

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**214096Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

## NDA/BLA Multi-disciplinary Review and Evaluation

**Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.**

[FDA will complete this section.]

<b>Application Type</b>	NME
<b>Application Number(s)</b>	NDA 214096
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<b>Division/Office</b>	Division of Oncology 2/OND
<b>Review Completion Date</b>	February 1, 2021
<b>Established Name</b>	tepotinib
<b>(Proposed) Trade Name</b>	Tepmetko
<b>Pharmacologic Class</b>	Kinase inhibitor
<b>Code name</b>	MSC2156119J
<b>Applicant</b>	EMD Serono, Inc.
<b>Formulation(s)</b>	Tablet
<b>Dosing Regimen</b>	450 mg orally once daily with food
<b>Applicant Proposed Indication(s)/Population(s)</b>	for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) (b) (4)
<b>Recommendation on Regulatory Action</b>	Accelerated Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

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OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRM=Division of Risk Management

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## Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BCRP	breast cancer resistance protein
BLA	biologics license application
CDRH	Center for Devices and Radiological Health
CF	capsule formulation
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CSR	clinical study report
CYP	cytochrome p450
DDI	drug-drug interaction
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
EQ-5D-5L	EuroQol Five Dimension Five Level Scale
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
FDA	Food and Drug Administration
FIH	first-in-human
GCP	good clinical practice
GLP	good laboratory practice
HCC	hepatocellular carcinoma
HRQoL	health-related quality of life
ICH	International Council for Harmonization
ILD	interstitial lung disease
IND	Investigational New Drug
IRC	Independent Review Committee

NDA/BLA Multi-disciplinary Review and Evaluation NDA 214096  
TEPMETKO, Tepotinib

ISS	integrated summary of safety
ITT	intent-to-treat
LBx	liquid biopsy
MAD	multiple ascending dose
MATE	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
<i>MET</i>	<i>MET</i> gene
<i>MET</i> ex14	<i>MET</i> exon 14
mDOR	median duration of response
mPFS	median progression-free survival
mOS	median overall survival
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OCT	organic cation transporter
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OR	objective response
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
Pd	pharmacodynamics
PD-L1	programmed cell death 1 ligand 1
P-gp	P-glycoprotein
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SOC	system organ class
TBx	tissue biopsy

NDA/BLA Multi-disciplinary Review and Evaluation NDA 214096  
TEPMETKO, Tepotinib

TF                      tablet formulation  
TEAE                  treatment-emergent adverse event



observed with tepotinib are reasonably likely to predict clinical benefit over existing treatments, even for treatment-naïve patients. Based on these findings, FDA expects that tepotinib will have, as described in section 505(d) of the Act, “the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

### 1.3. Benefit-Risk Assessment (BRA)

#### Benefit-Risk Summary and Assessment

Metastatic non-small cell lung cancer (NSCLC) is a fatal, incurable disease, with a 5-year survival rate of <10%. Mesenchymal-epithelial transition (MET) exon 14 skipping alterations have been identified as an oncogenic driver in NSCLC and have been reported to be present in 2-4% of all NSCLC tumors. In comparison to some other subpopulations of patients with targetable genomic tumor aberrations (i.e., EGFR mutation, ALK rearrangement), patients with NSCLC whose tumors harbor MET exon 14 skipping alterations tend to be older (median age around 70 years), similar to the general population of patients with NSCLC. Based on the limited data available for review, there is no indication that patients with NSCLC whose tumors harbor MET exon 14 skipping alterations have a higher response rate when treated with platinum-based chemotherapy and/or immunotherapy compared to the general population of patients with NSCLC. Capmatinib, another kinase inhibitor that targets MET, was granted accelerated approval by the FDA in May 2020 for the treatment of patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. To date, no targeted therapy specifically for the treatment of patients with NSCLC whose tumors have MET exon 14 skipping has been granted regular approval.

Tepotinib is a kinase inhibitor that targets MET, including the variant(s) with MET exon 14 skipping alterations. The proposed dosing regimen is 450 mg orally once daily (QD) with food. EMD Serono's proposed indication for tepotinib is "for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) [REDACTED] (b) (4) [REDACTED]."

The primary efficacy analysis population for this review comprises 152 patients with metastatic NSCLC whose tumors harboring MET exon 14 skipping alterations treated with tepotinib 450 mg QD in the multi-cohort clinical trial, the VISION Study. This population includes 83 patients with disease progression following one or two prior therapies ("previously treated") and 69 treatment-naïve patients. The confirmed overall response rate (ORR) assessed by blinded independent central review (BICR) in treatment-naïve patients was 43% (95% CI: 32, 56) and the median duration of response (DOR) was 10.8 months (95% CI: 6.9, NE), with 67% of the 31 responders having observed DOR of  $\geq 6$  months. In the previously treated population, the confirmed ORR per BICR was 43% (95% CI: 33, 55) and the median DOR was 11.1 months (95% CI: 9.5, 18.5), with 50% of the 37 responders having observed DOR of  $\geq 6$  months. These response rates, coupled with the durability of responses

observed, are reasonably likely to predict clinical benefit when considering the intended patient population.

Tepotinib appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. The most common ( $\geq 20\%$ ) adverse reactions were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea. Permanent discontinuation of tepotinib due to adverse reactions occurred in 20% of patients; the most frequent adverse reactions leading to permanent discontinuation were edema (5%), pleural effusion (2%), dyspnea (1.6%), general health deterioration (1.6%), and pneumonitis (1.2%). Safety issues identified as significant and serious during the NDA review were interstitial lung disease/pneumonitis and hepatotoxicity. These safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).

(b) (4)

approved labeling will state that there is no FDA-approved test for detection of MET exon 14 skipping alterations in NSCLC for selecting patients for treatment with tepotinib. EMD Serono has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect MET exon 14 skipping for identifying patients who may benefit from tepotinib.

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for accelerated approval. Tepotinib has a favorable benefit-risk profile in the indicated population based on the observed response rate and durable responses in a patient population with a life-threatening disease and an unmet medical need. While the ORR in the treatment-naïve population did not exceed that observed with available therapy of anti-PD-(L)1 antibody in combination with chemotherapy, the differing safety profile and option for treatment with a single agent administered orally make this a valuable treatment option for treatment-naïve patients. When considered in this context, the ORR and durable responses observed with tepotinib provide evidence indicating tepotinib is reasonably likely to predict clinical benefit over existing

treatments, even for treatment-naïve patients.

Given the relatively limited duration of follow-up and the number of patients in the primary efficacy analysis population for this application, the current data are considered adequate to support accelerated approval rather than regular approval. Due to the relatively low incidence of MET exon 14 skipping alterations in NSCLC, a randomized trial in this patient population is not feasible. To verify the clinical benefit of tepotinib in patients with NSCLC whose tumors harbor MET exon 14 skipping alterations, additional data will be obtained from the clinical trial which supported this approval, the VISION Study.

The review team’s regulatory recommendation is to grant tepotinib accelerated approval for the following indication: “For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.”

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>Lung cancer is the leading cause of cancer death in the U.S., with 80% to 85% of all lung cancer cases identified as non-small cell lung cancer (NSCLC).</li> <li>Mesenchymal-epithelial transition (MET) exon 14 skipping alterations have been identified as an oncogenic driver in NSCLC and have been reported in approximately 2-4% of NSCLC tumors.</li> <li>The 5-year survival rate for patients with metastatic NSCLC is &lt;10%. There is no randomized trial data available regarding survival specifically for patients with NSCLC whose tumors harbor MET exon 14 skipping alterations.</li> <li>Based on the limited data available for review, there is no indication that patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping have a higher response rate when treated with platinum-based chemotherapy and/or immunotherapy compared to the general population of patients with NSCLC.</li> </ul>	<p>Metastatic NSCLC harboring MET exon 14 skipping alterations is a life-threatening disease with poor survival.</p> <p>NSCLC harboring MET exon 14 skipping alterations is a rare subset of NSCLC; approximately 2- 4% of NSCLC tumors harbor MET exon 14 skipping alterations.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p style="text-align: center; color: blue;"><b>Current Treatment Options</b></p>	<ul style="list-style-type: none"> <li>• There is no therapy with regular approval specifically for the treatment of patients with NSCLC whose tumors harbor MET exon 14 skipping alterations. Capmatinib, another kinase inhibitor that targets MET, was granted accelerated approval by the FDA in May 2020 for the treatment of patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping.</li> <li>• Treatment options for patients with NSCLC whose tumors harbor MET exon 14 skipping alterations are the same as those used for NSCLC without a specific driver mutation identified.</li> <li>• For treatment-naïve patients this includes platinum-based chemotherapy and/or anti-PD- (L)1 antibody (including anti-PD-(L)1 antibody as a single agent or in combination with ipilimumab for PD-L1-positive NSCLC and in combination with ipilimumab and 2c of chemotherapy regardless of PD-L1 status). The highest ORRs, ranging from 48% to 58%, have been reported for platinum-based chemotherapy plus pembrolizumab (regardless of histology) and platinum-based chemotherapy plus atezolizumab with or without bevacizumab (for non-squamous NSCLC) with median durations of response ranging from 7.2 to 11.2 months.</li> <li>• For patients with progression of disease following platinum-based chemotherapy, treatment options include chemotherapy (single agent or docetaxel in combination with ramucirumab) associated with ORR 6-23% with median durations of response in the range of 4 to 9 months or single agent anti-PD(L)1 antibody if not received in the first-line setting, associated with ORR 14-20% with median durations of response in the range of 16 to 17 months.</li> </ul>	<p>There is an unmet medical need for patients with treatment-naïve and previously treated metastatic NSCLC whose tumors harbor MET exon 14 skipping alterations. This conclusion is based on the observed response rates, durations of response, and overall survival reported for therapies currently used in clinical practice for the treatment of this patient population.</p>
<p style="text-align: center; color: blue;"><b>Benefit</b></p>	<ul style="list-style-type: none"> <li>• The primary efficacy data supporting this NDA are from patients with NSCLC whose tumors harbor MET exon 14 skipping alterations either with progression following one or two prior therapies (“previously treated”) or who had received no prior therapy for metastatic NSCLC (“treatment-naïve) enrolled in the VISION study, a multicenter, non-randomized, open-label, multi-cohort study in patients with NSCLC with MET mutation and/or amplification.</li> </ul>	<p>The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORRs, along with the observed duration of responses, are clinically meaningful when considering the intended patient population.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• Among the 69 treatment-naïve patients, confirmed ORR per BIRC was 43% (95% CI 32, 56) with median DOR of 10.8 months (95% CI 6.9, NE).</li> <li>• Among the 83 patients who had received previous treatment, confirmed ORR per BIRC was 43% (95% CI: 33, 55) with median DOR of 11.1 months (95% CI 9.5, 18.5).</li> <li>• Given the relatively limited duration of follow-up for both treatment-naïve and previously treated patients in the primary efficacy analysis population for this application, the current data are considered adequate to support accelerated approval rather than regular approval.</li> <li>• A limitation of single arm trials is the potential for known and unknown patient selection bias.</li> </ul>	<p>While the ORR in the treatment-naïve population did not exceed that observed with available therapy of anti-PD-(L)1 antibody in combination with chemotherapy, the differing safety profile and option for treatment with a single agent administered orally make this a valuable treatment option for treatment-naïve patients. When considered in this context, the ORR and durable responses observed with tepotinib is <b>reasonably likely to predict clinical benefit</b> over existing treatments, even for treatment-naïve patients</p> <p>Additional data to verify the clinical benefit of tepotinib will be obtained from the clinical trial which supported this approval, the VISION study.</p> <p>Based on the demographic and baseline disease characteristics for the patients in the primary efficacy analysis population for this application, this population is comparable to the overall U.S. target population. Therefore, the benefit demonstrated in the VISION study is expected to extend to the post-market setting.</p>
<p><b>Risk and Risk Management</b></p>	<ul style="list-style-type: none"> <li>• The safety database for this NDA includes 448 patients with solid tumors who were treated with tepotinib at the recommended dose of 450 mg once daily, including 255 patients with NSCLC harboring METex14 skipping alterations from the VISION study. The safety data in this NDA is adequate to assess safety with reference to the overall U.S. target population.</li> <li>• Permanent discontinuation of tepotinib due to adverse reactions occurred in 20% of patients. The most frequent adverse reactions leading to permanent discontinuation of tepotinib were edema (5%), pleural effusion (2%), dyspnea</li> </ul>	<p>Although tepotinib can cause severe/serious toxicities, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. Tepotinib will be prescribed by oncologists who know how to monitor, identify, and manage such toxicities. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>(1.6%), general health deterioration (1.6%), and pneumonitis (1.2%).</p> <ul style="list-style-type: none"> <li>While 44% of patients had tepotinib dosing interrupted for adverse reaction, dose reductions due to adverse reactions occurred in 30% of patients.</li> <li>The most common adverse events (AEs) were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea.</li> <li>Safety issues considered significant and serious enough to warrant inclusion in the Warnings and Precautions section of the USPI for tepotinib are interstitial lung disease/pneumonitis and hepatotoxicity.</li> <li>In a single arm study such as the VISION study, a direct comparison of tepotinib-associated toxicity versus toxicity observed with current standard of care therapy (chemotherapy, anti-PD(L)1 antibodies) is not possible.</li> </ul>	

### 1.4. Patient Experience Data

**Patient Experience Data Relevant to this Application (check all that apply)**

X	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	
	X Patient reported outcome (PRO)	<b>Section 8.1.2 Study Results under Efficacy Results – Secondary or exploratory COA (PRO) endpoints</b>

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<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	

**X**

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Cross-Disciplinary Team Leader

## 2 Therapeutic Context

### 2.1. Analysis of Condition

#### The Applicant's Position:

Lung cancer remains the leading cause of cancer death in men and the second leading cause of cancer death in women worldwide, with 2.1 million new cases and 1.8 million deaths estimated globally for 2018 (Ferlay 2018). In the US, lung cancer is the second most common type of cancer, with 228,820 new lung cancer cases and 135,720 deaths projected to occur in 2020 (Siegel 2020).

Non-small cell lung cancer (NSCLC) accounts for 85% of all globally diagnosed lung cancer cases (Navada 2006; Sher 2008). There is a high unmet medical need in NSCLC, especially in patients with oncogenic-driven tumors. When untreated, NSCLC proves fatal in most patients within 1 year or less (Wao 2013). Up to one-fifth of NSCLC patients may not receive any treatment due to their older age, higher disease stage, or comorbidity (Rios 2018). Most newly diagnosed NSCLC patients have advanced disease: the proportion of NSCLC patients with Stage IV disease at diagnosis differs from region to region and has been reported in the range of 47% to 55% and Stage III disease at diagnosis in the range of 25% to 30% (Walters 2013).

