007; Turke 2010). Therefore, INSIGHT 2 investigates concomitant inhibition of both targets with the combination of the highly selective MET inhibitor tepotinib and osimertinib, in patients with EGFRm+ and MET amplified, locally advanced or metastatic NSCLC who have progressed on first-line osimertinib. It will also assess the contribution of tepotinib to the osimertinib and tepotinib combination therapy in the same population but no formal statistical comparison between the combination arm and the monotherapy arm is planned.

The strong addiction on the EGFR pathway is also demonstrated by 2 clinical phenomena observed in subsets of EGFRm+ NSCLC patients. A disease flare was seen in patients having discontinued their EGFR inhibitor treatment after relapse (Chaft 2011). Moreover, single responses were noted in patients following wash-out and re-start of EGFR TKI treatment after previous relapse on EGFR TKIs (Cappuzzo 2016). Therefore, patients who are identified as MET amplification positive and who had documented progression on previous EGFR TKI treatment are recommended to continue treatment with the EGFR TKI beyond progression in line with current clinical guidelines (NCCN version 3, 2019) and criteria as defined by Jackman 2010 until they either receive the experimental treatment as defined in this study, or in the case of non-eligibility, a follow-up treatment as discussed with their physician.

While there is a strong scientific rationale for the combined MET and EGFR inhibition in EGFR TKI resistant MET amplified NSCLC as supported by available results from several clinical studies (Yang 2017; Ahn 2017; Wu 2018; Cheng 2018), the final population eligible for this personalized targeted treatment is obviously small. It is estimated that only 2% to 5% of the overall

NSCLC population is positive for MET amplification after osimertinib relapse and therefore suitable to receive the study intervention. For this reason, the current design has been chosen to cope not only with the feasibility issues regarding recruitment of participants into this study but also with expectations of the participants having gone through the stringent entry criteria for this study. The decision for not including a standard of care control arm also considers the experience from the previous INSIGHT (NCT01982955) study, which the Sponsor performed in a comparable study population and which had to be prematurely halted due to difficulties recruiting participants into the randomized controlled study. The tepotinib monotherapy arm in the study is required in order to assess the contribution of tepotinib to the osimertinib and tepotinib combination in participants with EGFRm+ NSCLC who have relapsed on previous first-line osimertinib due to MET amplification. Only 12 MET amplification positive by centrally confirmed FISH (TBx) participants are required for the monotherapy arm. A formal statistical comparison between the combination and the monotherapy arm will not be performed. For participants in the randomized part of the study, verification of disease progression by IRC is required. Participants who are randomized to the tepotinib monotherapy will have the opportunity to switch over to the combination of tepotinib plus osimertinib if they experience disease progression according to RECIST Version 1.1 reported by investigator and verified by IRC. Until progression is verified by IRC and the switch over to the combination of tepotinib plus osimertinib takes place, tepotinib monotherapy can be continued, if judged appropriate by the Investigator. However, if disease progression is not verified by IRC, the participant must discontinue study intervention.

Previous clinical data clearly point to a much higher predictivity of MET amplification as a marker for patient stratification compared with MET overexpression in the EGFR TKI resistance setting. Tepotinib has already been investigated in a combination with the 1st generation EGFR TKI gefitinib in advanced EGFRm+ NSCLC patients. In this previous study participants were selected based on Met protein overexpression or gene copy number gain/MET amplification. While the respective overall intention-to-treat population had PFS similar to that of the platinum doublet chemotherapy control arm, the predefined subset of MET amplified patients showed highly significant differences in PFS with a hazard ratio of 0.13 (90% CI 0.04, 0.43) with median PFS in the tepotinib/gefitinib arm of 16.6 months (90% CI 8.3, not estimable) compared with a median PFS in the control arm of 4.2 months (90% CI 1.4, 7.0). This observation is also in line with previous failure in development programs by competitors such as onartuzumab, which only relied on Met or HGF protein overexpression for patient stratification and could not show benefit in a Phase III lung cancer study (Garber 2014).

In the INSIGHT 2 study, MET amplification status after progression on first-line osimertinib must be confirmed centrally by FISH (TBx) or centrally by blood-based next generation sequencing (LBx). In the case of local TBx FISH MET amplification testing, sites must provide the minimum required tumor tissue samples for central confirmation of MET status by FISH at Screening (or at Prescreening) but central confirmation is not mandated prior to the start of study treatment. A MET gene copy number ≥ 5 and/or a MET/CEP7 ratio ≥ 2 will be regarded as MET FISH positive.

In parallel with the clinical development activities, a companion diagnostic strategy for LBx based testing is in place including a methodology being monitored closely.

4.3 Justification for Dose

The dose selected for osimertinib is 80 mg once daily, which is the dose approved for the treatment of patients with EGFRm+ NSCLC and in agreement with the SmPC and osimertinib label. A dose reduction to 40 mg once daily is allowed but only if required based on individual safety and tolerability in line with the osimertinib label.

The primary dose to be evaluated for tepotinib is 500 mg once daily, which is the dose and regimen used in monotherapy as well as in the combination with gefitinib in 4 Phase II studies so far. Tepotinib doses up to 1400 mg once daily were administered in the tepotinib first in human (FIH) study without defining a maximum tolerated dose. Selection of the 500 mg once daily dose is based on a translational modelling approach using preclinical PK, pharmacodynamic, and tumor growth data combined with clinical PK and pharmacodynamic data from patients enrolled in the FIH study (Xiong 2015). Thereby, a tepotinib concentration could be defined that results in a 95% inhibition of the MET receptor which is achieved by > 90% of patients with the 500 mg once daily dosing (Xiong 2015).

Both drugs, osimertinib and tepotinib, have shown safety and tolerability in monotherapy in their FIH studies, which allowed dosing beyond the selected treatment doses, ie, 80 versus 240 mg osimertinib and 500 versus 1400 mg tepotinib. In addition, for both drugs there are clinical results available showing that a combination of an EGFR and MET inhibitor is safe to be used without change in the predefined treatment doses. In addition, the safety profile, especially between the 1st generation EGFR TKI (including gefitinib) and the 3rd generation EGFR TKI (including osimertinib) is also considered comparable (Soria 2018; Mezquita 2018), which may also allow to draw the conclusion that the combination of tepotinib and osimertinib may have a manageable risk for unexpected toxicity.

Therefore, based on the available clinical information of both drugs, a once daily dose of 500 mg tepotinib and 80 mg osimertinib will be assessed in the study. If this dose and regimen can be confirmed in the safety run-in by the SMC, the study will continue with the dose and regimen of 500 mg tepotinib and 80 mg osimertinib once daily. Based on safety, tolerability, and PK results in the safety run-in, the SMC may also decide to reduce the tepotinib dose to 250 mg, which is the lower dose that is still defined to be pharmacologically active.

Exposure to neither osimertinib nor tepotinib is subject to ethnic differences. Food has been shown to increase osimertinib exposure to a clinically insignificant degree (Planchard 2016). The drug combination or tepotinib monotherapy will therefore be administered after food intake, eg, a normal breakfast, as done in previous studies with tepotinib.

Results of the safety run-in treatment part

During the safety run-in treatment period of the MS200095-0031 study, two SMC meetings took place, the first on 05 May 2020 and the second on the 11 August 2020.

In the first SMC meeting, 3 participants who had completed Cycle 1 of treatment with the combination of tepotinib at the dose of 500 mg once daily together with osimertinib 80 mg once daily, were evaluated. No DLTs were noted and the SMC members unanimously confirmed to

continue the safety run-in treatment part without modification, until at least 3 more participants are enrolled in the study. The Investigators agreed with the decision of the SMC members.

In the second and final SMC meeting, 6 participants who had completed Cycle 1 of treatment with the combination of tepotinib at the dose of 500 mg once daily together with osimertinib 80 mg once daily, were evaluated (3 of those 6 participants had newly completed Cycle 1 of treatment since the first SMC meeting). No DLTs were noted with the data evaluated until 11 August 2020. The SMC members unanimously confirmed to continue enrollment in the expansion part of the study with a RP2D of 500 mg tepotinib and 80 mg osimertinib. The Investigators agreed with the decision of the SMC members and no further patients were included into the safety run-in treatment part of the MS200095-0031 study.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including all scheduled procedures (including survival follow-up).

The end of the study is defined as the date of study intervention discontinuation by all participants (due to either disease progression, undue toxicity, or withdrawal, and, therefore, are not likely to benefit from the study intervention any longer) and two thirds of the participants have died or were followed up for at least 3 years, whatever occurs first. After the end of the study a final analysis, including an analysis of efficacy and safety, will be conducted in all participants.

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant has provided written informed consent, as indicated in Appendix 2 (Study Governance).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are ≥ 18 years of age (or having reached the age of majority according to local laws and regulations, if the age of majority is > 18 years of age [ie, ≥ 20 years of age in Japan]), at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Are participants with the following:

a) Locally advanced or metastatic NSCLC histology (confirmed by either histology or cytology) with documented activating EGFR mutation.

b) Presence of at least 1 independently verified measurable lesion in accordance with RECIST Version 1.1, that can be accurately assessed at Baseline with ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), which is suitable for accurate repeated measurements and that preferably was not previously irradiated or biopsied.

c) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a minimum life expectancy of 12 weeks.

d) Acquired resistance on previous first-line osimertinib. Participants must meet both of the following 2 criteria:

- Radiological documentation of disease progression on first-line osimertinib.
- Objective clinical benefit documented during previous osimertinib therapy, defined by either partial or complete radiological response, or durable stable disease (SD) (SD should last > 6 months) after initiation of osimertinib.

e) Have received only first-line osimertinib as a prior line of therapy in the noncurative advanced or metastatic NSCLC setting.

f) MET amplification as determined by either FISH testing (central or local) on tumor tissue (TBx) or central blood-based next generation sequencing (LBx). Tumor and blood samples must be collected following progression on prior first-line osimertinib at Prescreening.

