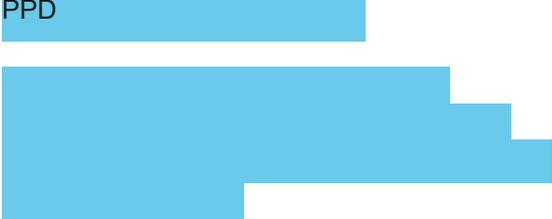


## Clinical Trial Protocol

<b>Clinical Trial Protocol Number</b>	EMR200095-006
<b>Title</b>	A Phase Ib/II Multicenter, Randomized, Open Label Trial to Compare Tepotinib (MSC2156119J) Combined with Gefitinib Versus Chemotherapy as Second-line Treatment in Subjects with MET Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation and Having Acquired Resistance to Prior EGFR-Tyrosine Kinase Inhibitor (EGFR-TKI) Therapy
<b>Short Title</b>	Tepotinib with Gefitinib in Subjects with Locally Advanced or Metastatic NSCLC (INSIGHT)
<b>Trial Phase</b>	Ib/II
<b>IND Number</b>	CCI
<b>EudraCT Number</b>	2016-001604-28
<b>Coordinating Investigator</b>	PPD 
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**Clinical Trial Protocol Version**

27 November 2017 / Version 8.0 (Global)

**Replaces Version**

30 September 2016 / Version 7.0 (Global)  
(Amendment no. 6)

**Current Clinical Trial Protocol  
Amendment**

27 November 2017 / Amendment no. 7 (Global)

- [REDACTED] -

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## Previous Protocol Amendments

Protocol amendments included in this protocol:

- Amendment no. 1 (Substantial); 15 April 2014 (Global)
- Amendment no. 2 (Substantial); 05 February 2015 (Global)
- Amendment no. 3 (Substantial); 15 June 2015 (Global)
- Amendment no. 4 (Substantial); 15 February 2016 (Global)
- Amendment no. 5 (Substantial); 08 April 2016 (Global; not distributed in Asia to study sites, ethic committees and health authorities, but submitted to FDA for input on regulatory requirements of assay for patient selection)
- Amendment no. 6 (Substantial); 30 September 2016 (Global)
- Amendment no. 7 (Substantial); 27 November 2017 (Global).

### Signature Page

#### Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial (EudraCT: 2016-001604-28; IND: CCI).

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#### Coordinating Investigator

I agree to conduct the clinical trial (EudraCT: 2016-001604-28; IND: CCI) in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

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## Principal Investigator Signature

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

**Clinical Trial Protocol Version/Date** 27 November 2017 / Version 8.0

**IND Number** CCI

**EudraCT Number** 2016-001604-28

**Center Number**

**Principal Investigator**

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, ICH Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.

I will not deviate from the clinical trial protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some regulatory Health Authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or Investigational Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore 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.

---

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Date of Signature

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Position (job title)

Address of Institution

Telephone number

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**List of Abbreviations**

<b>Abbreviation</b>	<b>Definition</b>
ADME	Absorption, Distribution, Metabolism, and Elimination
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ASBI	Average Symptomatic Burden Index
AST	Aspartate Aminotransferase
AUC <sub>0-∞</sub>	Area under the Curve from Time Zero to Infinity
AUC <sub>0-t</sub>	Area under the Curve from Time Zero to Time T
AUC <sub>0-tau</sub>	Area under the Curve Within 1 Dosing Interval
AUC <sub>extra</sub>	Area under the Curve Excreted
BCRP	Breast Cancer Resistance Protein
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
C <sub>avg</sub>	Average Plasma Concentration
CFDA	Chinese Food and Drug Administration
CHF	Congestive Heart Failure
CI	Confidence Interval
CL/F	Apparent Body Clearance of the Drug from Plasma
C <sub>last</sub>	Calculated Plasma Concentration at the Last Sampling Time Point
C <sub>max</sub>	Maximum Concentration
c-Met	Mesenchymal-Epithelial Transition Factor Gene
C <sub>min</sub>	Minimum Concentration
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation (%)
CrCl	Creatinine Clearance
DBP	Diastolic Blood Pressure
DLT	Dose-Limiting Toxicity

<b>Abbreviation</b>	<b>Definition</b>
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EGFRm+	EGFR-TKI Sensitizing Mutation
EGFR-TKI	EGFR-Tyrosine Kinase Inhibitors
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
CCI	
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin-Fixed Paraffin-Embedded
FIM	First-In-Man
GCN	c-Met Gene Copy Number
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
HGF	Hepatocyte Growth Factor
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ISH	In Situ Hybridization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LCSS	Lung Cancer Symptom Scale
LLQ	Lower Level of Quantification

<b>Abbreviation</b>	<b>Definition</b>
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MET+	MET Diagnostic-positive (status)
MFI	Mean Fluorescence Intensity
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OCT	Organic Cation Transporter
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
Pd	Pharmacodynamics
PET	Positron Emission Tomography
PFS	Progression Free Survival
Pgp	P-glycoprotein
CCI	
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
PT	Prothrombin Time
QD	Once Daily
QoL	Quality of Life
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SMC	Safety Monitoring Committee

<b>Abbreviation</b>	<b>Definition</b>
SmPC	Summary of Product Characteristics
SOC	System Organ Class
StD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Apparent Terminal Half-Life
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
$t_{max}$	Time to Maximum Concentration
TTSP	Time-to-Symptom Progression
CCI	[REDACTED]
[REDACTED]	[REDACTED]
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
V/F	Volume of Distribution
$V_{ss}/F$	Volume of Distribution at Steady State
$V_z/F$	Apparent Volume of Distribution Associated to the Terminal Phase
WBC	White Blood Cells
$\lambda_z$	Apparent Terminal Rate Constant

## 1 Synopsis

<b>Trial title</b>	<p>A Phase Ib/II Multicenter, Randomized, Open Label Trial to Compare Tepotinib (MSC2156119J) Combined with Gefitinib Versus Chemotherapy as Second-line Treatment in Subjects with MET Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Harboring EGFR Mutation and Having Acquired Resistance to Prior EGFR-Tyrosine Kinase Inhibitor (EGFR-TKI) Therapy</p> <p>Short Title: Tepotinib (MSC2156119J) with Gefitinib in Subjects with Locally Advanced or Metastatic NSCLC (INSIGHT)</p>
<b>Trial number</b>	EMR200095-006
<b>Sponsor</b>	<p><b>For all countries except USA and Japan:</b> Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany</p> <p><b>For sites in the USA:</b> EMD Serono Research &amp; Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA 01821-3936, USA</p> <p><b>For sites in Japan:</b> Merck Serono Co., Ltd Arco Tower. 1-8-1 Shimomeguro Meguro-ku. Tokyo 153-8926. Japan</p>
<b>Phase</b>	Ib/II
<b>IND Number</b>	CCI
<b>EudraCT Number</b>	2016-001604-28
<b>Trial center(s)/country(ies)</b>	<p><b>Phase Ib:</b> Selected sites in mainland China, South Korea, Taiwan, and other Asian countries</p> <p><b>Phase II:</b> 51 sites worldwide</p>
<b>Planned trial period (first enrollment-last subject out)</b>	December 2013 to June 2018

<b>Trial objectives</b>	<b>Primary Objectives</b>  <i>Phase Ib</i> <ul style="list-style-type: none"><li>• To determine the recommended Phase II dose (RP2D) of tepotinib when used in combination with gefitinib (at the approved standard dose of 250 mg) when administered orally once daily (QD) over a 21-day cycle in subjects with MET diagnostic-positive status (MET+) advanced NSCLC.</li></ul> <i>Phase II</i> <ul style="list-style-type: none"><li>• To evaluate whether the efficacy in terms of progression free survival (PFS) of second-line tepotinib in combination with gefitinib is superior to pemetrexed+cisplatin/carboplatin in subjects with T790M negative, MET+ locally advanced or metastatic NSCLC harboring an epidermal growth factor receptor (EGFR) mutation and having acquired resistance to first-line EGFR-TKI therapy including gefitinib, erlotinib, icotinib or afatinib.</li></ul> <b>Secondary objectives</b>  <i>Phase Ib</i> <ul style="list-style-type: none"><li>• To characterize the pharmacokinetics (PK) of tepotinib when given in combination with gefitinib;</li><li>• To characterize the PK of gefitinib when given in combination with tepotinib;</li><li>• To assess the safety and tolerability of tepotinib in combination with gefitinib;</li><li>• To evaluate preliminary antitumor activity of tepotinib in combination with gefitinib.</li></ul> <i>Phase II</i> <ul style="list-style-type: none"><li>• To evaluate the safety and tolerability of tepotinib in combination with gefitinib;</li><li>• To evaluate the efficacy of tepotinib in combination with gefitinib in T790M negative, MET+ subjects;</li><li>• To evaluate the antitumor activity of tepotinib in combination with gefitinib in T790M positive, MET+ subjects in a separate single-arm cohort (mainland China sites only);</li></ul>
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	<ul style="list-style-type: none"><li>• To assess patient-reported outcomes (PROs) with respect to quality of life (QoL), as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, Version 3.0), and time-to-symptom progression (TTSP), as measured by Lung Cancer Symptom Scale (LCSS).</li></ul> <p><b>Exploratory Objectives</b></p> <p><i>Phase Ib</i></p> <p><b>CCI</b></p> <ul style="list-style-type: none"><li>• To assess biomarkers that may correlate with antitumor activity, including, but not limited to, markers of the Mesenchymal-Epithelial Transition Factor Gene (c-Met) pathway activation (eg, hepatocyte growth factor [HGF] levels, and c-Met mutations), and other relevant oncogenic pathways.</li></ul> <p><i>Phase II</i></p> <p><b>CCI</b></p> <ul style="list-style-type: none"><li>• To investigate biomarkers of c-Met pathway activation and other relevant oncogenic pathways in serum and tumor tissue and their potential correlation with prognosis and the activity of tepotinib in combination with gefitinib;</li></ul> <p><b>CCI</b></p>
<p><b>Trial design and plan</b></p>	<p><b>Phase Ib</b></p> <p>The Phase Ib stage of the study comprises 2 parts, the standard “3+3” dose escalation cohorts, and an additional cohort for subjects from the mainland China sites.</p> <p>This Phase Ib part that contains the “3+3” dose escalation cohorts is a multicenter, open label, dose escalation phase. A standard “3+3” dose escalation design with a dose escalation and a dose confirmation phase will be used. The criteria for dose escalation and de-escalation rules are based on the occurrence of dose-limiting toxicities (DLTs) during Cycle 1. Other clinically relevant safety issues, as well as emerging</p>

PK data, should also be considered as necessary when making dosing decisions. A Safety Monitoring Committee (SMC) will perform periodic safety review and will be responsible for making the decision to escalate (or de-escalate) the dose level after all subjects in the preceding cohort have completed the first cycle of treatment and subject data during this cycle have been evaluated.

The anticipated dose cohorts of tepotinib are 300 and 500 mg QD. Gefitinib will be coadministered at standard dose (250 mg QD).

Rich PK sampling will be performed in Phase Ib to characterize the PK of tepotinib and gefitinib.

In addition, and separate from the “3+3” trial cohorts, up to 3 evaluable subjects will be enrolled in a separate cohort at one dose level below the RP2D at selected sites in mainland China.

## Phase II

The Phase II stage of the study also comprises two parts, randomized part and non-randomized part.

The randomized part is a multicenter, open label, active-control part to evaluate the efficacy and safety of tepotinib+gefitinib compared to that of pemetrexed+cisplatin/carboplatin in T790M negative, MET+ subjects. This part will be conducted once the RP2D for tepotinib+gefitinib has been defined in Phase Ib. A total of approximately 156 eligible subjects were planned to be enrolled. From study start to approval of Protocol Version 7.0, subjects were randomized at a 1:1 ratio to either the experimental arm (tepotinib+gefitinib) or the control arm (pemetrexed+cisplatin). From the approval of Protocol Version 7.0 onwards, subjects were randomized at a 2:1 ratio to either the experimental arm (tepotinib+gefitinib) or the control arm (pemetrexed+cisplatin/carboplatin). The Sponsor subsequently decided to halt enrollment. The sites were notified about the enrollment halt on 25 May 2017. The last subject was randomized on 12 June 2017. Until then 55 subjects had been randomized.

The Sponsor’s decision to halt further enrollment is due to the difficulties experienced in identifying subjects who meet the eligibility criteria of the trial. In spite of increased efforts, the enrollment rate did not improve to an extent that would allow for completion of the trial in a reasonable time frame. The decision is not based on any safety concerns. Accordingly, the benefit-risk ratio for all subjects continuing the trial remains unchanged.

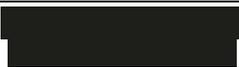
The primary endpoint, PFS in the randomized part, and the secondary efficacy endpoints based on tumor response, will be assessed by Investigator/site radiologist using the Response Evaluation Criteria in

	<p>Solid Tumors (RECIST), Version 1.1. In addition, an Independent Review Committee (IRC) will evaluate tumor response independently for both parts (ie, randomized and non-randomized).</p> <p>In addition to and separate from the randomized part of the trial in T790M negative and MET+ subjects, the safety and efficacy of tepotinib+gefitinib will be evaluated in a single-arm cohort (non-randomized part) of up to 15 subjects with MET+ T790M positive NSCLC (mainland China sites only). For this single-arm cohort, the Sponsor may conduct administrative interim analyses at time points that are not specified in the protocol for internal planning purposes. By the time of the enrollment halt, all 15 subjects with MET+ T790M positive NSCLC had been enrolled.</p> <p>For both parts (ie, randomized and non-randomized), an Independent Data Monitoring Committee (IDMC) will monitor the efficacy and safety data.</p> <p>CCI [REDACTED]</p>
<p><b>Planned number of subjects</b></p>	<p><b>Phase Ib:</b> Approximately 15 to 18 subjects following a “3+3” dose escalation design, and an additional up to 3 evaluable subjects from the mainland China sites.</p> <p><b>Phase II:</b></p> <ul style="list-style-type: none"> <li>• Approximately 156 subjects were planned to be enrolled in the randomized part with T790M negative and MET+ status. The Sponsor subsequently decided to halt enrollment. The sites were notified about the enrollment halt on 25 May 2017. The last subject was randomized on 12 June 2017. Until then 55 subjects had been randomized.</li> <li>• Up to 15 subjects in the single-arm cohort with T790M positive and MET+ status (mainland China sites only). By the time of the enrollment halt, all 15 subjects with MET+ T790M positive NSCLC had been enrolled.</li> </ul>
<p><b>Schedule of visits and assessments</b></p>	<p>Subjects will be screened for up to 28 days prior to study treatment. Informed consent will be obtained prior to performing any trial assessment.</p> <p>In Phase Ib, subjects will receive tepotinib in combination with gefitinib QD until progressive disease (PD)/intolerable toxicities/withdrawal from treatment.</p>

	<p>In the randomized part of Phase II from study start to approval of Protocol Version 7.0, subjects were randomized at a 1:1 ratio stratified by type of MET+ and prior EGFR-TKI treatment to receive either tepotinib+gefitinib QD or pemetrexed+cisplatin. From the approval of Protocol Version 7.0 onwards, subjects were randomized at a 2:1 ratio to either the tepotinib+gefitinib or pemetrexed+cisplatin/carboplatin using the same stratification factors as described above. Treatment will be discontinued for PD, intolerable toxicity, or withdrawal from the treatment. In addition, for subjects in the control arm not receiving pemetrexed continuation maintenance, the maximal number of pemetrexed+cisplatin/carboplatin is 6 cycles.</p> <p>In the single-arm cohort of Phase II, subjects will receive tepotinib+gefitinib QD. Treatment will be discontinued for PD, intolerable toxicity, or withdrawal from the treatment.</p> <p>In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Cases that may be considered for treatment beyond progression include subjects with slow (“smoldering”) progression after an initial partial response (PR)/complete response (CR), provided there are no clinical symptoms and no new lesions. If, in selected subjects, the Investigator wants to <u>continue</u> the treatment beyond progression although new lesion(s) have been documented, this must be discussed and agreed with the Sponsor, and documented in the appropriate designated electronic case report form (eCRF) section. The Investigator has to ensure that all safety data are collected, as per protocol, in the same manner as before progression, with the exception of the QoL questionnaires, which shall not be collected for this subject group. RECIST Version 1.1 radiographical assessment will follow institutional practice guidelines, however, tumor assessment information will not be recorded in the eCRF and there will be no further documentation collected for any new lesion and/or clinical symptoms of PD after first PD.</p> <p>Discontinuation of treatment beyond PD is at the discretion of the treating physician. If the subject develops new lesions or clinical symptoms, the benefit of continuing treatment with the study drugs should be discussed with the Sponsor. Please refer to Section 5.4.2. For analysis of the primary endpoint, only the first progression event is used.</p> <p>Subjects who stop all trial treatments will have an End-of-Treatment visit within 14 days of the last dose, the completion of treatment cycle, or the day when it is determined to permanently discontinue the study treatment. A Safety Follow-up visit will occur at 30 ± 3 days after the last dose for safety monitoring. If a subject withdraws from the treatment for reasons other than PD, additional follow-up visits for tumor assessments will be performed until disease progression, or the</p>
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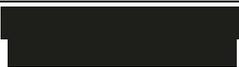


	<p>end of the trial, whichever comes first. In Phase II, there will also be survival follow-up assessments to collect subjects' survival information every 3 months <math>\pm</math> 2 weeks until death or the end of the trial, whichever comes first.</p> <p>Following the enrollment halt, subjects were offered the option to continue the trial following the current protocol after discussion with their Investigator. Subjects in prescreening/screening and who were eligible had been offered to be enrolled in the trial. Subjects who decided to continue treatment continued on their originally allocated treatment, at their most recent dose according to the protocol. Safety monitoring and data collection will continue without modification through to the end of the trial.</p>
<p><b>Diagnosis and main inclusion and exclusion criteria</b></p>	<p><i>Note: only main inclusion and exclusion criteria are listed below; for a full list of criteria, refer to the protocol Section 5.3.1 and Section 5.3.2.</i></p> <p><b>Main Inclusion Criteria</b></p> <p><b>Phase Ib</b></p> <ul style="list-style-type: none"> <li>a) Histologically or cytologically confirmed advanced NSCLC, regardless of histology subtype, which failed on gefitinib for reasons other than toxicity or compliance;</li> <li>b) Availability of a fresh or archived pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples). For subjects who have had at least 1 prior anticancer treatment, a biopsy obtained between failure of the most recent anticancer treatment and enrollment is mandatory;</li> <li>c) MET+ status, as determined by the central laboratory, ie, c-Met overexpression as determined by immunohistochemistry (IHC) (ie, IHC 2+ or IHC 3+);</li> <li>d) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.</li> </ul> <p><b>Phase II</b></p> <ul style="list-style-type: none"> <li>a) Locally advanced or metastatic NSCLC other than predominantly squamous histology (confirmed by either histology or cytology);</li> <li>b) Activating mutation of the EGFR receptor (documented, or as determined by the central laboratory);</li> <li>c) Acquired resistance on first-line EGFR-TKI therapy including gefitinib, erlotinib, icotinib, or afatinib;</li> </ul>



	<p>d) EGFR T790M status (as determined by the central laboratory, using a validated PCR test);</p> <ul style="list-style-type: none"> <li>• T790M negative status for the randomized part</li> <li>• T790M positive status for the single-arm cohort (mainland China sites only)</li> </ul> <p>e) Availability of a fresh or archived tumor tissue (excluding fine needle aspiration and cytology samples) obtained between documentation of acquired resistance to EGFR-TKI therapy including gefitinib, erlotinib, icotinib, or afatinib and enrollment is mandatory;</p> <p>f) MET+ status, as determined by the central laboratory, ie, c-Met overexpression as determined by IHC (ie, IHC 2+ or IHC 3+) and/or c-Met amplification and/or increased c-Met gene copy number (GCN), both determined by ISH;</p> <p>g) ECOG PS of 0 or 1.</p> <p><b>Exclusion Criteria (Phase Ib and Phase II)</b></p> <p>a) Estimated life expectancy &lt; 3 months;</p> <p>b) Inadequate bone marrow, liver or renal functions;</p> <p>c) Prior chemotherapy, biological therapy, radiation therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of trial treatment (<i>Phase Ib only</i>);</p> <p>d) Prior systemic anticancer treatment with chemotherapy or other agents targeting the EGFR pathway excluding gefitinib, erlotinib, icotinib, and afatinib for advanced NSCLC (one course of chemotherapy regimen for [neo]adjuvant purpose, or one course of chemoradiation for Stage IIIa disease is allowed) (<i>Phase II only</i>).</p>
<p><b>Investigational Medicinal Product(s): dose/mode of administration/ dosing schedule</b></p>	<p><b>Phase Ib:</b> For “3+3” dose escalation cohorts, tepotinib will be administered orally at 300 or 500 mg (or potentially, at a lower dose level, depending on the decision of the SMC) QD, in combination with gefitinib at 250 mg.</p> <p>For the additional up to 3 evaluable subjects from the mainland China sites, tepotinib will be administered orally one dose level below the RP2D QD, in combination with gefitinib at 250 mg.</p> <p><b>Phase II:</b> Tepotinib will be administered orally at the RP2D QD, in combination with gefitinib at 250 mg.</p>

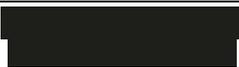
<p><b>Reference therapy(ies): dose/mode of administration/dosing schedule</b></p>	<p>Subjects in Phase II in the control arm of the randomized part will be treated on Day 1 of each 21-day cycle. The subjects will receive pemetrexed at 500 mg/m<sup>2</sup>, administered as an intravenous infusion over 10 minutes.</p> <p>The Investigator is free to choose either pemetrexed+cisplatin or pemetrexed+carboplatin for the individual subject. Cisplatin will be administered at 75 mg/m<sup>2</sup>, typically as an intravenous infusion over 2 hours, beginning approximately 30 minutes after the end of pemetrexed administration. At the Investigator's discretion, carboplatin will be administered at either AUC5 or AUC6 as an intravenous infusion over 1 hour, beginning about 30 minutes after the end of pemetrexed administration.</p> <p>These are common administration protocols. For further administration details, Investigators are requested to check / take into account current medical and local administration guidelines / treatment protocols as well as respective SmPCs and to discuss upfront with the Sponsor the treatment regimens they wish to select.</p>
<p><b>Planned treatment duration per subject</b></p>	<p><b>Phase Ib and Phase II:</b> In both phases, subjects may continue to receive tepotinib+gefitinib QD until PD, intolerable toxicity, or withdrawal from treatment.</p> <p>In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Discontinuation of treatment beyond PD is at the discretion of the treating physician. If the subject develops new lesions or clinical symptoms, the benefit of continuing treatment with the study drugs should be discussed with the Sponsor.</p> <p><b>Phase II:</b> In the control arm, pemetrexed+cisplatin/carboplatin will be administered on Day 1 of each cycle for:</p> <ul style="list-style-type: none"> <li>• Either up to 6 cycles, or</li> <li>• 4 cycles of pemetrexed+cisplatin/carboplatin followed by pemetrexed maintenance.</li> </ul>
<p><b>Primary endpoints</b></p>	<p>The primary endpoints for each part of the trial are as follows:</p> <p><b>Phase Ib:</b></p> <ul style="list-style-type: none"> <li>• Incidence of subjects experiencing at least 1 DLT in Cycle 1. (ie, 21 days after the first dose of trial medication);</li> <li>• Incidence and type of other adverse events (AEs).</li> </ul>



	<p><b>Phase II:</b></p> <ul style="list-style-type: none"> <li>• PFS in the randomized part, assessed by Investigator/site radiologist according to RECIST Version 1.1.</li> </ul> <p>PFS time is defined as the time, in months, from randomization to either the first observation of documented PD per RECIST Version 1.1 or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment.</p>
<p><b>Secondary endpoint(s)</b></p>	<p>The secondary endpoints of the trial are as follows.</p> <p>Secondary endpoints related to safety:</p> <ul style="list-style-type: none"> <li>• Drug exposure;</li> <li>• Incidence and type of Treatment-Emergent Adverse Events (TEAEs), toxicity grades as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0); treatment-related TEAEs, serious AEs (SAEs), treatment-related SAEs, TEAEs with toxicity Grade <math>\geq 3</math>, treatment-related TEAEs <math>\geq 3</math>, and TEAEs leading to permanent treatment discontinuation;</li> <li>• Incidence and reasons for deaths within 30 (<math>\pm 3</math>) days after the last dose of study drug;</li> <li>• Safety laboratory tests graded by NCI-CTCAE (Version 4.0);</li> <li>• Vital signs, 12-lead electrocardiogram (ECG) changes, physical examination, including change in body weight, and ECOG PS.</li> </ul> <p>Other secondary endpoints include:</p> <ul style="list-style-type: none"> <li>• PFS assessed by IRC in the randomized part of Phase II;</li> <li>• PFS assessed by Investigator and IRC in the single-arm cohort of Phase II;</li> </ul> <p>In the single-arm cohort, PFS time is defined as the time, in months, from the first administration of the trial treatment to either the first observation of documented PD per RECIST Version 1.1 or occurrence of death due to any cause within 84 days of either the first administration of the trial treatment or the last tumor assessment.</p> <ul style="list-style-type: none"> <li>• Overall survival (OS) time, defined as the time, in months, from randomization/the first administration of the trial treatment to the date of death in randomized part of Phase II/single-arm cohort of Phase II;</li> </ul>

	<ul style="list-style-type: none"> <li>• Tumor response as measured by objective response (OR) and disease control based on RECIST Version 1.1;</li> <li>• PK (Phase Ib only): <math>AUC_{0-t}</math>, <math>AUC_{0-tau}</math>, <math>C_{max}</math>, <math>C_{avg}</math>, <math>C_{min}</math>, <math>t_{max}</math>, <math>AUC_{0-\infty}</math>, <math>CL/F</math>, <math>V_z/F</math>, <math>V_{ss}/F</math>, <math>\lambda_z</math> and <math>t_{1/2}</math> (when appropriate);</li> <li>• Health-related quality of life (HRQoL) endpoints (Phase II only) will be assessed using the EORTC QLQ-C30 (Version 3.0), and LCSS questionnaires.</li> </ul>
<p><b>Exploratory endpoints</b></p>	<p><b>CCI</b></p> <ul style="list-style-type: none"> <li>• Exploratory biomarkers include biomarkers that may correlate with antitumor activity, including, but not limited to, markers of c-Met pathway activation (eg, HGF levels, and c-Met mutations), other relevant oncogenic pathways.</li> </ul> <p><b>CCI</b></p>
<p><b>Statistical methods (includes sample size calculation)</b></p>	<p><b>Sample Size Calculation:</b></p> <p>In Phase Ib, the total number of subjects planned in the “3+3” dose escalation cohorts is approximately 15 to 18, on the basis of the “3+3” dose escalation method with 2 dose cohorts: 3 or 6 in the dose escalation cohort and a potential for 3 or 12 subjects in the dose confirmation cohort (if dose de-escalation does not occur). The final sample size depends on the number of subjects who experience DLTs at each dose level, emerging safety and available PK data, and the decision from the SMC meeting.</p> <p>In addition, separately from the “3+3” dose escalation cohorts, up to 3 evaluable subjects will be enrolled in the mainland China sites.</p> <p>In the randomized Phase II part, the initial sample size planning required 111 PFS events (assessed by Investigator) to ensure 80% power with a two-sided significance level of 10% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio of 0.6. Assuming a median PFS time of 5 months in subjects in the control arm, a hazard ratio of 0.6 represents a 3.3 months increase, resulting in a median PFS time of 8.3 months for the experimental arm. A total of 156 subjects were planned to be randomized to receive tepotinib+gefitinib or pemetrexed+cisplatin/carboplatin. From study start to approval of Protocol Version 7.0, subjects were randomized at a 1:1 ratio to</p>

	<p>receive tepotinib+gefitinib or pemetrexed+cisplatin. From the approval of Protocol Version 7.0 onwards, subjects were randomized at a 2:1 ratio to receive either tepotinib+gefitinib or pemetrexed+cisplatin/carboplatin.</p> <p>The Sponsor subsequently decided to halt enrollment. The sites were notified about the enrollment halt on 25 May 2017. The last subject was randomized on 12 June 2017. Until then 55 subjects had been randomized.</p> <p>In the single-arm cohort of Phase II with MET+ T790M positive subjects, up to 15 subjects were planned to be enrolled (mainland China sites only). By the time of the enrollment halt, all 15 subjects with MET+ T790M positive NSCLC had been enrolled.</p> <p><b>Statistical Analyses:</b></p> <p>The primary analysis of the Phase II part will be conducted once all subjects have either been treated for at least 6 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first.</p> <p>For the randomized Phase II part, the primary analyses will test the equality of PFS time, as assessed by Investigator, between treatment arms, based on the intent-to-treat (ITT) population, applying a two-sided stratified log-rank test at a significance level of 10% and taking into account for the stratification factors used for randomization, type of MET+ and prior EGFR-TKI.</p> <p>Through Phase Ib and Phase II, continuous variables will be tabulated using the following summary statistics: number of non-missing values, mean, standard deviation (StD), median, the 25<sup>th</sup> and 75<sup>th</sup> percentiles, and the minimum and maximum values. Confidence intervals (CIs) will be presented where appropriate. Categorical variables will be tabulated using frequencies and percentages.</p> <p>An IDMC will be established for periodic evaluations of the clinical trial to ensure continued subject safety as well as the validity and scientific merit of the study. More detailed information can be found in Section 8.</p>
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## 2 Sponsor, Investigators and Trial Administrative Structure

Merck KGaA, Darmstadt, Germany (for all countries except USA and Japan), EMD Serono Research & Development Institute, Inc. (for USA), and Merck Serono Co., Ltd (for Japan) will be the Sponsor of this clinical trial of mesenchymal-epithelial transition factor gene (c-Met) inhibitor, tepotinib. Pemetrexed, cisplatin and carboplatin will be supplied to 51 sites worldwide by the respective study center or by the Sponsor, according to local laws and regulations. Tepotinib and gefitinib will be provided centrally by the Sponsor. The Sponsor will perform quality audits.