A wide variety of human malignancies exhibit aberrant activation of the mesenchymal-epithelial transition factor (MET)/hepatocyte growth factor (HGF) pathway, which is associated with aggressive cancer phenotypes (Moosavi 2019). In NSCLC, poor prognosis has been especially seen with genetic alterations of the MET gene (*MET*) (Tong 2016). In contrast to overexpression of MET and HGF, which may be triggered by the tumor disease, *MET* exon 14 (*MET*ex14) skipping alterations have been identified to drive development of NSCLC via oncogenic activation of MET. A characteristic of oncogenic drivers in NSCLC is their apparent mutual exclusivity with other oncogenic drivers, which has also been shown for *MET*ex14 (Schrock 2016). Therefore, *MET*ex14 is considered a predictive marker for NSCLC and early testing is recommended to instruct selection of respective therapies.

In US-based studies with screening of *MET* alterations in patients with lung cancer, the prevalence of *MET*ex14 skipping alterations has been reported at around 3%. Overall, the assessment of prevalence of *MET*ex14 skipping alterations in the US population was based on 3 studies, which included representative populations with an adequate sample size: Schrock 2016 which identified 298 *MET*ex14 NSCLC patients in a total of 11,205 lung cancer cases (2.7%), Awad 2019 which described a prevalence of approximately 3% from 1,141 patients with lung cancer, and Sabari 2018 which identified 147 patients in a total population of 2,896 patients with NSCLC (5.0%).

After morphological diagnosis of NSCLC, current clinical guidelines strongly recommend performing molecular testing prior to the initiation of a treatment for advanced disease ([National Comprehensive Cancer Network \[NCCN\] Version 4 2020](#); [Kalemkerian 2018](#); [Planchard 2018](#)). If a predictive oncogenic marker such as EGFR, ALK, ROS1, BRAF, RET, or *METex14* is identified in a patient with NSCLC, treatment with the respective approved targeted agents is recommended instead of potential chemotherapy and/or immune checkpoint inhibitors. This recommendation is based on the observation that efficacy of these available non-targeted therapies may be negatively influenced by the presence of an oncogenic driver such as EGFR and ALK but also *METex14* in NSCLC ([Gainor 2016](#); [Sabari 2018](#)).

*METex14* skipping alterations in NSCLC give rise to an aberrant signaling receptor that is targetable with selective MET inhibitors. There are no available therapies in the US that specifically target *METex14* skipping alterations. Very recently, the selective MET inhibitor capmatinib received accelerated approval in a line agnostic, metastatic *METex14* NSCLC population by the US FDA ([capmatinib US prescribing information](#)). Among the efficacy population of 97 patients including 28 treatment-naïve and 69 previously treated patients with NSCLC *METex14*, there were 47 responders after capmatinib treatment. The available non-targeted therapies for patients harboring *METex14* skipping alterations are considered unsatisfactory with limited clinical benefit ([NCCN Version 4 2020](#)). This still underlines the high unmet medical need for selective treatment options in the metastatic NSCLC *METex14* population independent of prior therapy.

**The FDA's Assessment:**

FDA agrees with EMD Serono's analysis of condition, as described.

## 2.2. Analysis of Current Treatment Options

### The Applicant's Position:

NSCLC is a serious and life-threatening disease. At the time of diagnosis, most patients with NSCLC present with advanced disease, at which point curative treatments such as surgical resection are not feasible. For the selection of therapies for advanced NSCLC, current clinical guidelines strongly recommend performing molecular testing prior to the initiation of an anticancer drug (NCCN Version 4 2020; Kalemkerian 2018; Planchard 2018). If a predictive oncogenic marker such as EGFR, ALK, ROS1, BRAF, RET or *MET*ex14 is identified in an NSCLC patient, treatment with the respective approved targeted agents is to be applied, when possible. In non-oncogenic altered NSCLC, biomarker testing for immune-oncology therapy is similarly important to enable decisions for immune checkpoint inhibitor monotherapy or combinations with chemotherapy (Hanna 2020).

A characteristic of oncogenic drivers in NSCLC is their apparent mutual exclusivity, which has also been shown for *MET*ex14 skipping alterations (Schrock 2016). Therefore, targeted treatment for other oncogenic driver alterations is not considered available therapy for NSCLC harboring *MET*ex14 skipping alterations. Instead, non-targeted therapies are considered available therapies, although the presence of oncogenic drivers including *MET*ex14 might reduce their efficacy as shown for immune checkpoint inhibitors (Gainor 2016; Sabari 2018; NCCN Version 4 2020). Current clinical guidelines refer to the following treatment categories for non-targeted NSCLC treatments, taking into account the dependence on programmed cell death 1 ligand 1 (PD-L1) expression status and potential contraindications (NCCN Version 4 2020; Hanna 2020):

- Checkpoint inhibitors in combination with platinum-containing chemotherapy, such as pembrolizumab in combination with carboplatin and pemetrexed, with an objective response rate (ORR) of 48% and a median progression-free survival (mPFS) of 8.8 months (pembrolizumab US PI).
- Checkpoint inhibitor monotherapy, such as pembrolizumab in metastatic NSCLC with PD-L1 expression (TPS  $\geq$  1%) or ineligibility for chemotherapy, with an ORR of 27% and an mPFS of 5.4 months (pembrolizumab US PI).
- Platinum-doublet chemotherapy combinations in case of contraindications to immune checkpoint inhibitors, with an ORR of about 30% and a median time to progression of 4 to 6 months (NCCN Version 7 2019).

After initial treatment for metastatic NSCLC, the following therapies are recommended in case the patient experienced disease progression on or after platinum-containing chemotherapy:

- Checkpoint inhibitor monotherapy with either pembrolizumab, atezolizumab or nivolumab; a best ORR of 20% was noted for nivolumab with an mPFS of 3.5 months (nivolumab US PI).

- Combination of docetaxel with ramucirumab with an ORR of 23% and an mPFS of 4.5 months ([ramucirumab US PI](#)).

Clinical guidelines also recommend considering the patient's performance status, age, and disease severity, with regards to the safety and administrative burden of the available immune- and chemotherapy-based agents. This may be of particular importance for *METex14* NSCLC, as the disease generally manifests in elderly patients ([Schrock 2016](#); [Tong 2016](#)) who are more prone to comorbidities and frailty. Platinum- and pemetrexed-based chemotherapy is characterized by hemato-, renal- and neuro-toxicity, as well as risk of tumor lysis syndrome; cardiotoxicity and severe cutaneous reactions have been reported upon treatment with docetaxel ([docetaxel US PI](#)). Patients receiving immune checkpoint inhibitors often experience hypersensitivity and immune-related reactions (such as thyroiditis, pneumonitis or interstitial lung disease [ILD]; [Suzuki 2020](#)), which can be life-threatening. These therapies are mostly administered at the hospital and require frequent visits and monitoring, as well as dose adjustments ([atezolizumab US PI](#); [Azoury 2015](#); [carboplatin US PI](#); [cisplatin US PI](#); [Cole 2019](#); [docetaxel US PI](#); [pembrolizumab US PI](#)).

In the absence of an available targeted therapy for *METex14* NSCLC in the US, patients may need to rely on immune checkpoint inhibitor-based or platinum chemotherapy-based treatments. However, the efficacy of available non-targeted therapies may be negatively influenced by the presence of an oncogenic driver ([NCCN Version 4 2020](#)). These observations underscore the high unmet medical need for efficacious and well-tolerated selective treatments with a convenient mode of administration for patients with advanced NSCLC harboring *METex14* skipping alterations. Tepotinib is a highly selective, targeted therapy, with substantial and sustainable efficacy, tolerable and manageable safety profile, and a convenient mode of administration, offering an effective therapeutic solution to address the high unmet need for this life-threatening disease.

**The FDA's Assessment:**

FDA agrees with EMD Serono's analysis of current treatment options for metastatic NSCLC. Additional options for the initial treatment of metastatic NSCLC, approved in May 2020, include nivolumab in combination with ipilimumab for patients with metastatic NSCLC whose tumors express PD-L1 (ORR 36%) and nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (ORR 38%). The Applicant's position stated in the last sentence above is not relevant to this section of the review.

### 3 Regulatory Background

Unless stated otherwise, the strength representation in this document corresponds to tepotinib hydrochloride hydrate and is consistent with the terminology used in nonclinical and clinical CTD modules, nonclinical and clinical reports, as well as statistical outputs.

To this end, "500 mg tepotinib" corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (the free base form), and "250 mg tepotinib" corresponds to 250 mg tepotinib hydrochloride hydrate and is equivalent to 225 mg tepotinib (the free base form). The active ingredient is tepotinib hydrochloride hydrate and the active moiety is tepotinib (free base; refer to Module 3, Section 2.S.1.2).

#### 3.1. U.S. Regulatory Actions and Marketing History

##### The Applicant's Position:

Tepotinib is an NME and is not currently marketed in the US.

##### The FDA's Assessment:

FDA agrees that tepotinib is not approved or currently marketed in the United States. Tepotinib received regulatory approval in Japan (March 2020) and is marketed in Japan for the treatment of patients with unresectable, advanced or recurrent NSCLC with *MET*ex14 skipping alterations.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

##### The Applicant's Position:

**Table 1: Key Interactions with FDA**

Interaction	Description
Pre-IND/Pre-Phase III; November 2015	Discuss the clinical development program for tepotinib in NSCLC; IND 128073
Agreed Initial Pediatric Study Plan (iPSP); September 2016	 (b) (4)

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Interaction	Description
Type C (CMC); May 2017 Type C; July 2017	<div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> <p>Designation of drug substance starting materials. Acceptability of clinical pharmacology and nonclinical plans intended to support future marketing applications for tepotinib for the 2 proposed indications above.</p>
Preliminary Breakthrough Designation request; March 2018	Receive FDA advice on preliminary clinical activity data available to support a potential breakthrough designation request for advanced (Stage IIIB/IV) NSCLC with <i>METex14</i> skipping alterations.
Type C meeting; March 2018	Bioequivalence study proposal to support switching from TF2 to TF3.
Type C meeting; August 2018	To align on data package for accelerated (FDA) approval of tepotinib in patients with advanced or metastatic (Stage IIIB/IV) <i>METex14</i> -NSCLC.
Breakthrough designation status; September 2019	Acceptability of data to support full breakthrough designation in <i>METex14</i> -NSCLC patients; breakthrough designation granted.
Type C meeting; September 2019	Discuss product comparability to support introduction of a new product formulation during generation of confirmatory evidence.
Type C meeting; September 2019	Align on a pathway to support registration of tepotinib, via accelerated approval pathway for treatment of patients with NSCLC with <i>METex14</i> skipping alterations; Align on a plan for confirmatory evidence generation to support regular approval; Agency input on product comparability to support introduction of a new product formulation during generation of confirmatory evidence; Agency input on data format and content to facilitate dossier planning.
Amended Agreed iPSP; December 2019	Indication: for the treatment of patients with advanced NSCLC whose tumors harbor <i>METex14</i> skipping alterations.
Type B, Pre-NDA (CMC) meeting; January 2020	To discuss and reach an agreement regarding the drug product dissolution method as well as the content and structure of the proposed NDA as it relates to the Quality submission package.
Type B meeting (nonclinical package); February 2020	To reach an agreement regarding the sufficiency of the planned nonclinical package to support the proposed NDA.
Type B, Pre-NDA meeting; May 2020	To reach an agreement on the NDA package that will be used to support an accelerated approval, including the content and format of a complete application.
RTOR Teleconference; May 2020	To reach an agreement on the proposed RTOR submission strategy.

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CMC=Chemistry, Manufacturing, and Controls, EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor, iPSP=initial Pediatric Investigation Plan, METex14=*MET* exon 14, NDA=New Drug Application, NSCLC=non-small cell lung cancer, RTOR=Real-Time Oncology Review, TF=Tablet Formulation.

The FDA's Assessment:

FDA was not able to verify the CMC meeting listed on May 2017 mentioned above in the Key Interactions with FDA. Furthermore, the July 2017 Type C meeting was a Written Response Only (WRO) and the Meeting Minutes for acceptability of clinical pharmacology and nonclinical plans intended to support future marketing applications were issued in September 2017. The bioequivalence study proposal to support switching from TF2 to TF3 as a Type C meeting in March 2018 was cancelled after the applicant received the preliminary comments in May 2018. The meeting in August 2018 listed as a Type C meeting was an end of phase 2 (EOP2) meeting to align data package for accelerated FDA approval of tepotinib in patients with advanced or metastatic (Stage IIIB/IV) *MET* exon14 NSCLC.

This review was conducted under Project Orbis which provides a framework for concurrent submission and review of oncology drugs among international partners. For this application, a modified Project Orbis was undertaken because of the timing of submission to other regulatory agencies. FDA collaborated with HC Canada, HAS Singapore, TGA Australia, and Swissmedic Switzerland.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1 Office of Scientific Investigations (OSI)

The review division (DO2) and OSI selected two clinical investigators, Drs. Paul Paik (Site 104) and Xiuning Le (Site 152) as well as the (b) (4) central imaging contract research organization (CRO), for clinical inspections. Drs. Enriqueta Felip Font (Site 601) was also selected using risk-based approach including high enrollment and efficacy results; however, the scheduled inspection of Dr. Font in Spain was cancelled because of the COVID-19 pandemic.

Dr. Paul Paik (Site 104) had screened 22 patients and enrolled 14, all in Cohort A, with a subset of 9 patients enrolled at the site prior to April 2, 2019. This was the first FDA inspection for this investigator and no significant data discrepancies were identified between source records at the site and the submitted data listings. There was no under-reporting of adverse events or protocol deviations. The inspection found no regulatory violations at the site.

Dr. Xiuning Le (Site 152) had screened 29 patients and enrolled 12 patients into the study. Two of the enrolled patients at the site are in the efficacy analysis population for the submission. No significant data discrepancies were identified. There was no under-reporting of adverse events or protocol deviations. The inspection found no regulatory violations at the site.

(b) (4) was contracted to conduct the independent radiology review for the VISION study and was inspected as a data audit and surveillance inspection. There were three patients who had an incorrect response assessment in the data listings due to a protocol deviation occurring from November 13, 2018 to December 12, 2019 whereby source data (cytology reports) were not sent (b) (4). The missing cytology reports were subsequently sent (b) (4); however, this occurred after the January 1, 2020 data cutoff and the delayed cytology results were not incorporated into the endpoint evaluations. A total of 11 patients were affected. The inspection revealed that this deviation affected the response assessments for 3 of the 11 patients. The sponsor corrected the discrepancies and submitted updated data within the September 3, 2020 submission (with a July 1, 2020 data cutoff.) The changes in response based on the corrected data improved the outcome of the drug for Subject (b) (6) and worsened the outcome for Subjects (b) (6). Please refer to the review from the FDA OSI Reviewer, Michele Fedowitz for additional details. OSI concluded that the issue of cytology reports not being sent (b) (4) was fixed and it was a mistake from the CRO (b) (4). EMD Serono identified, corrected, and incorporated a new process in place to prevent future lapses.