- Submission of tumor tissue and blood sample obtained after progression on first-line osimertinib, is mandatory for all patients for MET amplification testing.
- Submission of tumor tissue during Prescreening or Screening is mandatory for patients with tumor tissue tested by local FISH, to confirm MET amplification status. Central confirmation is not mandated prior to the start of study treatment.

Weight

Not applicable.

Sex

3. Are male or female

a) Female participants:

Are **not** pregnant or breastfeeding, and at least 1 of the following conditions applies:

- **Not** a woman of childbearing potential (WOCBP)

OR

- If a WOCBP, use a highly effective contraceptive method (ie, with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
  - Before the first dose of the study intervention(s), if using hormonal contraception:

    1. has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

    OR

    2. Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

  AND
  - A barrier method, as described in Appendix 3.
- During the intervention period
- After the study intervention period (ie, after the last dose of study intervention is administered) for at least 2 months after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

  The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Have a negative serum pregnancy test, as required by local regulations, within 28 days before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.4.

The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

b) Male participants:

Agree to the following during the study intervention period and for at least 4 months after the last dose of study intervention:

- Refrain from donating sperm

PLUS, either:

- Abstain from intercourse with a WOCBP

OR

- Use a male condom: when having sexual intercourse with a WOCBP, who is **not** currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak.

Informed Consent

4. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Spinal cord compression or brain metastasis unless asymptomatic, stable or not requiring steroids for at least 2 weeks prior to start of study intervention. Prior radiotherapy or surgery for brain metastases such as stereotactic radiosurgery/gamma knife must have been completed ≥ 2 weeks, all others ≥ 4 weeks prior to start of therapy. Participants with leptomeningeal disease are ineligible.
2. Any unresolved toxicity Grade 2 or more according to NCI-CTCAE version 5, from previous anticancer therapy with the exception of alopecia.
3. Need for transfusion within 14 days prior to the first dose of study intervention.
4. Participants who have brain metastasis as the only measurable lesion
5. Inadequate hematological function:
    - Hemoglobin < 8.5 g/dL
    - Neutrophils < 1.5×10^9/L
    - Platelets < 100×10^9/L.
6. Inadequate liver function:
    - Total bilirubin > 1.5 × ULN
    - AST/ALT/ALP > 3 × ULN
    - For participants with liver metastases:
        i. Total bilirubin > 1.5 × ULN
        ii. AST/ALT/ALP > 5 × ULN
        iii. For participants with bone metastases: ALP > 5 × ULN.

7. Inadequate renal function:

    - Renal impairment as evidenced by serum creatinine ≥ 1.5 × ULN, or creatinine clearance (CrCl) < 30 mL/min calculated by the Cockcroft-Gault formula (24-hour CrCl might be requested by the Investigator for confirmation, if calculated CrCl is < 50 mL/min. In such case, participants with 24-hour CrCl < 30 mL/min should be excluded).

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

8. History of ILD or interstitial pneumonitis including radiation pneumonitis that required steroid treatment.
9. Impaired cardiac function:

    - Left ventricular ejection fraction < 45% defined by echocardiography
    - Grade 4 arrhythmia (NCI-CTCAE v5.0)
    - Unstable angina pectoris
    - Congestive Heart Failure New York Heart Association III and IV
    - Myocardial infarction, stroke, or transient ischemic attack within the last 6 months prior to study entry.

10. Corrected QT interval by Fredericia (QTcF) > 470 ms for women and > 450 ms for men at Screening. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives, or any concomitant medication known to prolong the QT interval and cause Torsade de Pointes.
11. Hypertension uncontrolled by standard therapies (not stabilized to < 150/90 mmHg).
12. Contraindication to the administration of osimertinib.
13. Medical history of liver fibrosis/cirrhosis.
14. Past or current history of neoplasm other than NSCLC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, benign prostate neoplasm/hypertropia, or other cancer curatively treated and with no evidence of disease for at least 5 years.
15. Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the tested product.
16. Major surgery within 28 days prior to Day 1 of study intervention.
17. Known human immunodeficiency virus positivity.

18. Known hypersensitivity to any of the study intervention ingredients.

Prior/Concomitant Therapy

19. Prior treatment with other agents targeting the HGF/MET pathway such as crizotinib, capmatinib, savolitinib, foretinib, glesatinib, cabozantinib, merestinib, onartuzumab, rilotumumab, emibetuzumab, and ficlatuzumab.
20. Participants currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study intervention) medications or herbal supplements known to be potent inducers of CYP3A4.

Prior/Concurrent Clinical Study Experience

21. Participation in another interventional clinical study (except those participants who were solely involved in other studies where the investigational product was osimertinib in the first-line of therapy) within the 30 days prior to randomization/first dose.

Diagnostic Assessments

Not applicable.

Other Exclusions

22. Substance abuse, active infection, or other acute or chronic medical or psychiatric condition or laboratory abnormalities that might increase the risk associated with study participation at the discretion of Investigators.
23. Legal incapacity or limited legal capacity.
24. Any other reason that, in the opinion of the Principal Investigator, precludes the participant from participating in the study.

5.3 Lifestyle Considerations

On days when PK samples are to be drawn, participants should be instructed to attend the study visit in a fasted state (minimum 6 hours fasting; plain water consumption is acceptable), with no breakfast and prior to taking their dose of tepotinib and osimertinib. After a predose PK blood sample is drawn, the assigned dose of tepotinib and osimertinib should be taken after breakfast. No further food should be consumed until 2 hours after the dose (water is allowed).

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

5.4 Screen Failures

Prescreening

Generally, repeat of Prescreening is not permitted. However, in case of administrative errors or the provided TBx and/or LBx sample cannot be evaluated at the central testing laboratory, the TBx and/or LBx sample may be collected again (but always after progression on first-line osimertinib and before initiation of study intervention) from a participant without obtaining new consent for Prescreening and using the already assigned participant number.

Screening

Generally, individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. However, the Sponsor may be re-approached by the Investigator for an individual participant and may grant an exception to repeat screening procedures. This participant must have a confirmed MET amplification as defined in this protocol but may have failed other inclusion or exclusion criteria in the initial screening. In this case, the rescreened participants will be assigned a new participant number.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol. In this protocol, this refers to tepotinib and osimertinib combination therapy or tepotinib monotherapy.

Note: Osimertinib is an approved drug (Tagrisso). While this protocol describes the use of osimertinib in this study, more comprehensive information about osimertinib can be found in the prescribing information/SmPC and other reference sources. Investigators are advised to also take this information into account.

6.1 Study Intervention(s) Administration

Study Intervention Name:	Tepotinib and osimertinib combination, or tepotinib monotherapy
Dose Formulation:	Tepotinib: 250 mg tablets. Osimertinib: 80 mg (and 40 mg) tablets.
Unit Dose Strength(s)/Dosage Level(s):	Tepotinib 500 mg (2 tablets of 250 mg) per day, orally, in cycles of 21-day duration. Osimertinib (Tagrisso): 80 mg once daily. A dose reduction to 40 mg once daily is allowed if required based on individual safety and tolerability in line with the prescribing information.
Route of Administration:	Oral with food
Dosing Instructions:	Participants will take tepotinib at the assigned dose together with osimertinib at the approved dose of 80 mg, orally once daily, approximately at the same time (± 2 hours), preferentially each morning immediately after food intake with a full glass of water (approximately 200 mL). Participants assigned to the monotherapy tepotinib treatment will take tepotinib at the 500 mg once daily dose (as currently used in the single agent Phase II study). Participants will be instructed to swallow the tablets wholly and to avoid biting or breaking the tablets or attempting to dissolve in water before taking the dose. For comprehensive dosing instructions refer to Section 6.6.
Supplier/Manufacturer:	Tepotinib: manufactured by Merck Healthcare KGaA. Osimertinib: manufactured by AstraZeneca. Tepotinib and osimertinib are to be supplied by Merck Healthcare KGaA.

Packaging and Labeling	A description of pharmaceutical properties and composition of the formulation is provided in the IB for tepotinib and in the SmPC for osimertinib. Each container will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines. Tepotinib and osimertinib kits will be supplied in a ready-to-use format for dispensing to the participant. No additional preparation or labeling steps will be required. Additional details of packaging, including quantity per container and anticipated length of supply per container, and labeling of the study interventions will be defined in a separate Pharmacy Manual.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff. Any deviations from the recommended storage conditions (refer to the Pharmacy Manual for details) should be immediately reported to the Sponsor, and the study interventions should not be used until authorization has been received from the Sponsor. Tepotinib and osimertinib must not be used for any purpose other than the study. For details regarding special handling instructions of the study interventions refer to the Pharmacy Manual and the osimertinib prescribing instructions.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
  - Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, container numbers, expiry dates, and the participant numbers.

- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Operations Manual.
- The administration of tepotinib or osimertinib to participants who have not been enrolled into the study is not covered by the study insurance.
- Disposal of study intervention should be according to local regulations and institutional guidelines.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

This study is performed two-arm, open-label. Once the participant meets all the inclusion and none of the exclusion criteria, the Investigator or delegate will request the study treatment assignment using the Interactive Voice Response System (IVRS). Eligible participants with MET amplification identified centrally or locally by FISH (TBx) will be randomized at a 2:1 ratio to either combination therapy with tepotinib and osimertinib or tepotinib monotherapy. Participants in the Republic of Korea will not undergo randomization but will be assigned exclusively to the combination of tepotinib plus osimertinib, and therefore will not be treated with tepotinib monotherapy. The randomization is implemented in order to assure an objective assignment to the combination and monotherapy to avoid any influence of participant's characteristics on the decision for treatment. The assignment to the two arms will continue until 12 participants with centrally confirmed (FISH testing) MET amplification are included in the monotherapy arm. Afterwards all enrolled participants will receive the combination treatment.

Approximately 20 participants with MET amplification identified by central blood-based next generation sequencing (LBx) only are expected to be assigned to the combination of tepotinib plus osimertinib.

An IRC is implemented to strengthen objectivity and consistency in the evaluation of the primary endpoint.

In addition, an Independent Data Monitoring Committee (IDMC) of external experts will perform periodic reviews and assess benefit risk of the overall study including all participants. This independent review is considered to also improve the overall quality of the data.

Participant numbers will be assigned in the appropriate format and will reflect study number, site number and participant identification. Participant numbers will not be reassigned to other participants or reused in this study. If a participant is replaced, the replacement will be enrolled

with a unique participant number. If a participant is allowed to be re-screened for the study, a new participant number will have to be assigned.

6.4 Study Intervention Compliance

Acceptable compliance for this study will be defined in the Monitoring Plan.

Each participant will record on a diary card the number of tablets and dosage of tepotinib/osimertinib taken daily including actual time of intake. This diary card will be returned to the Investigator site at each visit.

Participants may be withdrawn from the study intervention in the event of noncompliance that is deemed by the Investigator or Sponsor to compromise participant safety or study integrity (refer to Section 7.1 and Section 8.4).

Participants should be instructed to bring with them to each visit both opened and unopened tepotinib/osimertinib packages, in order to allow the assessment of compliance with study intervention. Tepotinib/osimertinib administration must be recorded in the electronic Case Report Form (eCRF), as applicable.

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (eg, medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

The study will be performed at a clinical research site with personnel trained in basic or immediate life support. Equipment and other agents (epinephrine and prednisolone equivalents, etc.) will be available at the site in case of allergic reactions.

6.5.2 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

The only permitted medications are the following, but restrictions may apply:

- Concomitant medications that have a narrow therapeutic window and are known to be transported by P-gp (eg, rivaroxaban, apixaban, ranolazine, talinolol, and digoxin), BCRP (eg, rosuvastatin), OCT2, MATE1, and MATE2 (eg, dofetilide and metformin), OATP1B1 and OCT1 are permitted. However, cautionary use and close monitoring of signs of changed tolerability due to potentially increased exposure is advised.

- Refer to Appendix 3 for contraceptive methods for WOCBP and female partners with childbearing potential of male study participants. Accordingly, WOCBP enrolled in the study are to use effective contraception during study intervention and for 2 months after final dose. Males and their female partners are to use effective contraception for 4 months after final dose.
- Supportive treatment, eg, bisphosphonates, agents for improving appetite, if initiated prior to study entry can continue. Change in dose/schedule on study is discouraged.
- Symptomatic treatment of brain metastasis with anticonvulsants known to have a reduced risk for drug interactions such as lamotrigine, levetiracetam, pregabalin, or valproic acid.

The Investigator will record all concomitant medications/procedures taken by the participant during the study, from the date of signature of main informed consent, in the appropriate section of the eCRF.

6.5.3 Prohibited Medicines

Any additional concomitant therapy or procedure that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

The following are not permitted during the study:

- Any other concomitant cancer drug therapy, including chemotherapy, biological therapy, hormonal therapy for anticancer purposes, targeted therapy, or any investigational product other than tepotinib and osimertinib as defined in this protocol
- Any concomitant medication known to prolong the QT interval and cause Torsade de Pointes (refer to Appendix 8)
- Drug(s), for which the package insert/SmPC includes a contraindication for P-gp (eg, dabigatran, aliskiren, colchicine), BCRP, OCT1, OCT2, MATE1, MATE2, or OATP1B1 inhibiting drugs
- Drug(s) that are known to be potent inducers of CYP3A or P-gp and thereby may decrease efficacy of osimertinib and tepotinib, including carbamazepine, phenytoin, rifampicin, and Saint John's wort.

Use of prohibited medicines for any reason must result in withdrawal of the participant from this study. For further details with regard to drug-drug interactions, refer to the tepotinib IB.

6.5.4 Other Interventions

Participants may receive palliative radiotherapy, eg, for painful bone metastasis. However, the use of any localized radiation therapy during the study should be discussed with the Sponsor (or delegate) on a case-by-case basis considering the influence on imaging assessments of target/non-target lesions.

6.6 Dose Selection and Modification

Participants assigned to the combination of tepotinib plus osimertinib will take tepotinib at the assigned dose and dose regimen (dose for the overall study confirmed by SMC after the safety-run in) together with osimertinib at the approved dose of 80 mg, orally once daily, approximately at the same time (± 2 hours), preferentially each morning immediately after food intake with a full glass of water (approximately 200 mL).

Participants assigned to the tepotinib monotherapy treatment will take tepotinib at the 500 mg once daily dose (as currently used in the Phase II single agent VISION study), approximately at the same time (± 2 hours), preferentially each morning immediately after food intake with a full glass of water (approximately 200 mL).

The dose of 500 mg tepotinib once daily is the labeled dose of tepotinib in US and Japan for patients with NSCLC with METex 14 skipping alterations. The proposed administered dose of 500 mg tepotinib corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (free base form). The 250 mg tepotinib corresponds to 250 mg tepotinib hydrochloride hydrate and is equivalent to 225 mg tepotinib (free base form).

Participants will be instructed to swallow the tablets whole and to avoid biting or breaking the tablets or attempting to dissolve them in water before taking the dose.

Refer to Section 5.3 for food restrictions prior to PK sampling.

If a participant misses taking a scheduled dose of study drug, within a window of 12 hours, it is acceptable to take the dose. If it is more than 12 hours after the scheduled dose time, the missed dose should not be taken, and participants should be instructed to take the next dose at the next scheduled time.

If a participant vomits after taking their study drug, they should not make up for this dose, but should take the next scheduled dose.

If intolerable toxicities are observed and judged by Investigator to be related to either or both components of the study combination intervention, dose reduction of either or both components will be permitted, if criteria for participant withdrawal from study intervention have not been met. Thereby, the Investigator should notify the Sponsor (or delegate) immediately and each case should be discussed including the reason for dose reduction.

In case a dose reduction is necessary, the study intervention will be administered as follows:

If there is a Grade 3 or higher AE related to either or both components of the combination intervention, dose interruption of either or both components will be permitted for up to 3 weeks. If this AE is not recovered to Grade ≤ 2 or baseline values after 3 weeks of interruption, the participant may have to permanently discontinue osimertinib, tepotinib, or both drugs. If this AE recovered to Grade ≤ 2 or baseline values in less than 3 weeks, continuation of intervention can be restarted at the same dose or at a lower dose of the respective study interventions. In case of osimertinib, a lower dose of 40 mg is available. In case of tepotinib, depending on the RP2D, a reduction to 250 mg or change in dose regimen is possible. The Investigator is also permitted to reduce the dose of osimertinib and tepotinib for AEs that he/she deem related to the intervention

but is also allowed to escalate back again if the clinical condition allows. Immediate notification of the Sponsor (or delegate) is mandatory.

Further guidance on dose modification of osimertinib is given in Table 3, following information as provided in the Tagrisso EU SmPC dated 28 August 2018. Since this table only provides a snapshot of current available knowledge the Investigator is advised to consider any update of osimertinib information given in respective SmPC revisions.

Table 3 Recommended Dose Modifications for Tepotinib and Osimertinib

Target organ	Adverse reaction[a]	Dose modification
Pulmonary	ILD/Pneumonitis.	Permanently discontinue osimertinib and tepotinib.
Cardiac	QTc interval greater than 500 ms on at least 2 separate ECGs.	Withhold osimertinib until QTc interval is less than 481 ms or recovery to baseline if baseline QTc is greater than or equal to 481 ms, then resume at the reduced 40 mg dose.
	QTc interval prolongation with signs/symptoms of serious arrhythmia.	Permanently discontinue osimertinib[b]
	Symptomatic congestive heart failure	Permanently discontinue osimertinib[b]
Body	Edema Grade 1 or 2	Dose level of tepotinib can be maintained
	Edema Grade 3	The dose of tepotinib must be interrupted until edema recovers to ≤ Grade 2 or baseline but for no more than 21 days. After recovery the patient can restart at the same dose or at 250 mg daily. If edema Grade 3 reoccurs the tepotinib dose must be interrupted again until edema recovers to ≤ Grade 2 or baseline but for no more than 21 days. After recovery, tepotinib must then be dose reduced to 250 mg daily (if the previous dose was 500 mg daily). If edema Grade 3 reoccurs at 250 mg dose, tepotinib must be permanently discontinued.
	Generalized edema Grade 4	Permanently discontinue tepotinib
Pancreas	Pancreatic enzyme elevation Grade ≥3	See detailed instruction in Section 6.8.
Other	Any other adverse reaction of Grade ≥3	The dose of tepotinib must be interrupted until event resolves to ≤ Grade 2 or baseline but for no more than 21 days. After recovery, tepotinib may be restarted at 1 dose level below: 250 mg daily.