The Coordinating Investigator <sup>PPD</sup> [REDACTED]

[REDACTED], represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonization (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are on pages 4 and 5 of this protocol.

The contract research organization (CRO) responsible for the conduct of the trial (including trial management, monitoring, biostatistics, and data management) will be <sup>PPD</sup> [REDACTED]

[REDACTED] will undertake the operational aspects of this trial. Details of any transferred trial-related duty and function to <sup>PPD</sup> [REDACTED] and associated procedures are defined in writing in a Project Addendum.

A Safety Monitoring Committee (SMC) (see Section 6.2.2) will perform periodic reviews to evaluate the safety of the subjects who follow “3+3” dose escalation method in Phase Ib. Details of the safety monitoring process will be specified in a dedicated SMC charter.

The SMC will not be responsible for safety evaluation of the up to 3 evaluable subjects in the additional cohort of subjects from the mainland China sites of Phase Ib. Sponsor experts including, but not limited to, medical responsible, safety responsible and pharmacokineticist, as well as the coordinating Investigator, will review the safety profile of the up to 3 evaluable subjects in the additional cohort. See details in Section 5.1.

An Independent Data Monitoring Committee (IDMC) (see Section 8.6) will perform periodic reviews to evaluate the safety of the subjects participating in Phase II. Details of the data monitoring process will be specified in a dedicated IDMC charter. The first IDMC review took place after dosing of about 25% of the subjects. As the Sponsor decided to halt enrollment no further IDMC reviews will take place.

An Independent Review Committee (IRC) will conduct a blinded review of the images of all subjects participating in Phase II part using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 based on a separate charter outlining details of the review process.

### 3 Background Information

Lung cancer remains the leading cause of cancer death world-wide. Approximately 85% of the subjects have non-small-cell lung cancer (NSCLC), most of these subjects 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 subjects with epidermal growth factor receptor (EGFR) mutation, including the oral EGFR-tyrosine kinase inhibitors (EGFR-TKI) gefitinib, erlotinib, icotinib, and afatinib. 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 (1).

Among all the mechanisms identified for the development of resistance, the main reason is a secondary mutation in the EGFR gene (T790M mutation) and amplification of the c-Met proto-oncogene. In about 50% of cases, resistance is due to the occurrence of a secondary mutation in EGFR (ie, T790M mutation) (2).

Amplification of c-Met was initially reported to account for up to 20% of tyrosine kinase inhibitor (TKI) acquired resistance subjects. In more recent studies, however, c-Met amplification has been identified in only 5% of specimens (3). c-Met overexpression/amplification and EGFR T790M mutation are two independent mechanisms of acquired drug resistance in NSCLC subjects progressing on EGFR-TKI treatment. The likelihood of progressing subjects to respond to tepotinib is, therefore, higher in MET diagnostic-positive (MET+) subjects which are negative for T790M. This occurs by a different molecular pathway from T790M (4). c-Met protein expression and c-Met gene mutation may, also, be abnormal in NSCLC, and are associated with poor prognosis (5).

Therefore, the inhibition of the c-Met pathway has become a potential novel therapeutic strategy in NSCLC.

#### 3.1 Tepotinib-Summary of Nonclinical and Clinical Studies

Tepotinib (MSC2156119J) is a potent, highly selective c-Met inhibitor with a favorable pharmacokinetic (PK) profile in humans allowing once daily (QD) dosing. It inhibits growth and induces regression of hepatocyte growth factor (HGF)-dependent and HGF-independent susceptible tumor models, and is currently under investigation in several trials. Refer to the current Investigator's Brochure (IB) for further information regarding the nonclinical and clinical programs and guidance for the Investigator.

##### 3.1.1 Nonclinical Evaluation

Nonclinical studies indicate that tepotinib is a highly selective adenosine triphosphate-competitive c-Met inhibitor, which effectively inhibits c-Met signaling in tumors. Tepotinib exhibited marked inhibitory activity on the growth of mouse tumors and of human tumor xenografts and frequently led to complete regression of established tumors. This antitumor effect was observed in 2 types of clinically relevant models: 1) tumor cells in which c-Met activation was ligand independent, ie, tumors harboring c-Met amplification or activating mutation; 2) tumors in which c-Met and HGF were co-expressed, thereby creating an autocrine positive feedback loop.

Results of the nonclinical safety pharmacological studies conducted in compliance with the ICH Guideline 7A/7B suggest a favorable nonclinical safety profile for tepotinib.

On the basis of presently available results of the animal *in vivo* and *in vitro* studies, there are no reservations from a toxicological point of view against studying tepotinib in cancer subjects.

### 3.1.2 Clinical Experience

Until 30 September 2016, five clinical trials were completed:

1. Three clinical pharmacology trials in 79 healthy volunteers (EMR200095-002, EMR200095-007 and MS200095-0012) and
2. Two Phase I trials in 161 subjects with different advanced solid tumors (EMR200095-001 and EMR200095-003).

Four trials in subjects with indications hepatocellular carcinoma (EMR200095-004 and EMR200095-005) and NSCLC (EMR200095-006 and MS200095-0022) are ongoing.

Healthy volunteers (see 1. above) well tolerated a single or up to 3 single doses of tepotinib at different dose levels up to 500 mg. All treatment-emergent adverse events (TEAEs) were mild to moderate, except one Grade 3 asymptomatic lipase elevation in 1 subject. Treatment emergent adverse events did not show a pattern across the 3 trials. No serious adverse events (SAEs) were reported and no subjects died. No clinically significant findings with regard to laboratory parameters, vital signs and ECG, including QTcF values were noted.

In subjects with solid tumors (see 2. above), tepotinib was generally well tolerated at different dose levels up to 1400 mg QD. The most frequent ( $\geq 15\%$ ) TEAEs, irrespective of a relationship to tepotinib, were fatigue, decreased appetite, constipation, peripheral edema, nausea, vomiting, hypoalbuminemia and abdominal pain. The most frequent ( $\geq 5\%$ ) TEAEs with toxicity Grade  $\geq 3$  were fatigue and pulmonary embolism and the most frequently ( $\geq 3\%$ ) reported SAEs were abdominal pain, constipation, nausea and small intestinal obstruction ascites. No death was considered to be related to trial treatment. With the exception of lipase/amylase elevations, no safety findings with regard to laboratory tests, vital signs and ECG were noted.

First clinical experience from EMR200095-001, EMR200095-003 and the safety run-in Phase Ib part of EMR200095-004, EMR200095-005 and EMR200095-006 provided first signs of clinical efficacy of tepotinib supporting its further clinical development in hepatocellular carcinoma and NSCLC and other potential indications.

A more detailed description of the safety and efficacy of tepotinib from completed and ongoing trials is provided in the Investigator's Brochure.

#### 3.1.2.1 Clinical Experience in Asian Population

In the Japanese Phase I trial EMR200095-003 a total of 12 subjects were enrolled and received at least one dose of study drug; 3 subjects each received 215 mg and 300 mg p.o. QD, and 6 subjects received 500 mg p.o. QD.

No DLT was observed in any of the subjects treated with study medication. Treatment-emergent AEs of any grade were reported in 11 (92%) of 12 subjects; treatment-related TEAEs were reported in 5 (42%) subjects. The most frequently reported TEAEs ( $\geq 30\%$  of all subjects or  $\geq 4$  subjects) by preferred term were constipation and decreased appetite in 6 subjects, each (50%), nausea in 5 (42%) subjects, and fatigue, hypoalbuminemia, edema peripheral, and vomiting in 4 (33%) subjects, each. Common treatment-related TEAEs were amylase increased, lipase increased, hypoalbuminemia, fatigue and dysgeusia in 2 subjects each.

Grade  $\geq 3$  TEAEs were reported in total of 7 (58%) subjects. Grade 3 TEAEs were ascites, decreased appetite, dyspnea, urinary tract obstruction, and hyponatremia. Grade 4 TEAEs were lipase increased, altered state of consciousness and dyspnea. Of these, treatment-related Grade  $\geq 3$  TEAEs were Grade 4 lipase increased in 2 subjects and Grade 3 hyponatremia in 1 subject.

Serious AEs were reported in total of 4 (33%) subjects: altered state of consciousness, dyspnea, and decreased appetite and malaise. Apart from altered state of consciousness, all SAEs reported were recovered/resolved. In addition, 1 subject had serious dyspnea that was ongoing at death (25 days after last study treatment) due to progressive disease. All SAEs reported in this study were considered unrelated to the treatment by the Investigator.

No subject had TEAEs resulting in permanent treatment discontinuation. Grade 4 lipase increased occurred in 2 subjects and was considered treatment-related.

No notable change was observed in laboratory tests over time except for decrease in mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV). National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or 4 laboratory parameters were lymphocyte ratio (lower than lower limit of normal range = low), alkaline phosphatase (ALP),  $\gamma$ -glutamyl transferase ( $\gamma$ -GTP), glucose (higher than upper limit of normal range = high), sodium (low), and triacylglycerol lipase.

No clinically notable abnormalities or abnormal changes were found in vital signs and other safety observations.

Currently available data does not indicate an impact on QTc by tepotinib. High variability within and between subjects in QTc observed in the First-In-Man (FIM) trial is likely due to co-morbidity, comedication and/or electrolyte disturbances in such a subject population with advanced cancers. Specific safety measures consisting of frequent electrocardiogram (ECG) monitoring which, at some time points is paired with PK sampling, are included in the current trial.

The assessment of TEAEs, laboratory parameters, and ECG results does not indicate any differences in the safety profile for Asian subjects compared with non-Asian subjects. Although the conclusions are limited due to the small number of Asian subjects, the use of 500 mg tepotinib daily in clinical trials may be justified in Asian subjects.

### 3.2 Rationale for the Study Design

The FIM study identified the safety and tolerability of tepotinib monotherapy and the nonclinical studies demonstrated mechanism of dual inhibition of c-Met and EGFR pathways after acquired resistance to first-line EGFR-TKI treatment.

In the randomized Phase II part of the present study, the antitumor activity of tepotinib will be evaluated in combination with an EGFR-TKI (gefitinib) and compared to standard chemotherapy (pemetrexed+cisplatin/carboplatin). The Phase Ib dose escalation part of the study, which precedes Phase II, is considered a safety run-in that will determine the proper dose of tepotinib in combination with EGFR-TKI (gefitinib).

The non-randomized Phase II part will provide exploratory data on the combination of tepotinib and gefitinib in MET+ T790M positive tumors (mainland China sites only).

A detailed discussion of the trial design is provided in Section 5.2.

### 3.3 Risk Benefit Assessment

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the nonclinical and clinical data available to date, the conduct of the trial is considered justifiable using the dose(s) and dosage regimen(s) of the IMP as specified in this clinical trial protocol.

In the ongoing and completed trials, tepotinib shows a favorable safety profile. For monotherapy, a RP2D of 500 mg QD has been determined. This RP2D is defined as a biologically active dose, based on PK/Pd modeling and supported by data on target inhibition from paired tumor biopsies, rather than as a safety defined MTD. However, since the RP2D of tepotinib administered with an EGFR-TKI as combination therapy has not been determined, a safety run-in phase will start dose escalation at 300 mg, thereby allowing for an additional safety step before exposing subjects to the full RP2D.

Available evidence suggests that c-Met overexpression/amplification is associated with acquired resistance in NSCLC subjects progressing on EGFR-TKI treatment. Analysis of progressing tumors revealed they are likely a mixture of EGFR-TKI sensitive clones and resistant clones. EGFR-TKI sensitive clones are very susceptible to EGFR-TKI, but rarely eradicated, re-administration or continuation of EGFR-TKI can therefore effectively suppress the expansion of drug sensitive clones (7). Thus, simultaneous inhibition of both pathways holds the promise to overcome this resistance (Section 5.2). Moreover, in a single-arm Phase Ib/II trial, the addition of INC280 (a highly selective c-Met inhibitor) to gefitinib showed promising clinical activity in MET+ NSCLC subjects resistant to EGFR-TKIs, which supports the therapeutic potential of c-Met-targeting agents (8).

In an effort to further improve benefit-risk ratio of the trial, only subjects with MET+ tumors will be enrolled (both in Phase Ib and Phase II), this enable to investigate the efficacy and safety of the compound in the most relevant population and turned out further exposure to non-targeted population.

Since gefitinib is not active on the T790M mutation, the likelihood of progressing subjects to respond to tepotinib is expected to be higher in MET+ subjects who are negative for T790M and this will therefore be the target population for the randomized part of the Phase II trial.

Doublet chemotherapy consisting of pemetrexed+cisplatin ensures the benefit of subjects randomized to the control arm in Phase II as this chemotherapeutic regimen is the most active platinum doublet in subjects with NSCLC (9), and magnitude of benefit has been confirmed in EGFR-TKI sensitizing mutation (EGFRm+) subjects in another Phase III trial (10). Carboplatin has a similar effect on progression free survival but a different toxicity profile when compared with cisplatin (11). Although carboplatin showed a tendency for a smaller response compared to cisplatin, this difference diminished when both platinum compounds were compared in combination treatments. Multiple clinical trials have shown a beneficial role for maintenance therapy in select groups. Pemetrexed maintenance will be an option for subjects who have not progressed after the completion of 4 cycles of chemotherapy with pemetrexed+cisplatin/carboplatin, in line with the current guideline and clinical practice (12, 13).

Overall, in the ongoing and completed trials, tepotinib was well tolerated (refer to the current IB). Asymptomatic elevation of pancreatic enzymes are an important risk associated with the administration of tepotinib and have been reported for a number of other TKIs with molecular targets other than c-Met (eg, sunitinib, imatinib, sorafenib). Potential risks associated with study drug application from nonclinical studies are hepatobiliary toxicity and drug-drug interaction with P-glycoprotein (Pgp) inducing or inhibiting drugs as well as Breast Cancer Resistance Protein (BCRP), OATP1B1, OCT1, OCT2, MATE1 and MATE2 transported drugs.

As long as safety measures described in the protocol are strictly followed, it is reasonable to believe that the potential benefit of tepotinib in addition to gefitinib outweighs its risk; furthermore, there will be an SMC assessing the ongoing safety in Phase Ib and an IDMC which continues to regularly monitor safety in Phase II.

The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the trial unjustifiable.

This clinical trial will be conducted in compliance with the clinical trial protocol, Good Clinical Practice (ICH Topic E6, GCP), the Japanese ministerial ordinance on GCP and any additional applicable regulatory requirements.

## 4 Trial Objectives

### 4.1 Primary Objectives

The primary objectives are:

#### *Phase Ib*

- To determine the RP2D of tepotinib when used in combination with gefitinib (at the approved standard dose of 250 mg) when administered orally QD over a 21-day cycle in subjects with MET+ advanced NSCLC.

### *Phase II*

- To evaluate whether the efficacy in terms of progression free survival (PFS) of second-line tepotinib in combination with gefitinib is superior to pemetrexed+cisplatin/carboplatin in subjects with T790M negative, MET+ locally advanced or metastatic NSCLC harboring an EGFR mutation and having acquired resistance to first-line EGFR-TKI therapy including gefitinib, erlotinib, icotinib, or afatinib.

## **4.2 Secondary Objectives**

### *Phase Ib*

- To characterize the PK of tepotinib when given in combination with gefitinib;
- To characterize the PK of gefitinib when given in combination with tepotinib;
- To assess the safety and tolerability of tepotinib in combination with gefitinib;
- To evaluate preliminary antitumor activity of tepotinib in combination with gefitinib.

### *Phase II*

- To evaluate the safety and tolerability of tepotinib in combination with gefitinib;
- To evaluate the efficacy of tepotinib in combination with gefitinib in T790M negative, MET+ subjects;
- To evaluate the antitumor activity of tepotinib in combination with gefitinib in T790M positive, MET+ subjects in a separate single-arm cohort (mainland China sites only);
- To assess patient-reported outcomes (PROs) with respect to quality of life (QoL), as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, Version 3.0), and time-to-symptom progression (TTSP), as measured by Lung Cancer Symptom Scale (LCSS).

## **4.3 Exploratory Objectives**

The exploratory objectives are:

### *Phase Ib*

**CCI**

- To assess biomarkers that may correlate with antitumor activity, including, but not limited to, markers of the c-Met pathway activation (eg, HGF levels, and c-Met mutations), and other relevant oncogenic pathways.

## Phase II

CCI

- To investigate biomarkers of c-Met pathway activation and other relevant oncogenic pathways in serum and tumor tissue and their potential correlation with prognosis and the activity of tepotinib in combination with gefitinib;

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## 5 Investigational Plan

### 5.1 Overall Trial Design and Plan

#### Phase Ib

The Phase Ib stage of the study comprises 2 parts, the standard “3+3” dose escalation cohorts, and an additional cohort for subjects from the mainland China sites.

#### “3+3” Dose Escalation Cohorts

The Phase Ib part that contains the “3+3” dose escalation cohorts is a multicenter, open label part to determine the RP2D of tepotinib in combination with gefitinib in subjects with MET+, advanced NSCLC.

A standard “3+3” dose escalation design with a dose escalation and a dose confirmation phase will be used. In principle, the criteria for dose escalation and de-escalation rules are based on the occurrence of DLTs during Cycle 1. However, other clinically relevant safety issues, as well as emerging PK data should also be considered as necessary when making dosing decisions. A SMC will be responsible for making the decision to escalate (or de-escalate) the dose level after all subjects in the preceding cohort have completed the first cycle of treatment and all subjects’ data during this cycle have been evaluated.

The first dose level of tepotinib (300 mg QD) has been set to be 1 dose level lower than the RP2D from the FIM trial (500 mg QD). Therefore, the anticipated dose cohorts of tepotinib in this trial are 300 and 500 mg. Gefitinib will be coadministered at the standard dose (250 mg QD).

The criteria for decisions concerning dose escalation or de-escalation are discussed in detail in Section 6.2.1. Dose escalation beyond the target RP2D of tepotinib will not be pursued unless there is reasonable concern that it might not be biologically active and if the safety data do not preclude further dose escalation. The SMC (Section 6.2.2) may also elect to evaluate a lower dose. Rich PK sampling will be performed to characterize the PK of tepotinib and gefitinib when given as combination therapy.

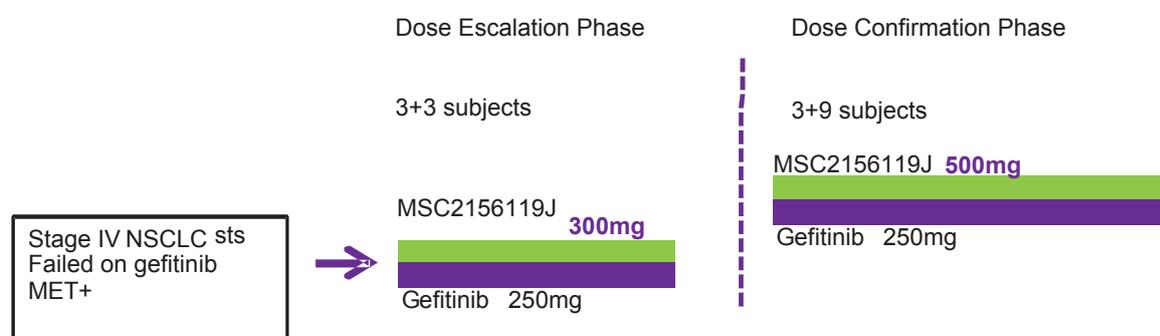
## Treatment Duration

There will be a screening period of up to 28 days prior to study treatment to assess subjects' eligibility except for MET status. Some subjects may have a prescreening period which extends beyond 28 days for the determination of MET status. Eligible subjects will be enrolled into the trial and then enter the treatment period. Subjects will receive tepotinib in combination with gefitinib QD. Subjects who stop treatment with both components of the combination therapy will have an End-of-Treatment visit within 14 days of the last dose, the completion of treatment cycle, or the day when it is determined to permanently discontinue the study treatment.

A 30-day Safety Follow-up visit will occur at  $30 \pm 3$  days after the last dose. If a subject withdraws from the treatment for reasons other than progressive disease (PD), additional follow-up visits for tumor assessments will be performed until progression.

The trial design is presented graphically in [Figure 5.1](#).

**Figure 5.1 Phase Ib Design (“3+3” Dose Escalation Cohorts)**



MSC2156119J = tepotinib; sts=subjects

## Chinese (Mainland) Subject Cohort

Up to 3 evaluable subjects will be enrolled in the mainland China sites separately and will be tested at tepotinib one dose level below the RP2D QD. An additional cohort for subjects from the mainland China sites is included to meet a request from the Chinese Food and Drug Administration (CFDA) following clinical trial amendment review. The aim of this cohort is to collect preliminary data of the safety and PK of tepotinib administered in combination with gefitinib in subjects from mainland China sites. All subjects in this cohort will be evaluated with the same criteria as the other subjects in the dose escalation cohort. Subjects who are not fully evaluable will be replaced (Section 5.6). The Sponsor experts (see Section 2) as well as the coordinating Investigator will take the responsibility of evaluating safety and available PK data at the last subject's completion of Cycle 1. If any subject experiences an event listed in Section 6.2.3, and if this event is classified as related to tepotinib, this may trigger a decision of the treating physician and the coordinating Investigator to enroll more subjects, after discussing with the Sponsor. The safety data from the additional cohort of subjects from the mainland China sites will not be used for DLT evaluation and/or RP2D/MTD determination.

## Phase II

The Phase II stage of the study also comprises two parts, randomized part and non-randomized part (single-arm cohort). This phase will be conducted once the RP2D for tepotinib+gefitinib has been defined in Phase Ib.

The randomized part is a multicenter, open label, active-control part to evaluate the efficacy and safety of tepotinib+gefitinib compared to that of pemetrexed+cisplatin/carboplatin in T790M negative, MET+ subjects. Subjects with MET+ and T790M negative locally advanced or metastatic NSCLC who harbor the EGFR mutation and have acquired resistance to first-line EGFR-TKI therapy including gefitinib, erlotinib, icotinib, or afatinib will be enrolled in this part of the trial.

A total of approximately 156 eligible subjects were planned to be enrolled in the randomized part. From study start to approval of Protocol Version 7.0, subjects were randomized at a 1:1 ratio to either the experimental arm (tepotinib+gefitinib) or the control arm (pemetrexed+cisplatin). From the approval of Protocol Version 7.0 onwards, subjects were randomized at a 2:1 ratio to either the experimental arm (tepotinib+gefitinib) or the control arm (pemetrexed+cisplatin/carboplatin). They were stratified by type of MET+ (protein overexpression immunohistochemistry [IHC] 2+ vs. protein overexpression IHC 3+ vs. gene amplification and/or increased c-Met gene copy number (GCN), both by in situ hybridization [ISH]; see [Appendix H](#)) and prior EGFR-TKI treatment (gefitinib vs. erlotinib vs. icotinib vs. afatinib). Subjects who have the co-existence of amplification and/or increased c-Met GCN as well as overexpression were included in the amplification and/or increased c-Met GCN group.

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

The Sponsor's decision to halt further enrollment is due to the difficulties experienced in identifying subjects who meet the eligibility criteria of the trial. In spite of increased efforts, the enrollment rate did not improve to an extent that would allow for completion of the trial in a reasonable time frame. The decision is not based on any safety concerns. Accordingly, the benefit-risk ratio for all subjects continuing the trial remains unchanged.

Following the enrollment halt, subjects were offered the option to continue the trial following the current protocol after discussion with their Investigator. Subjects in prescreening/screening and who were eligible had been offered to be enrolled in the trial. Subjects who decided to continue treatment continued on their originally allocated treatment, at their most recent dose according to the protocol. Safety monitoring and data collection will continue without modification through to the end of the trial.

In addition to and separate from the randomized part of the trial in T790M negative and MET+ subjects, the safety and efficacy of tepotinib+gefitinib will be evaluated in a single-arm (non-randomized) cohort of up to 15 subjects with MET+ T790M positive NSCLC (mainland China sites only). By the time of the enrollment halt, all 15 subjects with MET+ T790M positive NSCLC had been enrolled. The rationale for inclusion of this cohort is provided in [Section 5.2](#). For this single-arm cohort, the Sponsor may conduct administrative interim analyses at time points that are not specified in the protocol for internal planning purposes.

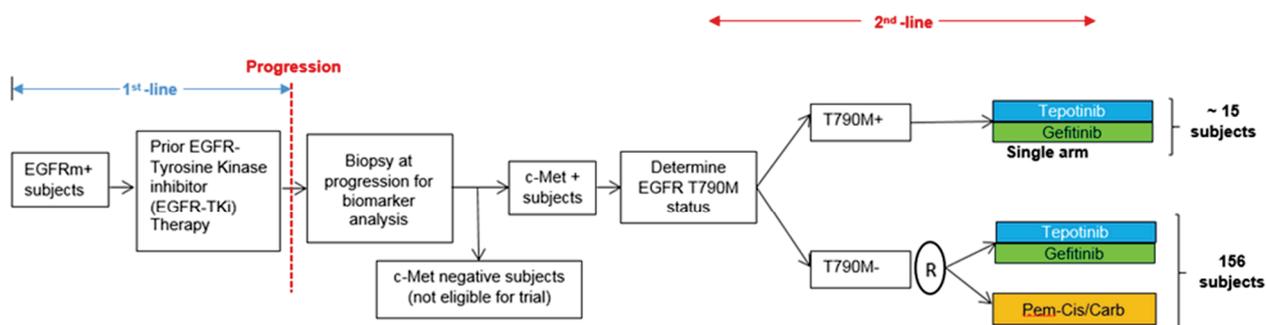
The primary endpoint, PFS in the randomized part, and the secondary efficacy endpoints based on tumor response, will be assessed by the Investigator/site radiologist using RECIST, Version 1.1. In addition, an IRC will evaluate tumor response independently for both parts (ie, randomized and non-randomized), of which the results will serve as sensitivity analysis at the end of the trial.

For both parts (ie, randomized and non-randomized), an IDMC will monitor the efficacy and safety data.

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For both parts (ie, randomized and non-randomized), at specified time points (Appendix A, Appendix B), subjects will be asked to complete QoL questionnaires, including LCSS (Appendix K), EORTC QLQ-C30 (Appendix L), and CCI evaluations by themselves. Subjects will need to complete the QoL questionnaires at the investigational center prior to the initiation of any other trial activities (including RECIST Version 1.1 assessments) or active treatments, and prior to any contact with the Investigator. The design of Phase II is summarized in Figure 5.2.

**Figure 5.2 Trial Design for Phase II**



Abbreviations: EGFR: epidermal growth factor receptor; EGFRm+: EGFR-TKI sensitizing mutation; R: randomization; Pemetrexed/Cis/Carb: pemetrexed+cisplatin/carboplatin (pemetrexed plus either cisplatin or carboplatin).

**Treatment Duration**

There will be an up to 28 day screening period to assess subject eligibility prior to randomization/the first administration of the study treatment, except for MET and T790M status. Some subjects may have a prescreening period which extends beyond 28 days for the determination of MET and T790M status. Eligible subjects will receive either tepotinib+gefitinib QD, or pemetrexed+cisplatin/carboplatin for:

- Either up to 6 cycles of pemetrexed+cisplatin/carboplatin, or
- 4 cycles of pemetrexed+ cisplatin/carboplatin followed by pemetrexed maintenance.