Based on the results of the three completed inspections, the clinical data generated from these three investigator sites appear to be reliable and adequate in support of this NDA.

#### 4.2. Product Quality

The CMC review team confirmed that the proposed impurity levels for the three related impurities are qualified and analytical methods are adequately validated. All methods except for the high-performance liquid chromatography (HPLC) and Headspace gas chromatography methods are compendial. Retest date of 30 months may be granted when stored at the proposed storage conditions.

#### 4.3. Clinical Microbiology

Not applicable for this application.

#### 4.4. Devices and Companion Diagnostic Issues

At the time of submission, the Applicant intended to seek approval of tepotinib for the treatment of patients with MET exon 14 skipping metastatic NSCLC (b) (4)

[Redacted]

[Redacted] (b) (4)

Given the efficacy of tepotinib in patients with metastatic NSCLC harboring METex14 skipping alterations, the low prevalence of the biomarker in patients with NSCLC, and the availability of non-companion diagnostic testing, the clinical review team determined that it is in the best interest of U.S. patients to approve tepotinib (b) (4)

[Redacted] approved labeling will state that there is no FDA-approved test for detection of MET exon 14

skipping alterations in NSCLC for selecting patients for treatment with tepotinib. EMD Serono has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect MET exon 14 skipping for identifying patients who may benefit from tepotinib.

## 5 Nonclinical Pharmacology/Toxicology

### 5.1. Executive Summary

The mesenchymal-epithelial transition factor (c-Met) receptor is a widely expressed cell surface receptor that upon phosphorylation induces activation of several downstream signaling cascades including the Ras/ERK and PI3K/AKT pathways. c-Met and its ligand hepatocyte growth factor (HGF) have been implicated in carcinogenesis and tumor progression by promoting cancer cell proliferation, survival, migration and invasion, tumor angiogenesis, and resistance to other cancer therapies. c-Met signaling in tumor cells can be activated by autocrine or paracrine HGF as well as c-Met amplification or mutation. A diverse set of mutations (point mutations, insertions/deletions) affecting the exon-intron boundaries of exon 14 of the MET gene (METex14 skipping alterations) can occur in non-small cell lung cancer (NSCLC) and in other cancer indications. METex14 skipping alterations causes alternative splicing and to deletion of the entire exon 14-encoded sequences on the mRNA and protein level leading to loss of the intracellular, juxtamembrane domain of MET, thereby leading to loss of negative regulatory elements controlling MET kinase activity and MET protein expression levels. METex14 alterations were shown to result in oncogenic activation of MET and to be associated with sensitivity to MET inhibitors (Frampton et al., 2015; Awad et al., 2016).

Tepotinib (EMD 1214063) is a small molecule inhibitor of the c-Met receptor with an established pharmacologic class of kinase inhibitor. In biochemical kinase screening assays tepotinib inhibited wild type c-Met with an  $IC_{50}$  of 1.7 nM and, at a concentration of 0.1  $\mu$ M, showed greater than 84% inhibition of Met variants arising from point mutations in the kinase domain or the juxtamembrane domain, such as T992I, V1092I, T1173I, and M1250T. In an in vitro investigation of potential off-target activity, tepotinib inhibited the melatonin ML2 receptor and imidazoline I1 receptor with  $IC_{50}$  values of 2.4 and 35 nM, respectively. Based on a maximum concentration ( $C_{max}$ ) of 1050 ng/mL and human protein binding of approximately 98%, the free concentration of tepotinib is  $\sim$  40 nM, therefore, these concentrations are potentially clinically relevant in patients treated at the once daily oral dose of 450 mg. The major human metabolite, M506 (MSC2571109A), which accounts for approximately 31% of human exposure, did not demonstrate off-target activity at clinically relevant concentrations. In cellular assays using lung cancer cell lines, tepotinib inhibited ligand-dependent c-Met phosphorylation with an  $IC_{50}$  of 5.4 nM and M506 inhibited ligand-induced c-MET phosphorylation with  $IC_{50}$  values ranging from 13 to 26 nM. In cancer cell lines harboring c-Met gene amplifications and high levels of constitutive c-Met phosphorylation, incubation with tepotinib led to dose-dependent inhibition of c-Met phosphorylation with  $IC_{50}$  values ranging from 1.1 to 2.9 nM. In addition, tepotinib inhibited downstream signaling such as activation of Gab1, Akt, or ERK with  $IC_{50}$  values ranging from 0.02 to 3.4 nM as well as HGF-dependent

colony formation, cell migration, and anchorage dependent growth. Tepotinib inhibited cellular proliferation in cells that overexpress c-Met due to gene amplification with an  $IC_{50}$  of 6.3 nM, but inhibited proliferation of cells with normal c-Met expression with greater than 400-fold less sensitivity ( $IC_{50} = 2.8 \mu M$ ) in the absence of HGF stimulation.

Considering the intended clinical indication for the treatment of patients with NSCLC with METex14 skipping alterations, the Applicant evaluated the anti-tumor activity of tepotinib against tumors with METex14 skipping alterations both with and without MET gene amplification or tumors containing only MET gene amplification without the skip alteration. In mice implanted with human tumor cell lines harboring METex14 skipping alterations with and without gene amplification, maximal anti-tumor activity occurred at doses as low as 6 mg/kg once daily, leading to complete tumor regression in 100% of mice bearing tumors with both the METex14 skipping alteration and gene amplification. At a daily dose of 100 mg/kg tepotinib decreased tumor volume in mice bearing tumors with METex14 alterations without gene amplification approximately 80%, suggesting increased sensitivity of tumors with both METex14 skipping alterations and gene amplification. Tepotinib had little to no effect on tumor growth in transgenic HGF mice bearing tumors with oncogenic EGFR kinase domain mutations, despite high c-Met expression and MET activation. M506, the major active metabolite of tepotinib, did not have anti-tumor activity in vivo even at dose levels that led to higher exposure of M506 compared to tepotinib despite showing transient inhibition of MET phosphorylation, suggesting that the metabolite contributes little to tepotinib activity.

Tepotinib also showed anti-tumor activity against tumor explants derived from human brain metastases of primary tumors with high MET gene amplification in orthotopically implanted mice, indicating that tepotinib can elicit an anti-tumor response across the blood brain barrier (BBB); tepotinib was present in brain tissue following a 24-hour IV infusion study despite the lack of radio-labelled tepotinib exposure in the brains of healthy animals after a single low dose (6 mg/kg) oral exposure study. Tepotinib-related anti-tumor activity was comparable to that of commercially available oral c-Met inhibitors capmatinib and crizotinib in mice bearing the same explants as subcutaneous tumors. In addition, tepotinib led to decreases in both the number of lung metastases and the size of the primary hepatic tumor in mice orthotopically implanted with a MET amplified and constitutively active human hepatocellular tumor cell line. The Applicant evaluated the effects of tepotinib on vital organ function in a panel of in vitro and in vivo safety pharmacology studies. Since Met signaling is necessary for skin wound healing, the Applicant investigated oral tepotinib at dose up to 50 mg/kg for up to 10 days and showed that the drug did not negatively impact wound healing in mice with a 5 mm-thick excision wound. In cardiovascular safety studies neither tepotinib nor M506 exhibited the potential to induce QT prolongation in vitro and there were no changes in cardiovascular parameters, including QT, in rats or dogs in single-dose safety pharmacology studies at doses up to 70 mg/kg or in repeat-dose toxicology studies in dogs at doses up to 30 mg/kg (~0.3 times the human

exposure at the 450 mg dose) for 39 weeks, though the highest tested doses in these studies resulted in exposures lower than the human exposure at the 450 mg dose. CNS functions were not altered with single doses of tepotinib up to 200 mg/kg in rats or in repeat-dose toxicology studies in dogs up to 40 mg/kg/day. No CNS toxicities have been reported in patients treated with tepotinib. Finally, while in vitro assays suggested a potential for tepotinib-mediated phototoxicity, a subsequent single-dose in vivo study in pigmented rats did not show increased eye or skin toxicity at doses up to 1500 mg/kg, indicating that warning for phototoxicity is not warranted.

To assess the safety of tepotinib, the Applicant conducted GLP-compliant toxicology studies of up to 26-weeks in Sprague Dawley rats and 39 weeks Marshall Beagle dogs. Both species experienced liver toxicity following tepotinib exposure, with dose-dependent elevated liver enzymes (AST, ALT, and/or ALP), histopathologic changes, liver enlargement, and, in the 28-day rat study supporting the initial first-in-human trial, periportal edema. Liver enzyme increases are also a common clinical event. Liver toxicity was reversible in both species upon withdrawal of the drug. In both species, TK analysis showed greater tepotinib exposure over time, indicating drug accumulation and higher exposures in females than in males.

In a 26-week toxicology study, rats received tepotinib orally at doses of 15, 45, or 135 mg/kg per day (corresponding to 0.04, 0.06, and 0.13 times the clinical AUC of 22,200 ng\*hr/mL at the 450 mg daily dose) for 26 weeks, followed by an 8-week recovery period. There were subtle increases in inorganic phosphate with concomitant dose-dependent increases in alkaline phosphatase. Males exposed to tepotinib had reduced thymic size. Females had significantly increased size of ovaries and adrenal glands. While tepotinib had no clear effect on respiratory parameters in rats at doses up to 200 mg/kg in single dose studies or in the repeat-dose toxicology studies in either species, there were histopathological findings in the lung in rats, predominantly at the high dose level. In females at the 135 mg/kg group findings included macroscopic discoloration of the lungs, as well as microscopic alveolar aggregation, fibrosis with foam cells, and focal alveolar hemorrhage. One male in the 135 mg/kg group and 1 female in the 15 mg/kg recovery group had chronic necrotizing lung inflammation; pneumonitis and interstitial lung disease occurs clinically and is included in the warnings section of the label. In a 28-day study in rats at the high dose level of 90 mg/kg exposure in female rats was approximately half of the human exposure at the 450 mg clinical dose; additional findings at this dose included increased weight gain without increased food consumption, suggestive of edema. In a second 28-day study in rats conducted to qualify impurities the Applicant included an assessment of the M506 metabolite following administration of an impurity-spiked formulation of tepotinib. At a tepotinib dose of 450 mg/kg (resulting in exposures in female rats approximately equal to the human exposure at the 450 mg dose), the lung, liver, and intestinal tract were target organs. At the highest tested dose of 2000 mg/kg, animals were sacrificed early, apparently due to gastric toxicity, primarily a lack of gastric motility. At the non-lethal

tepotinib dose of 450 mg/kg, exposures to the metabolite in females were as high as 3070 h\*ng/mL (~40% of the 7530 h\*ng/mL exposure in patients at the proposed clinical dose) providing evidence of reasonable exposure of the metabolite in animals to support its safety in the proposed patient population.

Dogs received 3, 10, or 30 mg/kg of tepotinib via oral administration of a hard gelatin capsule every day for 39 weeks, followed by a 12-week recovery period. Exposures at the high dose of 30 mg/kg were approximately 0.3 times (females) to 0.15 times (males) the AUC in humans at the 450 mg clinical dose. Dogs experienced dose-dependent increases in vomiting and diarrhea. Males in the 30 mg/kg group had lower food consumption and did not gain as much weight as dogs in other groups. Four animals in the high-dose group had increased lacrimation (tearing). In addition to the liver, pathology findings in tepotinib-exposed dogs were generally mild and included changes in adrenal glands (decreased cortical vacuolation) and bile duct (hyperplasia, lymphoplasmacellular infiltrates). Females at all dose levels experienced milky retention in mammary glands. Though exposures in dog studies were significantly lower than exposures in humans and there were no mortalities in dogs at the highest doses tested in studies of 28 days or longer, the liver and bile duct findings appear to predict human hepatic findings and GI toxicity precluded higher dosing.

In a standard genotoxicity battery, neither tepotinib nor the major metabolite M506 were positive in either the Ames or the in vitro micronucleus assay regardless of metabolic activation. Tepotinib was also negative in the in vivo micronucleus assay. Dedicated carcinogenicity studies were not conducted with tepotinib, as they are not needed to support the use of a drug intended to treat patients with advanced cancer.

To assess the potential developmental and reproductive toxicity, the Applicant conducted two embryo-fetal development studies of oral tepotinib dosed daily during organogenesis on Gestation Days (GD) 6-18 in New Zealand White (NZW) rabbits at doses of 0.5, 5, and 25 mg/kg (Study 1) or 50, 150, and 450 mg/kg (Study 2). At 450 mg/kg/day, 4 of 11 animals were found dead and another 3 died prematurely. Remaining rabbits in the 450 mg/kg group (approximately 75% of the clinical tepotinib AUC exposure of 22,200 ng\*hr/mL at the 500 mg daily dose) were euthanized early due to morbidity. At the 150 mg/kg dose level (about 50% of the human exposure) two dams had complete abortions resulting in an average 33% post-implantation loss for the dose level. At dose levels  $\geq$  5 mg/kg there was an increased frequency of skeletal abnormalities, including misshapen scapula and clavicle, malpositioned calcaneus and talus, malrotated hind paw, and incomplete ossification of sternebra. One fetus from a dam at the 0.5 mg/kg dose level had an ectopic kidney and 1 fetus from a dam at the 5 mg/kg dose level had spina bifida. Because of the clear fetal toxicity at doses resulting in exposures less than the human exposure at 450 mg daily clinical dose, studies in a second species were not warranted. Based on data from the embryo-fetal development studies a warning for embryo-

fetal toxicity is included in the label for TEPMETKO. No studies were conducted or necessary to investigate the presence of tepotinib in milk. As many drugs are secreted in breastmilk, the label includes a warning not to breastfeed during treatment with TEPMETKO and for 1 week after the final dose. From a pharmacology/toxicology perspective, there are no outstanding issues that would prevent the approval of tepotinib in patients with metastatic NSCLC (b) (4)

## 5.2. Referenced NDAs, BLAs, DMFs

### The Applicant's Position:

None.