ECG: electrocardiogram; ILD: interstitial lung disease.

a Adverse reactions graded by NCI CTCAE v5.0

b In the case of permanent discontinuation of tepotinib or osimertinib due to toxicity, participants must permanently discontinue study treatment.

Any clinical circumstances leading to dose modifications and which are not covered by above criteria may be grounds for dose reductions or intervention interruptions and should be discussed with the Sponsor on a case-by-case basis.

6.7 Study Intervention after the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for patients with NSCLC.

6.8 Special Precautions

The study will be performed at a clinical research site with personnel trained in basic or immediate life support. Equipment and other agents (epinephrine and prednisolone equivalents, etc.) will be available at the site in case of allergic reactions. In case of localized radiation therapy this should be discussed with the Sponsor (or delegate) on a case-by-case basis.

6.9 Management of Specific Adverse Events, Adverse Events of Special Interest or Adverse Drug Reactions

Tepotinib

Specific Adverse Events

Interstitial Lung Disease

Interstitial lung disease or ILD-like adverse reactions have been reported in the clinical study program with tepotinib in patients with NSCLC.

Participants should be monitored for pulmonary symptoms indicative for ILD or ILD-like reactions. Tepotinib should be withheld and participants should be promptly investigated for alternative diagnosis or specific etiology of ILD. Tepotinib must be permanently discontinued if ILD is confirmed and the participant be treated appropriately.

Edema

Edema has been reported frequently in the study program. It is an identified risk for treatment with tepotinib. Other AEs related to fluid retention, such as generalized edema and pleural effusion have been observed. To gain further information to the occurrence and resolution of edema, any AEs of edema, the current edema status or AE resolution is to be specifically documented at each visit.

In the case of edema, please follow the advice provided in Table 3 in Section 6.6.

Asymptomatic Pancreatic Enzyme Elevation

If an asymptomatic lipase/amylase elevation of Grade ≥ 3 occurs, the participant will undergo clinical evaluation for the presence of signs and symptoms typical of acute pancreatitis and for

other risk factors for pancreatitis. In addition, a computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of the abdomen will be performed to assess the pancreas. The Sponsor (or delegate) will be notified of the outcome of the CT/MRI. Dosing with study treatment can continue during the evaluation period unless the clinical evaluation indicates pancreatitis. If there is no clinical or radiological evidence of pancreatitis, treatment with tepotinib should be continued, particularly if there is a potentially positive benefit for the individual participant. However, the continuation of study treatment for the participant will be individually discussed with the Investigator on a participant by participant basis.

In case of dose reduction (Section 6.6), the Investigator should notify the Sponsor immediately and each case should be discussed on a case-by-case basis, providing the reason for dose reduction.

For further information on tepotinib please refer to the tepotinib IB.

Adverse Event of Special Interest (AESI)

Adverse events suggestive of drug-induced liver injury including hepatic/liver failure and hepatitis (non-infectious) are considered AEs of special interest (AESIs) and will be reported to the Sponsor (or delegate) in an expedited fashion (refer to Section 8.3).

Osimertinib

For information on osimertinib please refer to the osimertinib prescribing information.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Participants must be discontinued from study intervention when they meet one of the following criteria:

- Pregnancy (Section 8.3.5)
- ILD/pneumonitis
- Objective disease progression as per RECIST Version 1.1 as per Investigator or participant is no longer receiving clinical benefit.

For participants in the randomized part of the study, verification of disease progression by IRC is required. Participants who are randomized to the tepotinib monotherapy will have the opportunity to switch over to the combination of tepotinib plus osimertinib if they experience disease progression according to RECIST Version 1.1 reported by investigator and verified by IRC. Until progression is verified by IRC and the switch over to the combination of tepotinib plus osimertinib takes place, tepotinib monotherapy can be continued, if judged appropriate by the Investigator. However, if disease progression is not verified by IRC, the participant must discontinue study intervention. Participants who permanently discontinue tepotinib monotherapy due to an AE,

withdraw consent, or for any reason other than progressive disease, will not be eligible to switch over to the combination of tepotinib plus osimertinib.

The Investigator must consider discontinuation of study intervention if he/she believes it is in the best interest of the participant or when a participant meets one of the conditions outlined below:

- Abnormal liver function as defined by the occurrence of Hy's law defined as aminotransferases > 3 × ULN, ALP < 2 × ULN, total bilirubin ≥ 2 × ULN, with no other reason to account for these abnormalities
- Grade 4 QTcF increase associated with signs and symptoms of serious arrythmia
- Grade ≥ 3 lipase and/or amylase elevation with signs and symptoms suggestive of pancreatitis or if pancreatitis is confirmed based on clinical or radiological signs.

The Investigator may consider discontinuation of study intervention when a participant has an increase in QTcF interval greater than 500 ms on at least 2 separate ECGs in line with Table 3.

The Schedule of Activities specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed. The reason for study intervention discontinuation should be recorded. If the participant discontinues at a scheduled visit, the EoT assessment can be performed on that day.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request.
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator must document this in the site study records.
- The participant may be withdrawn by the Investigator due to participation in another clinical study.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- The Schedule of Activities specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed. The Investigator will secure the safety of the study participants and make every attempt to collect data.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Schedule of Activities.
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 (Study Governance).
- Procedures conducted as part of the participant's routine medical care (eg, blood count) and obtained before signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.
- On days when PK samples are to be drawn, participants should be instructed to attend the study visit in a fasted state, with no breakfast and prior to taking their dose of tepotinib/osimertinib.
- The following assessments and information will be obtained at Prescreening after Prescreening informed consent (or where applicable optional consents) has been given (to occur prior to screening, but not time limited):
  - Documentation of relapse to first-line osimertinib
  - Documentation of EGFR alterations
  - Documentation of NSCLC histology

- Demographic characteristics, including age, gender, height, weight, race and ethnicity
- Smoking status

Collection of tumor biopsy material to determine MET amplification. Only tissue biopsy material which was collected after progression on first-line osimertinib is eligible. Submission of tumor tissue and blood sample obtained after progression on first-line osimertinib, is mandatory for all patients for MET amplification testing during Prescreening. In the case of previous local FISH testing for MET amplification, participants who are identified MET amplification positive are required to provide tumor tissue during Prescreening or Screening for central confirmation. Central confirmation is not mandated prior to the start of study treatment (Section 8.8).

- Blood Collection for central blood-based next generation sequencing (LBx) to determine MET amplification.
- Note: In case of administrative, operational or logistical errors, insufficient TBx material available/provided from previous local FISH testing or if the provided TBx or LBx sample could not be evaluated at the testing laboratory, repeat collections of TBx and/or LBx may be performed without the need to obtain a new written informed consent for Prescreening. In all cases samples for TBx/LBx MET amplification testing must be collected after progression on first-line osimertinib relapse until prior to first study intervention is eligible.
- Tissue collected after progression on first-line osimertinib is recommended to be provided (if available and allowed locally) from all participants for central next generation sequencing TBx MET amplification testing.

- The following assessments and information will be obtained during the screening period (Days -28 to -1) after signing the study consent and, where applicable, optional informed consents:
  - Demographic characteristics
  - Medical and disease history (including prior lines of therapy, and time to progression, best overall response (BOR) and duration of response on all line[s] of therapy prior to entry to the study)
  - ECOG performance status and life expectancy assessment
  - Independent confirmation of measurable disease by independent radiologists, in accordance with the RECIST Version 1.1 criteria (Appendix 7)
  - Brain imaging
  - Chest X-ray (not necessary if chest CT is performed as part of the tumor assessment at Screening)
  - Laboratory parameters, ECG, vital signs, and AEs
  - Serum pregnancy test.

- Collection of tumor tissue for central confirmation (central FISH TBx) of MET amplification, in the case of participants who are locally identified MET amplification positive by FISH testing
- Full physical examination
- Ophthalmology examination
- Echocardiogram
- Patient reported outcomes (PROs)

8.1 Efficacy Assessments and Procedures

Complete tumor assessment of all lesions by radiographic modality (using RECIST Version 1.1) is required. CT or MRI of the chest and abdomen (including imaging of the whole of the liver and adrenal glands), must be conducted to evaluate disease in these locations. Additional anatomical areas, such as the pelvis or other body areas in question, should be investigated in case of suspicion of presence of metastases based on signs, symptoms, biochemical results and/or non-study imaging of individual participants.

In addition, all participants must have brain imaging by MRI with IV contrast enhancement, including T2/FLAIR sequences of the brain, at Screening and at Follow-up in participants with brain metastases confirmed by IRC on the baseline brain scan. For participants who are enrolled in the study and present with brain metastasis when possible, the MRI assessment shall include Coronal 3D Gd-T1WI, Axial TSE/T2WI, Axial FLAIR, Axial T1WI, Axial Gd-T1WI, and Coronal 3D Gd-T1WI. MRI may be performed without contrast enhancement, if contrast is contraindicated. At Screening and during the Follow-up visits, if brain MRI is not clinically feasible, CT of the brain with IV contrast enhancement may be used; CT may be performed without contrast enhancement, if contrast is contraindicated.

During the follow-up, tumors will be assessed every 6 weeks (± 7 days) following the Cycle 1 Day 1 visit until 9 months, and every 12 weeks (± 14 days) thereafter according to RECIST Version 1.1, until disease progression as per Investigator, death, study withdrawal, or withdrawal of consent. Both IRC and Investigator assessments will be conducted. For participants in the randomized part of the study, verification of disease progression by IRC is required. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during the study. Tumor assessment according to RECIST Version 1.1 at EoT Visit is requested only if last tumor assessment was performed ≥ 6 weeks within the first 9 months, or ≥ 12 weeks after 9 months prior to EoT Visit.