Treatment will discontinue upon PD, intolerable toxicity, withdrawal from the treatment, or, for subjects in the control arm not receiving pemetrexed maintenance only, the completion of

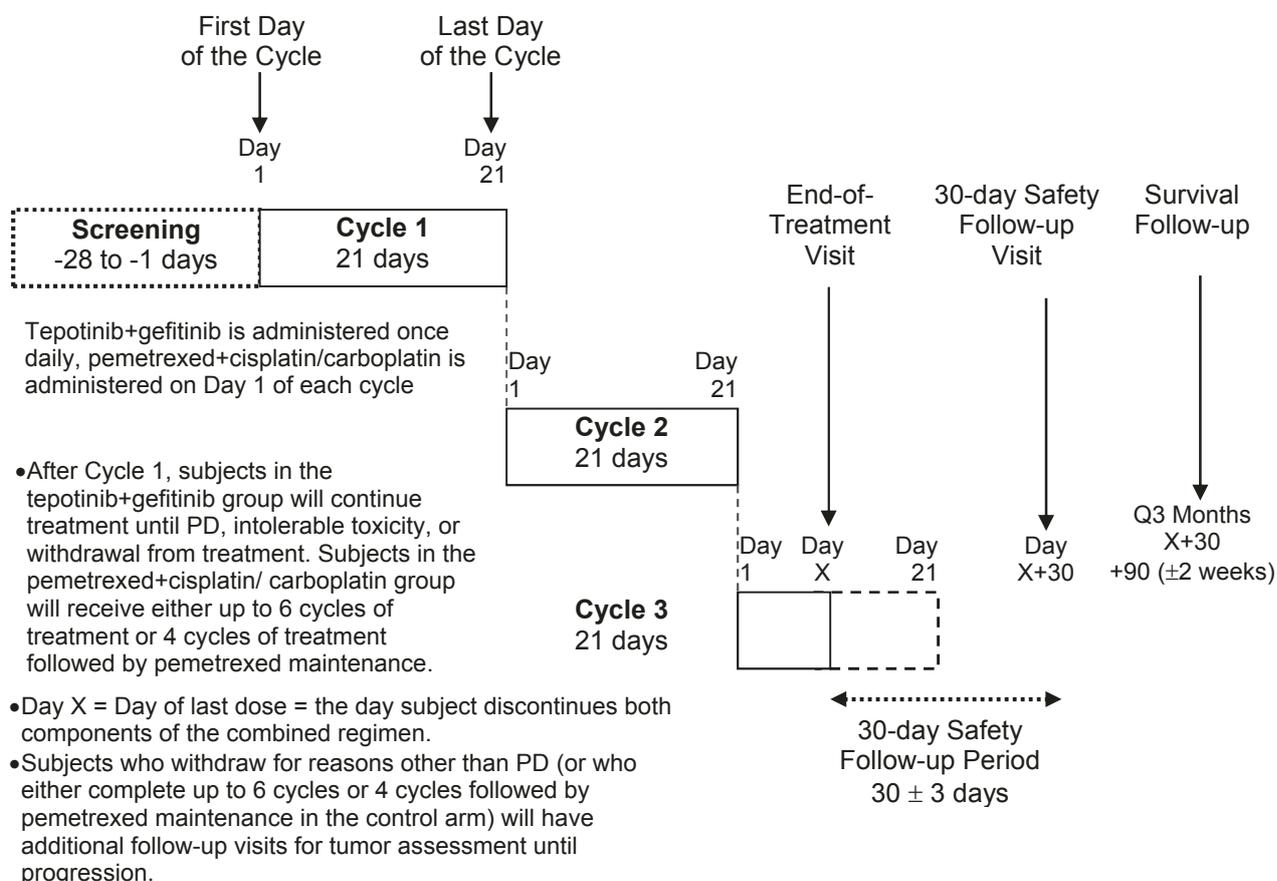
up to 6 cycles of chemotherapy with pemetrexed+cisplatin/carboplatin. In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Please refer to Section 5.4.2.

Subjects who stop treatment with all trial treatment will have an End-of-Treatment visit within 14 days of the last dose, the completion of treatment cycle, or the day when it is determined to permanently discontinue the study treatment. A 30-day Safety Follow-up visit will occur at  $30 \pm 3$  days after the last dose for safety monitoring. If a subject withdraws from the treatment for reasons other than PD, additional follow-up visits for tumor assessments will be performed until they have PD. There will also be survival follow-up assessments to collect subjects' survival information every 3 months  $\pm 2$  weeks until death or the end of the trial, whichever comes first.

Subjects who experience PD after having completed 6 cycles of chemotherapy or who prematurely have to stop their chemotherapy or who cannot continue their experimental or maintenance treatment due to toxicity or other reasons as specified in Section 5.4.2 will either have an End-of-Treatment visit within 14 days of the last dose, or at the completion of the respective treatment cycle, or the day when it is determined to permanently discontinue the study.

A schematic of the flow of events for each subject is displayed in Figure 5.3.

**Figure 5.3 Treatment Duration in Phase II**



Note: for subjects who receive tepotinib+gefitinib in Phase II, treatment beyond progression may be considered.

## 5.2 Discussion of Trial Design

In the completed and ongoing trials, tepotinib shows a favorable safety profile. For monotherapy, a RP2D of 500 mg QD has been determined in the FIM study. This RP2D is defined as a biologically active dose, based on PK/Pd modeling and supported by data on target inhibition from paired tumor biopsies, rather than as a safety defined MTD. However, since the RP2D of tepotinib together with an EGFR-TKI as combination therapy has not been determined, a safety run-in phase will start dose escalation at 300 mg, thereby allowing for an additional safety step before exposing subjects to the full RP2D.

In this study, subjects will receive combination therapy of tepotinib+gefitinib. Based on the available drug metabolism and PK data from both compounds, no major drug-drug interaction is expected, however, PK of both compounds will still be evaluated in Phase Ib. Meanwhile, taking into account the potential difference in drug metabolism and PK in Asian ethnicity, de-escalating to the second lower level, will be open for SMC decision by carefully considering PK and safety data explored in preceding cohorts.

Doses exceeding 500 mg QD will not be pursued unless there is a reasonable concern that 500 mg QD might not be biologically active in Asian subjects and the safety and/or PK data do not preclude further dose escalation. Continuous QD administration of tepotinib for 21 consecutive days was determined, after consideration of nonclinical data and the FIM trial as the most appropriate treatment regimen for this trial.

In the current plan, the highest dose level of tepotinib is set at 500 mg, which is in line with the RP2D defined in the FIM study. The definition of the RP2D (ie, 500 mg) in the FIM study was based on the following criteria and considerations (refer to the current IB):

1. Based on the results from a nonclinical PK/Pd and tumor growth model, the analysis of target inhibition phospho-c-Met in on-treatment subject biopsies, and from a population PK model, the 500 mg QD dose achieves target inhibition  $\geq 95\%$  and results in sufficiently high steady state (trough) exposure levels in  $\geq 90\%$  of subjects to induce activity in tumors with varying degrees of sensitivity to c-Met inhibition. Further support for this recommendation can be found in the current IB.
2. The SMC evaluated results from an expanded cohort of 14 subjects that were treated with 500 mg tepotinib QD administered over a 21-day cycle. No DLTs were observed in the 12 evaluable subjects. Of the 2 subjects who were not evaluable, 1 subject was replaced due to the AE of Grade 2 bacteremia (assessed by the Investigator as not related to tepotinib) and the other subject was replaced due to disease progression.
3. The 500 mg QD dose is, therefore, considered to be safe and in the biologically active range and will be used as the target dose level (ie, RP2D) in subsequent clinical trials with tepotinib.

In-house data and published evidence suggest the simultaneous inhibition of both pathways is necessary for subjects with MET+ tumors, and that these subjects require treatment combining both a c-Met and an EGFR inhibitor (14, 15). In tumors from subjects with acquired resistance to EGFR-TKI, the original activating mutation is still found in addition to the T790M resistance mutation, indicating that the original oncogenic driver is still present and therefore requires continued inhibition. It is hypothesized that the tumor may evade therapeutic pressure from

single pathway inhibition by switching the signaling to the other pathway. In house nonclinical data which demonstrated activity of tepotinib and EGFR-TKI combination regimen in MET+, T790M negative xenograft models after acquired resistance also provide compelling evidence. Based on the knowledge mentioned above, monotherapy with tepotinib or EGFR-TKI alone as active control is not justified.

In subjects with good performance status (PS) and acquired resistance to EGFR-TKI, the current standard treatment is platinum-based doublet chemotherapy (12). The majority of subjects with NSCLC harboring EGFR mutation have a non-squamous histology. The available evidence indicates that cisplatin in combination with pemetrexed is a preferred option for this histological subtype. Studies have indicated better survival and favorable safety profile when compared with gemcitabine+cisplatin (16). Moreover, some clinical trials in an EGFRm+ population have used pemetrexed+cisplatin as active control (17); thus, using this doublet regimen facilitates the verification of external validity in the future and allows for easier indirect comparison across trials.

This study will enroll subjects who are MET+. Initial scientific evidence (31) indicates that even tumors with relatively small MET gene copy number gains can develop resistance to EGFR TKIs, though remaining sensitive to c-Met inhibitors. Therefore, MET+ is defined as c-Met overexpression and/or c-Met amplification and/or increased c-Met GCN. Although there is little doubt on the driving role of c-Met amplification in the acquired resistance to EGFR inhibition, the role that c-Met overexpression plays in this field remains less established. However, in a single-arm Phase Ib/II trial, the addition of INC280 (a highly selective c-Met inhibitor) to gefitinib showed promising clinical activity in MET+ NSCLC subjects resistant to EGFR-TKIs. This suggests that c-Met overexpression (IHC2+, 3+) is predictive of benefit from the dual inhibition of c-Met and EGFR pathways (18). We hypothesize that c-Met overexpression is another indicator of c-Met pathway activation leading to acquired resistance to EGFR inhibition, and that it thus warrants being regarded as a potential predictive biomarker for dual inhibition of c-Met and EGFR pathways in this setting.

As previously mentioned, the T790M mutation has been identified as playing an important role and is frequently detected in EGFR-TKI acquired resistance. Growing evidence also indicates that the T790M mutation is associated with better prognosis. In-house nonclinical data indicate that a cell line carrying the T790M mutation was sensitive to EGFR and c-Met dual inhibition (cetuximab+tepotinib), suggesting that T790M mutation subjects may still benefit from this dual inhibition. However, there is scant data to predict how tepotinib+gefitinib may perform in subjects with the T790M mutation. If both c-Met overexpression/amplification and T790M mutation are present in the same subject, the contribution of each of the two resistance mechanisms to the overall resistant phenotype is currently unknown.

Therefore, the initial trial design considered enrollment of a broad population of subjects progressing on the first generation EGFR-TKI gefitinib. However, recent data from third generation EGFR-TKIs (AZD9291/CO-1686) on T790M positive subjects who have failed a first generation EGFR-TKI showed impressive efficacy (objective response rate 58% - 64%) (19, 20). Therefore, several large global Phase III trials with a strong focus on the Asian region are ongoing. Since these trials may lead to a change in the standard of care in T790M positive subjects, and, thus, in the composition of the control arm in controlled studies, it has been decided to focus the randomized part of the present study on subjects who have failed EGFR-TKI therapy including gefitinib, erlotinib, icotinib, and afatinib and are T790M negative.

In conclusion, only T790M negative subjects will be randomized to chemotherapy in the present study, but, in order to collect preliminary data on safety and antitumor activity in T790M positive subjects, up to 15 subjects with T790M mutation will be treated with tepotinib+gefitinib in a single-arm cohort (mainland China sites only).

### 5.2.1 Inclusion of Special Populations

Not applicable.

## 5.3 Selection of Trial Population

### 5.3.1 Inclusion Criteria

#### Phase Ib

For inclusion in Phase Ib, all of the following inclusion criteria must be fulfilled:

1. Histologically or cytologically confirmed advanced NSCLC, regardless of histology subtype, which failed on gefitinib for reasons other than toxicity or compliance;
2. Availability of a fresh or archived pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples). For subjects who have had at least 1 prior anticancer treatment, a biopsy obtained between failure of the most recent anticancer treatment and enrollment is mandatory (details of tumor tissue collection are described in Section 7.6.2);
3. MET+ status, as determined by the central laboratory, ie, c-Met overexpression as determined by IHC (ie, IHC 2+ or IHC 3+) and/or c-Met amplification as determined by ISH;
4. Signed, written informed consent by subject or legal representative prior to any study-specific screening procedure;
5. Male or female,  $\geq 18$  years of age (or minimum age of legal consent consistent with local regulations, if minimum is  $> 18$  years of age);
6. Measurable disease in accordance with RECIST Version 1.1;
7. Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1.

#### Phase II

For inclusion in Phase II, all of the following inclusion criteria must be fulfilled:

1. Locally advanced or metastatic NSCLC other than predominantly squamous histology (confirmed by either histology or cytology);
2. Activating mutation of the EGFR receptor (documented, or as determined by the central laboratory);

3. EGFR T790M status after acquired resistance to first line EGFR-TKI therapy including gefitinib, erlotinib, icotinib, or afatinib treatment (as determined by the central laboratory, using a validated PCR test);
  - T790M negative status for the randomized part
  - T790M positive status for the single-arm cohort (mainland China sites only)
4. Acquired resistance using the Jackman criteria (21) on first-line EGFR-TKI therapy including gefitinib, erlotinib, icotinib, or afatinib, subjects must meet both of the following 2 criteria defined as following:
  - a. Radiological documentation of disease progression while on continuous treatment with first-line gefitinib, erlotinib, icotinib, or afatinib within the last 30 days prior to disease progression (refer to Section 7.3 for additional information):
    - i. Evidence of central nervous system (CNS) recurrence only while on first-line gefitinib, erlotinib, icotinib, or afatinib is not considered as acquired resistance;
    - b. Prior objective clinical benefit defined by either partial or complete radiological response, or durable SD (SD should last > 6 months) after initiation of first-line gefitinib, erlotinib, icotinib, or afatinib;
5. Availability of a fresh or archived tumor tissue (excluding fine needle aspiration and cytology samples) obtained between documentation of acquired resistance to gefitinib, erlotinib, icotinib, or afatinib (as defined in inclusion criterion 4) and enrollment is mandatory (details of tumor tissue collection are described in Section 7.6.2);
6. MET+ status, as determined by the central laboratory, ie, c-Met overexpression as determined by IHC (ie, IHC 2+ or IHC 3+) and/or c-Met amplification and/or increased c-Met GCN, both determined by ISH (defined in Section 7.6.2);
7. Signed, written informed consent by subject or legal representative prior to any study-specific screening procedure;
8. Male or female,  $\geq 18$  years of age (or minimum age of legal consent consistent with local regulations, if minimum is > 18 years of age);
9. Measurable disease in accordance with RECIST Version 1.1;
10. ECOG PS of 0 or 1;
11. Eligible to start doublet chemotherapy consisting either of pemetrexed+cisplatin or pemetrexed+carboplatin.
12. Interval between documentation of radiological PD on first-line gefitinib, erlotinib, icotinib, or afatinib and first dose of study drug shall not exceed 60 days.

## 5.3.2 Exclusion Criteria

### Phase Ib

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

#### Cancer Related

1. Symptomatic metastasis of brain and/or CNS, uncontrolled with antiepileptics and requiring steroids, unless treated and stable without steroids for at least 10 days within 4 weeks prior to the first dose of trial treatment;
2. Any unresolved toxicity more than NCI-CTCAE (Version 4.0) Grade 2 from previous anticancer therapy;
3. Estimated life expectancy < 3 months;
4. Need for transfusion within 14 days prior to the first dose of trial treatment;
5. Prior chemotherapy, biological therapy, radiation therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of trial treatment.

#### Laboratory Values and Organ Function

1. Inadequate hematological function:
  - Hemoglobin < 8.5 g/dL
  - Neutrophils <  $1.5 \times 10^9/L$
  - Platelets <  $100 \times 10^9/L$ ;
2. Inadequate liver function:
  - Total bilirubin >  $1.5 \times$  upper limit of normal (ULN)
  - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >  $3 \times$  ULN;

For subjects with liver metastases:

  - Total bilirubin >  $1.5 \times$  ULN
  - AST/ALT >  $5 \times$  ULN
3. Known pre-existing interstitial lung disease;
4. Inadequate renal function:
  - Renal impairment as evidenced by serum creatinine  $\geq 1.5 \times$  ULN, or creatinine clearance (CrCl) < 60 mL/min calculated by the Cockcroft-Gault formula (24 hour CrCl might be requested by the Investigator for confirmation, if calculated

CrCl is < 60 mL/min. In such case, subjects with 24 hour CrCl < 60 mL/min should be excluded)

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

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

## General

### 1. Impaired cardiac function

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

2. Hypertension uncontrolled by standard therapies (not stabilized to <150/90 mmHg);

3. Contraindication to the administration of gefitinib;

4. Medical history of liver fibrosis/cirrhosis;

5. Past or current history of neoplasm other than NSCLC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years;

6. Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the tested product;

7. Major surgery within 28 days prior to Day 1 of trial treatment;

8. Known human immunodeficiency virus positivity;

9. Substance abuse, active infection, or other acute or chronic medical or psychiatric condition or laboratory abnormalities that might increase the risk associated with study participation at the discretion of Investigators;

10. Female subjects who are pregnant or lactating, or men and women of reproductive potential not willing or not able to employ a highly effective method of birth control/contraception to prevent pregnancy until the end of study. A highly effective

method of contraception is defined as those, alone or in combination, that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly (see [Appendix N](#)). This requirement begins 2 weeks before receiving the first trial treatment and ends 3 months after receiving the last treatment;

11. Known hypersensitivity to any of the trial treatment ingredients;
12. Legal incapacity or limited legal capacity;
13. Any other reason that, in the opinion of the Principal Investigator, precludes the subject from participating in the trial;
14. Participation in another interventional clinical trial (except those subjects who were solely involved in other trials where the investigation product was gefitinib, erlotinib, icotinib, or afatinib) within the 30 days prior to randomization/first dose.

### ***Phase II***

Subjects are not eligible for Phase II if they fulfill any Phase Ib exclusion criteria listed above. Additional exclusion criteria, listed below, apply to Phase II only.

### **General**

Any contraindication to the administration of either pemetrexed+cisplatin or pemetrexed+carboplatin.

### **Cancer Related**

1. Prior systemic anticancer treatment with eg. chemotherapy or any other agents excluding gefitinib, erlotinib, icotinib, and afatinib for advanced NSCLC (one course of chemotherapy regimen for [neo]adjuvant purpose, or one course of chemoradiation for Stage IIIa disease is allowed);
2. Prior treatment with other agents targeting the HGF/c-Met pathway.

## **5.4 Criteria for Subject Withdrawal**

### **5.4.1 Withdrawal from the Trial**

Subjects are free to discontinue the trial at any time without giving a reason. A subject must be withdrawn in the event of:

- Withdrawal of the subject's consent,
- Participation in any other trial using an investigational drug or intervention during the subject's participation in this trial.

If a subject fails to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, every effort should be made to complete the investigations scheduled for the End-of-Treatment visit, focusing on the most relevant assessments. The appropriate electronic case report form (eCRF) section must be completed.

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

#### 5.4.2 Withdrawal from Trial Therapy

Withdrawal from trial therapy is defined as permanently discontinuing study treatment in the event of any of the following:

- Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, in the judgment of the Investigator and/or Sponsor;
- AEs, if discontinuation of trial treatment is desired or considered necessary by the Investigator and/or subject;
- Dose delay time is more than 21 days at the permitted lowest dose due to any reason;
- Pregnancy;
- Noncompliance with administration of tepotinib, gefitinib or chemotherapy, as defined in Section 6.2.4;
- Initiation of a new systemic anticancer therapy as described in Section 6.5.2;
- Documented progression of the disease (but see following paragraphs for treatment beyond progression).

In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Cases that may be considered for treatment beyond progression include subjects with slow ("smoldering") progression after an initial partial response (PR)/complete response (CR), provided there are no clinical symptoms and no new lesions. If, in selected subjects, the Investigator wants to continue the treatment beyond progression although new lesion(s) have been documented, this must be discussed and agreed with the Sponsor, and documented in the appropriate designated eCRF section. The Investigator has to ensure that all safety data are collected, as per protocol, in the same manner as before progression. RECIST Version 1.1 radiographical assessment will follow institutional practice guidelines, however, tumor assessment information will not be recorded in the eCRF and there will be no further documentation collected for any new lesion and/or clinical symptoms of PD after first PD.

Discontinuation of treatment beyond PD is at the discretion of the treating physician. If the subject develops new lesions or clinical symptoms, the benefit of continuing treatment with the study drugs should be discussed with the Sponsor.

For analysis of the primary endpoint, only the first progression event is used.

If subjects withdraw from treatment without documented PD, every effort should be made to continue tumor assessments until objective PD, start of new anticancer treatment or withdrawal of consent.

Subjects who stop treatment with both components of the combination therapy will have an End-of-Treatment visit within 14 days of the last dose, the completion of treatment cycle, or the day when it is determined to permanently discontinue the study treatment.

## 5.5 Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to an unfavorable risk-benefit judgment of tepotinib+gefitinib, for example:
  - Evidence of inefficacy;  
*(Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or nonclinical examinations, eg, toxicology.)*
  - Safety findings that preclude further continuation of the trial.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons;
- Poor enrollment making completion of the trial within an acceptable time frame unlikely;
- Discontinuation of development of tepotinib.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of Health Authorities.

## 5.6 Replacement of Discontinued Subjects

Subjects withdrawn from Phase Ib may be replaced if they are not fully evaluable for the assessment of the primary endpoints. "Not fully evaluable" is defined as:

- Subjects who discontinue the trial prematurely during Cycle 1 for reasons other than a DLT. Such reasons could include, for example, withdrawal of consent, not meeting the eligibility criteria, noncompliance with follow-up, early disease progression, or unrelated AEs;
- Subjects who do not receive at least 80% (ie, < 17 treatment days) of planned cumulative doses of tepotinib+gefitinib during Cycle 1, for reasons other than AEs or DLTs.

Subjects withdrawn in Phase II will not be replaced.

## 5.7 Definition of End of Trial

The end of the trial is defined as the time point in Phase II part when the last subject discontinued treatment and completed the subsequent safety follow-up visit.

The Sponsor decided to halt enrollment. The sites were notified about the enrollment halt on 25 May 2017. The last subject was randomized on 12 June 2017. Until then 55 of 156 subjects with MET+ T790M negative NSCLC planned to be enrolled had been randomized. By that time, all 15 subjects planned to be enrolled in the single-arm cohort (mainland China sites only) of up to 15 subjects with MET+ T790M positive NSCLC had been included in the study.

Following the enrollment halt, subjects were offered the option to continue the trial following the current protocol after discussion with their Investigator. Subjects who decided to continue treatment continued on their originally allocated treatment, at their most recent dose according to the protocol. Safety monitoring and data collection will continue without modification through to the end of the trial.

## 6 Investigational Medicinal Product(s) and Other Drugs Used in the Trial

The term “Investigational Medicinal Product” or “IMP” refers to the investigational drug undergoing trial, ie, tepotinib and gefitinib. Subjects in both Phase Ib and Phase II will take tepotinib in combination with gefitinib. The active comparators in Phase II is pemetrexed infusion followed by infusion with cisplatin or carboplatin.

NOTE: Other medications and fluids are given as part of supportive care or to accompany the administration of pemetrexed and cisplatin or carboplatin. While some general information is discussed in this protocol, this document is not a comprehensive source of information regarding the use of pemetrexed and cisplatin or carboplatin. Please refer to the prescription information/summary of product characteristics (SmPC) and other reference sources for questions relating to pemetrexed, cisplatin, carboplatin, and accompanying medication.

### 6.1 Description of Investigational Medicinal Product(s)

Tepotinib, CCI [REDACTED] is supplied as 100 mg and 25 mg film-coated tablets.

The percentage of active ingredient in the white, round, film-coated tablet is approximately 26%. CCI [REDACTED]

[REDACTED] All excipients used are of compendial grade. Supplier’s certificates show that there is no transmissible spongiform encephalopathy risk.

Gefitinib (Iressa®) is provided as a 250 mg tablet and is ready for use. The actual appearance and composition of the product may depend on the respective marketed products sourced for the participating countries.

## 6.2 Dosage and Administration

### Phase Ib

For each dose cohort, a fixed dose and administration will be applied. The assigned dose of tepotinib will be administered daily, supplied as 100 mg (and 25 mg, if applicable) film-coated tablets. Tepotinib will be administered with gefitinib (250 mg).

For “3+3” dose escalation cohorts, the first dose level of tepotinib will be 300 mg QD, which is 1 level lower than the target dose of RP2D (500 mg QD) from the FIM trial. The planned second dose level will be 500 mg QD. However, depending on the safety profile and emerging PK data of tepotinib+gefitinib, a lower dose of tepotinib may be investigated.

For additional up to 3 evaluable subjects from the mainland China sites, tepotinib will be administered orally one dose level below the RP2D, in combination with gefitinib at 250 mg.

Subjects will take their assigned doses of tepotinib and gefitinib orally, in the morning approximately at the same time, immediately after breakfast, with a full glass of water (approximately 200 mL) every day of each 21 day treatment cycle.

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

On days when PK samples are to be drawn, subjects should be instructed to attend the trial visit in a fasted state, with no breakfast and prior to taking their dose of tepotinib and gefitinib. After a predose PK blood sample is drawn, the assigned dose of tepotinib and gefitinib should be taken following breakfast. No further food should be consumed until 2 hours after the dose (water is allowed).

### Phase II

For the single-arm and the experimental arm in the randomization part, tepotinib (at the RP2D determined in Phase Ib) will be administered orally with gefitinib (250 mg) QD with food in the morning approximately at the same time, immediately after breakfast, with a full glass of water (approximately 200 mL). If the dosing on scheduled time is missed, tepotinib and/or gefitinib should be taken with the next meal, if possible; however, an administration time delay > 12 hours on the current day should not be performed. Subjects will take tepotinib and gefitinib continuously throughout the 21 day cycle.

All subjects in the randomization part of Phase II are permitted to receive folic acid and B12 intramuscular injection during screening period. After randomization, only subjects in the control arm will continue comedications for pemetrexed (eg, vitamin B12 and folic acid, see Section 6.4.1). A corticosteroid should be administered on the day prior to, day of, as well as on the day following pemetrexed administration to reduce treatment-related dermatologic toxicity (Section 6.4.1.1). Subjects should receive pretreatment and posttreatment hydration for cisplatin. All comedications will be administered per local package insert/SmPC.

For the control arm of the randomization part, subjects will receive pemetrexed 500 mg/m<sup>2</sup> as an intravenous infusion over 10 minutes. Cisplatin 75 mg/m<sup>2</sup> will be administered as an intravenous infusion over 2 hours beginning approximately 30 minutes after the end of pemetrexed administration.

Based on the subject's medical condition the Investigator may also choose carboplatin instead of cisplatin in combination with pemetrexed. In addition, the Investigator may decide for a carboplatin dose of either AUC5 or AUC6. Generally carboplatin is administered as an intravenous infusion over 1 hour, beginning about 30 minutes after the end of pemetrexed administration. The Investigator is allowed to change the platinum component, ie, from cisplatin to carboplatin and vice versa, during the trial based on the subject's medical condition.

Subjects in the control arm will be treated on Day 1 of each 21 day cycle for up to 6 cycles of pemetrexed+cisplatin/carboplatin or 4 cycles of pemetrexed+cisplatin/carboplatin followed by pemetrexed maintenance, in line with the SmPC for pemetrexed, cisplatin, or carboplatin, respectively. Pemetrexed 500 mg/m<sup>2</sup> as maintenance monotherapy will also be administered on Day 1 of each 21-day cycle following the completion of 4 cycles of doublet chemotherapy with the same administration method stated previously.

Common protocols for the administration of pemetrexed, cisplatin, and carboplatin are mentioned above. However, for further administration details, Investigators are also requested to check / take into account current medical and local administration guidelines / treatment protocols, as well as respective SmPCs.

On days when PK samples are to be drawn, subjects who receive tepotinib+gefitinib should be instructed to attend the trial visit in a fasted state, with no breakfast and prior to taking their dose of study medication. After a predose PK blood sample is drawn, the assigned doses of tepotinib and gefitinib should be taken following breakfast. No further food should be consumed until 2 hours after the dose (water is allowed).

## 6.2.1 Dose escalation Assessment Process (Phase Ib)

For "3+3" dose escalation cohorts, the trial will adopt the classical "3+3" dose escalation design consisting of a dose escalation phase and a dose confirmation phase. Dose escalation (or potentially dose de-escalation) decisions are based on the occurrence of DLTs (defined in Section 6.2.3) during Cycle 1 in the first 3 to 6 subjects. Other clinically relevant safety issues and emerging PK data should also be considered when making a decision.

### Dose Escalation Phase

For the first dose cohort (tepotinib 300 mg/day + gefitinib 250 mg/day):

- If no subject out of the first 3 experiences a DLT during Cycle 1, dose escalation will proceed to the higher dose cohort (500 mg);
- If 1 subject out of the first 3 experiences a DLT during Cycle 1, 3 additional subjects will be enrolled at 300 mg;
  - if none of the additional 3 subjects experiences a DLT; dose escalation will proceed to the higher dose cohort (500 mg), or
  - if 1 or more of the additional 3 subjects experiences a DLT, the dose will be identified as intolerable, and the SMC will determine whether to step down to a lower dose level or discontinue the study. This decision will be made by a consideration of the DLTs, other clinically relevant safety issues, and emerging PK data;

- If 2 or more subjects out of the first 3 experience a DLT during Cycle 1, the dose will be identified as intolerable, and the SMC will determine whether to step down to a lower dose level or discontinue the study. This decision will be made by a consideration of the DLTs, other clinically relevant safety issues, and emerging PK data.