## 5.3. Pharmacology

### Primary pharmacology

#### The FDA's Assessment (all data entered by FDA):

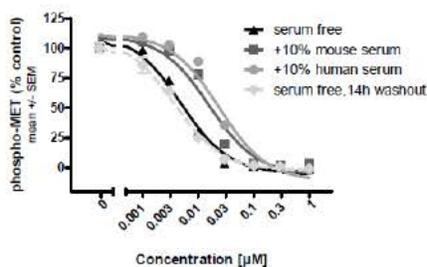
##### In vitro pharmacology

The Applicant assessed the ability of tepotinib to inhibit MET and at least 400 other kinases in a series of kinase screens (PSR-NCETech-EMD1214063-001, PSR-NCETech-EMD1214063-002, 20150521-EMD-RC-KP-38, PSR-NCETech-EMD1214063-003, and SER1071). In these screens, 10  $\mu$ M of tepotinib inhibited ALK, Axl, Blk, Ron, and TrkB by greater than 50%. Further analysis showed that 1  $\mu$ M of tepotinib still inhibited Axl, IRAK4, TrkA, and TrkC by greater than 50%, with IRAK4 and TrkC inhibited at greater than 75% in one, but not in a second, kinase screen at the same concentration. In a 298-panel radiometric Eurofins kinase screen (SER1071 study), however, 0.1  $\mu$ M of tepotinib did not inhibit any kinase unrelated to MET. In a second screen exploring the 0.1  $\mu$ M concentration of the drug (20150521-EMD-RC-KP-38), tepotinib inhibited wild type MET by greater than or equal to 99% at 1 and 0.1  $\mu$ M and inhibited MET variants T992I, V1092I, T1173I, and M1250T at greater than 80% at both concentrations. Tepotinib inhibited c-Met with an  $IC_{50}$  of 1.7 nM.

The Applicant evaluated the ability of tepotinib (EMD 1214063) to inhibit HGF-induced and ligand-independent c-Met phosphorylation and downstream signal transduction in Study PSR-NCETech-EMD1214063-001. Incubation of A549 lung cancer cells with 100 ng/mL recombinant human HGF in serum-free media led to increased c-Met phosphorylation; pre-incubation with tepotinib for 30-45 minutes prior to stimulation with HGF led to dose-dependent inhibition of c-Met phosphorylation with an  $IC_{50}$  of 5.4 nM. A 30-45 min incubation of A549 cells with tepotinib and then subsequent removal of extracellular tepotinib led to inhibition of HGF-induced c-Met phosphorylation for more than 14 hours, with an  $IC_{50}$  of 5.3 nM. The addition of 10% (v/v) murine or human serum shifted  $IC_{50}$  values to 21 and 23 nM, respectively, for

inhibition of HGF-induced c-Met phosphorylation (Figure 1). Investigators also determined the ability of the major circulating human metabolite, M506 (MSC2571109A), to inhibit HGF-induced c-MET phosphorylation in A549 cells in the same manner as described above. Similar to the parent compound, M506 inhibited HGF-induced c-MET phosphorylation with IC<sub>50</sub> values of 13 and 26 nM using 2 different batches of the metabolite (Study ONCIRA00346CK; data not shown).

**Figure 1: Tepotinib inhibited HGF-induced c-Met phosphorylation in A549 lung cancer cells**



(Excerpted from Study PSR-NCETech-EMD1214063-001)

The Applicant evaluated the effects of tepotinib on ligand-independent c-Met phosphorylation using EBC-1 lung, and GLT-16 and Hs746T gastric cancer cell lines, all of which harbor c-Met gene amplifications and display high levels of constitutive c-Met phosphorylation. Incubation of these cell lines with tepotinib for 45 minutes led to dose-dependent inhibition of c-Met phosphorylation with IC<sub>50</sub> values of 1.1 nM (EBC-1), 2.9 nM (GTL-16), and 2.5 nM (Hs746T). The Applicant also assessed the effects of tepotinib-mediated inhibition of c-Met phosphorylation on downstream signal transduction via Western blotting using phospho-site specific antibodies for Gab-1, Akt, Erk1/2, and on c-Met itself. IC<sub>50</sub> values for inhibition of downstream signaling were in the nanomolar to subnanomolar range (Table 2).

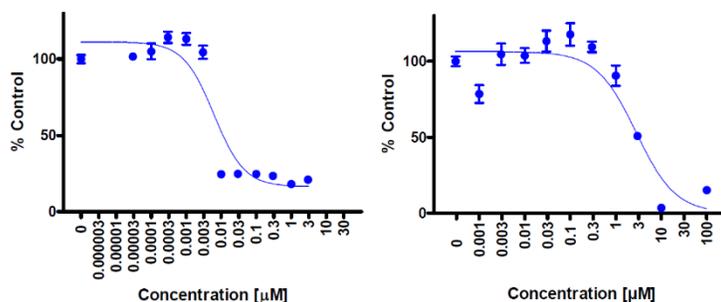
**Table 2: Tepotinib inhibited HGF-mediated and ligand-independent c-Met phosphorylation and activation of downstream signaling proteins**

Inhibition of c-Met phosphorylation				
	A549*	EBC-1	GLT-16	Hs746T
IC <sub>50</sub> (ELISA)	5.3 nM	1.1 nM	2.9 nM	2.5 nM
IC <sub>50</sub> (Western)	-	9.2 nM	4.8 nM	1.0 nM
Inhibition of downstream signaling				
IC <sub>50</sub> (Gab1)	-	3.4 nM	1.9 nM	0.4 nM
IC <sub>50</sub> (Akt)	-	1.6 nM	ND	0.04 nM
IC <sub>50</sub> (ERK)	-	0.75 nM	ND	0.02 nM

\*HGF-mediated c-MET phosphorylation. EBC-1 – NSCLC with MET gene amplification. GLT-16 – gastric cancer with MET gene amplification. Hs746T – gastric cancer with MET gene amplification and METex14 skipping. '-' = not conducted. ND = levels of pAKT and pERK in GLT-16 cells could not be detected in sufficient amounts to allow for reliable quantification.

In Study PSR-ONC-EMD1214063-002, the Applicant evaluated the effect of tepotinib on proliferation, cell migration, and anchorage independent growth in cell lines with ligand-dependent and independent c-Met signaling. For cell proliferation studies, investigators incubated cells seeded in 96 well plates with a concentration range of tepotinib (0.1 nM to 30  $\mu$ M) for 48 hours and measured live cells using a colorimetric enzyme assay. Tepotinib inhibited the viability of MKN-45 gastric cancer cells that overexpress c-Met due to gene amplification with an  $IC_{50}$  of 6.2 nM; however, tepotinib had little effect on the gastric cancer cell line SNU-16 with normal c-Met gene expression, with inhibition only at much higher concentrations ( $IC_{50}$  = 2.8  $\mu$ M; Figure 2).

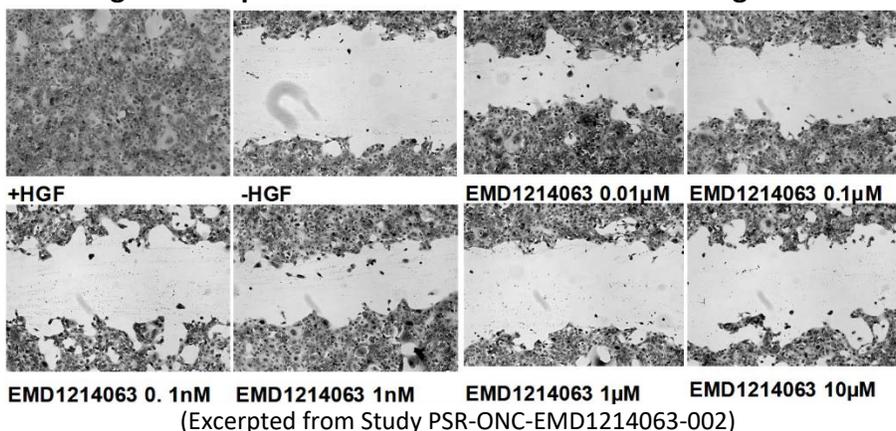
**Figure 2: Tepotinib inhibited proliferation of MKN-45 (left) and SNU-16 (right) cells**



(Excerpted from Study PSR-ONC-EMD1214063-002)

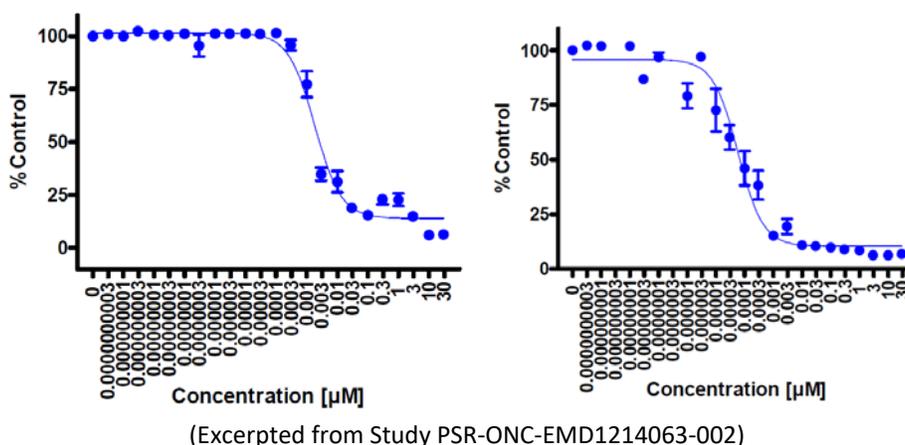
In an assay to assess cell migration, investigators pre-treated a dense cellular layer of H441 lung cancer cells with tepotinib at concentrations ranging from 0.1 nM to 10  $\mu$ M for 1 hour then scratched the cell layer with a pipette tip and removed media to replace it with media containing HGF (100 ng/mL) with or without tepotinib for an additional 24 hours. HGF induced cell migration demonstrated by the lack of scratch visibility at the 24-hour imaging timepoint; however, the addition of tepotinib inhibited HGF-induced cell migration (recovery from the scratch) at concentrations as low as 0.1 nM (Figure 3).

**Figure 3: Tepotinib inhibited HGF-induced cell migration**



The Applicant assessed the effects of tepotinib on anchorage independent growth using S114 cells which express human c-Met and human HGF and can form colonies in soft agar. Investigators plated cells in solidified agar and overlaid the agar with tepotinib containing media on Days 1 and 8 or only on Day 8. Tepotinib treatment resulted in a dose-dependent inhibition of further colony growth in cells treated on only Day 8 with an IC<sub>50</sub> of 1.8 nM. Inhibition was more pronounced when treated on both Days 1 and 8 with IC<sub>50</sub> < 1 nM (Figure 4).

**Figure 4: Inhibition of S114 anchorage independent growth by tepotinib treatment on Day 8 only (left) or Days 1 and 8 (right)**

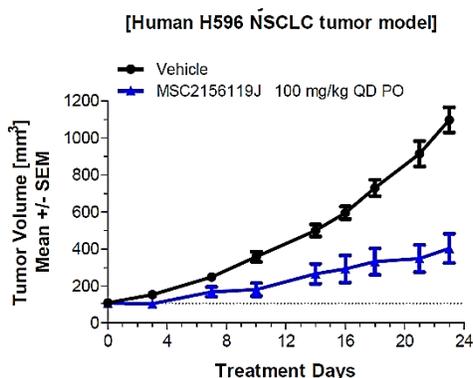


### In vivo pharmacology

In Study ONC207-1-83MFH the Applicant evaluated the anti-tumor activity of tepotinib in a mouse xenograft model using human H596 NSCLC cells which carry a METex14 skipping alteration with normal MET gene copy number and dependency on HGF. Investigators treated

humanized HGF SCID-1 female adult mice (10/group) bearing H596 tumors (~100-150 mm<sup>3</sup>) orally once daily for 23 days with vehicle or 100 mg/kg tepotinib. Treatment with tepotinib led to an approximately 80% decrease in tumor volume compared to controls and no toxicities or deaths occurred during the treatment (Figure 5).

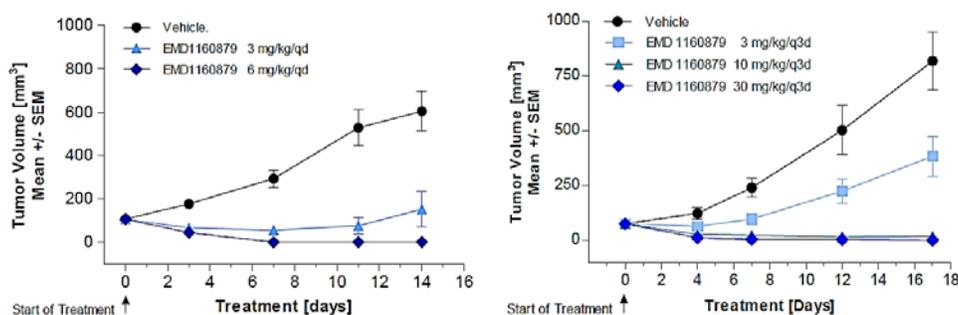
**Figure 5: Daily tepotinib decreased tumor growth in mice bearing H596 tumors**



MSC2156119J = EMD 1214063, tepotinib HCl (clinical candidate).  
(Excerpted from Study ONC207-1-83MFH)

In adult female CD-1 mice bearing Hs746T gastric cancer cells (METex14 skipping alteration plus concomitant high-level MET gene amplification), treatment with daily tepotinib at doses of 3 and 6 mg/kg led to tumor regression in 5/10 and 10/10 mice, respectively; administration once every 3 days at doses of 3, 10, and 30 mg/kg also resulted in decreased tumor growth compared to controls with complete tumor regression at doses ≥6 mg/kg (Figure 6; Study PSR-ONC-EMD1214063-004).