When a pleural effusion occurs as an adverse event and is punctured, cytology should be evaluated for malignancy and the results communicated to the IRC for consideration of their assessment, as outlined in the IRC charter.

Participants who withdraw from the study intervention for reasons other than PD or death will have additional visits for tumor assessments every 6 weeks until 9 months, and every 12 weeks

thereafter. A ± 7-days time window is permitted for these additional follow-up visits until 9 months, and ± 14 days thereafter. Reasons for study termination should be recorded if this visit is the last visit for the participant. Recording of any new anticancer therapy will be made (a tumor assessment is mandatory before initiating the new therapy).

Survival follow-up is to be performed every 3 months ± 2 weeks at clinic visit or by telephone contact. Participants' survival information will be collected. Recording of any new anticancer therapy will be made until death. For patient reported outcomes (PROs) (EuroQol Five Dimension Five Level Scale [EQ-5D-5L], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30] and Non-small Cell Lung Cancer Symptom Assessment Questionnaire [NSCLC-SAQ]), the questionnaires will be completed at Screening (or at Day 1 of Cycle 1 prior to any other intervention or drug intake if it was missed at Screening) and every 6 weeks from Cycle 1, Day 1 until 9 months and every 12 weeks thereafter until disease progression, death, study withdrawal, or withdrawal of consent. At all visits indicated including EoT and Safety Follow-up, every effort should be made to have the questionnaires completed by the participant prior to the initiation of any other study activities (including RECIST Version 1.1 assessments) or active treatment and prior to any contact with the Investigator.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, echocardiograms, chest X-ray (or CT scan), and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give Prescreening informed consent (Prescreening ICF) and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

Apart from the Investigator, safety data will also be assessed continuously by the Sponsor medical monitoring activities, as well as by the following committees:

- Safety Data Committee: for dose definition during the safety run-in (refer to Section 4.1 and Appendix 2).
- Independent Data Monitoring Committee: periodic reviews on safety and efficacy data; (refer to Section 4.1 and Appendix 2).

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. In addition, skin examination is to be performed. Height (measured during Prescreening) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the cardiovascular, neurologicaland respiratory symptoms and the skin.

- Sufficient ophthalmological examination (including visual acuity and fundus) should be performed at Screening and end of treatment/withdrawal, or in case of any visual symptom (including blurred vision). Any clinically significant examination results, including results confirmed by the ophthalmologist, should be reported as AEs. Photographs should be taken to record any clinically significant findings. Ophthalmological examination results should be collected in the eCRF. Patients with corneal ulcer have to discontinue study treatment
- Investigators should pay special attention to clinical signs related to previous serious illnesses, including ILD, pancreatitis, and cardiovascular diseases.

8.2.2 Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure and weight will be assessed; height will be assessed at Pre-Screening only.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured preferably in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rates. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Participants will rest for 5 minutes in a semi-supine or supine position before the reading is taken. For study discontinuation criteria involving clinically significant QTcF findings, refer to Section 7.1.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5, at the time points listed in the Schedule of Activities. All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

  The tests will be performed by the local laboratory. It is required that these local laboratories are certified, perform and document interlaboratory testing at regular time intervals and provide a list of normal range laboratory values including units as defined by international system of units (SI). A 3-day window for collection of blood and urine samples scheduled to be collected on Day 1 of Cycle 1 is permitted.

  In sites in China, laboratory assessments (e.g., lipase) can be performed in a local or a central laboratory, depending on the availability of the test in the local laboratory.

The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor.

- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- Methods for sample identification during shipping and handling, as well as sampling methods, processing and storage of samples are detailed in the local Laboratory Manuals.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the time points specified in the Schedule of Activities during study intervention administration.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 4.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (from time of signature of the Prescreening ICF) and continues until Safety Follow-up Visit (30 ± 3 days after the last dose of tepotinib/osimertinib).

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 4, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and all nonserious AEs of special interest must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

Adverse events are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the Safety Follow-up Visit (30 ± 3 days after the last dose of tepotinib/osimertinib). All SAEs ongoing at the Safety Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 4 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

Details regarding the monitoring and management of AEs and AESI can be found in Section 6.9.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

- For sites outside Japan:

  The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the independent ethics committee (IEC)/institutional review board (IRB) that approved the study.

  In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or suspected unexpected serious adverse reactions [SUSARs]). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

- For sites in Japan:

  The Investigator must report SAEs (particularly deaths) in accordance with applicable site-specific requirements to the IRB that approved the study.

  In accordance with ICH GCP and the Japanese ministerial ordinance on GCP, the Sponsor/designee will immediately inform all the study Investigators and the Heads of the study sites of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. In line with respective applicable regulations, the Sponsor/designee will immediately inform all the study Investigators and the Heads of the study sites of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or

SUSARs). In addition, per applicable regulations, the Sponsor/designee will inform the study Investigators and the Heads of the study sites of all SAEs which were reported to the health authorities. In accordance with the Japanese regulatory requirements concerning safety reporting the Investigator should place copies of the Safety Reports in the Investigator Site File. The Head of the study site should also maintain copies of safety reports appropriately.

- For all sites:

  When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

  For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (eg, resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the CRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4, section on Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities.

Investigators must actively follow up, document, and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose of tepotinib or osimertinib which exceeds the daily dose that is defined in this clinical study protocol will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

Even if it not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4, section on Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities.

8.5 Pharmacokinetics

- The following PK parameters will be calculated, when appropriate:

Symbol	Definition
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$C_{L/f}$	The apparent total body clearance of study intervention following extravascular administration, taking into account the fraction of dose absorbed. $C_{L/f}$ = Dose $_{po}$ /$AUC_{0-\infty}$. Either the observed or predicted $AUC_{0-\infty}$ should be used, depending on the study specific requirements.
C_{max}	Maximum observed concentration
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
$V_{z/F}$	The apparent volume of distribution during the terminal phase following extravascular administration, based on the fraction of dose absorbed. $V_{z/f}$ = Dose/($AUC_{0-\infty}$*λ_z) following single dose. $V_{z/f}$ = Dose/(AUC_{τ}*λ_z) following multiple dose.

- Whole blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of tepotinib and metabolites, as specified in the Schedule of Activities. Samples for rich PK sampling (safety run-in only) will be obtained at Cycle 1 Day 1 and Cycle 1 Day 15 (at predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after tepotinib administration). Samples for sparse PK sampling will be obtained at Cycle 1 Day 1 and Cycle 2 Day 1 (at predose, 1.5, and 4 hours after tepotinib administration). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.
- The quantification of tepotinib and metabolites in plasma will be performed using a validated method. Concentrations will be used to evaluate the PK of tepotinib.
- Whole blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of osimertinib and metabolites, as specified in the Schedule of Activities. Time points for PK sampling are the same as described for tepotinib. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.
- The quantification of osimertinib and metabolites in plasma will be performed using a validated assay method. Concentrations will be used to evaluate the PK of osimertinib.

- For participants in the safety run-in, a maximum total blood volume for PK analysis of 250 mL will not be exceeded. For participants in the overall study a maximum total blood volume for PK analysis of 80 mL will not be exceeded.
- Remaining samples collected for analyses of tepotinib and osimertinib concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Details on collected blood volumes, processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Concentrations and clinical data from this study will be merged with available data from other clinical studies to perform the respective Population PK analyses and the analysis results will be reported separately from the clinical study report.

8.6 Pharmacodynamics

Refer to Section 8.8 for biomarker assessments. No specific pharmacodynamic assessments will be carried out.

8.7 Pharmacogenetics

- Where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants. Participation in pharmacogenetic research is optional. Participants who do **not** wish to participate in the pharmacogenetic research may still participate in the study.
- In the event of DNA extraction failure, a replacement sample for pharmacogenetic testing may be requested from the participant. Additional informed consent will not be required to obtain a replacement sample.
- Appendix 6 provides further information on pharmacogenetic research.

8.8 Biomarkers

Collection of participant samples for biomarker research is either a mandatory or optional part of this study and is governed by the appropriate ICF.

MET amplification status must be assessed centrally by FISH (TBx) and centrally by blood-based next generation sequencing (LBx) in participants with EGFRm+ NSCLC with documented relapse on previous first-line osimertinib.

MET amplification status for enrolment can be also be locally assessed by FISH (TBx) on material collected after progression on first-line osimertinib. For a local TBx FISH MET positive test to be acceptable for eligibility, the following criteria must be met:

1. The TBx FISH assay cut-off for MET amplification meets the criteria specified by the Study Sponsor. Specifically, a MET gene copy number ≥ 5 and/or a MET/CEP7 ratio ≥ 2 will be regarded as MET FISH positive.

2. The local FISH assay must evaluate both MET gene copy number and MET/CEP7 ratio.Sites must provide the information on the local FISH assay used.
3. Sites must provide during Prescreening or Screening the minimum required tumor tissue for central confirmation of MET amplification. Central confirmation is not mandated prior to the start of study treatment.

Please see Section 4.1 for the assignment of the participants to the investigation treatment based on the test used for defining MET amplification status.