For the second dose cohort (tepotinib 500 mg/day + gefitinib 250 mg/day):

- If no subject of the first 3 treated at 500 mg experiences a DLT during Cycle 1, the SMC may decide to enroll 9 additional subjects at the same dose level for a total of 12 subjects.
- If 1 subject out of first 3 experiences a DLT during Cycle 1, 3 additional subjects will be enrolled at the same dose cohort;
  - if none of the additional 3 subjects experiences a DLT; 6 additional subjects will be enrolled at the same dose cohort, or
  - if 1 or more of the additional 3 subjects experience a DLT, the dose will be de-escalated to the lower dose level;
- If 2 or more subjects out of the first 3 experience a DLT during Cycle 1, the dose will be de-escalated to the lower dose level.

### **Dose Confirmation Phase**

After the dose has been determined by the SMC, the cohort at that dose level will be expanded to up to 12 subjects by recruiting an additional 6 to 9 subjects (final subject number depends on those subjects already treated in the dose escalation phase) to confirm the RP2D. A SMC meeting will be held after all 12 subjects have completed Cycle 1. In addition, recruitment will be stopped and an ad hoc SMC meeting will be convened if at any time 33% of subjects or more experience a DLT:

- If 33% or more of up to 12 subjects experience DLTs at the second (500 mg) dose cohort; the dose will be de-escalated to a lower dose level (300 mg), or
- If 33% or more of up to 12 subjects experience DLTs at the first dose cohort (300 mg); the dose will be identified as intolerable, the SMC will determine whether to step down to a lower dose level or discontinue the study by considering other clinically relevant safety issues and emerging PK data.
- If less than 33% of up to 12 subjects experience DLTs at either dose cohort, the dose level will be identified as RP2D.

### **Dose De-escalation**

For dose de-escalation at tepotinib 300 mg/day, 1 step down to a lower dose level is permitted at the discretion of the SMC by considering DLTs, other safety concerns, and available PK data.

For dose de-escalation at tepotinib 500 mg/day, 2 steps down to 300 mg and a further decrease to a lower dose level are permitted at the discretion of SMC by considering DLTs, other safety concerns, and available PK data.

## 6.2.2 Safety Monitoring Committee

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

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

When 3 subjects have completed Cycle 1 at each dose cohort, new enrollment to this trial is paused in each of the dose cohorts. A full safety data set (all AEs, laboratory data, ECG data, and vital signs) and available PK data will be submitted to the SMC, which evaluates the data and confirms the DLT incidence. Depending on the incidence of DLTs, the SMC will determine whether to recruit additional subjects, or de-escalate to next dose level, or discontinue the study. The details of this process will be described in the SMC Charter.

The ad hoc SMC meetings can be performed at any time in case a safety concern should arise.

Dose de-escalation rules as described in Section 6.2.1 will be followed by the SMC.

Further information describing a scope of work and procedures for the SMC will be provided in the SMC Charter, and a separate statistical analysis plan (SAP) for the SMC will be established prior to the start of recruitment.

## 6.2.3 Definition of DLT

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

Using the NCI-CTCAE (Version 4.0), a DLT is defined as any of the following toxicities that occur at any dose level and judged to be related to tepotinib by the Investigator and/or the Sponsor:

- Grade 4 neutropenia for more than 7 days;
- Grade  $\geq$  3 febrile neutropenia for more than 1 day;
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with non-traumatic bleeding;
- Grade  $\geq$  3 uncontrolled nausea/vomiting and/or diarrhea despite adequate and optimal treatment;
- Grade  $\geq$  3 any non-hematological AE, except the aforementioned gastrointestinal events and alopecia; however, a DLT is defined specifically for the following cases:

- Grade  $\geq 3$  liver AE requiring a recovery period of more than 7 days to the baseline or to Grade 1 (This criterion is not limited to the liver function tests. Other liver AE eg, jaundice or hepatic encephalopathy suggestive of liver failure should be also considered);
- Grade  $\geq 3$  lipase and/or amylase elevation with confirmation of pancreatitis, either based on clinical or radiological signs will be considered as DLT. An isolated lipase and/or amylase elevation of  $\geq$  Grade 3 without clinical or radiological evidence of pancreatitis will not be classified as DLT (for related topics, see below “Asymptomatic Elevation of Serum Lipase and/or Amylase”).

### **Asymptomatic Elevation of Serum Lipase and/or Amylase**

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

All cases of asymptomatic lipase and/or amylase elevations of Grade  $\geq 3$  will be reported as Adverse Events of Special Interest (AESI) to the Sponsor (or delegate) in an expedited fashion (see Section 7.4.1.1).

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

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

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

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

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

subjects with this tumor type. Otherwise, treatment with tepotinib+gefitinib should be discontinued.

#### **6.2.4 Missed Doses and Dose Adjustment**

Subjects who miss more than approximately 20% of doses planned during Cycle 1 (ie, > 4 days) for reasons other than adverse drug reactions or DLTs will not be fully evaluable for the assessment of the primary endpoints of Phase Ib. These subjects will be replaced with new subjects for assessment of DLT.

The overall safety assessment will be performed based on the full data set from all subjects who take at least 1 dose of any trial medication.

Subjects will not make up any missed dose unless the entire tablet is seen if vomiting occurs immediately after administration of the study drug. An administration time delay  $\leq 12$  hours compared to the scheduled administration time is permitted; however, if the time delay is  $> 12$  hours, study drug should not be administered on the current day.

#### **Dose Reduction**

If intolerable toxicities are observed and judged by Investigator to be related to either or both components of combination therapy, dose reduction of either or both components will be permitted, depending on the type and severity of toxicity encountered (based on NCI-CTCAE Version 4.0), provided that criteria for subject withdrawal from study treatment have not been met.

#### Tepotinib

Dose reductions of 1 or 2 levels may be applied, depending on the RP2D identified from the Phase Ib part. If 500 mg is identified as the RP2D of tepotinib in combination with gefitinib, and the subject has a toxicity at that dose, the dose may be reduced on a case-by-case basis to 300 mg. It should be noted that if such a situation arises, the Investigator should notify the Sponsor immediately and inform on a case-by-case basis, providing the reason for dose reduction. In case the Investigator needs to consider further dose reduction in response to toxicity, the Investigator should notify the Sponsor prior to modifying the dose further to a lower dose level of 200 mg.

The following dose reduction guidelines for tepotinib are recommended. Clinical circumstances which are not covered by below criteria may be grounds for dose modification. For all situations pertaining to dose reduction, the Investigators should notify the Sponsor on a case-by-case basis, providing the reason for dose reduction.

Under the following circumstances, the tepotinib dose should be temporarily interrupted until the AE recovers to Grade 1 (or less) or to baseline values. Following the interruption, subjects can be re-challenged at the next lower dose level, as described above.

- Grade 4 neutropenia for more than 7 days;
- Grade  $\geq 3$  febrile neutropenia for more than 1 day;
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with non-traumatic bleeding;

- Grade  $\geq 3$  uncontrolled nausea/vomiting and/or diarrhea despite adequate and optimal treatment for more than 3 days;
- Grade  $\geq 3$  any nonhematological AE, except the aforementioned gastrointestinal events and alopecia; however, the following cases are specifically defined:
  - Grade  $\geq 3$  liver AE requiring a recovery period of more than 7 days to return to the baseline grade or to Grade 1 (or less);
  - Grade  $\geq 3$  lipase and/or amylase elevation with confirmation of pancreatitis (for related topics, see above “Asymptomatic Pancreatic Enzyme Elevation”)
  - Recurrence of Grade  $\geq 2$  AEs after re-challenging despite adequate and optimal treatment of the AE.

Under the following circumstances, the dosing should be continued in combination with the appropriate supportive treatment:

- Grade 1 AE;
- Well tolerated Grade 2 AEs;
- Lipase and/or amylase elevation without confirmation of pancreatitis.

For the other circumstances not previously mentioned, the dose may be interrupted temporarily until recovery to Grade 1 (or less) or baseline grade and the same dose could be restarted after recovery.

### Gefitinib

The Investigators may modify the dose schedule of gefitinib in response to any clinically relevant AE with a causal relationship with gefitinib. The dose schedule adjustment of gefitinib should follow its package insert. A table with general guidance for dose modification for common AEs related to gefitinib is provided in [Appendix J](#). General recommendations for the management of diarrhea and skin toxicities related to gefitinib are provided in [Appendix I](#).

### Pemetrexed, cisplatin, or carboplatin

Investigators may follow local package insert/SmPC, their own clinical judgment and their own institutional guidelines for dose modifications of pemetrexed, and cisplatin or carboplatin.

### **Dose Interruption**

Subjects may discontinue 1 component of trial therapy and continue the other if, in the opinion of the Investigator; the subject may derive benefit from treatment. The Investigator must discuss this with the Sponsor on a case by case basis.

AEs assessed by the Investigators to be exclusively related to the subject’s underlying disease or medical condition/concomitant treatment are not considered in the decisions for dose reduction.

## Treatment beyond PD

Refer to Sections 5.4.2 and 7.1.3.9.

### 6.2.5 Intrasubject Dose Escalation

In Phase Ib, subjects will stay at their assigned dose level (except for dose modification due to tolerability issues) throughout their treatment period, unless there is a sufficient reason to allow intrasubject dose escalation. Only subjects who tolerate treatment well in prior cycles at their assigned dose levels will be considered as candidates for intrasubject dose escalation, and dose escalations may occur only after these subjects have the first tumor assessment. Any intrasubject dose escalation must be agreed to by the Sponsor on a case-by-case basis.

AEs reported after intrasubject dose escalation will not be included in the DLT assessment and will not be used for the definition of RP2D. In analyses and summaries, data from these subjects will be analyzed based on assigned dose.

Intrasubject dose escalation to a higher dose level beyond RP2D will not be permitted after the RP2D is defined.

No intrasubject dose escalation is permitted in Phase II.

### 6.3 Assignment to Dose Level (Phase Ib) or Phase II

#### Subject Allocation

Phase Ib is planned to be conducted at selected sites in mainland China, South Korea, Taiwan, and other Asian countries. Subjects will be assigned sequentially to the available dose cohort.

At the time of Amendment 7 approval, Phase II was being conducted in 51 sites worldwide. Randomization of the randomized part of Phase II will be performed centrally by using an interactive voice response system (IVRS). Up to 15 T790M positive and MET+ subjects will be assigned in a single-arm cohort (mainland China sites only) by using an IVRS.

#### Subject Number

- The subject numbers will be assigned in the appropriate format and will reflect study number, site number and subject number.

Subject numbers will not be reassigned to other subjects or reused in this trial. If a subject is replaced, the replacement will be enrolled with a unique subject number.

### 6.4 Other Drugs to be used in the Trial

In addition to the treatment with tepotinib and commercially available gefitinib in Phase Ib and Phase II, commercially available pemetrexed in combination with either cisplatin or carboplatin will be the active comparators in Phase II. The actual appearance and composition of the product may depend on the respective marketed products sourced for the participating countries.

## 6.4.1 Comedications for Phase II

For subjects who receive pemetrexed in combination with either cisplatin or carboplatin in the randomized part of Phase II, as with most cytotoxic regimens, these drugs are preceded and accompanied by supportive care. Some important supportive care measures are described below.

NOTE: As comedications for pemetrexed (oral folic acid, vitamin B12 intramuscular injection) will need to be delivered in the week before first delivery of chemotherapy, this comedication is permitted in all subjects after signing the informed consent form (ICF) and before randomization/the first administration of the trial treatment. After that, only subjects in the control arm of the randomized part will continue comedications for pemetrexed.

### 6.4.1.1 Comedications for Pemetrexed

#### Vitamin Supplementation

All subjects in the randomized part of Phase II are permitted to receive folic acid and first B12 intramuscular injection during screening period, as noted in the section above. After randomization/first administration of the trial treatment, only subjects in the control arm in the randomized part of Phase II will continue comedications for pemetrexed (eg., vitamin B12 and folic acid). All comedications will be administered per local package insert/SmPC.

Subjects should receive oral folic acid or a multivitamin containing folic acid on a daily basis. For the week (ie, 7 days) preceding the first dose of IMP/active comparator, there should be at least 5 doses of folic acid. In the control arm, dosing should continue for the full course of the treatment, and for 3 weeks (ie, 21 days) following the last dose of pemetrexed to be administered.

Subjects should receive vitamin supplementation with vitamin B12 intramuscular injection to reduce hematologic and gastrointestinal toxicity. Subjects should be given an intramuscular injection of vitamin B12 (1000 µg) in the week preceding the first dose of IMP/active comparator, 3 weeks after the first vitamin B12 intramuscular injection (in Cycle 1), and then around every 9 weeks for subjects in the control arm. The vitamin B12 administered orally cannot substitute the vitamin B12 intramuscular administration.

#### Corticosteroid administration

A corticosteroid should be administered on the day prior to, day of, as well as on the day following pemetrexed administration to reduce treatment-related dermatologic toxicity. The amount of corticosteroid to be administered should be equivalent to, for example, 4 mg of dexamethasone. The corticosteroid should be administered orally twice a day.

### 6.4.1.2 Comedications for Cisplatin

See local package insert/SmPC for details on dosing regarding comedications for subjects in the control arm for cisplatin.

## Pretreatment hydration

For pretreatment hydration, local package insert/SmPC for cisplatin will be followed. For example, subjects should receive pretreatment hydration with 1-2 L of fluid to be infused for 8-12 hours prior to cisplatin administration to initiate diuresis. Additionally, adequate subsequent hydration should be ensured to maintain diuresis for the first 24 hours following administration (refer to [Section 6.4.3](#)).

## Pre-emesis

The administration of the antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC, [22](#)).

### 6.4.1.3 Comedications for Carboplatin

See local package insert/SmPC for details on dosing regarding comedications for subjects in the control arm for carboplatin.

## Pre-emesis

The administration of the antiemetic treatment should follow the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in cancer (MASCC, [22](#)).

### 6.4.2 Pemetrexed

General instructions for pemetrexed:

- Pemetrexed dosing should be performed in accordance with its product labeling and use at the site.
- Pemetrexed will be administered on Day 1 of each 21-day cycle at a dose of 500 mg/m<sup>2</sup>.
- Pemetrexed is typically diluted in 100 mL normal saline and administered via IV infusion over 10 minutes. It should not be administered with calcium-containing IV fluids such as Lactated Ringer's solution.
- Pemetrexed will be centrally labeled and supplied by the Sponsor or prescribed by the Investigator, according to local laws.
- Body surface area (BSA) should be calculated based on a standard formula—such as the Mosteller formula ([23](#)):

$$\text{BSA (m}^2\text{)} = ([\text{Height(cm)} \times \text{Weight(kg)}] / 3600)^{1/2} \quad \text{eg, BSA} = \text{square root}(\text{cm} \cdot \text{kg} / 3600)$$

$$\text{or in inches and pounds: } \text{BSA (m}^2\text{)} = ([\text{Height(in)} \times \text{Weight(lbs)}] / 3131)^{1/2}$$

- Pemetrexed dose modifications should be conducted according to the locally approved product label.

### 6.4.3 Cisplatin

General instructions for cisplatin:

- Cisplatin dosing should be performed in accordance with its product labeling and use at the site.
- Subjects should be well hydrated before receiving cisplatin.
- Subjects must receive adequate antiemetic treatment prior to receiving cisplatin.
- Cisplatin will be centrally labeled and supplied by the Sponsor or prescribed by the Investigator, according to local laws.
- Cisplatin infusion should start approximately 30 minutes after completion of the pemetrexed infusion.
- Cisplatin will be administered on Day 1 of each 21-day cycle at a dose of 75 mg/m<sup>2</sup>, for up to 6 cycles or, **in case of pemetrexed continuation maintenance**, for 4 cycles followed by pemetrexed maintenance (for BSA calculation see Section 6.4.2).
- Cisplatin is typically diluted in 250 mL normal saline and administered via IV infusion over 120 minutes.
- Cisplatin dose modifications will be conducted according to its locally approved product label.
- In addition, prior to each dose of cisplatin, monitoring for hearing loss via audiometry should be performed, as clinically indicated.

### 6.4.4 Carboplatin

General instructions for carboplatin:

- Carboplatin dosing should be performed in accordance with its product labeling and use at the site.
- Subjects must receive adequate antiemetic treatment prior to receiving carboplatin.
- Carboplatin will be centrally labeled and supplied by the Sponsor or prescribed by the Investigator, according to local laws.
- Carboplatin will be administered on Day 1 of each 21-day cycle at a dose of AUC5 or AUC6 at the discretion of the Investigator.
- Carboplatin is typically diluted in 5% glucose or 0.9% sodium chloride and administered via IV infusion over 60 minutes.
- The Calvert formula used to determine individual carboplatin dosage:  
*[Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m<sup>2</sup>.]*

Dose (mg) = target AUC (mg/mL x min) x [GFR mL/min + 25]

Generally the Cockcroft Gault calculation can be used to calculate creatinine clearance/GFR. However care should be taken if creatinine level is not felt to truly reflect renal function as in extremes of BSA. Creatinine clearance should be capped at 125 mL/min for carboplatin dosing as recommended by FDA (24). In this respect a maximum carboplatin dose (mg) =

target AUC (mg·min/mL) x (150 mL/min), for example for a target AUC = 5, the maximum dose is  $5 \times 150 = 750$  mg.

- Carboplatin dose modifications should be conducted according to its locally approved product label.

## 6.5 Concomitant Medications and Therapies

### 6.5.1 Permitted Medicines

Any medication (other than those excluded by the clinical trial protocol) that are considered necessary for the subjects' welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

The Investigator will record all concomitant medications/procedures taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the eCRF. Any additional concomitant therapy that becomes necessary during the trial 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.

In order to avoid disease flare, it is highly recommended to continue first-line EGFR-TKI treatment (with gefitinib, erlotinib, icotinib, or afatinib) after documented disease progression until the day before first dose of chemotherapy or first dose of tepotinib/gefitinib.

The following are permitted:

- Concomitant medications that have a narrow therapeutic window and are known to be transported by Pgp (eg, rivaroxaban, apixaban, ranolazine, talinolol, digoxin), BCRP (eg, rosuvastatin), or OCT1 are permitted, but should be used with caution.
- Concomitant medications that are known to inhibit Pgp (eg, itraconazole, telaprevir, clarithromycin, ketoconazole, and conivaptan) are permitted but should be used with caution.

The Investigator may decide not to include a subject in the trial, if the subject cannot withdraw a drug that is advised to be used with caution as defined above. If the Investigator decides to enroll a subject who is treated with a drug that should be used with caution, close safety monitoring is advised.

### 6.5.2 Non-permitted Medicines and Procedures

Any additional concomitant therapy that becomes necessary during the trial 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 trial:

- Any other approved or investigational systemic anticancer treatment including, but not limited to, Traditional Chinese Medicine, chemotherapy, biological response modifiers, hormones, or immunotherapy;

- Given gefitinib administration, concomitant use of known potent CYP3A4 inducers, such as phenytoin, carbamazepine, rifampicin, barbiturates, or St John's Wort should only take place with caution;
- Drug(s), for which the package insert/SmPC includes a contraindication for Pgp (eg, dabigatran, aliskiren, colchicine), BCRP, OCT1, OCT2 and Multidrug and Toxin Extrusion protein (MATE) 1 inhibiting drugs, must not be combined with tepotinib;
- Drug(s) that are known to induce Pgp and thereby may decrease efficacy of Tepotinib such as drugs known to induce Pgp (eg, avasimibe, carbamazepine, phenytoin, rifampin, Saint John's Wort);
- Any drug contraindicated for administration of gefitinib, pemetrexed, cisplatin, or carboplatin;
- Simultaneous participation in another clinical treatment study protocol;
- Experimental or systemic anticancer therapy, except for localized radiotherapy for pain control provided the localized radiotherapy does not compromise tumor assessments of target lesions
- Initiation of a new systemic anticancer therapy for any reason, except as stated above, must result in withdrawal of the subject from the treatment. If a subject requires a non-permitted medication more than 21 days other than an anticancer drug, this treatment may be allowed at the discretion of Investigator, if warranted by the subject's medical condition. The subject should be advised to contact the Investigator before starting the non-permitted medicine, and should not take tepotinib concurrently.

## 6.6 Packaging and Labeling

Packaging and labeling will be in accordance with Manufacture of Investigational Medicinal Products (Annex 13, Volume 4), applicable local regulatory requirements, and applicable Good Manufacturing Practice (GMP) Guidelines.

Tepotinib tablets will be supplied in aluminum-aluminum blisters. A blister sheet contains tablets of 100 mg (and 25 mg if applicable) tepotinib suitable to support the dose escalation setting of the trial. The blisters will be packed in a suitable carton box which is labeled with (but not limited to) the following required information: trial number, number of tablets per box, storage condition, the word "for clinical trial use," batch number, and the Sponsor's name.

Gefitinib (Iressa®) is provided as 250 mg tablets and is ready for use. Gefitinib will be packed in a suitable carton box which is labeled with (but not limited to) the following required information: trial number, number of tablets per box, storage condition, the word "for clinical trial use," batch number, and the Sponsor's name. Pemetrexed (Alimta®) is provided as 100 or 500 mg powder for preparation of a concentrate for solution for infusion. Cisplatin and carboplatin are provided as generic products.

Pemetrexed, cisplatin and carboplatin will be supplied by the study center or by the Sponsor, according to local laws and regulations.

## 6.7 Preparation, Handling and Storage

The pharmacy or designee will receive tepotinib, gefitinib, pemetrexed, cisplatin, and carboplatin labeled and packaged according to the local regulatory requirements and storage requirements. Tepotinib and the co-administered marketed gefitinib are formulated as tablets and are ready for use. The responsible pharmacist will dispense the necessary amount of tepotinib and gefitinib until the next visit to each subject. Pemetrexed, cisplatin, and carboplatin are supplied as marketed formulations, which, depending on the type of formulation, require further preparation before infusion. This preparation will be carried out by a certified pharmacist or by adequately trained personnel on behalf of the Investigator. Detailed guidance will be provided in a MOP.

The drug supplies will be recorded in a drug inventory and stored in a locked cabinet, protected from environmental extremes until use in the trial.

**CCI** [REDACTED] For the storage conditions of gefitinib, pemetrexed, cisplatin, and carboplatin please refer to information provided with the medication. Any deviation from the recommended storage conditions should be immediately reported to the Sponsor, and the medication should not be used until authorization has been received from the Sponsor.

## 6.8 Investigational Medicinal Product Accountability

The pharmacist/delegate who is assigned by the Principal Investigator of the trial site is responsible for ensuring accountability for IMP (tepotinib and gefitinib) and/or active comparator (pemetrexed, cisplatin, or carboplatin), including reconciliation of drugs and maintenance of drug records.

After the conclusion of the trial contract with the site, the Sponsor (or designee) may deliver the IMP to the assigned pharmacist/delegate at the trial site.

- Upon receipt of IMP/active comparator, the pharmacist/delegate will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained for the Investigator Site File or Pharmacy File.
- The dispensing of IMP/active comparator will be carefully recorded on the appropriate drug accountability forms provided by the Sponsor/CRO and an accurate accounting will be available for verification by the Sponsor/CRO monitor at each monitoring visit.
- IMP/active comparator accountability records will include:
  - Confirmation of IMP/active comparator delivery to the trial site;
  - The inventory at the site of IMP/active comparator provided by the Sponsor and prepared at the site;
  - The use of each dose by each subject (diaries for subjects who receive tepotinib+gefitinib; infusion records for the control arm of the randomized part in Phase II);
  - Disposition of unused IMP/active comparator;
  - Dates, quantities, batch numbers, expiry dates and (for IMP/active comparator prepared at the site) formulation, as well as the subjects' trial numbers;

- The assigned pharmacist/delegate should maintain records adequately document:
  - That the subjects were provided the doses specified by the clinical trial protocol/amendment(s);
  - That all IMP/active comparator provided by the Sponsor was fully reconciled.

Unused IMP/active comparator must not be discarded or used for any purpose other than the present trial. IMP/active comparator that has been dispensed to a subject must not be re-dispensed to a different subject.

The Sponsor/CRO monitor will periodically collect the IMP/active comparator accountability forms and will check all returns (both unused and used containers) authorizing their destruction by the trial site.

## **6.9 Assessment of Investigational Medicinal Products Compliance**

For those in Phase Ib and subjects who receive tepotinib+gefitinib in Phase II, each subject will record on a diary card the number and dosage of tepotinib and gefitinib taken daily and the time the tablets were taken. This diary card will be returned to the Investigator site at each visit.

Subjects should be instructed to bring with them to each visit both opened and unopened tepotinib+gefitinib packages, in order to allow the assessment of compliance with trial treatment. The tepotinib+gefitinib administration must be recorded as applicable.

Pemetrexed, cisplatin, and carboplatin are administered as intravenous infusions. The administration of these products must be recorded.

## **6.10 Method of Blinding**

Not applicable, both Phase Ib and Phase II will be carried out in an open label manner.

## **6.11 Emergency Unblinding**

Not applicable.

## **6.12 Treatment of Overdose**

An overdose is defined as any dose greater than the daily dose level at which the subject is being treated. Any overdose must be recorded in the trial medication section of the eCRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported to the Sponsor's Global Drug Safety department in an expedited manner using the appropriate reporting form (see Section 7.4.1.4).

In case of an overdose that needs to be treated, the Investigator should use his/her clinical judgment for the management of the overdose.

## 6.13 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice, and depending on the subject's individual medical needs.

## 7 Trial Procedures and Assessments

Trial periods and assessments apply to both Phase Ib and Phase II, except where noted.

### 7.1 Schedule of Assessments

A chart of all treatment visits and assessments are presented in [Appendix A](#) and [Appendix B](#). Details of the visits and assessments performed are provided in their respective sections. Assessments will be performed on an outpatient basis. However, hospitalization may be needed on PK sampling days in Phase Ib as well as prior to administration of pemetrexed+cisplatin or pemetrexed+carboplatin on Day 1 of each treatment cycle in Phase II. In addition, if clinically indicated, subjects may be hospitalized for evaluation at the discretion of the Investigator.

#### 7.1.1 Informed Consent

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator should ensure that the subject or the subject's legal representative has provided written informed consent(s) according to the procedure described in [Section 9.2](#). A separate written informed consent is required for those subjects who go through the prescreening period to determine MET and/or T790M status.

#### 7.1.2 Screening Period

Subjects who have a prescreening to determine MET and/or T790M status must sign a separate ICF before any prescreening study procedures will be performed. Demographic data, medical history, and disease history will be collected in addition to MET and/or T790M status during prescreening.

Screening procedures must be performed within 28 days prior to study treatment of Phase Ib and Phase II, except for MET and T790M status (if applicable). Some subjects may have a prescreening period which extends beyond 28 days for the determination of MET and T790M status (if applicable). Screening procedures include the following: physical examination, demography, height, medical history including EGFR mutation status, weight, vital signs, pretreatment tumor biopsy, 12-lead ECG, ECOG PS, laboratory assessments (laboratory assessments should be repeated if the last assessment is more than 7 days prior to the planned date for the first dose, and must be performed by the central laboratory), recording of concomitant medications/procedures and assessments of AEs from the time of consent, and tumor imaging to evaluate each subjects' eligibility for participation in the trial. A screening ICF must be obtained before any screening procedures.

#### *Phase Ib and Phase II*

Assessments include the following:

- Eligibility evaluation (review of inclusion/exclusion criteria);

- Demography (see Section 7.2) and height (cm);
- Medical history, including EGFR mutation status;
- Pretreatment tumor biopsy (see Section 7.6.1);
- Physical examination/weight (kg);
- ECOG PS (see Section 7.4.4.2);
- Vital signs (see Section 7.4.4.3);
- 12-lead ECG (see Section 7.4.4.4);
- Chest X-ray (not necessary if thoracic CT performed);
- Hematology and coagulation (see Section 7.4.3.1);
- Biochemistry (see Section 7.4.3.2);
- Urinalysis (see Section 7.4.3.3);
- Serum pregnancy test for female subjects of child bearing potential;
- Complete tumor assessment of all lesions by radiographic or other modality (using RECIST Version 1.1) based on CT/MRI of the chest, abdomen, and pelvis to evaluate disease in these locations. CT/MRI of the head will be performed for subjects who have or are suspected to have CNS metastases (see Section 7.3);
- AE assessment;
- Concomitant medications/procedures.

Randomization must be performed after all inclusion and exclusion criteria have been checked and patient eligibility has been confirmed. The study treatment should be given on the day of randomization or the day following the randomization day.

### 7.1.3 Treatment Period

**Phase Ib:** Tepotinib+gefitinib will be coadministered QD over a 21 day cycle until PD/intolerable toxicity/withdrawal from treatment.