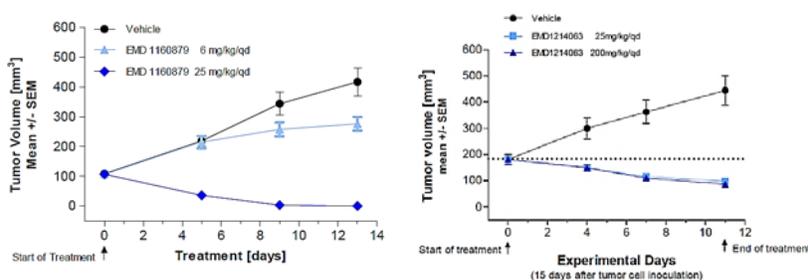
**Figure 6: Tepotinib led to tumor regression in mice bearing Hs746T gastric cancer tumors**



EMD 1160879 = tepotinib free base.  
(Excerpted from Study PSR-ONC-EMD1214063-004)

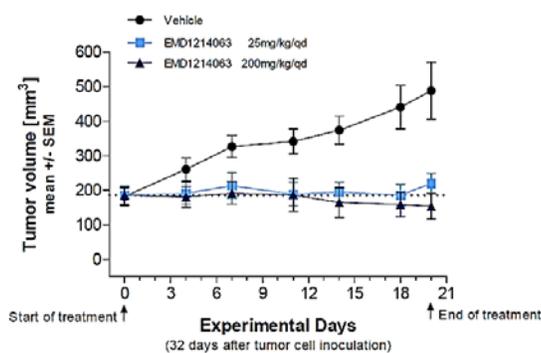
In adult female CD-1 mice bearing EBC-1 tumors (NSCLC cells expressing high-level MET amplification without METex14 alterations), daily oral tepotinib at 25 mg/kg led to tumor regression in 10/10 mice, with a less robust response at the 6 mg/kg dose (Figure 7; left panel). In another tumor model with high-level MET amplification without alterations (MKN-45 gastric cancer cells), once daily tepotinib at 25 or 200 mg/kg for 11 days inhibited tumor growth and resulted in tumor regression in 4/8 mice per group with no treatment related toxicities (Figure 7; right panel). In mice bearing subcutaneous H441 NSCLC tumors with constitutively active c-Met expression, tepotinib at 25 or 200 mg/kg once daily for 20 days inhibited tumor growth compared to vehicle control and induced partial regressions at the high dose (Figure 8). Tepotinib at 100 mg/kg daily for 5 days with 2 days off for 3 weeks led to complete tumor regression in 9/10 mice harboring MHCC97H (hepatocellular carcinoma) tumors that exhibit high-level MET gene amplification and constitutive activation of MET (data not shown in review; Study CrownBioMKGCP-S002-subcutanZW).

**Figure 7: Tepotinib inhibits tumor growth in MET-amplified EBC-1 (left) and MKN-45 (right) bearing mice**



EMD 1160879 = tepotinib free base. EMD 1214063 = tepotinib HCl (clinical candidate).  
(Excerpted from Studies PSR-ONC-EMD1214063-004 (EBC-1) and DOV-325-1-42-MFH (MKN-45))

**Figure 8: Inhibition of H441 tumor growth with daily oral tepotinib**

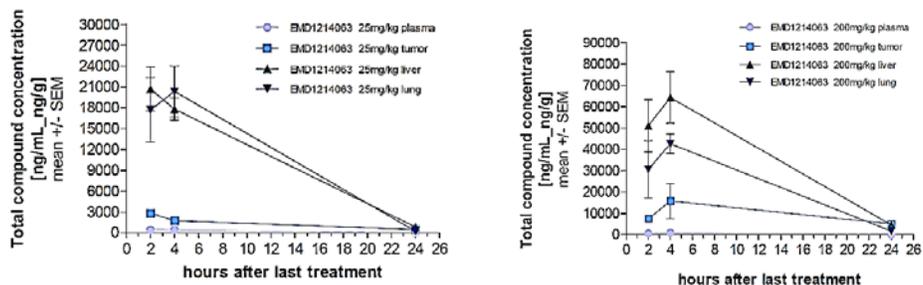


(Excerpted from Study DOV-190-1-66-MFH)

Evaluation of the distribution of tepotinib in mice bearing the MKN-45 or H441 (Figure 9) tumors showed that tepotinib levels in tumor and liver tissue or lung tissue were significantly

higher than levels in plasma at both dose levels in both models.

**Figure 9: Tepotinib levels in tumor, liver, lung and plasma in mice bearing H441 tumors**

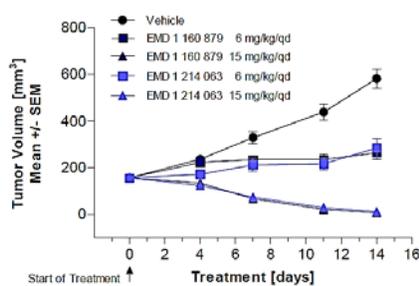


(Excerpted from Study DOV-190-1-66-MFH)

Tepotinib had little to no effect on tumor growth in transgenic HGF mice bearing HCC827 and PC9 NSCLC tumors, both of which have oncogenic EGFR kinase domain mutations, despite high c-Met expression and MET activation (data not shown in review; Studies ONC373-1-39MFH and ONC373-1-38MFH).

During development the Applicant changed the formulation of tepotinib and, as a result of a salt optimization program based on the free base EMD 1160879, switched synthesis of the compound to the more stable hydrochloride hydrate, EMD 1214063. Both forms showed equivalent tumor growth inhibitory activity human EBC-1 tumor bearing mice (Figure 10), and in vitro biochemical analysis showed the IC<sub>50</sub> values of EMD 1214063 (clinical candidate) and EMD 1160879 to be 1.7 and 3.6 nM, respectively.

**Figure 10: Comparison of tepotinib free base to tepotinib HCl in mice bearing human EBC-1 NSCLC tumors**



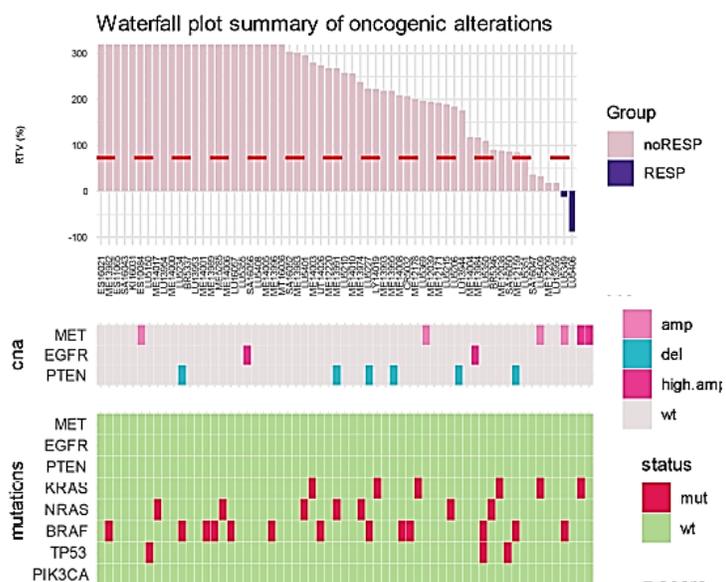
EMD 1160879 = tepotinib free base. EMD 1214063 = tepotinib HCl.

(Excerpted from Study PSR-ONC-EMD1214063-004)

The Applicant evaluated the anti-tumor activity of tepotinib (30 mg/kg once daily) in a screen against 63 tumor explants derived from human brain metastases (implanted subcutaneously in the right flank of adult female SCID mice) in a blind study without selection of tumors based on

a molecular marker profile. Duration of treatment ranged from 14-62 days based on tumor growth in the vehicle treated controls for each model, ending when vehicle control mice had tumors greater than 1500 mm<sup>3</sup>. Tepotinib induced tumor shrinkage in two models which subsequent molecular profiling indicated came from primary lung tumors, LU5349 and LU5406 that harbor high-level MET gene amplification; other tested tumors lacked MET amplification (Studies ONC20190605LC and ONC20190302CR; Figure 11).

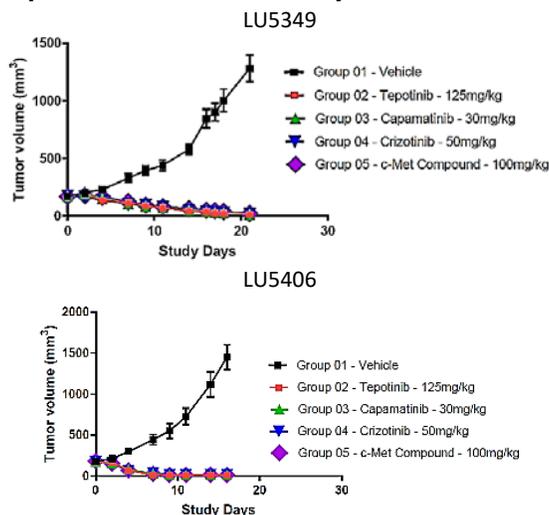
**Figure 11: Screen for tepotinib anti-tumor activity against human brain metastases models**



noRESP/RESP = no response/response to tepotinib as measured by tumor volume. Zero is considered baseline where tumors were approximately 150-250 mm<sup>3</sup> when treatment started. cna = copy number alterations. del = deletions. high.ampl = high amplification. wt = wild type. mut = mutations.  
(Excerpted from Study ONC20190302CR)

Further analysis of these two patient derived xenograft (PDX) lung cancer models (LU5406 and LU5349) showed that tepotinib (once daily, 125 mg/kg) had anti-tumor activity comparable to the commercially available oral c-Met inhibitors capmatinib (given BID, 30 mg/kg) and crizotinib (once daily, 50 mg/kg), and an in-house inhibitor, c-Met compound, (once daily, 100 mg/kg) in adult female SCID mice (n=5/dose group/tumor model) bearing subcutaneous tumors (Figure 12).

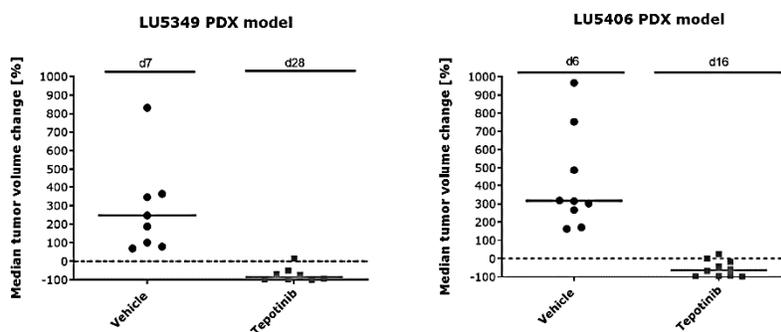
**Figure 12: Tepotinib led to complete tumor regression in 2 PDX lung cancer models with activity comparable to commercially available c-Met inhibitors**



(Excerpted from Study E0177-U1708)

The Applicant further evaluated the activity of tepotinib in orthotopically implanted LU5406 and LU5349 PDX models from NSCLC brain metastases. In female SCID mice with LU5406 or LU5349 cells injected into the brain (right frontal lobe), tepotinib administered once daily at 125 mg/kg for 16 or 28 days resulted in tumor regression with median tumor volume decreases of approximately 84 and 63% for LU5349 and LU5406, respectively, as measured by MRI (Figure 13).

**Figure 13: Effects of tepotinib on orthotopic brain metastases NSCLC models**



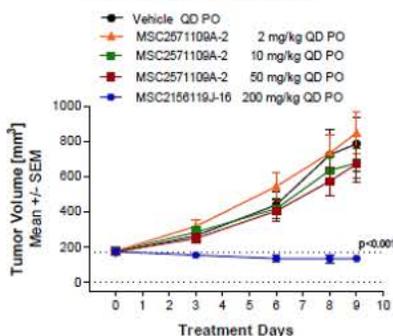
Vehicle control mice required early euthanasia due to tumor size/overall health.

(Excerpted from Study ONC-E0176-U1902-MFH)

Investigators evaluated daily (for 9 days) oral administration of tepotinib at 200 mg/kg and its major metabolite, M506 (MSC2571109A-2), at 2, 10, or 50 mg/kg in adult female Balb/C nude mice bearing subcutaneous KP-4 human pancreatic tumors which express HGF and c-Met in an

autocrine manner in Study onc402-3-12mfh. Daily treatment with 200 mg/kg tepotinib led to significant tumor growth inhibition, while M506 had no effect on tumor growth at any dose tested (Figure 14). Neither test article had a negative impact on body weight or mortality.

**Figure 14: Inhibition of human KP-4 tumor growth by daily treatment with tepotinib or the metabolite M506**



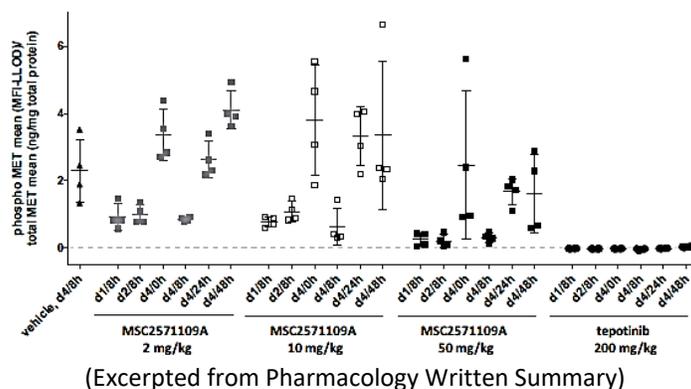
MSC2571109A-2 = M506. MSC2156116J-16 = tepotinib.  
(Excerpted from Study ONC402-3-12MFH)

Pharmacokinetic/pharmacodynamic evaluation of repeat dose administration of tepotinib at 200 mg/kg and M506 at 2, 10, or 50 mg/kg (Study ONC-401-1-12mfh) in mice bearing subcutaneous KP-4 tumors indicated that M506 exposure in tumor tissue was lower compared to plasma while tepotinib was increased in tumor tissues compared to plasma exposure. M506 levels transiently increased 2-8 hours post dose and dropped by 24 hours post dose indicating fast elimination of the metabolite (Table 3). Mice treated with tepotinib had a similar level of exposure to M506 as animals at the 50 mg/kg dose of M506. In addition, M506 transiently inhibited phospho-MET, while tepotinib inhibited MET phosphorylation for at least 24 hours post administration (Figure 15).