The following participant samples for biomarker research are required and will be collected from all participants in this study, as specified in the Schedule of Activities:

- For central testing, tumor biopsy (TBx) taken after progression on first-line osimertinib will be used to determine the MET amplification status by central FISH testing at Prescreening.
- For central confirmation, tumor biopsy (TBx) taken after progression on first-line osimertinib must be provided during Prescreening or Screening for participants enrolled using local FISH (TBx) results.
- For central testing, blood taken at Prescreening and after progression on first-line osimertinib, will be used to determine MET amplification status using central blood-based next generation sequencing (LBx).
- If available and allowed locally, tissue collected after progression on first-line osimertinib is recommended to be provided from all participants for central next generation sequencing TBx MET amplification testing. Material is to be collected during prescreening or screening. Further technical details are described in the appropriate laboratory manual.
- Blood for on-treatment ctDNA samples (optional for participants in China).
- Blood for exploratory biomarker evaluation (optional for participants in China).

Further technical details are described in the appropriate laboratory manual.

Optional sample for biomarker research may be collected from the participants when possible, where local regulations and IRB/IEC allow and if consent was given:

- Blood for optional pharmacogenetic testing (refer to Section 8.7 and Appendix 6)

Mandatory and optional blood samples will be tested for a possible link between biomarkers and the combined activity of tepotinib and osimertinib to evaluate antitumor activity and resistance of biomarkers including, but not limited to, markers of MET pathway activation (eg, HGF levels and MET mutations), and other relevant oncogenic pathways.

Details on tumor tissue requirements and blood volume collected, processes for collection and shipment of these samples can be found in a central Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.9 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

Details of the statistical analyses will be described in a separate Integrated Analysis Plan (IAP).

Regularly performed SMC assessments will be based on participant profiles. Interim analyses for the regular IDMC meetings will be a subset of the full set of tables, figures, and listings which will be prepared for the clinical study report (CSR). Details will be specified in the IAP and the IDMC charter.

The primary analysis will be conducted once all participants in the primary analysis set (participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH) have either been treated with the recommended Phase II dose of tepotinib and osimertinib for at least 9 months, died or have prematurely discontinued study intervention for any reason, whichever comes first.

The final analysis will be done 3 years after the last participant's first dose or when all participants have discontinued study intervention and two thirds of the participants have died, whichever comes first.

9.1 Statistical Hypotheses

No formal statistical hypotheses are being tested in this study. In particular there will be no formal comparison between the tepotinib and osimertinib combination arm and the tepotinib monotherapy arm. Descriptive statistics and graphical representations will be used to summarize the data. All data are displayed in listings.

9.2 Sample Size Determination

Safety run-in

A BOIN approach (Yuan 2016) with maximum 12 participants will be applied for the safety run-in. No formal sample size calculation was performed for this study period.

Combination treatment

The TATTON and INSIGHT studies (Sequist 2020; Cheng 2018) indicate encouraging antitumor activity in EGFRm+ NSCLC patients who have relapsed to previous EGFR TKI, with centrally confirmed MET amplification status. This justifies the choice of the MET amplified positive population as centrally assessed by FISH for the primary analysis.

An ORR of at least 50% is expected for the osimertinib and tepotinib combination in participants who have progressed on prior first-line osimertinib, as a confirmed BOR of PR or CR based on independent review. There is only limited data available to support this assumption. This assumption is based on an ORR of 67% observed in the subset of patients with MET amplified, NSCLC having received tepotinib and gefitinib after relapse on one prior EGFR TKI treatment (INSIGHT study, Cheng 2018) and also considers ORRs observed in the TATTON study after relapse to one prior EGFR TKI of 64% to 67% with the combination of osimertinib plus savolitinib (Sequist 2020).

While there is current controversy regarding reduced efficacy of checkpoint inhibitors in patients with EGFRm+ NSCLC (Soo 2018), chemotherapy regimens commonly tend to show slightly increased response rates in this selected population as indicated by ORRs of 34% and 31% with platinum doublet chemotherapy regimens in second-line treatments (Soria 2015, Ahn 2017). Based on these historical control data, an ORR of 35% is proposed as standard of care effect.

Assuming a true ORR of 50% for the combination treatment, a sample size of 80 patients in the primary analysis set leads to a 78% probability to observe a lower bound of the exact 2-sided 95% confidence interval of above 35%.

Monotherapy treatment

No formal sample size calculation was done for the monotherapy arm. A total number of 12 participants will be included in the tepotinib monotherapy arm. This leads to a precision of the ORR estimates as shown in Table 4.

Table 4 Confidence limits for the objective response rates in the monotherapy arm

Monotherapy arm (n=12)	
Observed ORR	**Corresponding exact 2-sided 95% CI**
1/12 (8.3%)	0.2% - 38.5%
2/12 (16.7%)	2.1% - 48.4%
3/12 (25.0%)	5.5% - 57.2%
4/12 (33.3%)	9.9% - 65.1%
5/12 (41.7%)	15.2% - 72.3%
6/12 (50.0%)	21.1% - 78.9%

CI: confidence interval; ORR: objective response rate.

Total number of participants

Enrollment will continue until 80 participants are included in the primary analysis set, ie, 80 participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH, are included into the tepotinib and osimertinib combination treatment arm.

It is anticipated that approximately 120 participants will be enrolled overall in the study.

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

All participants who provided informed consent for Prescreening/Screening will be analyzed in terms of participant disposition only.

Analysis Set	Description
Full Analysis Set (FAS)/Safety Analysis Population (SAF)	All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated and will be performed per treatment arm (and per dose level, in case multiple dose ranges were applied). Analyses of safety and efficacy will be based on this analysis set.
Primary Analysis Set for Efficacy (Primary FAS)	The primary analysis set for efficacy will consist of all FAS participants with advanced or metastatic EGFRm+ NSCLC and MET amplification, determined centrally by FISH. This analysis set supports the primary objective of the study.
Safety Run-In Analysis Set (SRIAS)	The SRIAS will include all participants treated in safety run-in who receive at least 75% of the tepotinib and osimertinib planned dose and complete the DLT period (3 weeks after start of treatment with study intervention), or who experience a DLT during the DLT period regardless of the received amount of each study intervention.
PK Analysis Set	All participants, who receive at least one dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable post-dose concentration. The PK population will include all participants: Who have completed all study periods without any relevant protocol deviations and factors likely to affect the comparability of PK results. With adequate study intervention compliance With evaluable PK data, ie, non-missing values for primary endpoints in each study period. If participants received prohibited concomitant therapy or medicines, as specified in Section 6.5, they will be excluded from the PK population. Relevant decisions will be made before database lock. All PK analyses will be based on this analysis set.

9.4 Statistical Analyses

Details of the statistical analyses will be described in a separate IAP.

Continuous variables will be summarized using descriptive statistics, ie, number of participants with non-missing values (n), mean, median, standard deviation, 2-sided 95% CIs where appropriate, 25th and 75th percentiles, minimum, and maximum.

Qualitative variables and rates will be summarized by counts and percentages along with 2-sided exact Clopper-Pearson 95% CIs. Unless otherwise stated, the calculation of proportions will be based on the sample size of the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

In general, the last measurement prior to first administration of study intervention will serve as the baseline measurement.

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

The independent review will be performed by an IRC which will conduct an independent review of the tumor assessment images of all participants using the same criteria based on a separate charter outlining details of the review process.

Non-compartmental computation as well as descriptive statistical analyses of PK parameters will be performed using the software Phoenix® WinNonlin® 6.3 or higher (Certara, L.P., Princeton, New Jersey) or equivalent software. All other statistical analyses will be performed using SAS® Version 9.2 or higher.

9.4.1 Efficacy Analyses

Primary and secondary efficacy endpoints will be analyzed by treatment arm for all participants in the FAS in accordance to the test (central or local TBx, or central LBx) used to define their MET amplification positivity.

T+ denotes a positive central test based on tissue biopsy (FISH) and L+ denote a positive central test based on liquid biopsy. The combined T+/L+ set denotes a positive central test based either on tissue or based on liquid or based on both tests.

All analyses will be done for T+, L+ as well as for the combined set T+/L+.

The following efficacy analysis sets are defined:

- Primary analysis set:
    - T+ participants, treated with the recommended Phase II dose of tepotinib and osimertinib or tepotinib monotherapy.

- Secondary analysis sets:
    - L+ participants, treated with the recommended Phase II dose of tepotinib and osimertinib or tepotinib monotherapy.
    - Combined T+/L+ participants, treated with the recommended Phase II dose of tepotinib and osimertinib or tepotinib monotherapy.

The efficacy outcome of participants who are detected to be MET amplification positive by local TBx but are negative based on central TBx and LBx, will only be listed.

Participants from the initial safety run-in who are treated with the recommended dose for the main treatment part will be included in the above analysis sets in accordance with the test with which they were defined to be MET amplification positive (central or local TBx, or LBx) and the treatment eligibility criteria of Version 2 of the Study Protocol (progression on first-line osimertinib).

Additionally, efficacy results for participants in the primary analysis set will be provided split by C797X status.

Intracranial response will be analyzed for potential participants with brain metastases as target lesions.

The following table specifies the definitions and analysis methods by endpoint, further details as well as further potential subgroup analyses will be specified in the IAP.