**Phase II:** Subjects will be treated with either tepotinib+gefitinib QD or pemetrexed+cisplatin/carboplatin on Day 1 of each cycle (for up to 6 cycles or 4 cycles followed by pemetrexed maintenance). After completion of 4 cycles of pemetrexed+cisplatin/carboplatin, pemetrexed monotherapy may be given on Day 1 of the subsequent cycles at the Investigator's discretion. Treatment will discontinue upon PD, intolerable toxicity, withdrawal from the treatment, or, for subjects in the control arm not receiving pemetrexed maintenance only, the completion of up to 6 cycles of pemetrexed+cisplatin/carboplatin. In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Discontinuation of treatment beyond PD is at the discretion of the treating physician. If the subject develops new lesions or clinical symptoms, the benefit of continuing treatment with the study drugs should be discussed with the Sponsor. Please refer to Section 5.4.2.

For subjects in the control arm, weight, hematology, biochemistry, and ECG should be performed within 3 days prior to treatment administration except for Cycle 1, unless stated otherwise.

- In Phase Ib, assessments and visits within  $\pm 3$  day time frame is permitted beginning with Cycle 3.
- In Phase II, assessments and visits within  $\pm 3$  day time frame is permitted beginning with Cycle 2.

### 7.1.3.1 Cycle 1, Day 1

#### *Phase Ib*

On Cycle 1, Day 1, the following assessments/treatment administrations will be performed:

- Drug dispensation;
- Vital signs
- Physical Examination/weight; ECOG PS; hematology and coagulation; biochemistry; urinalysis (only if screening assessments were performed  $> 7$  days prior to Day 1);
- 12-lead ECG (predose [within 30 minutes prior to dose] and 4 hours  $\pm 12$  minutes postdose, 10 hours  $\pm 30$  minutes postdose, and 24 hours postdose [within 30 minutes prior to next dose]);
- PK blood samples (predose and 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose);
- Tumor biopsy (excluding fine needle aspiration and cytology samples) optional, for subjects which did not provide a second pass at screening time point (also optional) for confirmation of target inhibition;
- Exploratory markers in plasma (predose only);

CCI

- AE assessment;
- Concomitant medications/procedures.

#### *Phase II*

Assessments will include the same assessments as in Phase Ib but with the following changes:

- ECOG PS; hematology and coagulation; biochemistry; and urinalysis on Cycle 1, Day 1 will not be performed;
- Complete the QoL questionnaires prior to the initiation of any other trial activities (including RECIST Version 1.1 assessments) or active treatments, and prior to any contact with the Investigator (see Section 7.7) on Cycle 1, Day 1;
- 12-lead ECG (predose [within 30 minutes prior to dose] in the control (chemotherapy) arm, predose [within 30 minutes CCI] and 4 hours  $\pm 10$  minutes postdose [CCI] 4-hour postdose sampling] in subjects who

receive tepotinib+gefitinib); ECGs will be collected in triplicate at the predose and 4 hour time points;

**CCI**

### **7.1.3.2 Cycle 1, Day 2**

#### ***Phase Ib***

The following assessments and examinations will be performed:

- Physical examination/weight;
- Vital signs;
- Hematology and coagulation;
- Biochemistry;
- AE assessment;
- Concomitant medications/procedures.

#### ***Phase II:***

No assessments and examinations will be performed.

### **7.1.3.3 Cycle 1, Day 8**

#### ***Phase Ib and Phase II***

The following assessments will be performed on Cycle 1, Day 8:

- Physical examination/weight;
- Vital signs;
- Hematology and coagulation;
- Biochemistry;
- AE assessment;
- Concomitant medications/procedures.

### **7.1.3.4 Cycle 1, Day 15**

#### ***Phase Ib and Phase II***

The following assessments will be performed on Cycle 1, Day 15:

- Vital signs;
- Physical examination/weight;

- 12-lead ECG (predose [within 30 minutes prior to dose] and 4 hours  $\pm$  10 minutes postdose, 10 hours  $\pm$  30 minutes postdose, and 24 hours postdose [within 30 minutes prior to next dose] in Phase Ib; predose only [ECGs collected in triplicate within 30 minutes prior to dose] in Phase II);
- PK blood samples (predose and 0.25, 0.5, 1, 2, 4, 8, 10 and 24 hours postdose [Phase Ib only]);
- Tumor biopsy (excluding fine needle aspiration and cytology samples) for confirmation of target inhibition (optional);
- Hematology and coagulation;
- Biochemistry;
- AE assessment;
- Concomitant medications/procedures.

### 7.1.3.5 Cycle 2, Day 1

#### *Phase Ib*

The following assessments/treatment administrations will be performed on Cycle 2 Day 1:

- Drug dispensation;
- Physical examination/weight;
- Vital signs;
- 12-lead ECG (predose only [within 30 minutes prior to dose]);
- Exploratory markers in plasma (optional, predose only);
- Hematology and coagulation;
- Biochemistry;
- Urinalysis;
- ECOG PS;
- AE assessment;
- Concomitant medications/procedures.

#### *Phase II*

Assessments include all assessments in Phase Ib, but with the following changes:

- 12-lead ECG (predose [within 30 minutes prior to dose] in the control [chemotherapy] arm, predose [within 30 minutes CCI ] and 4 hours  $\pm$  10 minutes postdose [CCI 4-hour postdose sampling] in subjects who receive tepotinib+gefitinib); ECGs will be collected in triplicate at the predose and 4 hour time points;

- Sparse PK sampling (within 60 minutes prior to dose and 1.5 hours  $\pm$  10 minutes and 4 hours  $\pm$  10 minutes postdose after ECG collection in subjects who receive tepotinib+gefitinib).

### **7.1.3.6 Cycle 2, Day 8**

#### ***Phase Ib***

On Cycle 2, Day 8 in Phase Ib, the following assessments will be performed:

- Physical examination/weight;
- Vital signs;
- Hematology and coagulation;
- Biochemistry;
- AE assessment;
- Concomitant medications/procedures.

#### ***Phase II***

No assessments will be performed on Cycle 2, Day 8 in Phase II.

### **7.1.3.7 Cycle 2, Day 15**

#### ***Phase Ib***

On Cycle 2, Day 15 in Phase Ib, the following assessments will be performed:

- Physical examination/weight;
- Vital signs;
- Hematology and coagulation;
- Biochemistry;
- AE assessment;
- Concomitant medications/procedures.

#### ***Phase II***

No assessments will be performed on Cycle 2, Day 15.

### **7.1.3.8 Cycles $\geq$ 3, Day 1**

#### ***Phase Ib and Phase II:***

On Cycles  $\geq$  3, Day 1 in both Phase Ib and Phase II, the following assessments/treatment administrations will be performed:

- Phase II only: Complete the QoL questionnaires prior to the initiation of any other trial activities (including RECIST Version 1.1 assessments) or active treatments, and prior to

any contact with the Investigator (see Section 7.7), on Day 1 of odd numbered cycles (Cycles 3, 5, 7, 9, 11, 13, 15, 17 and every 4 cycles thereafter until PD).

- Drug dispensation;
- Physical examination/weight;
- Vital signs;
- ECOG PS;
- 12-lead ECG (predose only [within 30 minutes prior to dose]; starting at Cycle 3, then performed every third cycle [Cycle 6, 9, 12, etc.] or as clinically indicated);
- Exploratory markers in plasma (Day 1 of Cycles 2, 4, 6, 8, 10 and 12 predose only, in subjects signing separate ICF);
- Hematology and coagulation;
- Biochemistry;
- Urinalysis;
- AE assessment;
- Concomitant medications/procedures;
- Tumor Assessment: A complete tumor assessment of all lesions using RECIST Version 1.1 will be performed on Day 1 of odd-numbered cycles (Cycles 3, 5, 7, 9, 11, 13, 15, 17, and every 4 cycles thereafter until PD).

### 7.1.3.9 Treatment Beyond Progressive Disease

In individual cases, treatment beyond progression may be considered for subjects on tepotinib+gefitinib. Cases that may be considered for treatment beyond progression include subjects with slow (“smoldering”) progression after an initial partial response (PR)/complete response (CR), provided there are no clinical symptoms and no new lesions. If, in selected subjects, the Investigator wants to continue the treatment beyond progression although new lesion(s) have been documented, this must be discussed and agreed with the Sponsor, and documented in the appropriate designated eCRF section. The Investigator has to ensure that all data are collected as required for Cycles  $\geq 3$ , Day 1 (see Section 7.1.3.8), in the same manner as before progression, with the exception of the QoL questionnaires, which shall not be collected for this subject group, and tumor assessments. RECIST Version 1.1 radiographical assessment will follow institutional practice guidelines, however, tumor assessment information will not be recorded in the eCRF and there will be no further documentation collected for any new lesion and/or clinical symptoms of PD after first PD.

Discontinuation of treatment beyond PD is at the discretion of the treating physician. If the subject develops new lesions or clinical symptoms, the benefit of continuing treatment with the study drugs should be discussed with the Sponsor. Please refer to Section 5.4.2. For analysis of the primary endpoint, only the first progression event is used.

### 7.1.3.10 End-of-Treatment Visit

An End-of-Treatment visit should be conducted within 14 days of the last dose of study treatment, the completion of treatment cycle, or the day when it is determined to permanently

discontinue the study treatment. If the subject discontinues from the study at a scheduled visit, the End-of-Treatment assessment can be performed on that day. A subject will have an End-of-Treatment visit only if they withdraw from treatment with both components of the combination therapy.

Note, for Phase II part of the study, at the End-of-Treatment visit, prior to the initiation of any other trial activities (including RECIST Version 1.1 assessments) or active treatments, and prior to any contact with the Investigator, subjects will need to complete the QoL questionnaires (see Section 7.7).

The following assessments will be performed at the End-of-Treatment visit if the last assessments were performed > 7 days prior to the visit. These will include:

- Vital signs;
- Physical examination/weight;
- ECOG PS;
- 12-lead ECG;
- Hematology and coagulation;
- Biochemistry;
- Urinalysis.

Other Assessments should also be performed at the End-of-Treatment visit:

- Exploratory markers in plasma;
- Tumor biopsy (Optional, whenever possible, the biopsy taken at progression on the last day of drug application [excluding fine needle aspiration and cytology samples] for determination of the MET status and analysis of potential resistance marker should be taken from the progressing lesion, provided that the lesion is accessible and there are no medical or safety reasons precluding a biopsy of the progressing lesion);
- Tumor assessment (For subjects whose last tumor assessment was performed  $\geq 6$  weeks before Cycle 17 and  $\geq 12$  weeks afterwards prior to this visit and has no radiological PD in previous visits);
- AE assessment;
- Concomitant medications/procedures;
- QoL assessment (Phase II only).

## 7.1.4 Post-treatment Follow-up Visit

### 30-Day Safety Follow-Up Visit (Phase Ib and Phase II)

The 30-day Safety Follow-up visit will be performed  $30 \pm 3$  days after subject discontinues both components of study treatment even if the subject starts on a new anticancer therapy.

Note, for Phase II part of the study, at the End-of-Treatment visit, prior to the initiation of any other trial activities (including RECIST Version 1.1 assessments), and prior to any contact with the Investigator, subjects will need to complete the QoL questionnaires. Subjects who terminate

their treatment early will be encouraged to return to the clinic for the 30-day safety follow-up visit. The following assessments will be performed:

- Physical examination/weight;
- Vital signs;
- ECOG PS;
- 12-lead ECG;
- Hematology and coagulation;
- Biochemistry;
- Urinalysis;
- Serum pregnancy test (for female subjects of child bearing potential)
- AE assessment;
- QoL assessment;
- Concomitant medications/procedures.

Ongoing or new AEs judged to be related to any trial medication will be followed until the event has resolved to the baseline grade, becomes stable, the subject is lost to follow-up, the subject withdraws consent, or it has been determined that the study treatment is not the cause of the AE, even if new anticancer treatment is initiated.

### **Additional Follow-Up Visits (Phase Ib and Phase II)**

If a subject withdraws from the treatment for reasons other than PD, or, for subjects in the control arm not receiving pemetrexed maintenance only, the completion of up to 6 cycles of pemetrexed+cisplatin/carboplatin, tumor assessments will be performed every 6 weeks until Week 51 (Cycle 17) and every 12 weeks after Week 51 until radiologically documented PD, death, end of trial, or start of a new anticancer therapy, whichever occurs first.

Note, for Phase II part of the study, at the End-of-Treatment visit, prior to the initiation of any other trial activities (including RECIST Version 1.1 assessments), and prior to any contact with the Investigator, subjects will need to complete the QoL questionnaires

The following assessments should be performed:

- Tumor Assessment;
- Recording of any new anticancer therapy (a tumor assessment is mandatory before initiating the new therapy);
- QoL assessment.

A  $\pm$  7 day time window is permitted for additional follow-up visits until Week 51 then a  $\pm$  14 day time window is permitted thereafter.

### **Trial Procedure Termination**

Trial procedure termination could occur at the 30-day safety follow-up visit or at an additional follow-up visit, whichever comes later. The following information needs to be documented in

source documents, and will be recorded in the eCRF: the date of discontinuation from trial procedures, and the primary reason for discontinuation from trial procedures.

### 7.1.5 Survival Follow-up (Phase II Only)

Information about subject survival will be collected by telephone interview/clinic visit every 3 months  $\pm$  2 weeks until death or the end of the trial, whichever comes first. Any new anticancer therapy given to the subject until death should be recorded.

After discontinuation of survival follow-up, the Investigator must document the primary reason for a subject's discontinuation from the survival follow-up in source document and record it in the eCRF, accordingly. For subjects who are lost to follow-up, the Investigator should show due diligence by documenting in the source documents steps taken to contact the subject.

## 7.2 Demographic and Other Baseline Characteristics

Prior to the first dosing (Cycle 1, Day 1), all subjects will have Screening and Baseline examinations to ensure their eligibility. Before any examination, they will be informed about the trial aims, procedures, and possible risks of taking the study drugs and the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent, according to the procedure described in Section 9.2.

The following Screening and Baseline assessments will be performed:

- Demographics: including date of birth, race, and gender. Height will also be recorded.
- Medical History: The medical history will include:
  - The starting and ending dates or duration of the medical incidences;
  - Concomitant illnesses at screening, including chronic diseases or abnormal conditions;
  - Previous relevant illnesses;
  - Major relevant surgery not related to the cancerous condition, as well as other relevant prior procedures;
  - Smoking status.
- Oncology History: includes date of diagnosis, tumor type, histological type and location, tumor, lymph nodes, metastasis (tumor, lymph nodes, metastasis status) classification, staging information at the initial histological diagnosis, previous treatments (surgery, radiotherapy, and systemic therapies), current symptoms, and tumor involvement at the time of screening.
- Medication History of Oncology: includes the starting and ending dates of previous anticancer therapies, the best response to each treatment (including both prescription and over-the-counter medications) and other relevant tumor-related interventions.

## 7.3 Assessment of Efficacy

### Tumor Assessment (Tumor Response Assessment)

Tumor assessment will be performed according to RECIST Version 1.1 (see [Appendix C](#)).

The Baseline tumor assessment is scheduled to be performed during the Screening period (see Section 7.1.2).

Computed tomography or MRI with contrast enhancement is recommended for tumor assessment. Imaging studies, including CT or MRI of the chest, abdomen and pelvis must be performed at Baseline in order to survey metastasis. At Baseline, the organs with metastatic disease and target and non-target lesions should be documented. CT/MRI of the head for subjects suggestive of CNS metastasis can be performed at Baseline. The bone scan and/or positron emission tomography (PET) could be considered for subjects suggestive of bone metastasis at baseline or when suspecting any bone metastasis during the study, however CT/MRI scan must be used for tumor assessment at the Baseline and at subsequent visits. The bone scan or PET cannot be used for tumor assessment.

Tumor response evaluations will be assessed by CT or MRI and other modalities at the end of every 2 cycles (every 4 cycles after Cycle 17). If the treatment cycle in the control or experimental arm is delayed, the scheduled tumor assessment should not be delayed and should still be performed every 6 weeks before Week 51 and every 12 weeks afterwards. This should include a complete assessment of all target and non-target lesions. In case of symptomatic progression, subjects should be evaluated by imaging studies thereafter. A CT or MRI must also be performed at the End-of-Treatment visit if subject's last tumor assessment was performed  $\geq 6$  weeks before Cycle 17 and  $\geq 12$  weeks afterwards prior to this visit. Evaluation of lesions should be based on images obtained by either CT or MRI. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during the trial. If a chest X-ray indicates metastatic disease while the subject is enrolled in this trial, a CT or MRI of the chest is required for confirmation. The assessment provided by the same physician or radiologist is recommended during the study.

All measurements should be recorded in metric notation. Tumor assessment will be performed according to RECIST Version 1.1 as described in [Appendix C](#). In Phase Ib, tumor evaluations will be done by the Investigator and site radiologist.

For the determination of progression to evaluate PFS in the randomized part of Phase II, tumor evaluations will be done by the Investigator and site radiologist (as a primary endpoint) as well as by the IRC (as a secondary endpoint).

For the determination of progression to evaluate PFS in the single-arm cohort of Phase II, tumor evaluations will be done by the Investigator and IRC.

If a subject drops out of the trial for a reason other than PD or death, further tumor assessments will be performed and the information will be used for PFS and other assessments based on tumor progression.

Subjects who withdraw from the trial for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging. X-rays may only be taken for documentation of PD in case of clear evidence of PD on the chest X-ray, when CT or MRI are not feasible for medical reasons.

For subjects receiving treatment beyond PD, RECIST Version 1.1 radiographical assessment will follow institutional practice guidelines, however, tumor assessment information will not

be recorded in the eCRF and there will be no further documentation collected for any new lesion and/or clinical symptoms of PD after first PD.

## **7.4 Assessment of Safety**

The safety profile of trial treatments will be assessed through the recording, reporting and analyzing of baseline medical conditions, AEs, AESIs, DLTs, physical examination findings including vital signs, ECG, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed from the time of the subject's signature of informed consent throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

### **7.4.1 Adverse Events**

#### **7.4.1.1 Adverse Event Definitions**

##### **Adverse Event**

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In cases of 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/intensity of each AE by referencing the NCI-CTCAE, Version 4.0 (publication date: 28 May 2009), 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 a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following 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

According to Sponsor convention, 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 described below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as a 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 (for example, sudden death, unexplained death), the death per se might be reported as an SAE. Investigators must also systematically assess the causal relationship of AEs to trial treatment (tepotinib and/or gefitinib in Phase Ib and Phase II; cisplatin, carboplatin, and/or pemetrexed in Phase II) using the following definitions.

Decisive factors for the assessment of causal relationship of an AE to the trial treatments include, but may not be limited to, temporal relationship between the AE and the trial treatments, known side effects of trial treatments, medical history, concomitant medication, course of the underlying disease, and trial procedures.

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

**Related:** Reasonably related to the trial treatment. The AE could medically (pharmacologically/clinically) be attributed to the trial treatments under study in this clinical trial protocol.

### **Abnormal Laboratory Findings and Other Abnormal Investigational Findings**

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

### **Serious Adverse Event**

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

- Results in death;
- Is life-threatening;

NOTE: The term "life-threatening" refers to an event in which the subject 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 prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is otherwise considered as medically important.

(NOTE: 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 subject 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 trial treatment is also considered an SAE as described in Section 7.4.1.4.

### **Events that Do Not Meet the Definition of a SAE**

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (eg, an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, 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 trial visit that do not worsen in severity or frequency during the trial 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 patient's general condition is more severe than expected and/or unless the outcome is fatal within the AE reporting period (as defined in Section 7.4.1.3). However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs or reported as SAEs, if they meet criteria for seriousness.

### **AEs of Special Interest**

Subjects might experience asymptomatic elevations in serum pancreatic enzyme (lipase and amylase) and such enzyme elevations of Grade  $\geq 3$  are considered AESIs in this trial.

When such AESI is not serious, a specific AESI form should be filled at the site and the Sponsor must be notified immediately (within 24 hours). Reporting process of an AESI should follow the same process for reporting SAEs (see Section 7.4.1.4).

Should the AESI be serious, a SAE Report Form, instead of the AESI Form should be filled and the procedure for reporting SAEs (see Section 7.4.1.4) should be followed.

In addition to SAEs, all non-serious DLTs (Phase Ib) will be promptly reported by the Investigator using the AE section of the eCRF.

### 7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject 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 non-serious AESI must be additionally documented and reported using the appropriate Report Form as described in Section 7.4.1.4.

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

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor/designee.

### 7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent) and continues through the trial's post treatment follow-up period, defined as  $30 \pm 3$  days with a Safety Follow-up visit. If the "30-Day Safety Follow-up Visit" was not performed (eg, the subject could not come back to the site for a visit), a telephone interview should be performed to document any AEs that occurred in this time period.

Any SAE assessed as related to trial treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration of trial treatment.

### 7.4.1.4 Procedure for 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 24 hours after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone. In these cases, a written report must be sent immediately thereafter by fax or e-mail. The reporting procedures and timelines are the same for follow-up cases. Names, addresses, telephone and fax numbers for SAE reporting will be included in the trial specific SAE Report Form.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

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/designee and (as applicable) to allow the Sponsor/designee to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible monitor, although in exceptional circumstances the Global 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 non-serious AESI, the Investigator will complete the AESI Report Form and send it to the Sponsor/designee within 24 hours after becoming aware of the event. Names, addresses, telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs have to be reported in an expedited manner as SAEs as outlined above.

### **Dose Limiting Toxicities (Phase Ib)**

Each event meeting the criteria of a DLT (see Section 6.2.3) has to be recorded in the eCRF within 24 hours after becoming aware of the event. Serious DLTs have to be reported in an expedited manner as SAEs as outlined above.

#### **7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators**

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

Trials conducted in countries other than Japan:

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor/designee will inform the Investigator of “findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC’s/IRB’s approval/favorable opinion to continue the trial.” In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

Trials to be conducted in Japan:

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

In accordance with ICH GCP and the Japanese ministerial ordinance on GCP, the Sponsor/designee will immediately inform all the trial Investigators and the Heads of the trial sites of “findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IRB’s approval/favorable opinion to continue the trial.” In particular and in line with respective applicable regulations, the Sponsor/designee will immediately inform all the trial Investigators and the Heads of the trial sites of AEs that are both serious and unexpected and are considered to be related to the administered product (“suspected unexpected serious adverse reactions” or SUSARs). In addition, according to applicable regulations, the Sponsor/designee will inform the trial Investigators and the Heads of the trial 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 trial site should also maintain copies of safety reports appropriately.

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 by the Sponsor/designee 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 trials 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.

#### **7.4.1.6 Monitoring of Subjects with Adverse Events**

AEs are recorded and assessed continuously throughout the study and are assessed for final outcome at the Post-treatment Follow-up Visit (30-Day Safety Follow-Up Visit). All SAEs and AESIs ongoing at the “30-Day Safety Follow-Up Visit” must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject 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.

#### **7.4.2 Pregnancy and In Utero Drug Exposure**

Only pregnancies considered by the Investigator as related to trial treatment (eg, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

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

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 subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

### 7.4.3 Laboratory Assessments

Samples will be sent to a central laboratory for analysis, and these values will be imported into the eCRF on a regular basis. The Investigator may also use local laboratory results for safety evaluations and real time individual dose adjustments. If clinically significant discrepancies or differences are deemed necessary to repeat a test at the Investigator's discretion, the follow-up testing must be done by the central laboratory.

It is essential that the Sponsor/designee be provided with a list of laboratory normal ranges before shipment of the trial drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the Sponsor/designee. An amount of blood volume for laboratory assessments is shown in [Appendix F](#).

#### 7.4.3.1 Hematology and Coagulation

Hematology and coagulation assessments, as described in [Table 7.1](#), will be performed during the course of this trial including the screening period (3 mL of blood for blood counts plus 4.5 mL for coagulation tests for a total of 7.5 mL).

**Table 7.1 Hematology and Coagulation Parameters**

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

Abbreviations: aPTT, activated partial thromboplastin time; Hb, hemoglobin; Hct, hematocrit; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cells; WBC, white blood cells.

### 7.4.3.2 Biochemistry

Biochemistry assessments, as described in [Table 7.2](#), will be performed during the course of this trial including the screening period.

**Table 7.2 Biochemistry Parameters**

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

- a. If calculated creatinine clearance during screening is < 60 mL/min, then 24-hour urine creatinine clearance might be requested by the Investigator for confirmation of renal impairment; must be performed at the central laboratory.

### 7.4.3.3 Urinalysis

Urinalysis assessments (dipstick) for Phase Ib and Phase II are presented in [Table 7.3](#). The dipstick urinalysis will be followed by microscopic examination if abnormal results are obtained.

**Table 7.3 Urinalysis Parameters**

Parameter
Blood
Glucose
Ketones
Leukocytes
Nitrites
pH
Proteins

## 7.4.4 Vital Signs, Physical Examinations, and Other Assessments

### 7.4.4.1 Physical Examinations

The physical examination will be identical to a general medical check-up comprising a whole body inspection (general appearance, skin/subcutaneous tissue, head, eyes, ears, nose, throat, neck, thyroid, respiratory, cardiovascular, peripheral vascular, lymphatic, lymph nodes/immunology, abdomen, musculoskeletal, neurological and psychiatric, palpation, percussion, and auscultation. Body weight (kg) should be recorded prior to treatment administration of chemotherapy. Any clinically significant abnormal findings or worsening of conditions previously recorded in the medical history must be documented in the eCRF.

### 7.4.4.2 ECOG PS

ECOG PS will be assessed according to the criteria described in [Appendix D](#), at the times described in [Appendix A](#) and [Appendix B](#).

### 7.4.4.3 Vital Signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (°C) will be measured in the study. SBP and DBP should be measured in seated position after 5 minutes resting (for individual subjects, measurements at different visits should be taken in the same position). On days when ECGs are also performed, vital signs should be taken after sitting for 5 minutes and immediately prior to each ECG recording.

### 7.4.4.4 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested at least for 5 minutes in a supine position. At least 5 to 7 beats for each lead run. All ECGs are taken in triplicate with up to 2 minutes between each ECG, immediately after measurement of vital signs, to monitor the heart rhythm and PR, QRS, QT, RR, and QTc intervals. For both phases of the study, QTc intervals will be corrected using Fridericia's formula (QTcF). For Phase II, QTc will be calculated in eCRF. Results of the ECG recordings will be included in the subject's eCRF.

## 7.5 Pharmacokinetics

For Phase Ib, plasma concentrations of tepotinib and gefitinib will be obtained on Day 1 and Day 15 of Cycle 1. Samples will be taken predose and at 0.25, 0.5, 1, 2, 4, 8, 10, and 24 hours postdose (the 24 hour postdose is equivalent to predose on Day 2 and Day 16, respectively). Altogether 4 mL (2 mL for tepotinib and 2 mL for gefitinib) of whole blood will be collected for each PK time point.

CCI



For both Phase Ib and Phase II, the plasma concentration of tepotinib will be determined by a validated liquid chromatography-tandem mass spectrometry method. The validation of the method will be presented separately.

In Phase Ib, the plasma concentration of gefitinib will be determined by a validated liquid chromatography-tandem mass spectrometry method. The validation of the method will be presented separately.

A laboratory manual will provide detailed instructions on proper sample collection, centrifugation, and further processing to plasma, storage, and shipment of PK samples. The eCRF will contain provisions for recording the protocol-specified nominal time of each specimen, as well as the actual time and date that the specimen was obtained. Recording of the test results in the eCRF is not required.

### 7.5.1 Body Fluids

All predosing samples should be taken within 60 minutes before each treatment administration.

In Phase Ib, whole blood (2 mL samples) will be collected in ethylenediamine tetracetic acid-coated tubes for tepotinib PK samples, and whole blood (2 mL samples) will be collected in heparin-coated tubes for gefitinib PK samples. In Phase II, whole blood (2 mL samples) PK samples will be taken for tepotinib only.

Details about the tumor and blood sampling and processing procedures, storage, and transportation will be provided in a separate laboratory manual. Values and changes over time in Pd and screening markers will be assessed during the trial. Sampling time points of blood samples are presented in [Appendix A](#) (Phase Ib) and [Appendix B](#) (Phase II) and detailed in [Appendix F](#). Blood sample volumes are presented in [Appendix G](#).

### 7.5.2 Pharmacokinetic Calculations

The following PK parameters will be calculated and summarized from the measured individual plasma concentrations of tepotinib and gefitinib using non-compartmental methods.