**Table 3: Average M506 and tepotinib concentrations in plasma and tumor tissue in mice bearing KP-4 tumors**

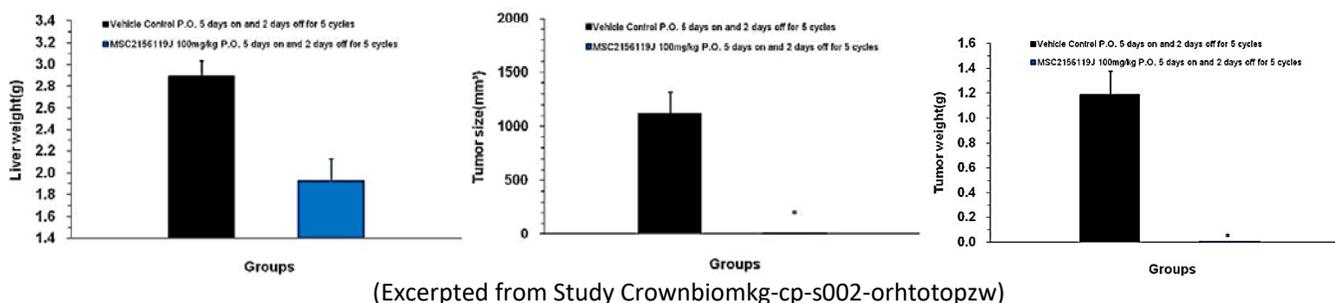
Test article administered	M506 treatment (50 mg/kg)					Tepotinib treatment (200 mg/kg)				
	D1/8 hours	D2/8 hours	D4/0 hours	D4/8 hours	D4/24 hours	D1/8 hours	D2/8 hours	D4/0 hours	D4/8 hours	D4/24 hours
M506 exposure										
Plasma ng/mL	192	266	3	209	7	164	156	19	175	14
Tumor ng/mL	90	113	BLOQ	104	BLOQ	70	66	7	81	15
Tepotinib exposure										
Plasma ng/mL	-	-	-	-	-	1010	784	77	996	61
Tumor ng/mL	-	-	-	-	-	10450	9503	2123	15525	1228

**Figure 15: MET phosphorylation levels in tumor tissue after administration of tepotinib or M506**



The Applicant evaluated the anti-tumor and anti-metastasis activity of tepotinib in mice bearing orthotopic MET amplified and constitutively active human hepatocellular MHCC97H tumors (Study Crownbiomkg-cp-s002-orhtotopzw). Investigators implanted 2-3 mm<sup>3</sup> tumor fragments into the left lobe of the liver of adult male Balb/c nude mice then, 7 days later, initiated oral administration of 100 mg/kg of tepotinib (5 days on 2 days off) for 5 weeks. Tepotinib treatment significantly decreased tumor size in the liver (Figure 16). In addition, tepotinib decreased the incidence of lung metastases in mice with orthotopic HCC tumors (Table 4).

**Figure 16: Liver weights with tumors (left), primary tumor size (mid), and tumor weight (right) in mice treated with vehicle or tepotinib**



**Table 4: Lung metastasis in mice bearing orthotopic HCC tumors and treated with vehicle or tepotinib for 5 weeks**

Group	Number of mice	Number of mice with lung metastasis <sup>#</sup>	Number of metastatic foci <sup>*</sup>
1	10	10	3.1±0.5
2	9	6	0.8±0.7

Note: data expressed as Mean ± SEM

(Excerpted from Study Crownbiomkg-cp-s002-orhtotopzw)

### Secondary Pharmacology

#### The Applicant's Position:

In a secondary pharmacodynamic in vivo study in mice, the once daily oral administration of up to 50 mg/kg tepotinib for 3 or 10 days had no effect on wound healing (i.e., wound width, visual severity score, wound area, percentage of re-epithelialization and granulation tissue maturity) in comparison to vehicle.

#### The FDA's Assessment:

Genetic deletion of the MET gene in the epidermis of mice led to lack of re-epithelialization of skin wounds suggesting that MET signaling is necessary for skin wound healing, thus the Applicant investigated the effect of oral tepotinib on healing of a 5 mm full-thickness excision skin wound in mice treated with 25 or 50 mg/kg tepotinib daily for 3 or 10 days (10/time point/per group; Study 08/237b) using histological assessments of wound width, wound area, re-epithelialization, and granulation tissue maturity. FDA agrees that daily oral administration up to 50 mg/kg for 3 or 10 days did not negatively impact wound healing in mice. The Applicant investigated potential off-target interactions of tepotinib free base at 10 µM against 143 cell receptors enzymes, transporters, and ion channels using both radioligand binding assays and enzymatic assays (Studies 8920141, 8920150, and 8920154); inhibition/activation greater than or equal to 50% inhibition/activation triggered further investigation (Studies 8920142 and 8920158). Tepotinib inhibited melatonin ML2 receptor and imidazoline I1 receptor with IC<sub>50</sub> values of 2.4 and 35 nM, respectively, compared to MET kinase with an IC<sub>50</sub>=1.7 nM. Tepotinib had antagonistic effects on alpha-2C (α<sub>2c</sub>; IC<sub>50</sub>=19 µM) adrenergic and muscarinic (M1, M2, M3; IC<sub>50</sub>=1.3, 22, 1.3 µM, respectively) receptors, and on norepinephrine (NE; IC<sub>50</sub>=2 µM) and dopamine (DA; IC<sub>50</sub>=0.55 µM) transporters. In a radioligand binding assay (Study 10002144), the major human metabolite M506 showed slightly greater than 50% inhibition or stimulation against adenosine A3 (activated, 58%) and muscarinic M1 and M2 (inhibited, 58 and 52%, respectively) receptors, suggesting the IC<sub>50</sub> is close to the 10 µM concentration, but did not inhibit ion channels by greater than 20% at 10 or 30 µM (Study MRS031115-1). M506 also inhibited PDE6 74.6% at the 10 µM concentration. Considering the

activity of M506 against these targets at 10  $\mu\text{M}$  was close to an  $\text{IC}_{50}$ , further evaluation of M506 at lower concentrations was not conducted and does not appear warranted.

### Safety Pharmacology

#### The Applicant's Position:

In vitro safety pharmacological investigations with tepotinib (free base) suggest no anticipated risk for potential off target effects at the proposed clinical dose of 500 mg.

#### *Cardiovascular function*

Tepotinib (hydrochloride hydrate) inhibited the Kv11.1 (hERG) channel current with an  $\text{IC}_{50}$  of 1.2  $\mu\text{M}$ , at a concentration 24-fold higher than the equivalent unbound maximum plasma concentration of the proposed clinical dose of 500 mg. Tepotinib (free base) inhibited the cardiac ion channel hNav1.5 up to 26% at 10  $\mu\text{M}$ . A slight increase (up to 11%) in the refractory period of guinea pig papillary muscles was recorded at 10  $\mu\text{M}$  and 30  $\mu\text{M}$  tepotinib (free base), which are more than 100-fold higher than the equivalent concentration in humans for the proposed dose of 500 mg.

Tepotinib (free base) showed no effects on heart rate and arterial blood pressure in rats by telemetry, and no relevant effects on regional and systemic hemodynamics in dogs. No effects on arterial blood pressure and electrocardiogram (ECG) derived parameters were seen in different repeat-dose toxicity studies in dogs with tepotinib (hydrochloride hydrate).

#### *Respiratory and Central Nervous System (CNS)*

No significant effects with tepotinib hydrochloride hydrate were seen on the respiratory system in male rats and on the CNS in a functional observation battery study in rats.

In vitro safety pharmacological investigations with the major metabolite MSC2571109A suggest no anticipated risk for potential off target or cardiovascular (QT prolongation) effects at the proposed clinical dose of 500 mg tepotinib.

In conclusion, in vitro and in vivo safety pharmacology studies with tepotinib, its free base or the metabolite MSC2571109A did not show any relevant off target, cardiovascular, respiratory, or CNS effects.

#### The FDA's Assessment:

#### *Cardiovascular function*

Investigators incubated HEK293 cells stably expressing human hERG potassium channel with tepotinib (0.3, 1, 3, or 10  $\mu\text{M}$ ) or the major human metabolite M506 (MSC2471109A; 0.1, 0.3, 1, 3, or 10  $\mu\text{M}$ ), 0.1% DMSO (negative control), and 100 nM Cisapride (positive control for metabolite study) or 60 nM Terfenadine and 0.5  $\mu\text{M}$  E-4031 (positive control and reference article for tepotinib study) and measured potassium current using the patch-clamp technique in GLP-compliant Studies 080415-DCC and RC10. Negative and positive controls behaved as expected. Tepotinib inhibited hERG potassium current with  $\text{IC}_{25}$ ,  $\text{IC}_{50}$ , and  $\text{IC}_{75}$  values of 0.4, 1.2,

and 3.4  $\mu\text{M}$ . Concentrations of MSC2471109A up to 3  $\mu\text{M}$  had no effect on hERG tail current, with the highest concentration of 10  $\mu\text{M}$  leading to a 25% inhibition of tail current. The Applicant further evaluated the effects of tepotinib at 3 and 10  $\mu\text{M}$  against 8 cardiac ion channels (hNav1.5, hKv1.5, hERG, hKv4.3/hKChIP2, Human L-Type Calcium (Cav1.2), hKCNQ1/hminK, and hKir2.1) using patch clamp (Study MSE-2008-005B). Tepotinib inhibited hERG up to 62% and hNav1.5 up to 46% at the 10  $\mu\text{M}$  concentration. Tepotinib up to 30  $\mu\text{M}$  had no effect on force of contraction in isolated guinea pig papillary muscle but, at concentrations between 10 and 30  $\mu\text{M}$ , did increase refractory period by 6-11% (Study GSP-IO-001-2007) compared to vehicle control.

In vivo evaluation of cardiovascular effects of oral tepotinib in normotensive male rats (Study GSP0001CVP) showed that 15 or 50 mg/kg/day for 8 days (n=6/group) did not affect heart rate, systolic, diastolic, or arterial pressure, motor activity, food or water consumption, or body weight, while the reference compound resulted in significant changes in all parameters at 50 mg/kg/day. In awake mongrel or Beagle dogs (n=5/dose group), administration of tepotinib at single oral doses of 30 or 70 mg/kg had no effect on arterial blood pressure, heart rate, or ECG including QT-interval (Study GSP0002ECG). In an open-chest study in dogs (Study PDA0018), intraduodenal administration of 70 mg/kg of tepotinib did not exert significant effects on any hemodynamic parameter. In addition, tepotinib administration up to 30 mg/kg/week in the chronic repeat dose toxicology study in Beagle dogs (reviewed fully in Section 5.5) had no effect on heart rate, blood pressure or ECG including QT-interval.

#### *Respiratory and CNS function*

Tepotinib administered at 25, 75, or 200 mg/kg to adult rats (n=8/group) had no effect on respiratory rate and volume, tidal volume, inspiratory, expiratory and relaxation time. Peak inspiratory- and expiratory rate for up to 240 min following administration was comparable to vehicle control, while the positive control theophylline led to expected stimulant effects on mechanical respiratory function (Study 08-198-4). In addition, tepotinib did not affect respiratory parameters in the repeat-dose toxicology studies in rats at doses up to 40 mg/kg/day for 4 and 13 weeks. In a study evaluating the potential effects of tepotinib on CNS function (Study T16160), single oral administration of doses up to 200 mg/kg in rats (5/sex/group) did not cause any changes in a functional observational battery, spontaneous locomotor activity, or body temperature. Positive controls haloperidol (3 mg/kg) and caffeine (20 mg/kg) led to expected changes in behavior and motor activity. Autonomic nervous system reflexes evaluated in the chronic repeat dose toxicity studies in dogs indicated that tepotinib up to 40 mg/kg/day had no effect on any parameter measured.

## 5.4. ADME/PK

### The Applicant's Position:

Tepotinib is a Biopharmaceutics Classification System (BCS) class IV drug with medium permeability in vitro. Oral bioavailability was moderate and the absorption rate was slow across nonclinical species. Exposure generally increased with increasing doses of tepotinib in rat and dog, and tended to be higher in female rats than males. Accumulation was minimal in rat and dose-dependent in dog. Tepotinib has high protein binding and a high volume of distribution indicating extensive distribution into tissues.

Tepotinib exhibits moderate to high clearance in non-primate animals, low clearance in monkey, and follows a simple metabolic pathway with only few metabolites found across species. The in vitro metabolism and proposed biotransformation pathway is consistent between human and the nonclinical safety species rat and dog. In human, tepotinib is moderately metabolized mainly by oxidation, and subsequent biotransformation to the major circulating metabolite MSC2571109A via 4 different routes involving alcohol dehydrogenase, aldehyde dehydrogenase, aldehyde oxidase, and cytochrome p450(CYP)3A4-metabolizing enzymes. MSC2571109A is formed in the rat and dog but represents a disproportionate metabolite. The contribution of MSC2571109A to the antitumor activity of tepotinib is considered not to be meaningful.

Biliary secretion is the major route of elimination of tepotinib in rat and tepotinib is mostly eliminated via feces in rat and dog.

### The FDA's Assessment (data presented by FDA):

FDA agrees that the in vitro metabolism of tepotinib is consistent between humans and the nonclinical safety species (dogs and rats) regarding the formation of the major metabolite M506.