Endpoint	Definitions and Statistical Analysis Methods
Primary	
Objective response (confirmed CR or PR) determined according to RECIST Version 1.1 as per IRC	Participants are identified as having an objective response if they achieve either a confirmed CR or PR from first administration of study treatment to first observation of PD. Confirmation needs to take place by a tumor assessment at least 4 weeks (28 days) after the tumor assessments initially indicating CR or PR. Objective response rate (confirmed CR or PR) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented. Corresponding summaries of BOR will also be provided.
Secondary	
Objective response (confirmed CR or PR) determined according to RECIST Version 1.1, as per Investigator	Participants are identified as having an objective response if they achieve either a confirmed CR or PR from first administration of study treatment to first observation of PD. Confirmation needs to take place by a tumor assessment at least 4 weeks (28 days) after the tumor assessments initially indicating CR or PR. Objective response rate (confirmed CR or PR) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented. Corresponding summaries of BOR will also be provided.
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. Confirmation needs to take place by a tumor assessment at least 4 weeks (28 days) after the tumor assessments initially indicating CR. Complete response rate (confirmed CR) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.

Endpoint	Definitions and Statistical Analysis Methods
Duration of response by IRC and by Investigator	For participants with objective response, duration of response 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 tumor assessment, whichever occurs first. Duration of response data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death) or for participants with an event after 126 days of the last tumor assessment. Participants who do not have a tumor assessment after objective response will be censored at the date CR/PR criteria are first met. Duration of response will be summarized descriptively. Kaplan-Meier plots as well as the corresponding number of events, 1st and 3rd quartile (Q1 and Q3), median, minimum and maximum from the Kaplan-Meier product-limit estimates of the survival function and survival rates at 3, 6, 9, 12, 15, and 18 months together with corresponding 95% CI will be presented.
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 if they achieve either a confirmed CR or PR (confirmation needs to take place by a tumor assessment at least 4 weeks [28 days] after the tumor assessments initially indicating CR or PR), or stable disease (SD) lasting at least 12 weeks (84 days). Disease control rate and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.
Progression free survival by IRC and by Investigator	Progression free survival (PFS) 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. 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. Participants who do not have a baseline tumor assessment or who do not have any post baseline tumor assessments will be censored at the date of the start of study treatment. PFS will be summarized descriptively. Kaplan-Meier plots as well as the corresponding number of events, first and third quartile (Q1 and Q3), median, minimum and maximum from the Kaplan-Meier product-limit estimates of the survival function and survival rates at 3, 6, 9, 12, 15, and 18 months together with corresponding 95% CI will be presented. PFS will only be analyzed for participants treated with the tepotinib and osimertinib combination.
Overall survival	Overall survival is defined as the time (in months) from first administration of study treatment to the date of death. For participants not known to be deceased at time of analysis, OS time will be censored at the last date the participant was known to be alive before data cutoff. Overall survival will be summarized descriptively. Kaplan-Meier plots as well as the corresponding number of events, first and third quartile (Q1 and Q3), median, minimum and maximum from the Kaplan-Meier product-limit estimates of the survival function and survival rates at 3, 6, 9, 12, 15, and 18 months together with corresponding 95% CI will be presented. Overall survival will only be analyzed for participants treated with the tepotinib and osimertinib combination.
Patient Reported Outcomes	Patient reported outcomes (EQ 5D 5L, EORTC QLQ-C30, NSCLC-SAQ) will be descriptively summarized in tabular and/or graphic format, as appropriate to the data.
Tertiary/Exploratory	
Intracranial response (CR or PR) by IRC	Participants with brain metastases as target lesions are identified as having an intracranial response if they achieve either a confirmed CR or PR from first administration of study treatment to first observation of PD. Confirmation needs to take place by a tumor assessment at least 4 weeks (28 days) after the tumor assessments initially indicating CR or PR.

Endpoint	Definitions and Statistical Analysis Methods
	Intracranial response rate (confirmed CR or PR) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented. The denominator for intracranial response rate will be the number of participants with brain metastases as target lesions.

9.4.2 Safety Analyses

All safety analyses will be performed on the SAF. All analyses will be presented by treatment arm and by dose level, if applicable, and participants will be analyzed as treated.

The safety analyses will also be done purely descriptively.

Endpoint	Statistical Analysis Methods
Primary (for the safety run-in)	
Occurrence of DLTs	Refer to Section 4.1 for the definition of DLTs The number and percentage of participants in the DLT analysis set during the DLT observation period will be tabulated.
Secondary	
Occurrence of AEs and treatment-related AEs and deaths during the study	Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities. Severity of AEs will be graded using the NCI-CTCAE (v5.0) toxicity grades. AEs related to study intervention will be defined as any AE considered as related to tepotinib and/or osimertinib. Missing classifications concerning study intervention relationships will be considered related to the study intervention. Any TEAEs will be summarized, ie, those events that are emergent during treatment having been absent prior to treatment or worsened relative to the pretreatment state and with onset dates occurring within the first dosing day of study intervention until 30 days after the last dose of study intervention (or switch over to combination treatment, whichever occurs first for the tepotinib monotherapy arm). Adverse events occurring after switch over will be described separately, details will be specified in the IAP. Following subtypes of TEAEs will be presented in summaries and tables according to System Organ Classes and Preferred Terms: • TEAEs • SAEs • TEAEs related to tepotinib and/or osimertinib • SAEs related to tepotinib and/or osimertinib • NCI-CTCAE Grade 3 or higher TEAEs • NCI-CTCAE Grade 3 or higher TEAEs related to tepotinib and/or osimertinib • TEAEs leading to tepotinib and/or osimertinib interruptions • TEAEs leading to permanent tepotinib and/or osimertinib discontinuation • TEAEs leading to deaths. • AESIs Deaths during the study will also be presented in summaries and tables. Adverse events of special interest are defined as events suggestive of drug-induced liver injury including hepatic/liver failure and hepatitis (non-infectious) and are

Endpoint	Statistical Analysis Methods
	collected in an expedited manner in the Global Drug Safety database for close monitoring.
Laboratory variables	Descriptive summaries over time of actual (absolute) laboratory values and changes from baseline will be presented. Gradable laboratory results will be classified by grade according to NCI-CTCAE (v5.0); non-gradable parameters will be classified as normal, high or low. Shift tables will be presented where applicable.
Vital signs, body weight, ECOG	Increase/decrease in vital signs (body temperature, heart rate, blood pressure and respiratory rate), ECOG performance status and body weight will be categorized and summarized descriptively in shift tables from Baseline to minimum and maximum on-treatment values.
ECG	Clinically significant, abnormal findings from 12-lead ECG during the treatment phase will be presented descriptively. Change from Baseline to worst on-treatment value will be summarized descriptively for the QTcF interval in accordance to ICH E14 criteria.

In the safety run-in, a BOIN design will support dose decisions starting with a tepotinib dose of 500 mg with the option to decrease to 250 mg as well as the option for re-escalation, with a target toxicity rate of 30% and a maximum number of 12 participants.

Participants who terminated study intervention will be summarized by primary reason for intervention discontinuation.

All deaths, deaths within 30 days after the last dose of study intervention, deaths within 60 days after the first dose of study intervention, split by primary reasons for death, will be tabulated.

Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination during and after study intervention will not be provided.

9.4.3 Other Analyses

PK and biomarker exploratory analyses will be specified in the IAP finalized before database lock. Integrated analyses across studies, such as the population PK analysis and pharmacodynamic analyses will be presented separately from the main CSR.

9.4.4 Sequence of Analyses

During the course of the study, the following steps are implemented:

- Two SMC meetings to assess safety and PK during safety run-in.
- Regular interim analyses for the IDMC to assess safety and efficacy of the participants after the safety-run in. Details will be specified in the IAP and the IDMC charter.
- These analyses are planned to be performed 90 days after 12 T+ participants have received the first dose of combination treatment, 90 days after 24 T+ participants in the combination treatment group and 12 T+ participants in the monotherapy have received the first dose of study intervention (ie, enrolment into monotherapy is completed), then 90 days after 48 T+

participants and 90 days after 72 T+ participants have received first combination dose as well as 90 days after complete enrollment of T+ participants.

- Primary analysis, conducted once all participants in the primary analysis set have either been treated with the recommended Phase II dose of tepotinib in combination with osimertinib for at least 9 months, died, or have prematurely discontinued study intervention for any reason, whichever comes first.
- Final analysis, done at the time point at which all participants have discontinued study intervention and two thirds of the participants have died, or after 3 years after the last participant's first dose, whichever occurs first.
- In addition to the analyses described above, further interim analyses at time points that are not specified in the protocol may be performed.

10 References

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11 Appendices

Appendix 1 Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-time Curve
BCRP	Breast Cancer Resistance Protein
BOIN	Bayesian Optimal Interval Design
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events Version 5.0
ctDNA	Circulating tumor Deoxyribonucleic Acid
CYP3A4	Cytochrome P450 3A4
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EGFRm+	Epidermal Growth Factor Receptor Mutation Positive
EoT	End of Treatment
EQ-5D-5L	EuroQol Five Dimension Five Level Scale
FAS	Full Analysis Set
FIH	First-in-Human
GCP	Good Clinical Practice
HGF	Hepatocyte Growth Factor
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease

IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRC	Independent Review Committee
IVRS	Interactive Voice Response System
LBx	Liquid Biopsy
MET	Mesenchymal-epithelial Transition Factor
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NSCLC	Non-small Cell Lung Cancer
NSCLC-SAQ	Non-small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient Reported Outcomes
Q1	1st Quartile
Q3	3rd Quartile
QLQ-C30	EORTC Core Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Stable Disease
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
US	United States
WOCBP	Woman/Women of Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- To enroll in this study, participants will first need to sign a Prescreening informed consent form (ICF). Once signed, Mesenchymal-epithelial Transition Factor (MET) amplification status will be assessed by liquid biopsy. Participants with positive MET amplification and who had progressed on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment should continue with the EGFR TKI beyond progression, until they either receive the experimental treatment as defined in this study or in the case of ineligibility, a follow-up treatment as discussed with their physician. In case of eligibility, participants should sign a second ICF at Screening.
- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on Good Clinical Practice (GCP); local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing, and inspection purposes.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

Approximately 100-120 study sites in Europe, Asia, and North America are planned to participate in this study.