- $C_{max}$ : observed maximum plasma concentration;
- $t_{max}$ : time to reach maximum plasma concentration;
- $\lambda_z$ : apparent terminal rate constant determined by log-linear regression analysis of the measured plasma concentrations of the terminal log-linear phase;
- $t_{1/2}$ : apparent terminal half-life, calculated by  $\ln 2/\lambda_z$ ;
- $AUC_{0-\infty}$ : area under the plasma concentration versus time curve from time zero to infinity.  $AUC_{0-\infty}$  will be calculated by combining area under the curve from time zero to time  $t$  ( $AUC_{0-t}$ ) and area under the curve excreted ( $AUC_{extra}$ ).  $AUC_{extra}$  represents an extrapolated value obtained by  $C_{last}/\lambda_z$ , where  $C_{last}$  is the calculated plasma concentration at the last sampling time point at which the measured plasma concentration is at or above the lower limit of quantification (LLQ). If the value of  $AUC_{extra}$  provides more than 20% of  $AUC_{0-\infty}$ , this parameter and all related parameters (eg, total body clearance of drug [CL] and volume of distribution associated to the terminal phase [ $V_z$ ]) will be rejected as implausible and not included for further statistical analysis;

- $AUC_{0-t}$ : area under the plasma concentration versus time curve from time zero to the last sampling time (ie, t) at which the concentration is at or above the LLQ.  $AUC_{0-t}$  will be calculated according to the mixed log-linear trapezoidal rule;
- $AUC_{0-\tau}$ : area under the plasma concentration versus time curve within 1 dosing interval.

Further derived PK parameters will be calculated, when appropriate:

- CL/F: apparent body clearance of the drug from plasma,  $CL = Dose/AUC_{0-\infty}$ ;
- $V_z/F$ : apparent volume of distribution associated to the terminal phase, calculated by  $Dose/(AUC_{0-\infty} * \lambda_z)$ ;
- $V_{ss}/F$ : volume of distribution at steady state, CL, mean resident time.

The PK evaluation shall be carried out under the responsibility of the Sponsor.

The PK variables will be analyzed descriptively for each treatment and administration separately. Descriptive statistics include number of subjects, arithmetic mean, geometric mean, standard deviation (StD), standard error of the mean, median, minimum, maximum and coefficient of variation (CV in %). The drug concentration in plasma at each sampling time will be presented on the original scale for all subjects who participated in the trial. Values below LLQ will be taken as zero for descriptive statistics of concentrations. Individual plasma concentration-time profiles (linear and semi-logarithmic scale) will be plotted by treatment. Mean plasma concentrations per treatment and administration will be plotted with StD using schedule time points. The weight-normalized PK parameters will be calculated if it would be appropriate.

Formal statistical hypotheses will not be performed. All statistical tests will be performed in an explorative way. All analyses will be based on the PK analysis set. Details of the statistical analyses will be described in the SAP.



## 7.6 Biopsies, Biomarkers, and Pharmacogenomics

Details about the tumor and blood sampling and processing procedures, storage, and transportation will be provided in a separate laboratory manual. Values and changes over time in Pd and stratification markers will be assessed during the trial. Sampling time points of blood samples for PK/Pd are detailed in [Appendix F](#). The storage period of tumor tissue and blood

will be up to 12 years after the end of the trial. During this time, it is possible that the samples/data/medical information will be re-analyzed for meta-analyses, post hoc analyses, or other investigations in the scope of the project by the Sponsor. After this period, the samples will be destroyed by the Sponsor.

## 7.6.1 Tumor Biopsies

### Pretreatment Biopsy

A pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples) is mandatory in both the Phase Ib and Phase II parts.

For the Phase Ib, tumor tissue will be collected for MET status diagnosis. For subjects who experienced at least 1 anticancer treatment, the biopsy should be obtained between failure of the most recent anticancer treatment and enrollment.

For the Phase II, tumor tissue will be collected for MET status diagnosis, T790M mutation status determination (if no documented result is already available), as well as EGFR mutation status confirmation (if no documented result is already available). The new biopsy should be obtained between documentation of acquired resistance to first-line gefitinib, erlotinib, icotinib, or afatinib and enrollment.

Whenever possible, the biopsy taken for determination of the MET status should be taken from the progressing lesion (primary or metastatic, whichever applies), provided that the lesion is accessible and there are no medical or safety reasons precluding a biopsy of the progressing lesion. Samples must be sent to the central laboratory prior to enrollment.

For pretreatment biopsy, 8 to 10 formalin-fixed paraffin-embedded (FFPE) sections ( $\geq 10\%$  viable tumor cells) or paraffin block with tumor tissue (preferable) are required, the minimal number of required sections will be re-evaluated after the Phase Ib. For subjects without documented EGFR mutation in the Phase II part, 10 to 15 FFPE sections are required.

### Optional Biopsies

The optional biopsies (excluding fine needle aspiration and cytology samples) include:

- Additional pretreatment biopsy second pass in screening period or pre-dose on Cycle 1, Day 1;
- On-treatment biopsy;
- End-of-Treatment biopsy.

Paired tumor biopsies are not mandatory, but highly recommended for subjects with accessible tumors (highest priority in Phase Ib). Paired tumor biopsies should be taken before the treatment period (preferentially as second pass when biopsy for screening purposes is taken) and during the treatment period (can be taken any time between Cycle 1, Day 15 and the beginning of Cycle 3). If a tumor shows progression after initial response to tepotinib+gefitinib, a third biopsy is highly desirable when progression is diagnosed at the End-of-Treatment visit (highest priority in Phase II).

For all subjects of Phase Ib and Phase II, the feasibility of a paired biopsy and End-of-Treatment biopsy should be regularly reviewed and any reasonable effort should be made to obtain these additional biopsies.

Analysis of MET status and related markers will be performed on the tumor samples after consent has been obtained from the subjects. Tumor biopsies will be performed for analysis of specific markers (see Section 7.6.2).

## 7.6.2 Tumor Tissue Biomarkers

The pretreatment tumor biopsies (excluding fine needle aspiration and cytology samples) will be assessed to investigate the following:

### 1) Selection biomarkers for both Phase Ib and Phase II: MET+ (cMET IHC for phase IB and cMET IHC and cMET FISH for the phase II)

MET+ status is based on:

c-Met overexpression determined by cMET IHC (IHC 2+ and IHC 3+)

and/or

Alterations of cMET gene copy numbers as determined by cMET ISH (ratio MET/CEN7  $\geq$  2.0 and/or GCN  $\geq$  5).

cMET protein overexpression will be tested prospectively in Phase IB and Phase II.

c-Met amplification will be tested retrospectively in Phase Ib and prospectively in Phase II; technical details are specified in the laboratory manual.

### 2) Selection biomarkers for Phase II: Absence of the EGFR T790M mutation.

T790M negative, MET+ subjects will be enrolled into the 2-arm randomized Phase II part of the trial and treated either with tepotinib + gefitinib or pemetrexed + cisplatin/carboplatin.

In mainland China, an additional single-arm cohort of n=15 T790M positive, MET+ subjects will be enrolled and treated with tepotinib + gefitinib.

The EGFR T790M mutation status will be assessed by a central laboratory, using a validated PCR test. Technical details are specified in the laboratory manual.

### 3) Exploratory biomarkers

They will include, but will not be limited to, markers of c-Met pathway activation (eg, HGF levels, c-Met mutations), and other relevant oncogenic pathways.

## 7.6.3 Blood Biomarkers

Blood samples (20 mL) will be collected at pre-treatment, concurrent with treatment Cycles 1, 2, 4, 6, 8, 10, 12, as well as at the EOT visit. Blood samples will be obtained at tumor assessment visits.

The aim of this sampling regimen is to facilitate molecular monitoring to study the relationship between molecular disease progression and clinical progression, a well-known benefit of the liquid biopsies. Liquid biopsy based molecular monitoring could be utilized as the basis for clinical decision making in the future to greatly improve subjects' treatment by reducing biopsy requirements.

Samples will be processed as appropriate or stored for exploration of potential new biomarkers based on future research or for new stratification biomarker identification by new technologies.

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## 7.7 Health Related Quality of Life Assessments

All subjects in Phase II are required to take part in all PRO assessments. The LCSS (see [Appendix K](#)), EORTC QLQ-C30 (see [Appendix L](#)), and CCI [REDACTED] will be completed by the subject before any procedures are performed, and at the time points noted in the Schedule of Assessments described in Section 7.1 and [Appendix B](#). Only countries/centers where validated local language(s) version of the subject scale of the questionnaires are available, will take part in the PROs assessments.

The Sponsor will provide training for relevant personnel (eg, key Investigators, clinical research assistants) in the administration of the questionnaires, so that subjects fill in the questionnaires as completely and accurately as possible. It is important that the significance and relevance of the data are explained carefully to participating subjects so that they are motivated to comply with data collection (25).

Questionnaires will be handed to the subject and should be completed at the investigational center, in approx. 20 to 30 minutes, prior to the initiation of any other trial activities or active treatments and prior to any contact with the Investigator. Efforts should be made at the investigational center (eg, by nominating a nurse) to ensure that fully completed questionnaires are obtained from every subject at each scheduled time point, so as to not delay any clinical assessments.

The measures are self-reported and the subject must complete the questionnaires in person and should not be given help from relatives/friends or clinic staff; help in interpreting the questions is not allowed. Subjects will be asked to fill in the questionnaires as completely and accurately as possible.

In case local regulations stipulate requirements regarding confidentiality of questionnaire completion (ie, completed questionnaires not to be seen by the clinic staff), all appropriate arrangements will be made at the investigational center to ensure confidentiality.

### 7.7.1 Lung Cancer Symptom Scale

The LCSS is a validated questionnaire consisting of an observer scale and a subject scale ([Appendix K](#)) used to specifically measure symptom changes relevant to QoL for individuals

undergoing treatment for lung cancer (26, 27, 28). In this trial, the subject scale will be used as a tool to help to determine TTSP. The 9-item questionnaire used to document subject-reported outcomes for a variety of lung cancer associated symptoms will be used in this trial. The data derived provides a level of detail in determining clinical benefit that is unavailable from the review of other endpoints.

The average symptomatic burden index (ASBI) will be used to determine differences in the two treatment arms in the randomized part of Phase II and to evaluate subjects in the single-arm cohort. The ASBI is the mean of all six symptom scores treated as a single domain. TTSP will be defined as an increase (worsening) of the ASBI score of 10% of the scale breadth (10 mm on a scale of 0-100 mm) from the baseline score.

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

### 7.7.2 EORTC QLQ-C30

The EORTC QLQ-C30 (Appendix L) is a questionnaire developed to assess the QoL of cancer subjects. The EORTC QLQ-C30 (Version 3.0) is available in 81 languages and has been used in trials worldwide. It is cancer specific and consists of 5 functional scales (physical, role, cognitive, emotional, social), 4 symptom scales (fatigue, pain, nausea, vomiting), a global health status scale, and several single items (including dyspnea, loss of appetite, and insomnia). The questionnaire consists of 30 multiple choice questions.

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## 8 Statistics

### 8.1 Sample Size

In Phase Ib, the total number of subjects in the “3+3” dose escalation cohorts is approximately 15 to 18, on the basis of the “3+3” dose escalation method with 2 dose cohorts: 3 or 6 in the dose escalation cohort and a potential for 3 or 12 subjects in dose confirmation cohort (if dose de-escalation does not occur). The final sample size depends on the number of subjects who experience DLTs at each dose level, safety and emerging available PK data and decision from the SMC meeting. In addition, separately from the “3+3” dose escalation cohorts, up to an additional 3 evaluable subjects will be enrolled in the mainland China sites.

In the randomization part of Phase II, the initial sample size planning required 111 PFS events (assessed by Investigator) to ensure 80% power with a two-sided significance level of 10% for rejecting the null hypothesis of equal treatment effect between treatment arms, assuming a true hazard ratio of 0.6. Assuming a median PFS time of 5 months in the control arm, a hazard ratio of 0.6 represents a 3.3 months increase, resulting in a median PFS time of 8.3 months for the experimental arm. With other assumptions: 1) accrual period of 39 months and follow-up period of 9 months; 2) randomization ratio of 2:1 (experimental vs. control arm); 3) overall drop-out rate of ~15%; 4) 1 non-binding futility analysis with futility boundary  $\alpha_0 = 0.81$  was planned to be performed after observation of 50% of PFS events. A total of approximately 156 subjects were planned to be randomized to receive tepotinib+gefitinib or pemetrexed+cisplatin/carboplatin. From study start to approval of Protocol Version 7.0, subjects were randomized at a 1:1 ratio to receive either tepotinib+gefitinib or pemetrexed+cisplatin. From the approval of Protocol Version 7.0 onwards, subjects were randomized at a 2:1 ratio to receive either tepotinib+gefitinib or pemetrexed+cisplatin. The Sponsor subsequently decided to halt enrollment. The sites were notified about the enrollment halt on 25 May 2017. The last subject was randomized on 12 June 2017. Until then 55 subjects had been randomized.

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

By the time of the enrollment halt, all 15 subjects with MET+ T790M positive NSCLC had been enrolled.

### 8.2 Randomization

Randomization will only occur in the randomized part of Phase II and has been performed centrally by using an IVRS.

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

- Type of MET+: protein overexpression IHC2+ vs. protein overexpression IHC3+ vs. gene amplification and/or increased c-Met GCN, both by ISH.
- Prior EGFR-TKI treatment: Gefitinib vs. erlotinib vs. icotinib vs. afatinib.

Please note that subjects with the co-existence of protein over expression and gene amplification and/or increased c-Met GCN were included in the amplification and/or increased c-Met GCN stratum.

## 8.3 Endpoints

### 8.3.1 Primary Endpoints

The primary endpoints are:

Phase Ib:

- Incidence of subjects experiencing at least 1 DLT in Cycle 1 (ie, 21 days after the first dose of trial medication);
- Incidence and type of other AEs.

Phase II:

- PFS assessed by Investigator in the randomized part of Phase II. PFS time is defined as the time (in months) from randomization to either the first observation of documented PD per RECIST Version 1.1 (as assessed by the Investigator) or occurrence of death due to any cause, whichever is latest, within 84 days of either randomization or the last tumor assessment.

Tumor assessments are performed according to RECIST Version 1.1 (see [Appendix C](#)).

### 8.3.2 Secondary Endpoints

The safety endpoints will comprise:

- Drug exposure;
- Incidence and type of TEAEs, toxicity grades as per NCI-CTCAE (Version 4.0); treatment-related TEAEs, SAEs, treatment-related SAEs, TEAEs with toxicity Grade  $\geq 3$ , treatment-related TEAEs  $\geq 3$ , and TEAEs leading to permanent treatment discontinuation;
- Incidence and reasons for deaths within 30 ( $\pm 3$ ) days after the last dose of study drug;
- Safety laboratory tests graded by NCI-CTCAE (Version 4.0);
- Vital signs, 12-lead ECG changes, physical examination, including change in body weight, and ECOG PS.

Other secondary endpoints include:

- PFS assessed by IRC in the randomized part of Phase II. PFS time is defined as the time (in months) from randomization to either the first observation of documented PD per RECIST Version 1.1 (as assessed by an IRC) or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment;
- PFS assessed by Investigator and IRC in single-arm cohort of Phase II. PFS time is defined as the time (in months) from the first administration of the trial treatment to either the first observation of documented PD per RECIST Version 1.1 (as assessed by the Investigator and IRC) or occurrence of death due to any cause within 84 days of either the first administration of the trial treatment or the last tumor assessment.
- OS time: OS time is defined as the time (in months) from randomization/the first administration of the trial treatment to the date of death in the randomized part of Phase II/ the single-arm cohort of Phase II;
- Tumor response as measured by objective response (OR) and disease control based on RECIST Version 1.1. OR is defined as CR or PR as the best overall response according to local radiological assessments from randomization/the first administration of the trial treatment to the first observation of PD. Responses do not require confirmation according to RECIST Version 1.1; disease control is defined as CR, PR, or SD as the best overall response according to local radiological assessments from the date of randomization/the first administration of the trial treatment to the first observation of PD. In the case of SD, measurements must have met the SD criteria at least once after entry at a minimum interval of 42 days after randomization/the first administration of the trial treatment;
- PK (Phase Ib only):  $AUC_{0-t}$ ,  $AUC_{0-\tau}$ ,  $C_{max}$ , average plasma concentration ( $C_{avg}$ ), minimum concentration ( $C_{min}$ ),  $t_{max}$ ,  $AUC_{0-\infty}$ ,  $CL/F$ ,  $V_z/F$ ,  $V_{ss}/F$ ,  $\lambda_z$  and  $t_{1/2}$  (when appropriate);
- Health related quality of life (HRQoL) endpoints (Phase II only) will be assessed using EORTC QLQ-C30 (Version 3.0) and TTSP as measured by LCSS.

### 8.3.3 Exploratory Endpoints

Exploratory endpoints in this trial are:

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- Exploratory biomarkers include biomarkers that may correlate with antitumor activity, including, but not limited to, markers of c-Met pathway activation (eg, HGF levels, and c-Met mutations), other relevant oncogenic pathways.

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## 8.4 Analysis Sets

- All Screening Analysis Set:

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

- DLT Analysis Set (Phase Ib part only):

The DLT Analysis Set includes all subjects who experienced a DLT during Cycle 1, or did not experience a DLT, and completed at least 80% of planned treatment during the DLT observation period (21 days after the first dose administered). Subjects who have been replaced during the Cycle 1 will be excluded from the DLT Analysis set (for replacement criteria, see Section 5.6).

The DLT Analysis Set will be used for evaluation of the number of subjects experiencing any DLTs at the end of each cohort and for the assessment of the RP2D in Cycle 1. Subjects who have been replaced during the Cycle 1 or who belong to the additional cohort for subjects from the mainland China sites will be excluded from the DLT analysis set (for replacement criteria, see Section 5.6).

- Safety Analysis Set:

In Phase Ib, the Safety Analysis Set includes all subjects who have received at least 1 dose of tepotinib or gefitinib. Subjects replaced for evaluation of DLT and subjects who are from mainland China sites will still be included in the Safety Analysis Set if they are treated at least once (ie, the above criteria is met).

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

In Phase Ib and Phase II, the Safety Analysis Set will be used for all summaries of safety data. Subjects will be allocated as treated.

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

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

The ITT Analysis Set consists of all subjects in randomized part of Phase II who were randomized to study treatment. Subjects will be allocated as randomized.

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

- QoL evaluable population (Phase II only):

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

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

- Subgroups of interest:

Other subgroups are considered to be of interest to explore the treatment effect of tepotinib+gefitinib in an exploratory manner. These could include (depending on the actual size of the subgroups):

- Age: < 65 years vs. ≥ 65 years;

- Gender: male vs. female;
- Type of MET: protein overexpression IHC2+ vs. protein overexpression IHC3+;
- Type of MET: gene amplification and/or increased c-Met GCN by ISH vs. neither gene amplification nor increased c-Met GCN;
- Histological subtype: adenocarcinoma vs. non-adenocarcinoma;
- Smoking history: never smokers vs. ever smokers.

- PK Analysis Set:

All subjects who have received at least 1 dose of the tepotinib or gefitinib and who have provided at least 1 plasma concentration measurement of tepotinib or gefitinib after the first dose.

- Pd Analysis Set:

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

## 8.5 Description of Statistical Analyses

### 8.5.1 General Considerations

As this study has 2 components, with 2 different objectives that will be investigated at different stages, the SAP will evolve over time to address the trial reporting needs.

Statistical analyses of the Phase Ib data will be carried out in a descriptive manner whereas Phase II has a confirmatory component when analyzing PFS time.

Statistical analyses will be performed using eCRF data in general. In Phase Ib, data will be analyzed after 21 days dosing of the last subject. The DLT population is the underlying data set for the MTD determination. In Phase Ib and Phase II, safety analyses will be performed according to the as-treated principle. Safety data will be descriptively analyzed on the Safety Analysis Set. AEs will be coded according to the current Medical Dictionary for Regulatory Activities (MedDRA) and reported by system organ class (SOC) and preferred term. The severity of AEs will be graded using NCI-CTCAE (Version 4.0) toxicity grades.

In Phase Ib and single-arm cohort of Phase II, efficacy analyses will be performed on the safety population. Safety Analysis Set will be primarily used in the analysis of baseline characteristic and efficacy. In the randomization part of Phase II, the analysis of efficacy endpoints in the ITT population requires a clinical cut-off date, which is determined by the date after the required number of events for the primary endpoint has been reported.

In randomized part of Phase II, the ITT Analysis Set will be primarily used in the analysis of baseline characteristic and efficacy. Analyses on ITT population will consider subjects' allocation to treatment arms as randomized.

In order to provide overall estimates of treatment effect, data will be pooled across centers. The factor center will not be considered in statistical models or for subgroup analyses because of high number of participating centers and the anticipated small number of subjects randomized in each center.

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

Continuous variables will be summarized using descriptive statistics, ie, number of subjects, mean, median, StD, 25<sup>th</sup> and 75<sup>th</sup> percentiles (Q<sub>1</sub>, Q<sub>3</sub>), minimum and maximum values. CIs will be presented where appropriate.

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

In general, in the randomized part of Phase II, the last measurement prior to or on the day of randomization will serve as the baseline measurement. In the Phase Ib and single-arm cohort of Phase II, the last measurement prior to or on the day of the first administration of the trial treatment will serve as the baseline measurement.

The primary analysis of the Phase II part will be conducted once all subjects have either been treated for at least 6 months, died or have prematurely discontinued trial treatment for any reason, whichever comes first.

The final analysis will be conducted once the last subject discontinued treatment and completed the subsequent safety follow-up visit.

Details of the statistical analyses will be defined in the SAP.

### **8.5.1.1 Protocol Deviations**

All protocol deviations, including inclusion/exclusion criteria violations and deviations during the trial, will be listed, even if they are believed not to influence any of the results. The SMC/IDMC meetings will evaluate potential protocol deviations that could affect the MTD/RP2D determination (Phase Ib) and Phase II. The definition of protocol deviations will be specified in the SMC/IDMC's charter or in the SMC/IDMC's SAP.

### **8.5.1.2 Missing Data**

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

Incomplete AE-related dates will be handled as follows:

- In case the onset date is completely missing or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of study treatment then the onset date will be replaced by the minimum of start of study treatment and AE resolution date;
- In all other cases the missing onset day or onset month will be replaced by 1;

- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date;
- In all other cases the incomplete stop date will not be imputed.

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

In individual subject data listings the documented date as given in the eCRF will be reported. If applicable, imputed values will be presented, and the imputed information will be flagged.

## **8.5.2 Analysis of Primary Endpoints**

### **8.5.2.1 Statistical Analysis of the Dose Escalation Cohort**

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

For final statistical analysis, the number and proportion of subjects in the DLT population who experienced DLT during the Cycle 1 of treatment with tepotinib+gefitinib will be presented by dose level. Subject disposition will be reported for each dose level, and subject profiles will be presented.

Listings and graphics of information which is relevant to the primary endpoint will be prepared for the SMC, for the purpose of determination of the MTD/RP2D of tepotinib+gefitinib, according to the content agreed and specified in the SMC's charter.

The MTD/RP2D will be determined as described in Section 6.2.1.

### **8.5.2.2 Statistical Analysis of Primary Endpoint of Phase II**

The primary endpoint of the randomized part of Phase II in this study is PFS as assessed by Investigator/site radiologist according to RECIST Version 1.1. PFS (assessed by Investigator/site radiologist) time is defined as the time (in months) from randomization to either the first observation of documented PD per RECIST Version 1.1 or death in T790M negative, MET+ subjects due to any cause within 84 days of either randomization or the last tumor assessment. If no progression or death is observed, or if death without previously documented PD is observed after more than 84 days of last tumor assessment without progression, the PFS time will be censored on the date of last tumor assessment or date of randomization, whatever occurs later. The 84-day time window represents 2 scheduled tumor assessments.

The primary analysis will test the equality of PFS time between treatment arms in the randomized part of Phase II, based on the ITT population, applying a two-sided stratified log-rank test at a significance level of  $\alpha = 10\%$ , taking into account for the strata used for randomization, ie, type of MET+ and prior EGFR-TKI.

The following null hypothesis is tested:

$$H_0: \lambda_A(t) = \lambda_B(t) \text{ versus } H_1: \lambda_A(t) = \theta \lambda_B(t), \theta \neq 1,$$

where  $\lambda(t)$  represents the hazard at time  $t$  and  $\theta$  the unknown constant of proportionality of hazards in the allocated treatment arms in the randomized part of Phase II (experimental and control arms).

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

Kaplan-Meier survival curves (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the corresponding two-sided 90% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (30), and CI for the survival function estimates at above defined time points will be derived directly from the Kaplan-Meier estimates. The estimate of the standard error will be computed using Greenwood's formula.

### 8.5.3 Analysis of Secondary Endpoints

#### 8.5.3.1 Progression-free Survival

In randomized part of Phase II, progression-free survival time (assessed by IRC) is defined as the time (in months) from randomization to either the first observation of PD or occurrence of death due to any cause within 84 days of either randomization or the last tumor assessment. If no progression or death is observed, or if death without previously documented PD is observed after more than 84 days of last tumor assessment without progression, the PFS time will be censored on the date of last tumor assessment or date of randomization, whatever occurs later. The 84-day time window represents time between 2 scheduled tumor assessments.

The same survival analysis methods will be employed as for the primary endpoint, PFS assessed by Investigator, PFS assessed by IRC will be further explored considering pre-defined subgroups (see Section 8.4).

In the single-arm cohort of Phase II, progression-free survival time (assessed by Investigator and IRC) is defined as the time (in months) from the first administration of the trial treatment to either the first observation of PD or occurrence of death due to any cause within 84 days of either the first administration of the trial treatment or the last tumor assessment. If no progression or death is observed, or if death without previously documented PD is observed after more than 84 days of last tumor assessment without progression, the PFS time will be censored on the date of last tumor assessment or date of the first administration of the trial treatment, whatever occurs later. The 84-day time window represents time between 2 scheduled tumor assessments.

For PFS time in T790M positive, MET+ subjects (single-arm cohort of Phase II), it will be presented in subject listings and analyzed using the Kaplan-Meier method in the safety analysis set.

### 8.5.3.2 Overall Survival (Phase II only)

In randomized part of Phase II, a preliminary analysis on OS may be performed when PFS, as assessed by Investigator is analyzed. Final OS analysis will be carried out when death has been reported in at least two-thirds of subjects.

Overall survival will be measured as the time (in months) between the date of randomization and the date of death. The analysis will be performed on the basis of the ITT population. OS time (in months) is defined as:

$$(\text{date of death or last date known to be alive} - \text{date of randomization} + 1)/30.4375.$$

For subjects not known to be deceased at time of analysis, the time between date of randomization and date of last contact or date of lost to follow-up, will be calculated, and used as a censored observation in the analysis. If this date is after the data cut-off, then the subjects will be censored at the date of data cut-off.

Treatment arms will be compared, based on ITT population, applying two-sided stratified log-rank test at a significance level of  $\alpha = 10\%$  taking into account for strata used for randomization, type of MET+ and prior EGFR-TKI.

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

In the single-arm cohort of Phase II, OS will be measured as the time (in months) between the date of the first administration of the trial treatment and the date of death. The analysis will be performed on the basis of the Safety Analysis Set.

Furthermore, OS time in subjects from the single-arm cohort of Phase II will be presented in subject listings and analyzed using the Kaplan-Meier method in the Safety Analysis Set.

### 8.5.3.3 Antitumor Activity

OR and disease control will be evaluated based on the ITT population in randomized part of Phase II and the Safety Analysis Set in the Phase Ib and the single-arm cohort of Phase II.

In the randomized part of Phase II, the OR rate is evaluated as the proportion of subjects having achieved CR or PR as the best overall response according to local radiological assessments from the date of randomization to the end of study treatment. Responses do not require confirmation according to RECIST Version 1.1.

In Phase Ib and single-arm cohort of Phase II, the OR rate is evaluated as the proportion of subjects having achieved CR or PR as the best overall response according to local radiological assessments from the date of the first administration of the trial treatment to the end of study treatment. Responses do not require confirmation according to RECIST Version 1.1.

The disease control rate is defined as the proportion of subjects having achieved CR, PR or SD as the best overall response according to local radiological assessments from randomization/the first administration of the trial treatment until the end of study treatment in the randomized part of Phase II/the single-arm cohort of Phase II and Phase Ib. In the case of SD, measurement

must have met the SD criteria at least once after study entry at a minimum interval of 42 days after randomization/the first administration of the trial treatment.

In randomized part of Phase II, the Cochran-Mantel-Haenszel test will be performed for analysis using the randomization strata, type of MET+ (protein overexpression IHC2+ vs. protein overexpression IHC3+ vs. gene amplification and/or increased c-Met GCN, both by ISH) and prior EGFR-TKI. The Cochran-Mantel-Haenszel will test the following 2-sided hypothesis:

$$H_0: \Psi=1 \text{ versus } H_1: \Psi \neq 1$$

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

In general, the OR rate and disease control rate will be presented for each treatment arm in the randomized part and the single-arm cohort in the non-randomized part of Phase II, as well as each dose level of the “3+3” dose escalation cohorts and the additional mainland China cohort of Phase Ib, including the corresponding 90% Clopper-Pearson CIs.

Duration of response will be presented descriptively.

Further exploratory analyses will be performed for the per-protocol population and predefined subgroup (see Section 8.4).

#### 8.5.3.4 Safety and Tolerability Analyses

The Safety Analysis Set will be used for summaries of demographic and baseline characteristics in Phase Ib and the single-arm cohort of Phase II, as well as for all summaries of safety data (except for DLT analysis) in both Phase Ib and Phase II.