Type of Study	Major Findings																		
<b>Protein Binding</b>																			
<p><b>Study DMPK 144-08:</b> In vitro binding of [<sup>14</sup>C]EMD 1214063 mouse, rat, rabbit, dog, monkey and human plasma</p> <p><b>Study 15-GR031-P0:</b> MSC2571109 (M506 Metabolite of Tepotinib) – In Vitro Protein Binding in Mouse, Rat, Dog, and</p>	<ul style="list-style-type: none"> <li>Tepotinib was ≥ 94% protein bound in all species tested at concentrations ranging from 0.3 to 10 μM</li> <li>Unbound fractions of the major metabolite were comparable in mouse, rat, and human, with a higher percentage available in dogs</li> </ul> <p style="text-align: center;">Plasma protein binding</p> <table border="1"> <thead> <tr> <th>Species</th> <th>% bound Tepotinib</th> <th>% unbound MSC2571109</th> </tr> </thead> <tbody> <tr> <td>Mouse</td> <td>97</td> <td>1.2</td> </tr> <tr> <td>Rat</td> <td>96</td> <td>1.0</td> </tr> <tr> <td>Rabbit</td> <td>96</td> <td>-</td> </tr> <tr> <td>Dog</td> <td>94</td> <td>2.5</td> </tr> <tr> <td>Monkey</td> <td>95</td> <td>-</td> </tr> </tbody> </table>	Species	% bound Tepotinib	% unbound MSC2571109	Mouse	97	1.2	Rat	96	1.0	Rabbit	96	-	Dog	94	2.5	Monkey	95	-
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Human Plasma and to HSA and AAG	<table border="1"> <tr> <td>Human</td> <td>98</td> <td>1.2</td> </tr> </table> <p>Similar binding occurred at 0.3, 1, and 10 μM of tepotinib in all species. ‘-’ metabolite measured in rabbit or monkey plasma.</p>	Human	98	1.2																																																																																								
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<b>Absorption</b>																																																																																												
<p><b>Study DMPK 75-08:</b> Pharmacokinetics of EMD 1160879 (Free Base) After Single Intravenous and Oral Administration of EMD 1214063 (Salt) to Male and Female Wistar Rats</p> <p><b>Study DMPK 74-08:</b> Pharmacokinetics of EMD 1160879 (Free Base) After Single Intravenous and Oral Administration of EMD 1214063 (Salt) to Male and Female NMRI Mice</p> <p><b>Study DMPK 72-08:</b> Pharmacokinetics of EMD 1160879 (Free Base) After Single Intravenous and Oral Administration of EMD 1214063 (Salt) to Female Beagle Dogs</p> <p><b>Study DMPK 73-08:</b> Pharmacokinetics of EMD 1160879 (Free Base) After Single Intravenous and Oral Administration of EMD 1214063 (Salt) to Female Cynomolgus Monkeys</p>	<ul style="list-style-type: none"> <li>Oral bioavailability after a single dose was 21.4 and 55.3% in male and female rats, respectively, and 32.0 and 40.7% in male and female mice, respectively</li> <li>Oral bioavailability after a single dose in female dogs was 22.1% and 24.5% in female monkeys</li> </ul> <p style="text-align: center;">Tepotinib in plasma of treated rats and mice</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="4">Rats</th> <th colspan="4">Mice</th> </tr> <tr> <th colspan="2">IV 3mg/kg</th> <th colspan="2">Oral 6mg/kg</th> <th colspan="2">IV 2mg/kg</th> <th colspan="2">Oral 5mg/kg</th> </tr> <tr> <th>Sex</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> <th>M</th> <th>F</th> </tr> </thead> <tbody> <tr> <td>C<sub>max</sub> (ng/mL)</td> <td>-</td> <td>-</td> <td>21.8</td> <td>66</td> <td>-</td> <td>-</td> <td>83.5</td> <td>52.2</td> </tr> <tr> <td>AUC<sub>0-tlast</sub> (h*ng/mL)</td> <td>276</td> <td>579</td> <td>121</td> <td>637</td> <td>576</td> <td>468</td> <td>449</td> <td>465</td> </tr> <tr> <td>T<sub>max</sub> (h)</td> <td>-</td> <td>-</td> <td>5.33</td> <td>4</td> <td>-</td> <td>-</td> <td>0.667</td> <td>1</td> </tr> <tr> <td>T<sub>1/2</sub> (h)</td> <td>-</td> <td>-</td> <td>2.61</td> <td>3.2</td> <td>-</td> <td>-</td> <td>2.57</td> <td>2.12</td> </tr> </tbody> </table> <p style="text-align: center;">M = Male; F = Female. IV = intravenous.</p> <p style="text-align: center;">Tepotinib in plasma of treated dogs and monkey</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="2">Dogs</th> <th colspan="2">Monkey</th> </tr> <tr> <th>IV 2mg/kg</th> <th>Oral 5mg/kg</th> <th>IV 2mg/kg</th> <th>Oral 5mg/kg</th> </tr> </thead> <tbody> <tr> <td>C<sub>max</sub> (ng/mL)</td> <td>-</td> <td>22.4</td> <td>-</td> <td>55.5</td> </tr> <tr> <td>AUC<sub>0-tlast</sub> (h*ng/mL)</td> <td>567</td> <td>330</td> <td>2550</td> <td>1620</td> </tr> <tr> <td>T<sub>max</sub> (h)</td> <td>-</td> <td>4</td> <td>-</td> <td>12</td> </tr> <tr> <td>T<sub>1/2</sub> (h)</td> <td>-</td> <td>7.64</td> <td>-</td> <td>10.2</td> </tr> </tbody> </table> <p style="text-align: center;">IV = intravenous.</p>	Parameter	Rats				Mice				IV 3mg/kg		Oral 6mg/kg		IV 2mg/kg		Oral 5mg/kg		Sex	M	F	M	F	M	F	M	F	C <sub>max</sub> (ng/mL)	-	-	21.8	66	-	-	83.5	52.2	AUC <sub>0-tlast</sub> (h*ng/mL)	276	579	121	637	576	468	449	465	T <sub>max</sub> (h)	-	-	5.33	4	-	-	0.667	1	T <sub>1/2</sub> (h)	-	-	2.61	3.2	-	-	2.57	2.12	Parameter	Dogs		Monkey		IV 2mg/kg	Oral 5mg/kg	IV 2mg/kg	Oral 5mg/kg	C <sub>max</sub> (ng/mL)	-	22.4	-	55.5	AUC <sub>0-tlast</sub> (h*ng/mL)	567	330	2550	1620	T <sub>max</sub> (h)	-	4	-	12	T <sub>1/2</sub> (h)	-	7.64	-	10.2
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<b>Study DMPK 133-08:</b> In Vitro Distribution of [14C]-EMD 1214063 in Whole Blood of Mouse, Rat, Rabbit, Dog, Monkey and Human	Investigators prepared whole blood aliquots from NMRI mouse, WU rat, White New Zealand rabbit, Beagle dog, Cynomolgus monkey, and human and spiked it with radioactive tepotinib at 0.1 or 1 μM and incubated for 10 min at 37°C and quantified radioactivity by liquid scintillation counting (LSC). In contrast to animals, human whole blood indicated a similar plasma and blood concentration resulting in a ratio of 1.0.																																																																																											

Type of Study	Major Findings																																
<p><b>Study DMPK 38-09:</b> Distribution by Whole Body Autoradiography After Single Oral Administration of <sup>14</sup>C-EMD 1214063 to Male Lister Rats</p> <p><b>Study DMPK 149-08:</b> Distribution and Metabolism After Single po Administration of [<sup>14</sup>C]-EMD 1214063 in Tumor-Bearing (Hs746) Female Nude CD-1 Mice</p> <p><b>Study DMPK 128-11:</b> Plasma and Brain Concentrations After Intravenous Infusion of MSC2156119J to Male Wistar Rats</p>	<p>Blood:plasma ratio of tepotinib at 1 μM</p> <table border="1" data-bbox="824 317 1198 594"> <thead> <tr> <th>Species</th> <th>Blood : Plasma Ratio</th> </tr> </thead> <tbody> <tr> <td>Mouse</td> <td>1.9</td> </tr> <tr> <td>Rat</td> <td>2.2</td> </tr> <tr> <td>Rabbit</td> <td>2.5</td> </tr> <tr> <td>Dog</td> <td>2.5</td> </tr> <tr> <td>Monkey</td> <td>2.2</td> </tr> <tr> <td>Human</td> <td>1.0</td> </tr> </tbody> </table> <p>Blood:plasma ratio was similar at 0.1 and 1 μM</p> <p><b>Oral (rat)</b></p> <ul style="list-style-type: none"> <li>The highest levels of [<sup>14</sup>C]-tepotinib after a 4 mg/kg oral dose were in the GI tract with low concentrations in the liver, lungs kidneys, urinary bladder, and eyes; levels increased between 1 and 6 hours post administration</li> <li>No radioactivity was detected in the brain or spinal cord and was negligible in the testes</li> <li>At 24 hours low levels were still detectable in large intestine, pigmented skin, and eye</li> </ul> <p><b>Oral (Hs746AT tumor bearing mice; 6 mg/kg)</b></p> <ul style="list-style-type: none"> <li>Radioactivity was below levels of quantification by 24-48 hours</li> <li>Highest concentrations were present in the stomach and small intestine 1 hour post dose</li> <li>High levels were present in the large intestine and stomach with moderate levels in the liver, lungs, kidneys, and small intestines 6 hours post dose</li> <li>Low levels were present in tumor tissue</li> <li>No radioactivity was present in brain tissues after oral administration</li> <li>Low levels were still present in tumor tissue at 96 hours post dose, with no plasma activity present</li> </ul> <p><b>Plasma to brain ratio</b></p> <ul style="list-style-type: none"> <li>After continuous IV administration of 3.66 mg/kg/hr for 24 hours in male rats the brain to plasma ratio was 2.87 <ul style="list-style-type: none"> <li>Plasma = 177 ng/mL</li> <li>Brain = 505 ng/g brain weight</li> </ul> </li> </ul>	Species	Blood : Plasma Ratio	Mouse	1.9	Rat	2.2	Rabbit	2.5	Dog	2.5	Monkey	2.2	Human	1.0																		
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<p><b>Study DMPK 96-08:</b> EMD 1214063 - Interspecies Comparison of in vitro Metabolism of Mouse, Rat, Dog, Rabbit, Monkey</p>	<ul style="list-style-type: none"> <li>The major human metabolite M506 was not detected in hepatocytes</li> </ul> <p style="text-align: center;"><b>Percent radioactivity in hepatocytes</b></p> <table border="1" data-bbox="669 1654 1354 1789"> <thead> <tr> <th>Metabolite</th> <th>Ms</th> <th colspan="2">Rat</th> <th>Rb</th> <th>Dg</th> <th>Mn</th> <th>Hu</th> </tr> <tr> <th></th> <th>M</th> <th>M</th> <th>F</th> <th>F</th> <th>M</th> <th>M</th> <th>M</th> </tr> </thead> <tbody> <tr> <td>M684</td> <td>18</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>M668</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>40.2</td> </tr> </tbody> </table>	Metabolite	Ms	Rat		Rb	Dg	Mn	Hu		M	M	F	F	M	M	M	M684	18	-	-	-	-	-	-	M668	-	-	-	-	-	-	40.2
Metabolite	Ms	Rat		Rb	Dg	Mn	Hu																										
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<p><b>Clinical Study Report EMR200095-007</b></p> <p><b>Study DMPK 155-08:</b> Pharmacokinetics and Excretion After Single Intravenous and Oral Administration of <sup>14</sup>C-EMD 1214063 to Wistar Rats</p> <p><b>Study G-A-VIV-18-023:</b> Tepotinib (MSC2156119J)-absorption, metabolism, and excretion in female dogs after single oral administration</p>	<p><b>Oral (rat)</b></p> <ul style="list-style-type: none"> <li>After oral administration of tepotinib total radiolabeled material excreted in feces: <ul style="list-style-type: none"> <li>78% in humans</li> <li>58 and 67% in male and female rats, respectively, during the first 24 hours</li> <li>91% in female dogs during a 192-hour post administration time period</li> </ul> </li> <li>Urinary excretion accounted for approximately: <ul style="list-style-type: none"> <li>14% in humans</li> <li>1.5 and 5% in male and female rats</li> <li>0.5% in female dogs</li> </ul> </li> </ul>																																																																																																	

## 5.5. Toxicology

### 5.5.1. General Toxicology

#### The Applicant's Position:

Tepotinib proved to have a low acute toxicity in both rats and mice with no evidence of clinical signs or toxic effects following a single oral administration of 2,000 mg/kg. The general toxicology program comprised pivotal repeat-dose toxicity studies of tepotinib as subacute (4 weeks), subchronic (13 weeks), and chronic studies (up to 26 weeks in rats and 39 weeks in dogs), including toxicokinetic and reversibility evaluations. Apart from the pilot T16146 1-week toxicology rat study performed with tepotinib free base, all pivotal studies were performed with tepotinib hydrochloride hydrate.

Gastrointestinal disorders including vomiting and diarrhea were frequently observed in repeat-dose toxicity studies in dogs at all tested doses (i.e.,  $\geq 2.5$  mg/kg/day).

The major identified target organ of toxicity in the repeat-dose toxicity studies was the liver/hepatobiliary system (rat and dog). Slight and dose-dependent statistically significant increases of liver enzyme values (i.e., alkaline phosphatase, alanine transaminase [ALT], aspartate transaminase [AST]) were observed in the repeat-dose toxicity studies in rat at doses  $\geq 15$  mg/kg/day. Mild liver cell hypertrophy (considered an adaptive non-adverse phenomenon) was seen in female rats at the dose of 135 mg/kg/day in the 26-week study. In addition, hepatocellular necrosis and mononuclear infiltrates were seen in a 4-week study at the high doses of 450 and 2,000 mg/kg/day. In dog, increased hepatic-biliary parameters (glutamate dehydrogenase [GLDH], ALT, AST, alkaline phosphatase, bilirubin [direct, total and indirect]) were seen in all repeat-dose toxicity studies. These increases correlated histologically with pronounced cholangitis, pericholangitis, and inflammatory infiltrates in the liver in the 4-week (40 mg/kg/day) and 39-week (30 mg/kg/day) dog studies.

In both species, all changes proved to be reversible or showed indications for reversibility. The total AUC in the chronic repeat-dose toxicity studies at the no observed adverse effect level (NOAEL) is approximately 4% of the exposure achieved in patients at the proposed clinical dose of 500 mg in both rats and dogs.

#### The FDA's Assessment (all data presented by FDA):

##### **Study title/ number: 26 Week Oral Toxicity Study in Rats Plus an 8 Week Recovery Period/ T16179**

- The target organs of toxicity were lung and liver
- Females had 1.5 – 2x higher exposure ( $C_{max}$  and AUC) than males at several time points

Conducting laboratory and location: Merck KGaA  
Darmstadt, Germany

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 15, 45, or 135 mg/kg daily for 26 weeks\*  
Route of administration: oral gavage  
Formulation/Vehicle: 0.25% aq. Hydroxypropyl methylcellulose (Methocel® K4M premium)  
Species/Strain: Wistar rats  
Number/Sex/Group: 20/sex/group  
Age: 8 weeks  
Satellite groups/ unique design: 3/sex/group for TK  
Deviation from study protocol affecting interpretation of results: None that affected interpretation of results

\*While the doses were low, with low exposure margins compared to human, the high dose is reasonably justified by clear toxicity in a 4-week rat study at a dose level of 450 mg/kg

**Observations and Results: changes from control**

Parameters	Major findings
<b>Mortality</b>	There were no drug-related deaths
<b>Clinical Signs</b>	Unremarkable
<b>Body Weights</b>	Unremarkable
<p>Mean Body Weights (26-Week Study; Rats)</p>	
<b>Ophthalmoscopy</b>	No significant drug-related findings
<b>Hematology</b>	The subset of T helper cells increased dose-dependently in females on week 26. The subset of T regulatory cells showed minor dose-dependent increase in males and decrease in females on week 5, which resolved to near-control values by week 13.

Hematology: % Change from Vehicle-Treated Control Group in Rats Exposed to Tepotinib							
		Male			Female		
	WEEK	15 mg/kg	45 mg/kg	135 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
WBC	5	9%	5%	13%	-9%	-6%	33%
	13	-4%	-2%	9%	-3%	0%	<b>36%</b>
	26	<b>10%</b>	0%	4%	-3%	-10%	<b>32%</b>
Th Cells %	26	4%	0%	14%	<b>-29%</b>	-20%	-16%
Tregs %	5	<b>36%</b>	-2%	-6%	9%	-2%	-17%
	13	-5%	<b>-30%</b>	-13%	-3%	-3%	-2%

<b>Clinical Chemistry</b>	<ul style="list-style-type: none"> <li>Males had minor increases in inorganic phosphate by week 13, which remained elevated through the recovery period</li> <li>Males and females had increased alkaline phosphatase</li> </ul>
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Clinical Chemistry: % Change from Vehicle-Treated Control Group in Rats Exposed to Tepotinib							
		Male			Female		
	WEEK	15 mg/kg	45 mg/kg	135 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
K	5	-2%	-2%	-1%	<b>-8%</b>	<b>-9%</b>	-3%
Inorganic Phosphate	5	0%	6%	<b>4%</b>	<b>-18%</b>	<b>-9%</b>	5%
	13	<b>13%</b>	<b>11%</b>	<b>14%</b>	-7%	3%	9%
	26	6%	<b>10%</b>	<b>12%</b>	-6%	1%	9%
ALP	5	6%	3%	10%	10%	10%	<b>39%</b>
	13	9%	6%	15%	13%	8%	<b>44%</b>
	20	23%	6%	<b>26%</b>	8%	0%	31%
	26	<b>22%</b>	14%	<b>25%</b>	11%	9%	<b>47%</b>

<b>Urinalysis</b>	Unremarkable
<b>Gross Pathology</b>	Males exposed to tepotinib had reduced thymic size observed upon necropsy. Two females in the high-dose group had discoloration of the lungs.