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registries:

ClinicalTrials.gov: to be confirmed

EudraCT: to be confirmed

Details of structures and associated procedures will be defined in a separate Operations Manual.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - The Japanese ministerial ordinance on GCP
  - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (eg, advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- The Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.

- Any protocol amendments (ie, changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (eg, unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participant. The Sponsor takes out insurance to fulfill the responsibility.

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a CSR in consultation with the Coordinating Investigator and any Steering Committee or other relevant study-appointed committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Any publications and presentations of the results either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication but maintains the right to delay publication to protect intellectual property rights.

Posting of data on ClinicalTrials.gov and EudraCT is planned and will occur 12 months after the last visit, or scheduled procedure, or another appropriate date to meet applicable requirements.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Operations Manual.
- For PRO data (eg, QoL and pain assessments), ePRO will be used.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once

quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.

- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, the Japanese ministerial ordinance on GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (ie, the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (ie, signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (eg, CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed, and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator (in Japan, a record retainer designated by the Head of the study site) ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the Monitoring Plan.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment
- The first act of recruitment is when the first site is opened and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound
  - If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

   For a female with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.
3. A postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
   - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP, and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- Oral
- Intravaginal
- Transdermal
- Injectable

- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study

intervention, known side effects of study intervention, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (eg, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (eg, anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs, AESIs, and DLTs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (eg, an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (ie, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the adverse event reporting period, as defined in Section 8.3.2 (Method of Detecting Adverse Events and Serious Adverse Events)

Adverse Events of Special Interest

- Adverse events suggestive of drug-induced liver injury including
    - Hepatic/liver failure
    - Hepatitis (non-infectious).

Other Adverse Events to be Reported Following a Specialized Procedure

- Any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form.
- The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE.
- Each event meeting the criteria of a DLT must be recorded in the CRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. If an AE constitutes a DLT this is documented accordingly.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the

Sponsor or its designee using the electronic SAE report form in the Electronic Data Capture (EDC) system.

Reporting of SAEs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an electronic SAE report form must be completed immediately thereafter.

Relevant pages from the CRF may be provided in parallel (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (eg, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will notify the Sponsor/designee by completing the electronic AESI Report Form in the EDC system within 24 HOURS after becoming aware of the event. Serious AESIs must be reported in an expedited manner as SAEs, as outlined above. Reporting of non-serious AESIs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper report form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

Dose-Limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 4.1, must be recorded in the CRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.

Appendix 5 Clinical Laboratory Tests

Table 5 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelets		Mean Corpuscular Volume	WBC Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes			
	Hemoglobin		MCH	
	Hematocrit			
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase	Bilirubin
	Creatinine	Sodium	Alanine Aminotransferase	Total Protein
	Glucose	Calcium (Total Calcium and Calculated [or Adjusted] and/or Ionized [or free] Calcium)	Alkaline phosphatase	Serum Cystatin (for sites where the test is available)
	Total Amylase	Lipase	Gamma-glutamyl transpeptidase	Albumin
Coagulation	aPTT (sec or ratio)	PT (sec or ratio)	INR (%)	
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 (Discontinuation of Study Intervention).				
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal).			
Other Screening Tests	• FSH (if **not** a WOCBP only) • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for a WOCBP). All study-required laboratory assessments will be performed by a local laboratory. It is required that these local laboratories are certified, perform and document interlaboratory testing at regular time intervals and provide a list of normal range laboratory values including units as defined by international system of units. For sites in China, laboratory assessments (e.g., lipase) can be performed in local or central laboratories, based on the availability in the local laboratories.			

MCH: mean corpuscular hemoglobin; WCB: white blood cells; aPTT: Activated partial thromboplastin time; PT: Prothrombin time; INR: Prothrombin Intl. Normalized Ratio; WOCBP: woman of childbearing potential.

Appendix 6 Pharmacogenetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact study intervention absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated.

  DNA samples will be analyzed for a better understanding of the mode of action of tepotinib and potential resistance occurring under tepotinib treatment. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

- In addition, DNA samples will be used for research related to resistance occurring under osimertinib treatment, a better understanding of MET inhibition in EGFR resistant NSCLC. They may also be used to develop tests or assays, including diagnostic tests related to tepotinib or osimertinib treatment, mechanism of action of tepotinib, EGFR resistant NSCLC and other conditions in the context of NSCLC. Pharmacogenetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

- The results of pharmacogenetic analyses may be reported in the CSR or in a separate study summary.

- Details on blood volume collected, processes for collection and shipment of these samples can be found in the Laboratory Manual. The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- Retention time and possible analysis of DNA sample after the study ends are specified in the respective ICF.

Appendix 7 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The text below was obtained from the following reference: Eisenhauer et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer.2009; 45:228-47.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and in Follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and recorded and measured at Baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline

sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All Baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

No photographs, no skin lesion measurement by calipers and no measurements on chest X-ray will be done in this study.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article cited above, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit; however, they must normalize for a participant to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between partial response and complete response (CR) in rare cases if required by protocol (eg, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse event (AE) of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

RESPONSE CRITERIA

Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the Baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms (CRFs) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For partial response, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at Baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at Baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

When the participant also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or partial response in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or partial response of target disease will therefore be extremely rare.

When the participant has only non-measurable disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's Baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at Baseline is considered a new lesion and will indicate PD. An example of this is the participant who has visceral disease at Baseline and while on study has a brain CT or MRI ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at Baseline.

If a new lesion is equivocal, eg, because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fludeoxyglucose positron emission tomography (FDG-PET) response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at Baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at Baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study intervention until the end of treatment taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of partial response or CR is needed to deem either 1 the 'BOR'.

The BOR is determined once all the data for the participant is known. Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a participant who has SD at first assessment, partial response at second assessment, and PD on last assessment has a BOR of partial response). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR*	CR	No	CR
CR	Non-CR/non-PD	No	Partial response
CR	Not Evaluated	No	Partial response
Partial response	Non-PD or not all evaluated	No	Partial response
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR: complete response; NE: not evaluable; SD: stable disease; PD: progressive disease.
See text for more details.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the eCRF.

In studies where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies, it is reasonable to consider a participant with time point responses of partial response-NE-partial response as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

Conditions that define 'early progression, early death, and inevaluability' are study-specific and should be clearly described in each protocol (depending on treatment duration, and treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. The use of FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of partial response and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, ie, in randomized studies (Phase II or III) or studies where SD or progression are

the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/partial response (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of participants achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Appendix 8 Examples of Drugs that Prolong QT Interval and Have a Known Risk of Causing Torsade de Pointe

Table 6 provides examples of drugs which prolong QTc and have a known risk for Torsade de Pointe.

Note: This is not an exhaustive list. If you have questions on a drug product not included in this list, please consult the prescribing information for the product.

Table 6 Examples of drugs with a known risk for Torsade de Pointe due to QTc prolongation

Aclarubicin	Droperidol	Oxaliplatin
Amiodarone	Erythromycin	Papaverine HCl (Intra-coronary)
Anagrelide	Escitalopram	Pentamidine
Arsenic trioxide	Flecainide	Pimozide
Astemizole	Fluconazole	Probucol
Azithromycin	Gatifloxacin	Procainamide
Bepridil	Grepafloxacin	Propofol
Chloroquine	Halofantrine	Quinidine
Chlorpromazine	Haloperidol	Roxithromycin
Cilostazol	Hydroquinidine, dihydroquinidine	Sevoflurane
Ciprofloxacin	Ibogaine	Sotalol
Cisapride	Ibutilide	Sparfloxacin
Citalopram	Levofloxacin	Sulpiride
Clarithromycin	Levomepromazine (methotrimeprazine)	Sultopride
Cocaine	Levomethadyl acetate	Terfenadine
Disopyramide	Levosulpiride	Terlipressin
Dofetilide	Mesoridazine	Terodiline
Domperidone	Methadone	Thioridazine
Donepezil	Moxifloxacin	Vandetanib
Dronedarone	Ondansetron	

Examples provided are based on information given by www.crediblemeds.org/new-drug-list/ (accessed 18 March 2019)

Appendix 9 Protocol Amendment History

The information for the current amendment is on the title page.

Appendix 10 Sponsor Signature Page

Study 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)
Regulatory Agency Identifying Numbers:	IND Number: 128073 ClinicalTrials.gov: NCT03940703 European Clinical Trials Database: 2019-001538-33
Clinical Study Protocol Version:	3.0/ 04 May 2021

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250, Darmstadt, Germany
Telephone number:	PPD
Fax number:	Not applicable
E-mail address:	PPD

Appendix 11 Coordinating Investigator Signature Page

Study 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)
Regulatory Agency Identifying Numbers:	IND Number: 128073 ClinicalTrials.gov: NCT03940703 European Clinical Trials Database: 2019-001538-33
Clinical Study Protocol Version:	3.0/ 04 May 2021
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 12 Principal Investigator Signature Page

Study 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)
Regulatory Agency Identifying Numbers:	IND Number: 128073 ClinicalTrials.gov: NCT03940703 European Clinical Trials Database: 2019-001538-33
Clinical Study Protocol Version:	3.0/04 May 2021
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:	
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	