Safety analyses will be performed according to as-treated principle. Any TEAE will be summarized, ie, those events that are emergent during treatment having been absent pretreatment, or worsen relative to the pretreatment state and with onset dates occurring within the first dosing day of study treatment until  $30 \pm 3$  days after the last dose of study treatment. No formal statistical comparisons are planned.

The extent of exposure to tepotinib, gefitinib, pemetrexed, cisplatin, or carboplatin will be characterized by time on treatment (weeks), cumulative dose, dose intensity, relative dose intensity (actual cumulative dose/planned dose), number of dose reductions, and number of dose delays.

AEs will be coded according to the MedDRA. Severity of AEs will be graded using NCI-CTCAE (Version 4.0) toxicity grade. The incidence and type of AEs, SAEs, AESIs, study treatment-related AEs and SAEs, AEs of Grade  $\geq 3$  by NCI-CTCAE, study treatment-related AEs of Grade  $\geq 3$  by NCI-CTCAE (Version 4.0), AEs leading to death, study treatment-related AEs leading to death, and AEs leading to treatment discontinuation, will be summarized in total and for each treatment group according to MedDRA SOC and preferred terms. AE summaries will be prepared for Cycle 1 and the whole treatment period.

All deaths and deaths within 30 ( $\pm 3$ ) days after last dose of study treatment as well as reasons for death will be tabulated.

Laboratory results will be classified according to NCI-CTCAE (Version 4.0). The worst on-treatment grades after the first dose of the study treatment will be summarized. Shifts in toxicity grades from treatment start to the highest grade will be displayed. Results for variables that were not part of the NCI-CTCAE (Version 4.0) will be presented as below, within and above the normal limits of the local laboratory. Only subjects with postbaseline laboratory values will be included in these analyses. The last measurement before study treatment will serve as the baseline measurement. Descriptive summaries of actual (absolute) laboratory values and changes from baseline will be presented.

Changes in body weight from Baseline to measurements during the treatment phase will be classified according to the NCI-CTCAE (Version 4.0) criteria. The highest change from baseline will be summarized.

Clinically significant, abnormal findings from 12-lead ECG during treatment phase will be descriptively presented.

Changes from Baseline to worst on-treatment value will be summarized descriptively for the QTc interval (including absolute changes and categorical shifts).

Vital signs (body temperature, pulse rate, blood pressure, respiratory rate) recorded at Baseline will be descriptively presented.

Baseline results of the physical examination will be presented. Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination during and after treatment will therefore not be provided.

The ECOG PS will be summarized descriptively by visit.

Further details on safety analyses will be specified in the SAP.

### **Statistical Analyses for the Dose Escalation Decision**

Within each dose level and upon completion of Cycle 1 of treatment by the last subject in the “3+3” dose escalation cohorts of Phase Ib, data from analyses will be presented to the SMC for a decision on dose escalation. These analyses will include safety data only from Cycle 1 and all safety data from subjects exposed to study combination above Cycle 1, including listings of AEs graded according to NCI-CTCAE (Version 4.0) and DLT, listings of laboratory data, vital signs, ECGs, as well as each subject’s demographics, disease history, and treatment compliance in Cycle 1. Any protocol deviation that could affect DLT will be monitored and reported at each SMC. The full data to be presented will be documented in detail in the SMC charter.

All subjects in the safety analysis set will be included in the listings. Subjects that have been replaced during Cycle 1 will be flagged.

#### **8.5.3.5 Pharmacokinetics**

Pharmacokinetic parameters for the Phase Ib and Phase II parts of the trial are described in Section 7.5.2. For PK evaluation of Phase Ib, individual plasma and mean ( $\pm$  StD) concentration time plots will be provided for each dose cohort using a linear and semi-logarithmic scale. CCI [REDACTED]

The plasma concentration data for tepotinib and gefitinib will be separately summarized descriptively per dose cohort and per time point. Descriptive statistics will include number of subjects, arithmetic mean, geometric mean, median, StD, minimum, and maximum values and CV in %. Mean plasma concentration-time profiles will be generated on both linear and semi-logarithmic scales using time values as scheduled.

The derived PK parameters will be summarized descriptively per dose cohort. Descriptive statistics will include number of subjects (N), arithmetic mean, geometric mean, median, StD, minimum, and maximum values and CV in %.

The potential drug accumulation will be evaluated according to an appropriate manner. Additionally, the PK/Pd relationship may be explored. Pd variables might be chosen based on the trial outcome; efficacy, as well as safety variables might be considered. Further details on PK analyses of Phase Ib will be provided in the SAP.

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The PK population includes all subjects who have received at least 1 dose of the tepotinib or gefitinib and who had at least 1 blood sample drawn that provide drug concentration data for PK evaluation.

## 8.5.4 Analysis of Safety

See Section 8.5.3.4.

## 8.5.5 Analysis of Quality of Life

### 8.5.5.1 General Considerations

The LCSS, EORTC QLQ-C30 (Version 3.0) and the CCI questionnaires are used in this study (see [Appendix K](#), [Appendix L](#) and CCI respectively).

#### Evaluability:

The analysis for PROs will be performed with the QoL evaluable population.

For QoL endpoints, subjects will be considered evaluable for LCSS, EORTC QLQ-C30 or CCI provided they have a baseline and at least one evaluable LCSS, EORTC QLQ-C30 or CCI questionnaire, and are also included in the QoL evaluable population.

To be considered evaluable at baseline, a questionnaire has to be filled in on Cycle 1 Day 1, before dosing. After Cycle 1 Day 1, to be considered evaluable in the treatment period, a questionnaire has to be completed on Day 1 of Cycles 3, 5, 7, 9, 11, 13, 15, 17 and every 4 cycles thereafter until disease progression, and on the End-of-Treatment visit. Questionnaires filled in during the first 5 days after the beginning of a treatment cycle will be considered non-evaluable as these questionnaires would be primarily influenced by the acute side-effects

of chemotherapy. In addition, questionnaires filled in “on-treatment”, but after the date of progression, will be considered non-evaluable.

QoL questionnaires are expected from all subjects who remain on-treatment at the scheduled assessments. The patterns of completion of questionnaires will be explored to investigate the magnitude of missing data and to explore the extent of intermittent missing data and monotone missing data. The reasons for missing evaluable questionnaires will be presented by scheduled assessment time-point and treatment arm in the randomized part and the single-arm cohort.

Additionally, no data of PRO will be collected for those subjects in Phase II who are allowed to continue the treatment beyond PD.

Compliance will be defined for each assessment period and overall as follows:

- (number of subjects with at least one evaluable QoL questionnaires)
- % Compliance =  $100 * (\text{number of subjects with at least one evaluable QoL questionnaires}) / (\text{number of subjects with at least one evaluable QoL questionnaire expected})$

### **8.5.5.2 Time-to-Symptom Progression as Measured by the Lung Cancer Symptom Scale**

As defined in Section 7.7.1, ASBI is the mean of the six symptom scores derived from the LCSS questionnaire. Symptom progression will be defined as an increase (worsening) of the ASBI score of 10% of the scale breadth (10 mm on a scale of 0-100 mm) from the baseline score on at least two consecutive assessments during the period when assessments are performed every 2 cycles and then every 4 cycles. Once the frequency of assessments is reduced to every 4 cycles, then an increase at only one assessment is required as proof of worsening.

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

For subjects without symptom progression still receiving treatment at the time of analysis, the date of the last LCSS assessment will be used to calculate TTSP and will be considered as a censored observation in the analysis. Subjects who have stopped trial treatment and who have not subsequently met the criteria for TTSP will be treated as censored observations at time of last follow-up LCSS assessment. Subjects dying from causes other than PD and who do not have symptom progression will be treated as censored observations at time of death.

Subjects who have missed two consecutive scheduled doses, without evaluable assessment for related visits and who were lost to follow-up thereafter will be considered as having clinically meaningful symptom progression. In that case, TTSP will be calculated from the date of Cycle 1 Day 1 until the date of the first missed administration of trial treatment.

In randomized part of Phase II, the analysis of TTSP, to examine a potential clinically meaningful delay in symptom progression, will be based on a 2 sided log rank test comparison stratified by the type of MET+ and prior EGFR-TKI treatment.

The analysis of LCSS will be to determine the differences in the two treatment arms in the randomized part of Phase II: the proportion of subjects with symptomatic progression, the area under the curve, TTSP for the individual symptoms scores, TTSP for the summary symptoms score, time to worsening for global HRQoL.

Data from subjects in centers where a validated local language version of the LCSS is not used will not be included in the analysis of TTSP.

In single-arm cohort of Phase II, TTSP will be analyzed in a descriptive way.

### 8.5.5.3 EORTC QLQ-C30

The EORTC QLQ-C30 comprises 30 questions and provides a multi-dimensional assessment of QoL. Fifteen multi-items or single item scales were derived from the initial 30 items as per the EORTC QLQ-C30 Scoring Manual: 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), 3 symptom scales (fatigue, nausea and vomiting, pain), 6 symptom single item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and 1 global health status or QoL scale. All the scores will be derived from mutually exclusive sets of items, with scale scores ranging from 0 to 100 after a linear transformation. Higher scores for functioning scales and for the global health status or QoL scale indicate a higher level of functioning and a better QoL respectively, whereas higher scores in symptom scales represent a higher level of symptoms.

The analysis of EORTC QLQ-C30 scores will be based on descriptive statistics on changes from baseline scores for the multi-item scales and single item measures for each treatment arm in the randomized part and the single-arm cohort of Phase II at each of the assessment points.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 8.5.6 Analyses of Further Endpoints

### 8.5.6.1 Pharmacodynamics and Predictive Biomarkers

The exploratory biomarkers analysis set will include all subjects who have provided at least 1 sample of blood and/or tumor biopsy.

Exploratory biomarker (Pd markers and genetic alterations of relevant cancer genes) will be assessed in serum and tumor tissue and their potential correlation with prognosis and the activity of tepotinib in combination with gefitinib.

As exploratory endpoints, a statistical analysis of the biomarkers will be described in the SAP or in the specific Biomarkers SAP and the results of the analysis will be provided in a separate report.

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## 8.6 Interim Analysis and Data Monitoring Committee

An IDMC will be formed from a group of three experts and will consist of at least 1 statistician and 1 oncologist who will not be participants in this trial. An IDMC charter and SAP will provide the details about the conduct of the IDMC meeting, frequency and decision making rules.

The IDMC will be responsible for periodic (as defined by the IDMC charter) evaluations of the clinical trial to ensure continued subject safety as well as the validity and scientific merit of the study.

The designated independent statistician will provide the IDMC with the safety summaries periodically for review. The IDMC will give a recommendation regarding further conduct of the trial. The Sponsor management will take the final decision if the IDMC recommends to stop the trial. After the enrolment halt the requirements for an IDMC do no longer exist and no further IDMC meetings will be conducted.

In addition, the Sponsor may conduct administrative interim analyses in the single-arm (non-randomized) cohort of up to 15 subjects with MET+ T790M positive NSCLC at time points that are not specified in the protocol for internal planning purposes.

## 9 Ethical and Regulatory Aspects

### 9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and any other applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

In 1998, the US Food and Drug Administration (FDA) introduced a regulation (21 CFR, Part 54) entitled “Financial Disclosure by Clinical Investigators”. For trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the IMP (named “covered trials” by the FDA), the Investigator and all sub-Investigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor’s product under study. This information is required during the trial and for 12 months following completion of the trial.

### 9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject’s participation in the trial is his/her written informed consent. The subject’s written informed consent to participate in the trial must be given before any trial-related activities are carried out.

With the cooperation of the Sponsor, and in accordance with the Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP (for study sites in Japan), and the ethical principles that have their origin in the Declaration of Helsinki, the Investigator will prepare the informed consent form and other written information to be used in obtaining informed consent from the trial subjects. The Sponsor should provide the Investigator with documents/information necessary for preparing the aforementioned written information and cooperate with the Investigator to prepare it. In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject of all pertinent aspects of the trial orally as well as in writing. The language used in the aforementioned oral and written information about the trial must be fully and readily understandable to lay persons.

Before consent may be obtained, the Investigator should provide the prospective subject (or the prospective subject’s legally acceptable representative if applicable) with ample time and opportunity to inquire about details of the clinical trial and to decide whether or not to participate in the trial. In such cases, the Investigator or the trial collaborator giving supplementary explanation should answer all questions about the trial to the satisfaction of the prospective subject or legally acceptable representative.

Depending on national regulations, a person other than the Investigator may inform the subject and sign the ICF, as above.

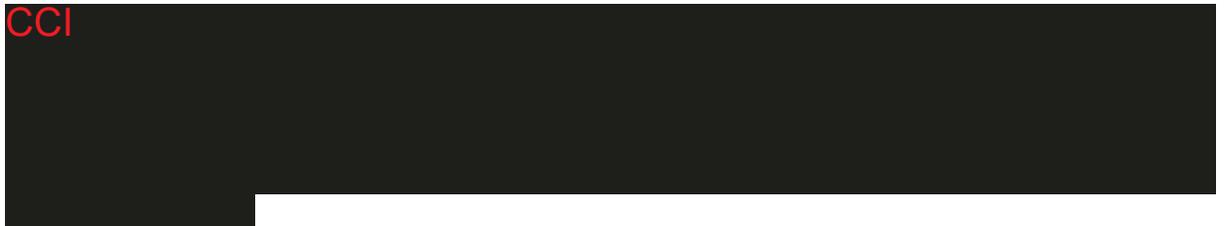
Where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and the Investigator.

For trials conducted in Japan: The trial collaborator giving supplementary explanation, where applicable, should sign, seal and date the informed consent form.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

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### 9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

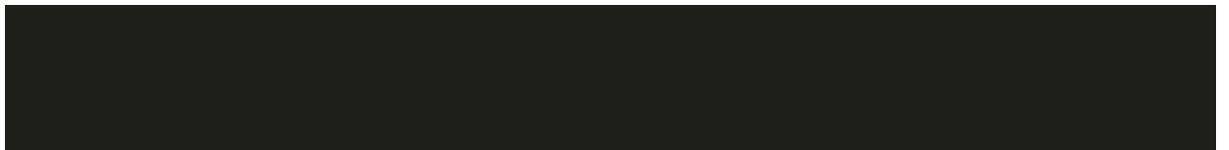
The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

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## 9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the Sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial; and this may include the possibility of emergency unblinding if needed, in case of blinded trials.

Clinical trial Investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, she/he will answer any questions. Any subsequent action (eg, unblinding) will follow the standard processes established for the Investigators.

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

## 9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

For trials conducted in Japan:

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

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

## **9.6 Independent Ethics Committee or Institutional Review Board**

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at the Sponsor.

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IEC/IRB, before implementation in case of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC/IRB during the course of the trial in accordance with national regulations and requirements.

For Japan sites:

The Sponsor initiates the trial at a site after obtaining written approval from the Head of the trial site based on favorable opinion/approval from the concerned IRB. The IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, its membership list, and names of members who were present and voted at the meeting. Written favorable opinion/approval should clearly identify the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version that were reviewed at the meeting. Where possible, copies of the meeting minutes should also be obtained.

Plans for any substantial amendments to the clinical trial will also be submitted to the concerned IRB before they are implemented (see Section 10.5). Relevant safety information will be submitted to the IRB during the course of the trial in accordance with national regulations and requirements.

## **9.7 Health Authorities**

The clinical trial protocol and any applicable documentation (eg, Investigational Medicinal Product Dossier, Subject Information, and ICF) will be submitted or notified to the Health Authorities in accordance with the regulations of the countries involved in the trial.

## 10 Trial Management

### 10.1 Case Report Form Handling

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered into a validated database. The data management department of the designated CRO, PPD, will be responsible for data processing, in accordance with the defined data management procedures, under the supervision of the Sponsor. Database lock will occur once quality control procedures and quality assurance procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

### 10.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. In particular, the following data should be available in this file:

- Subject's full name;
- Date of birth;
- Sex;
- Height;
- Weight;
- Medical history and concomitant diseases;
- Prior and concomitant therapies (including changes during the trial);
- Trial identification (Trial EMR200095-006);
- Date of subject's inclusion into the trial (ie, date of giving informed consent);
- Subject number in the trial;
- Dates of the subject's visits to the site;
- Any medical examinations and clinical findings predefined in the clinical trial protocol;
- All AEs observed in the subject;
- Date of subject's end of the trial, and
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, photographic negatives,

X-rays, CT or MRI, ECG recordings, laboratory value listings, a subject diary for the compliance to IMP administration, etc. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

The following information described in the eCRF is regarded as the source data.

- Any Investigator's comments,
- Subject number.

### **10.3 Investigator Site File and Archiving**

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the monitor, and must be ready for Sponsor audit, as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator (in Japan: a record retainer designated by the Head of the trial site) should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

### **10.4 Monitoring, Quality Assurance and Inspection by Health Authorities**

This trial will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, and any other applicable regulations. The site monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the tepotinib, and the subjects' original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

## 10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB (For Japan: through the Head of the trial site) for approval or favorable opinion. In such cases, the amendment will be implemented only after (For Japan: written approval from the Head of the trial site based on) approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation.

## 10.6 Clinical Trial Report and Publication Policy

### 10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH Topic E3 will be written by the Sponsor in consultation with the Coordinating Investigator.

### 10.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoints that will include data from all trial sites.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require presubmission review by the Sponsor.

The Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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### Appendix A Schedule of Assessments in Phase Ib

DAY	Screening <sup>aa</sup>	Treatment Period								EoT <sup>x</sup>	30-day Safety Follow-up Visit <sup>y</sup>	Additional Follow-Up Visit <sup>z</sup>
		Cycle 1 Day				Cycle 2 Day			Cycle ≥3 Day <sup>w ±3d</sup>			
	-28 to -1	1	2	8±1d	15±1d	1±1d	8±1d	15±1d	1	≤14 d of the Last Dose	±3d	±7d/ ±14d
Written Informed Consent	X											
Tepotinib+Gefitinib (IMP)		QD										
Drug Dispensation		X				X			X			
Demography <sup>bb</sup> , Height	X											
Medical History, Including EGFR Mutation Status <sup>bb</sup>	X											
Tumor Tissue Collection <sup>cc</sup> and Determination of MET Status	X <sup>a, b</sup>	X <sup>b</sup>			X <sup>b</sup>					X <sup>b</sup>		
Serum Pregnancy Test (If Applicable) <sup>c, cc</sup>	X										X	
Chest X-Ray	X <sup>d</sup>											
Physical Examination/Weight <sup>cc</sup>	X	X <sup>e</sup>	X	X	X	X	X	X	X	X <sup>f</sup>	X	
ECOG PS <sup>cc</sup>	X	X <sup>e</sup>				X			X	X <sup>f</sup>	X	
Vital Signs <sup>g, cc</sup>	X	X	X	X	X	X	X	X	X	X <sup>f</sup>	X	
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication/Procedure	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG <sup>h, cc</sup>	X	X <sup>i</sup>			X <sup>i</sup>	X <sup>i</sup>			X <sup>j</sup>	X <sup>f</sup>	X	
Hematology and Coagulation <sup>k, cc</sup>	X	X <sup>e</sup>	X	X	X	X	X	X	X	X <sup>f</sup>	X	
Biochemistry <sup>l, cc</sup>	X	X <sup>e</sup>	X	X	X	X	X	X	X	X <sup>f</sup>	X	
Urinalysis <sup>m, cc</sup>	X	X <sup>e</sup>				X			X	X <sup>f</sup>	X	
Tumor Assessment (RECIST Version 1.1) <sup>n, cc</sup>	X								X <sup>p</sup>	X <sup>q</sup>		X <sup>r</sup>
PK Blood Samples		X <sup>s</sup>			X <sup>s</sup>							
Exploratory Markers in Plasma		X <sup>t</sup>				X <sup>u</sup>			X <sup>u</sup>	X <sup>t</sup>		

CCI

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, End-of-Treatment; FFPE, Formalin-fixed paraffin-embedded; GGT, gamma-glutamyl transpeptidase; ICF, informed consent form; IMP, investigational medicinal product; MRI, magnetic resonance imaging; PD, progressive disease; CCI [REDACTED]; PK, pharmacokinetic; PT, prothrombin time; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

- a. Provision of a fresh or archived tumor biopsy (excluding fine needle aspiration and cytology samples). For subjects who experienced at least 1 anticancer treatment, biopsy obtained between failure of the most recent anticancer treatment and enrollment is mandatory. From the pretreatment biopsy, either FFPE tumor block (preferred) or 8 to 10 unstained slides must be sent to the central laboratory prior to enrollment for determination of MET+ status. The tumor tissue sample should have at least 10% viable tumor cells for the central laboratory to perform assessments. An associated pathology report must also be sent with the sample.
- b. Additional pre-treatment biopsy second pass in screening period or predose on Cycle 1, Day 1, on-treatment biopsy, and EoT biopsy. Paired tumor biopsies are not mandatory, but highly recommended for subjects with accessible tumors. Paired tumor biopsies should be taken before the treatment period (preferentially as second pass when biopsy for screening purposes is taken) and during the treatment period (can be taken any time between Cycle 1, Day 15 and the beginning of Cycle 3). If a tumor shows progression after initial response to tepotinib+gefitinib, a third biopsy is highly desirable when progression is diagnosed at the EoT.
- c. Only for women of childbearing potential, including those who have had a tubal ligation.
- d. Not necessary if thoracic CT is performed.
- e. Only if screening assessments were performed > 7 days prior to Day 1.
- f. Only if last assessments were performed > 7 days prior to end of treatment.
- g. Vital signs (pulse rate, systolic and diastolic blood pressure, body temperature, respiratory rate) are to be taken after at least 5 minutes rest in seated position. If vital signs and ECGs are taken at the same time, vital signs are to be taken immediately prior to each ECG recording.
- h. All ECGs to be taken as 12-lead resting ECGs in triplicate with up to 2 minutes between each ECG. ECGs are to be taken after at least 5 minutes rest in supine position.
- i. ECG recordings in Cycle 1, Day 1 and Cycle 1, Day 15 will be performed at predose (within 30 minutes prior to dose) and 4 hours ± 12 minutes postdose, 10 hours ± 30 minutes postdose, and 24 hours postdose (within 30 minutes prior to next dose). ECG recordings in Cycle 2, Day 1 will be performed at predose only (within 30 minutes prior to dose).
- j. Predose only (within 30 minutes prior to dose) after Cycle 3, ECGs will be performed every third cycle (ie, Cycle 3, 6, 9, 12, etc.) or as clinically indicated.
- k. Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelets, and coagulation (PT, aPTT, and INR).
- l. BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total bilirubin is abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, creatinine clearance, sodium, potassium, calcium, magnesium and glucose.
- m. Urinalysis: dipstick followed by microscopic examination if abnormal results are obtained.
- n. Complete tumor assessment of all lesions by radiographic or other modality (using RECIST Version 1.1). CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations. CT/MRI of the head at baseline for subjects who have or suspected to have CNS metastases.
- p. To be performed on Day 1 of Cycles 3, 5, 7, 9, 11, 13, 15, 17, and every 4 cycles thereafter until disease progression.
- q. Only if last tumor assessment was performed ≥ 6 weeks before Cycle 17 and ≥ 12 weeks afterwards prior to end of treatment.
- r. To be performed every 6 weeks until Cycle 17 and every 12 weeks after Week 51 until radiologically documented PD, death, end of trial, or starting a new anticancer therapy, whichever occurs first. Chest CT/MRI, other scans to document all sites of disease.
- s. Plasma concentrations of tepotinib and gefitinib will be obtained on Day 1 and Day 15 of Cycle 1. Samples will be taken predose and at 0.25, 0.5, 1, 2, 4, 8, 10 and 24 hours postdose.
- t. Blood sample (Cycle 1 Day 1 [predose] and during EoT visit).
- u. The on-treatment blood samples should be taken at cycles 2, 4, 6, 8, 10, and 12, at Day 1 pre-dose.

- w. All visits and assessments from Cycle 3 onwards may be performed  $\pm 3$  days to accommodate unforeseen delays, holidays, or vacations.
- x. Performed within 14 days of the last dose of study drug, the completion of treatment cycle, or the day when it is determined to permanently discontinue the study treatment; reason for treatment discontinuation should be recorded. If the subject discontinues from the study at a scheduled visit, the EoT assessment can be performed on that day. For subjects who withdraw from the treatment, only under the condition that subject stop administration for both components of the combination therapy, EoT visit is triggered.
- y. Performed at  $30 \pm 3$  days after the last treatment for all subjects who discontinue trial treatment permanently, including subjects who have completed an EoT visit. Reasons for study termination should be recorded if this visit is the last visit for subject. Ongoing or new AEs judged to be related to any trial medication will be followed until the event has resolved to the baseline grade, becomes stable, the subject is lost to follow-up, the subject withdraws consent, or it has been determined that the study treatment is not the cause of the AE, even if new anticancer treatment is initiated.
- z. Subjects who withdraw from the treatment for reasons other than PD have additional visits for tumor assessments. A  $\pm 7$  day time window is permitted for additional follow-up visits until Week 51 then  $\pm 2$  weeks thereafter. Reasons for study termination should be recorded if this visit is the last visit for subject. Recording of any new anticancer therapy will be made (a tumor assessment is mandatory before initiating the new therapy),
- aa. Subject eligibility evaluation (review of inclusion/exclusion criteria) will be checked. Some subjects may have a prescreening more than 28 days prior to first dose. Subjects who may have a prescreening to determine MET status must sign a prescreening ICF before any prescreening study procedures will be performed. MET status will be determined; and demographic data, medical history (including nicotine consumption), and disease history will be collected during the prescreening.
- bb. For some subjects who may have a prescreening ICF, this information will be recorded in prescreening.
- cc. Assessment can be repeated at the Investigator's discretion at unscheduled visits to assess the safety and tolerability of the IMP (tepotinib+gefitinib).

### Appendix B Schedule of Assessments in Phase II

DAY	Screening <sup>ee</sup>	Treatment Period					EoT <sup>aa</sup>	30 Day Safety Follow-up Visit <sup>bb</sup>	Additional Follow-up Visit <sup>cc</sup>	Survival Follow-up <sup>dd</sup>
		Cycle 1 Day		Cycle 2 Day <sup>z</sup> ±3d	Cycle ≥3 Day ±3d					
	-28 to -1	1	8 ±1d	15 ±1d	1	1	≤14 d of the Last Dose	±3d	±7d/±14d	
Written Informed Consent	X									
Randomization		X <sup>hh</sup>								
Comedication <sup>a</sup>	X <sup>a</sup>	Per local SmPC <sup>a</sup>								
Pemetrexed+cisplatin/carboplatin (comparator) <sup>a</sup>		Day 1 of each cycle								
Tepotinib+Gefitinib (IMP)		QD								
Drug Dispensation		X			X	X				
Demography, Height	X									
Medical History, Including EGFR Mutation Status	X									
Tumor Tissue Collection <sup>gg</sup> and Determination of MET+ and T790M Status	X <sup>b, c</sup>	X <sup>c</sup>		X <sup>c</sup>			X <sup>c</sup>			
Serum Pregnancy Test (If Applicable) <sup>d, gg</sup>	X							X		
Chest X-Ray	X <sup>e</sup>									
Physical Examination/Weight <sup>gg</sup>	X <sup>f</sup>	X	X	X	X <sup>g</sup>	X <sup>g</sup>	X <sup>h</sup>	X		
ECOG PS <sup>gg</sup>	X <sup>f</sup>				X	X	X <sup>h</sup>	X		
Vital Signs <sup>i, gg</sup>	X <sup>f</sup>	X	X	X	X	X	X <sup>h</sup>	X		
Adverse Events Assessment	X	X	X	X	X	X	X	X		
Concomitant Medication/Procedure	X	X	X	X	X	X	X	X		
12-lead ECG <sup>j, gg</sup>	X	X <sup>k</sup>		X <sup>l</sup>	X <sup>g, k</sup>	X <sup>g, m</sup>	X <sup>h</sup>	X		
Hematology and Coagulation <sup>n, gg</sup>	X <sup>f</sup>		X	X	X <sup>g</sup>	X <sup>g</sup>	X <sup>h</sup>	X		
Biochemistry <sup>p, gg</sup>	X <sup>f</sup>		X	X	X <sup>g</sup>	X <sup>g</sup>	X <sup>h</sup>	X		
Urinalysis <sup>q, gg</sup>	X <sup>f</sup>				X	X	X <sup>h</sup>	X		
Tumor Assessment (RECIST Version 1.1) <sup>r, gg</sup>	X					X <sup>s</sup>	X <sup>t</sup>		X <sup>u</sup>	
PK Blood Samples		X <sup>v</sup>			X <sup>v</sup>					
Exploratory Markers in Plasma		X <sup>w</sup>			X	X	X <sup>w</sup>			

	Screening <sup>ee</sup>	Treatment Period					EoT <sup>aa</sup>	30 Day Safety Follow-up Visit <sup>bb</sup>	Additional Follow-up Visit <sup>cc</sup>	Survival Follow-up <sup>dd</sup>
		Cycle 1 Day	Cycle 2 Day <sup>z</sup> ±3d	Cycle ≥3 Day ±3d						
DAY	-28 to -1	1	8 ±1d	15 ±1d	1	1	≤14 d of the Last Dose	±3d	±7d/±14d	
<b>CCI</b>										
Subject survival and anticancer therapies										X
HRQoL questionnaires <sup>ff</sup>		X				X <sup>ff</sup>	X	X	X	

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; EoT, End-of-Treatment; FFPE, formalin-fixed paraffin-embedded; GGT, gamma-glutamyl transpeptidase; HRQoL, health related quality of life; ICF, informed consent form; IMP, investigational medicinal product; MRI, magnetic resonance imaging; PD, progressive disease; **CCI**; PK, pharmacokinetic; PT, prothrombin time; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, summary of product characteristics.

- Regarding the comedications for pemetrexed, cisplatin, or carboplatin (see Section 6.4.1), all subjects are permitted to receive folic acid and first B12 intramuscular injection during screening period. After randomization, only subjects in the control arm in Phase II will continue comedications for pemetrexed (eg., vitamin B12 and folic acid). All comedications will be administered per local package insert/SmPC. In the control arm, dosing for folic acid should continue for the full course of the treatment, and for 3 weeks (ie, 21 days) following the last dose of pemetrexed to be administered. An intramuscular injection of vitamin B12 (1000 µg) will be administered around every 9 weeks per local package insert/SmPC. Subjects should receive pretreatment and posttreatment hydration for cisplatin per local package insert/SmPC.
- Provision of a fresh or archived pretreatment tumor biopsy (excluding fine needle aspiration and cytology samples). For subjects experienced at least 1 anticancer treatment, biopsy obtained between failure of the most recent anticancer treatment and enrollment is mandatory. Test done after progression of gefitinib, erlotinib, icotinib, or afatinib and more than 28 days prior to randomization/first administration of trial treatment is acceptable. From the pretreatment biopsy, either FFPE tumor block (preferred) or 10 to 15 unstained slides must be sent to the central laboratory prior to enrollment for determination of MET+/T790M status. The tumor tissue sample should have at least 10% viable tumor cells for the central laboratory to perform assessments. An associated pathology report must also be sent with the sample.
- Additional pre-treatment biopsy second pass in screening period or predose on Cycle 1, Day 1, on-treatment biopsy and EoT biopsy. Paired tumor biopsies are not mandatory, but highly recommended for subjects with accessible tumors. Paired tumor biopsies should be taken before the treatment period (preferentially as second pass when biopsy for screening purposes is taken) and during the treatment period (can be taken any time between Cycle 1, Day 15 and the beginning of Cycle 3). If a tumor shows progression after initial response to tepotinib+gefitinib, a third biopsy is highly desirable when progression is diagnosed at the EoT.
- Only for women of childbearing potential, including those who have had a tubal ligation.
- Not necessary if thoracic CT is performed.
- Should be repeated if the last assessment is more than 7 days prior to the planned date for first dose, and the laboratory assessment must be performed by the central laboratory.
- For control (chemotherapy) arm, weight, hematology, biochemistry, and ECG should be done within 3 days prior to treatment administration beginning with Cycle 2.
- Only if last assessments were performed > 7 days prior to EoT.
- Vital signs (pulse rate, systolic and diastolic blood pressure, body temperature, respiratory rate) are to be taken after at least 5 minutes rest in seated position. If vital signs and ECGs are taken at the same time, vital signs should be taken immediately prior to each ECG recording.
- All ECGs to be taken as 12-lead resting ECGs in triplicate with up to 2 minutes between each ECG. ECGs are to be taken after at least 5 minutes rest in supine position.

- k. On Cycle 1, Day 1 and on Cycle 2, Day 1 in subjects who receive tepotinib+gefitinib, ECG will be taken predose (within 30 minutes prior to PK predose sampling) and at 4 hours  $\pm$  10 minutes postdose [performed directly before PK 4-hour postdose sampling]. Predose only (within 30 minutes prior to dose) in control (chemotherapy) arm. ECGs will be collected in triplicate at the predose and 4 hour time points.
- l. Predose only (within 30 minutes prior to dose).
- m. Predose only (within 30 minutes prior to dose). After Cycle 3, ECGs will be performed every third cycle (ie, Cycle 3, 6, 9, 12, etc.) or as clinically indicated.
- n. Hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelets, and coagulation (PT, aPTT, and INR).
- p. BUN, creatinine, AST, ALT, GGT, total bilirubin (including direct fraction if total BR abnormal), lipase, amylase, total protein, albumin, alkaline phosphatase, creatinine clearance, sodium, potassium, calcium, magnesium and glucose.
- q. Urinalysis: dipstick followed by microscopic examination if abnormal results are obtained.
- r. Complete tumor assessment of all lesions by radiographic or other modality (using RECIST Version 1.1). CT or MRI of the chest, abdomen, and pelvis to evaluate disease in these locations. CT/MRI of the head at baseline for subjects who have or suspected to have CNS metastases.
- s. To be performed on Day 1 of Cycles 3, 5, 7, 9, 11, 13, 15, 17, and every 4 cycles thereafter until disease progression. For subjects receiving treatment beyond PD, RECIST Version 1.1 radiographical assessment will follow institutional practice guidelines, however, tumor assessment information will not be recorded in the eCRF and there will be no further documentation collected for any new lesion and/or clinical symptoms of PD after first PD.
- t. Only if last tumor assessment was performed  $\geq$  6 weeks before Cycle 17 and  $\geq$  12 weeks afterwards prior to EoT.
- u. To be performed every 6 weeks until Cycle 17 and every 12 weeks after Week 51 until radiologically documented PD, death, end of trial, or starting a new anticancer therapy, whichever occurs first. Chest CT/MRI, other scans to document all sites of disease.
- v. Sparse PK sampling (total of 6 samples) will be performed at within 60 minutes prior to dose and at 1.5  $\pm$  10 minutes and 4 hours  $\pm$  10 minutes postdose on Day 1 Cycle 1 and on Day 1 Cycle 2 in subjects who receive tepotinib+gefitinib.
- w. Blood samples (Cycle 1 Day 1 [predose] and during EoT visit).
- x. The on-treatment blood samples should be taken at cycles 2, 4, 6, 8, 10, and 12, at Day 1 pre-dose.
- z. All visits and assessments from Cycle 2 onwards may be performed  $\pm$  3 days to accommodate unforeseen delays, holidays, or vacations.
- aa. Performed within  $\leq$ 14 days of the last dose of study drug, the completion of treatment cycle, or the day when it is determined to permanently discontinue the study treatment. Reason for treatment discontinuation should be recorded. If the subject discontinues from the study at a scheduled visit, the EoT assessment can be performed on that day. A subject will have an End-of-Treatment visit only if they withdraw from treatment with both components of the combination therapy. A subject will have an End-of-Treatment visit only if he/she will withdraw from treatment with both components of the combination therapy.
- bb. Performed at 30  $\pm$  3 days after the last treatment for all subjects who discontinue trial treatment permanently, including subjects who have completed an EoT visit. Ongoing or new AEs judged to be related to any trial medication will be followed until the event has resolved to the baseline grade, becomes stable, the subject is lost to follow-up, the subject withdraws consent, or it has been determined that the study treatment is not the cause of the AE, even if new anticancer treatment is initiated.
- cc. If a subject withdraws from the treatment for reasons other than PD, or, for subjects in the control arm not receiving pemetrexed maintenance only, the completion of up to 6 cycles of pemetrexed+cisplatin/carboplatin, tumor assessments will be performed every 6 weeks until Week 51 (Cycle 17) and every 12 weeks after Week 51 until radiologically documented PD, death, end of trial, or start of a new anticancer therapy, whichever occurs first.
- dd. Information about subject survival will be collected by telephone interview/clinic visit every 3 months  $\pm$  2 weeks until death or the end of the trial, whichever comes first. Any new anticancer therapy given to the subject until death should be recorded.
- ee. Subject eligibility evaluation (review of inclusion/exclusion criteria) will be checked. Some subjects may have a prescreening more than 28 days prior to randomization/first administration of trial treatment. Subjects who may have a prescreening to determine MET and T790M status must sign a prescreening ICF before any prescreening study procedures will be performed. MET and T790M status will be determined; and demographic data, medical history (including nicotine consumption), and disease history will be collected during the prescreening.

- ff. PROs (LCSS, EORTC QLQ-C30 and CCI ): the questionnaires will be completed on Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17 and every 4 cycles thereafter until disease progression, and EOT. At the visits indicated, the questionnaires will be completed by the subject and prior to the initiation of any other trial activities (including RECIST Version 1.1 assessments) or active treatment. No PROs will be required for subjects receiving treatment beyond PD.
- gg. Assessment can be repeated at the Investigator's discretion at unscheduled visits to assess the safety and tolerability of the IMP/comparator.
- hh. Study treatment should be given on the day of randomization or the day following the randomization day.

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

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). *European Journal of Cancer*. 2009; 45: 228-247.

### Definitions

Response and progression will be evaluated in this trial 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  $\geq 15$  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  $\geq 10$  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 exam 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 noncystic lesions are present in the same subject, 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. Trial 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 organ, 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  $\geq 15$  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, saggital, 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  $\geq 10$  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 exam.

**Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial and  $\geq 10$  mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

**Chest X-ray:** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

**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 trial, 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 trials 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 subject 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 PSA 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 trials in ovarian cancer.

**Cytology, histology:** These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, 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 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 SD in order to differentiate between response (or SD) and PD.

## Response Criteria

### Evaluation of Target Lesions

**Complete Response (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 (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). 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).

**Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

*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 trial. 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 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 PR, 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 trial, 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.

Complete Response (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.

Progressive Disease (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 subject 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 PR 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 qualify 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 PR of target disease will therefore be extremely rare.

*When the subject has only non-measurable disease.* This circumstance arises in some Phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply 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 subjects 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 subject 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 (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject’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 trial 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 subject who has visceral disease at baseline and while on trial has a brain CT or MRI ordered which reveals metastases. The subject’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, for example 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 fluorodeoxyglucose positron emission tomography (FDG-PET) response assessments need additional trial, 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 OR is the best response recorded from the start of the trial treatment 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 best OR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject’s best OR 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 trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either the ‘best OR’.

The best OR is determined once all the data for the subject is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best OR of PR). 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 subject’s best response depends on the subsequent assessments. For example, a subject 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 subject 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	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
	Non-PD		
Not all evaluated		No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

\* CR = complete response; PR = partial response; SD = stable disease; and 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 subjects with CR may not have a total sum of ‘zero’ on the eCRF.

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

Subjects 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 trial therapy.

Conditions that define ‘early progression, early death and inevaluability’ are trial specific and should be clearly described in each protocol (depending on treatment duration, 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 trials where response is the primary endpoint, confirmation of PR 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 trials. However, in all other circumstances, ie, in randomized trials (Phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the trial 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 trial entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the trial protocol.

#### Duration of Overall Response

The duration of OR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on trial).

The duration of overall complete response 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 trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on trial (if the baseline sum is the smallest, this is the reference for calculation of PD).

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

Note: The duration of response and stable disease 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 trials are to be made.

## Appendix D Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

## Appendix E New York Heart Association (NYHA) Criteria

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

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

## Appendix F Blood Sampling Schedule for PK/Pd

### Phase Ib

Cycle	Day	Time points H = hours after dosing	PK	Pd/Biomarkers
			2 x 2 mL	20 mL
Cycle 1	Day 1	Pre dosing	X	X
		H 0.25	X	
		H 0.5	X	
		H 1	X	
		H 2	X	
		H 4	X	
		H 8	X	
		H10	X	
		H 24	X	
	Day 15	Same time points as Day 1	X	

All pre-dosing samples should be taken within 60 minutes before each treatment administration

### Phase II

Cycle	Day	Time points H = hours after dosing	PK	Pd/Biomarkers
			2 mL	20 mL
Cycle 1	Day 1	Pre dosing	X	X
		H 1.5	X	
		H 4	X	
Cycle 2,	Day 1	Same time points as Cycle 1	X	
Cycle 2, 4, 6, 8, 10, 12 and EoT	Day 1	Pre dosing		X

On days when PK samples are to be drawn, subjects should be instructed to attend the trial visit in a fasted state, with no breakfast and prior to taking their dose of study medication. After a predose PK blood sample is drawn, the assigned doses of tepotinib and gefitinib should be taken following breakfast. No further food should be consumed until 2 hours after the dose (water is allowed).

## Appendix G Blood Samples Volumes

### For Cycle 1

Sample Type	Volume of Blood (mL)		
	Cycle 1		Total
	Day 1	Day 15	
PK Phase Ib	36	36	72
PK Phase II	6	-	6
Pd/Biomarkers	20	-	20
<b>Total (mL) Phase Ib</b>	<b>62</b>	<b>36</b>	<b>98</b>
<b>Total (mL) Phase II</b>	<b>32</b>	<b>-</b>	<b>32</b>

An anticipated total blood sample volume of approximately 98 mL will be taken for Cycle 1 in Phase Ib.

An anticipated total blood sample volume of approximately 32 mL will be taken for Cycle 1 in Phase II.

### For Cycle 2, 4, 6, 8, 10 and 12, End of Treatment

Sample type	Volume of blood (mL)			
	Cycle 2	Cycle ≥ 3	End of Treatment	Total(mL)
	Day 1	Day 1		
PK Phase II	6	-	-	6
Pd/Biomarkers *	20*	20*	20	60
<b>Total (mL)</b>	<b>26</b>	<b>20</b>	<b>20</b>	<b>66</b>

An anticipated total blood sample volume of approximately 66 mL will be taken for Cycle 2, Cycle 3, subsequent cycles and End of Treatment in both Phase Ib and Phase II.

\*Seven on-treatment samples (1 cycle apart, ie, 1 in Cycle 2, 4, 6, 8, 10 and 12 and end of treatment in subjects signing separate ICF).

## Appendix H Scoring System for MET Immunohistochemistry

Diagnostic	Clinical Score	Scoring Criteria
Positive	3+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with strong intensity
	2+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with moderate intensity
Negative	1+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with weak intensity but < 50% tumor cells with moderate or high intensity
	0	Samples with no staining, or with < 50% tumor cells with membrane and/or cytoplasmic staining (could be combination of any staining intensities)

## Appendix I Gefitinib AE Management Guidelines

In all instances, it is recommended that subjects be instructed at time of starting drug therapy to call the Investigator/site if no improvement in symptoms has been observed after 24 hours of subject taking the recommended/optimal pharmacologic treatment.

### Abbreviations:

BSA: Body Surface Area

ADL: Activities of Daily Living.

*Instrumental ADL* refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

*Self-care ADL* refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden. (definitions per CTCAE Version 4.0)

### DIARRHEA

Subjects should be encouraged to drink 8 to 10 large glasses of clear liquids per day while on study in order to maintain adequate hydration

General dietary measures to limit impact of diarrhea could include:

Stop all lactose-containing products in subjects with evidence of lactose intolerance;

Eat frequent small meals if experiencing increased frequency of stools;

Consider low fat regimen enriched with bananas, rice, applesauce, and toast.

Diarrhea Management Guideline	
Grade of Event	Management / Next Dose
Grade 1: increase of < 4 stools per day over baseline;	Loperamide 4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the subject is diarrhea-free for at least 12 hours. (During the night the subject may take 4 mg of loperamide every 4 hours).  Fluid intake of at least 2 L should be maintained to avoid dehydration: subjects are to drink 8-10 large glasses of clear liquids. Consideration for maintenance of electrolyte balance would include electrolyte-containing drinks, broth, and clear juices.  <b><i>Study Treatment:</i></b> should be continued at same dose.

<b>Diarrhea Management Guideline</b>	
<b>Grade of Event</b>	<b>Management / Next Dose</b>
<p>Grade 2: increase of 4-6 stools per day over baseline;</p>	<p>Loperamide as above, or consider use of diphenoxylate hydrochloride and atropine sulfate formula (eg, Lomotil<sup>®</sup>, Diarced<sup>®</sup>, Co-Phenotrope<sup>®</sup>) at standard doses.</p> <p>Fluid intake of at least 2 L should be maintained to avoid dehydration.</p> <p>Monitor subject closely and consider intravenous hydration.</p> <p><b><u>Study Treatment:</u></b> If not improved to &lt; Grade 1 within 24 hours despite use of loperamide, hold treatment until Grade 1. If diarrhea of &gt; Grade 1 recurs after initial improvement, consider reduction of 1 dose level.</p>
<p>Grade 3: increase of ≥7 stools per day over baseline; or incontinence; or limiting self-care ADL: or hospitalization indicated</p>	<p>Oral therapy with diphenoxylate hydrochloride and atropine sulfate formula, or tincture of opium.</p> <p>Fluid intake of at least 2 L should be maintained, intravenously if necessary.</p> <p>Consider use of octreotide (Sandostatin) 100-150 µg subcutaneously twice daily with escalation to 500 µg three times daily.</p> <p>Consider hospitalization if does not improve to Grade 2 within 24 hours, or in presence of fever, abdominal pain, etc.</p> <p><b><u>Study Treatment:</u></b> Hold therapy. Upon resolution to ≤ Grade 1, resume therapy with consideration of reduction of 1 dose level</p>
<p>Grade 4: life-threatening</p>	<p>Maximal inpatient fluid and nutritional support, antibiotics as indicated in judgment of Investigator for fever, leukocytosis, marked dehydration, etc.</p> <p><b><u>Study Treatment:</u></b> Hold until ≤ Grade 1. Mandatory dose reduction of 1 dose level</p>

**DERMATOLOGIC TOXICITY**

Acneiform/ Papulopustular Rash:

<b>Acneiform/ Papulopustular Rash Management Guideline</b>	
<b>Grade of Event</b>	<b>Management</b>
<p><b>Grade 1:</b> &lt; 10% body surface area (BSA) papules and / or pustules (with or without symptoms of pruritus or tenderness)</p>	<p><b>Topical steroids *</b> <b>And</b> <b>Topical antibiotic bid</b> (clindamycin 1 - 2%, erythromycin 1% - 2%, metronidazole 1%)</p>
<p><b>Grade 2:</b> 10 to 30% BSA papules and / or pustules (with or without symptoms of pruritus or tenderness), or psychosocial impact, or limited instrumental ADL</p>	<p><b>Oral antibiotic for at least 4 weeks</b> (doxycycline 100 mg bid, minocycline 100 mg bid or oxytetracycline 500 mg bid); Stop topical antibiotic if being used <b>And</b> <b>Topical steroids *</b></p>
<p><b>Grade 3:</b> &gt; 30% BSA papules and / or pustules (with or without symptoms of pruritus or tenderness); <i>or</i> limiting self-care ADL: <i>or</i> associated with local super-infection with oral antibiotics indicated</p>	<p><b>Oral antibiotic for 4 weeks</b> (doxycycline 100 mg bid, minocycline 100 mg bid or oxytetracycline 500 mg bid) If infection suspected (yellow crusts, purulent discharge, painful skin/nares):     switch oral antibiotic to broad spectrum/gram negative cover for at least 10 days     consider skin swab for bacterial culture, <b>And</b> <b>Topical steroids (continue)*</b> Consider dermatology consultation</p>
<p>* Moderate/Low strength steroids include:</p>	<p><i>Triamcinolone acetonide 0.025%</i> <i>Desonide 0.05%</i> <i>Alclometasone 0.05% cream</i> <i>Fluticasone propionate 0.05%</i> For subjects intolerant or allergic to tetracycline antibiotics, use an antibiotic with <i>Staphylococcus</i> coverage (eg, cephalexin, sulfamethoxazole/ trimethoprim)</p>

## Appendix J Dose Modification for Gefitinib

AE/Grade	Gefitinib
Subjects should be instructed at time of starting drug therapy to call the Investigator/Site if no improvement in symptoms has been observed after 24 hours of subject taking the recommended/optimal pharmacologic treatment.	Gefitinib dose frequency and discontinuation should follow local standard of care practice.  Depending upon local practice, subjects with toxicities which in the Investigator’s opinion are clearly related to gefitinib, may have their dosing held until toxicity resolution or may have their dosing frequency reduced in accordance with local standard of care practice
Grade 4 neutropenia for more than 7 days  Grade $\geq$ 3 febrile neutropenia for more than 1 day;  Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding;	No change in dose frequency
Grade $\geq$ 3 uncontrolled nausea/vomiting and/or diarrhea despite adequate and optimal treatment for more than 3 days	Depending upon local practice, subjects with toxicities which in the Investigator’s opinion are clearly related to gefitinib, may have their dosing held until toxicity resolution or may have their dosing frequency reduced in accordance with local standard of care practice  Subjects with poorly tolerated diarrhea (sometimes associated with dehydration) drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose.
Grade $\geq$ 3 any nonhematological AE, except the aforementioned gastrointestinal events and alopecia;	Continue at Investigator discretion
Grade $\geq$ 3 liver AE requiring a recovery period of more than 7 days to return to the baseline grade or to Grade 2;	Continue at Investigator discretion
Grade $\geq$ 3 lipase and/or amylase elevation with confirmation of pancreatitis;	Continue at Investigator discretion

AE/Grade	Gefitinib
Clinically intolerable skin rash, acne or other skin symptoms	<p>Depending upon local practice, subjects with toxicities which in the Investigator’s opinion are clearly related to gefitinib, may have their dosing held until toxicity resolution or may have their dosing frequency reduced in accordance with local standard of care practice.</p> <p>Subjects with poorly tolerated skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg daily dose.</p>
Acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever)	Gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur. If Interstitial Lung Disease is confirmed, Gefitinib should be discontinued.
Eye symptoms	Subjects who develop onset of new eye symptoms such as pain should be medically evaluated and gefitinib therapy should be interrupted. After symptoms and eye changes have resolved, the decision should be made concerning reinstatement of the 250 mg daily dose.
Recurrence of Grade $\geq$ 2 AEs after re-challenging despite adequate and optimal treatment of the AE.	Continue at Investigator discretion
Grade 1 AE; Well tolerated Grade 2 AEs; Asymptomatic lipase and/or amylase elevation without confirmation of pancreatitis.	Continue at Investigator discretion

## Appendix K Lung Cancer Symptom Scale (LCSS): Subject Scale

A sample of the English version of the LCSS is provided below. Local language version will be available for trial subjects.

**Directions:** Please place a mark along each line where it would best describe the symptoms of your lung cancer DURING THE PAST DAY (within the last 24 hours).

Example Question	
How is the weather today?	
As good as it could be	As bad as it could be

1. How is your appetite?

As good as it  
could be \_\_\_\_\_ As bad as it  
could be

2. How much fatigue do you have?

None \_\_\_\_\_ As much as it  
could be

3. How much coughing do you have?

None \_\_\_\_\_ As much as it  
could be

4. How much shortness of breath do you have?

None \_\_\_\_\_ As much as it  
could be

5. How much blood do you see in your sputum?

None \_\_\_\_\_ As much as it  
could be

6. How much pain do you have?

None

As much as it  
could be

7. How bad are your symptoms from lung cancer?

I have none

As bad as they  
could be

8. How much has your illness affected your ability to carry out normal activities?

Not at all

So much that I  
can do nothing  
for myself

9. How would you rate the quality of your life today?

Very high

Very low

## Appendix L EORTC QLQ-C30 (Version 3.0)

A sample of the English version of the EORTC QLQ-C30 (Version 3.0) is provided below. Local language version will be available for trial subjects.



**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--	--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

**During the past week:**

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

**During the past week:**

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

1      2      3      4      5      6      7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

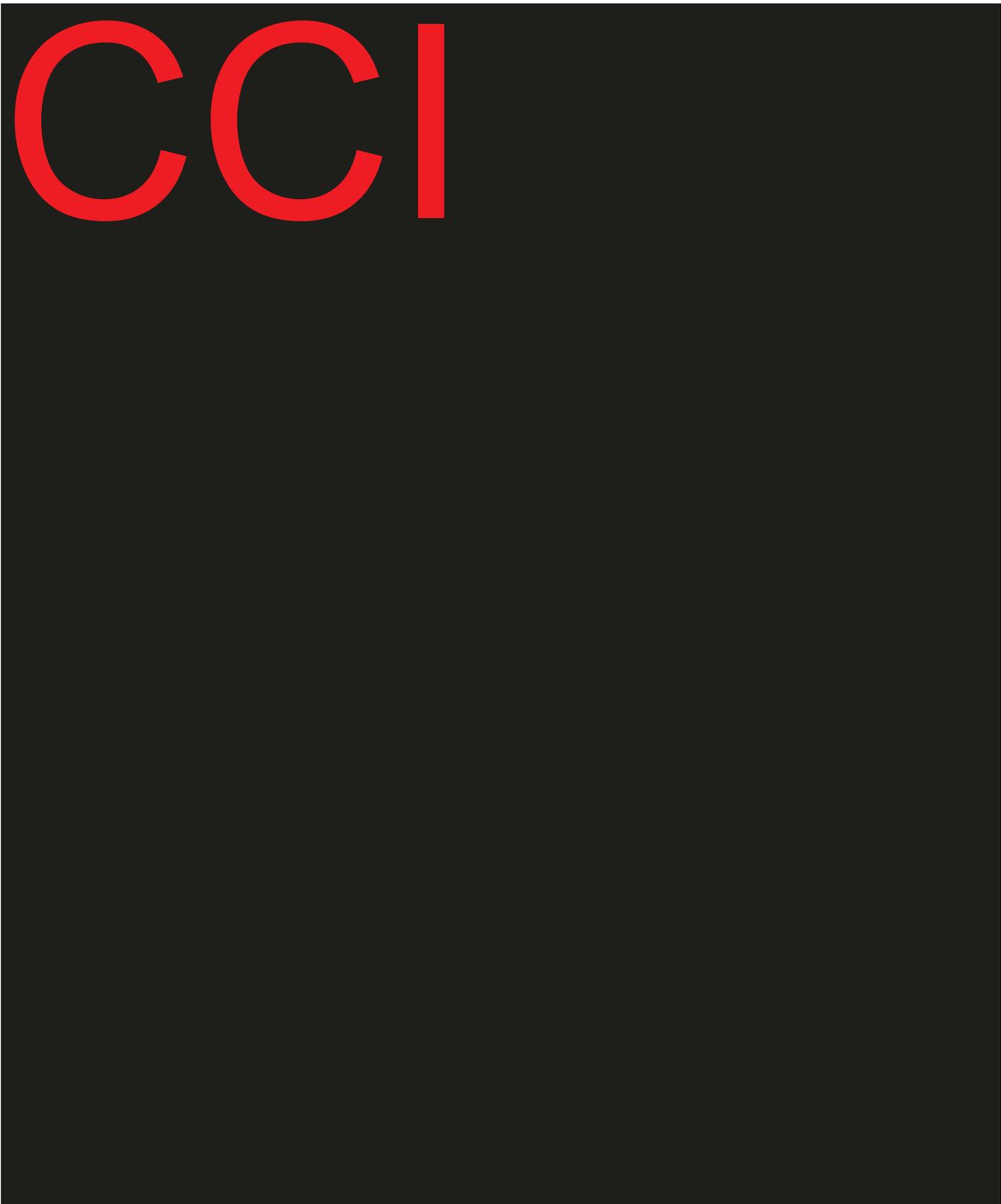
1      2      3      4      5      6      7

Very poor

Excellent



CCI



CCI

CCI

CCI

## Appendix N Contraceptive Guidance and Women of Childbearing Potential

### Definitions

#### Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

#### Women in the following categories are not considered women of childbearing potential

1. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

2. Premenarchal

3. Postmenopausal female

- Females who are postmenopausal (age-related amenorrhea  $\geq 12$  consecutive months and increased follicle-stimulating hormone [FSH]  $> 40$  mIU/mL), or who have undergone documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, FSH will be re-tested at Screening.
- Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

## Contraceptive Guidance

<b>Highly Effective Contraceptive Methods That Are User Dependent</b>
Failure rate of < 1% per year when used consistently and correctly.
<ul style="list-style-type: none"><li>• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<sup>b</sup><ul style="list-style-type: none"><li>• oral</li><li>• intravaginal</li><li>• transdermal</li></ul></li></ul>
<ul style="list-style-type: none"><li>• Progestogen-only hormonal contraception associated with inhibition of ovulation<sup>b</sup><ul style="list-style-type: none"><li>• oral</li><li>• injectable</li></ul></li></ul>
<b>Highly Effective Methods That Are User Independent</b>
<ul style="list-style-type: none"><li>• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<sup>b</sup></li><li>• Intrauterine device (IUD)</li><li>• Intrauterine hormone-releasing system (IUS)</li><li>• bilateral tubal occlusion</li></ul>
<ul style="list-style-type: none"><li>• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)</li></ul>
<ul style="list-style-type: none"><li>• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)</li></ul>
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case another highly effective (not hormone based) method must be utilized during the treatment period and for at least 3 months after the last dose of study treatment.