Necropsy Findings in Rats Exposed to Tepotinib									
		Male				Female			
Organ	Detail	0 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg	0 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
Lung	discolored (red/ white)								2
Thymus	small	1	2	5	2				1

<b>Organ Weights</b>	In females, the weight ratio of liver, ovaries, and adrenal gland increased as a function of tepotinib dose. Except for the ovaries, these increases resolved to near-control values during the recovery phase. In males, the relative organ to body weight ratio of the thymus decreased during exposure to tepotinib and did not resolve during the recovery phase.					
<b>%Change from Control in Organ to Body Weight Ratio Following 26-Week Exposure to Tepotinib in Rats</b>						
week 27	<b>Male</b>	<b>Female</b>				
<b>Organ</b>	<b>15 mg/kg</b>	<b>45 mg/kg</b>	<b>135 mg/kg</b>	<b>15 mg/kg</b>	<b>45 mg/kg</b>	<b>135 mg/kg</b>
Liver	4%	4%	4%	-3%	3%	9%*
Ovaries				-6%	6%	27%*
Adrenals	0%	9%	9%	7%	7%	29%**
Treatment phase; * p = 0.050; ** p = 0.010						
week 35	<b>Male</b>	<b>Female</b>				
<b>Organ</b>	<b>15 mg/kg</b>	<b>45 mg/kg</b>	<b>135 mg/kg</b>	<b>15 mg/kg</b>	<b>45 mg/kg</b>	<b>135 mg/kg</b>
Heart	-7%*	-7%	-4%	6%	6%	3%
Liver	-7%	-7%	-3%	-3%	-3%	0%
Thymus	-29%**	-29%*	-29%	0%	15%	0%
Ovaries				11%	0%	22%
Adrenals	0%	-10%	0%	-7%	-7%	13%
Recovery phase; * p = 0.050; ** p = 0.010						
<b>Histopathology</b>	Animals in the high-dose group had minimal to mild microscopic changes in the lung, lymph node, and liver					
Adequate battery: Yes						

**Rat Histopathology Following 26-Week Exposure to Tepotinib**

Organ	Detail	Severity	Male				Female			
			0 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg	0 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
Liver	Hypertrophy	Min								2
		Mild								1
	Hydropic change			1R	1R					1R
Lung	Alveolar aggregation	Min	1		1	1			3	2
		Mild				1				3
	Fibrosis with foam cells									1
	Hemorrhage, alveolar, focal				1					1
	Inflammation, necrotizing/chronic					1		1R		
LN, Mesenteric	Sinus histiocytosis	Min				1				
		Mild								3

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			Male				Female			
Organ	Detail	Severity	0 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg	0 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
		Mod						1		1

R = Recovery phase; all other data are dosing phase

<b>Toxicokinetics</b>	<ul style="list-style-type: none"> <li>Females had nearly 2x greater exposure than males at all time points examined</li> <li>Between Days 28 and 91, exposures were comparable</li> <li>In general, exposures increased less than dose-proportionally at all time points examined</li> </ul>
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**Mean TK Parameters in Rats Following 26-Week Exposure to Tepotinib**

Day	Dose	Sex	C <sub>max</sub> (ng/mL)	AUC <sub>24</sub> (h*ng/mL)
1	15 mg/kg	M	38.63	269.2
		F	78.59	580.8
	45 mg/kg	M	99.78	586.2
		F	124.18	951.3
	135 mg/kg	M	129.87	1251
		F	230.58	1855
Day	Dose	Sex	C <sub>max</sub> (ng/mL)	AUC <sub>24</sub> (h*ng/mL)
182	15 mg/kg	M	61.32	534.8
		F	66.03	937.3
	45 mg/kg	M	90.12	809.9
		F	135.54	1312.1
	135 mg/kg	M	101.28	1522.7
		F	201.9	2909.2

**Study title/ number: 39 Week Oral Toxicity Study in Beagle Dogs with a 12 Week Recovery Period/ 13-DA009-N0**

- Dogs had dose-dependent hepatobiliary toxicity which was reversible during recovery
- The target organs were liver, GI tract, and adrenal gland
- Males and females in the low- and mid-dose groups had comparable exposures, while females had nearly 2x higher exposure than males in the high dose group after Day 176

Conducting laboratory and location: Merck KGaA  
Darmstadt, Germany

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 3, 10, or 30 mg/kg daily for 39 weeks  
Route of administration: Gelatin capsule by mouth  
Formulation/Vehicle: 0.25% aq. Hydroxypropyl methylcellulose (Methocel® K4M premium)  
Species/Strain: Beagle Dogs  
Number/Sex/Group: Terminal = 5/Sex/Group

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Version date: January 2020 (ALL NDA/ BLA reviews)

**Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.**

Age: Recovery = 2/Sex/Group  
10 to 10.5 months  
Satellite groups/ unique design: 1<sup>st</sup>, 3<sup>rd</sup>, and 5<sup>th</sup> dog from each treatment group  
Deviation from study protocol: None that affected interpretation of results  
affecting interpretation of results:

**Observations and Results: changes from control**

Parameters	Major findings
Mortality	There were no drug-related deaths
Clinical Signs	Dogs exhibited dose-dependent increases in abnormal stool, vomiting, diarrhea, and lacrimation.

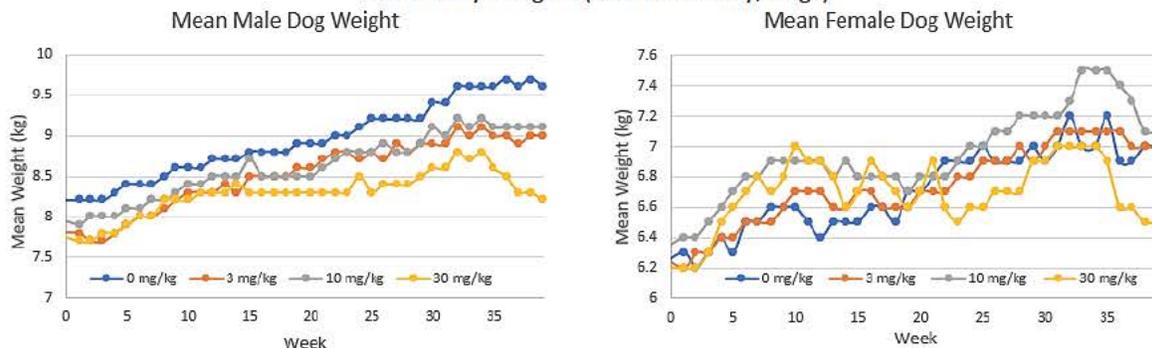
**Clinical Signs in Dogs Exposed to Tepotinib**

Sign	Male				Female			
	0 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg	0 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
abnormal stool (+/- red material/ soft/ mucous)	2	4, 1R	5	5		2	4	5
diarrhea (+/- red coloring/ mucous)	1	1	4	5	1	1	2	5
vomiting		4, 1R	5	5	1	1	3	5
lacrimation increased, eye				1			1	3

# of animals exhibiting clinical signs; R indicates recovery period

Body Weights	Major findings
	Males in the 30 mg/kg group did not gain as much weight as dogs in other groups Males in the 30 mg/kg group had lower food consumption than dogs in other groups

**Mean Body Weights (39-Week Study; Dogs)**



<b>Ophthalmoscopy</b>	Unremarkable																																																																																									
<b>Hematology</b>	<ul style="list-style-type: none"> <li>Males had a dose-dependent decrease in PTT through week 38, compared to controls.</li> <li>Males and females had increased reticulocyte counts from week 5 through 38, compared to controls.</li> <li>Females in the 30 mg/kg group had significantly higher (i.e. 2x) reticulocyte counts compared to male counterparts from week 5 through 26.</li> </ul>																																																																																									
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	38R	39.6%	42%	63%**	8%	55%	41%																																																																																			
<b>Neu</b>	5	7.5%	-4%	-17%	3%	9%	39%*																																																																																			
	26	1.2%	-14%	-40%*	13%	24%	2%																																																																																			
R indicates Recovery phase; *p<0.05; **p<0.01																																																																																										
<b>Clinical Chemistry</b>	Liver enzymes increased dose-dependently as early as 2 weeks after initial exposure and remained elevated into the recovery phase. Alkaline phosphatase was particularly increased in females in the 30 mg/kg group.																																																																																									

**Clinical Chemistry: % Change from Vehicle-Treated Control Group in Dogs Exposed to Tepotinib**

		Male			Female		
TEST	WEEK	3 mg/kg	10 mg/kg	30 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
ALP	7	-2%	-9%	-3%	15%	20%	49%*
	38R	30%	22%	151%	52%	17%	181%
ALT	2	34%	20%	104%	9%	3%	77%*
	7	41%	26%	82%**	24%	57%	68%**
	18	10%	26%	126%**	8%	33%	127%**
	26	9%	31%	136%	17%	14%	163%*
	38R	27%	35%	174%	10%	5%	163%**
AST	7	9%	14%	34%	22%	16%	5%
	26	27%	18%	49%	26%	13%	62%**

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TEPMETKO, Tepotinib

TEST	WEEK	Male			Female		
		3 mg/kg	10 mg/kg	30 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
	38R	29%	21%	132%	30%	15%	35%*
GLDH	7	27%	41%	117%	20%	63%	97%**
	18	19%	36%	134%**	2%	35%	140%**
	26	14%	16%	125%	-5%	7%	169%**
	38R	29%	30%	191%	-4%	-6%	163%*

<b>Urinalysis</b>	Unremarkable				
<b>Gross Pathology</b>	Macroscopic observations of organ discoloration were limited to animals in the 10- and 30 mg/kg groups.				
<b>Gross Pathology Findings in Tepotinib-Treated Dogs</b>					
			Male	Female	
Organ/ Tissue	Observation	Severity	30 mg/kg	10 mg/kg	30 mg/kg
Adrenal gland	grey color				2
Liver	white hilus; bile duct	min	1R		1
		mild	1, 1R		
		marked	1		2
Mammary gland	discoloration; yellow	Min			1
	increased size; multifocal	mild		1	1
Only affected groups are shown. R indicates Recovery phase					
<b>Organ Weights</b>	Females had dose-dependent liver enlargement and decrease in thymus weight				

**%Change in Organ Weight Relative to Body Weight Following 39-Week Exposure to Tepotinib in Dog**

(%) terminal	Male			Female		
Organ/ Tissue	3 mg/kg	10 mg/kg	30 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
liver	-1%	-11%	5%	6%	2%	18%
spleen	27%	6%	-6%	0%	-3%	8%
thymus	-7%	21%	3%	44%	26%	13%
testes (M)/ ovaries (F)	13%	-24%	-7%	-30%	-38%	-5%
adrenals	0%	-13%	0%	23%	-5%	0%
thyroid	-22%	-22%	10%	12%	12%	12%

(%) recovery	Male			Female		
Organ/ Tissue	3 mg/kg	10 mg/kg	30 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
liver	6%	5%	11%	-6%	-12%	-13%
spleen	38%	0%	27%	8%	-9%	3%

NDA/BLA Multi-disciplinary Review and Evaluation NDA 214096  
TEPMETKO, Tepotinib

thymus	-13%	5%	47%	42%	41%	73%
testes (M)/ ovaries (F)	29%	22%	0%	-9%	63%	0%
adrenals	34%	29%	15%	-14%	-30%	-14%
thyroid	0%	25%	-33%	0%	0%	-22%

<p><b>Histopathology</b> Adequate battery: Yes Peer Review: Yes (internal)</p>	<p>There were few aberrant histological observations. Most pathologies resolved during the recovery phase, except for periductal liver fibrosis in the 30 mg/kg group and milky retention of the mammary gland in the 3 mg/kg group.</p>
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**Dog Histopathology Following 39-Week Exposure to Tepotinib**

Organ/ Tissue	Observation	Severity	Male		Female			
			0 mg/kg	30 mg/kg	0 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
Adrenal gland	decreased/ diffuse cortical vacuolation	mild		1				3
Kidney	increased vacuolation; tubuli recti	mild				1	1	1
Liver	bile duct hyperplasia, papillary, epithelium	mod		2				3
	lymphoplasmacellular infiltrates; bile duct; multifocal	mild		2				
	periductal fibrosis	mild		1R				1R
		mod		2				3
	cholangioles proliferation; diffuse periportal	min		1				2
		mod		1				1
	hemosiderin pigmentation; periportal	min		1				1
	bile pigmentation; canaliculi; centrilobular	mild						1
kupffer cell activation; diffuse	mild		1					
Mammary gland	milky retention	min				1		2
		mild				1R	2	1

Only affected groups and controls are shown. R indicates recovery phase

<p><b>Toxicokinetics</b></p>	<ul style="list-style-type: none"> <li>Males and females had comparable exposures in 3 and 10 mg/kg groups</li> <li>In 30 mg/kg group, females had nearly 2x the exposure of males on Days 176 and 267</li> <li>Exposure (Cmax and AUC) increased over 267 days, indicating accumulation</li> </ul>
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<b>Mean TK Parameters in Dogs Following 39-Week Exposure to Tepotinib</b>				
<b>Day</b>	<b>Dose (mg/kg)</b>	<b>Sex</b>	<b>C<sub>max</sub> (ng/mL)</b>	<b>AUC<sub>24</sub> (h*ng/mL)</b>
1	3	M	20.5	205
		F	20.2	183
	10	M	57.2	538
		F	57.1	485
	30	M	92.1	1020
		F	98.5	1110
<b>Day</b>	<b>Dose (mg/kg)</b>	<b>Sex</b>	<b>C<sub>max</sub> (ng/mL)</b>	<b>AUC<sub>24</sub> (h*ng/mL)</b>
267	3	M	21.8	213
		F	25	267
	10	M	76.9	898
		F	105	1370
	30	M	254	3420
		F	554	6380

#### **General toxicology; additional studies**

Dr. Whitney Helms reviewed the 28-day repeat-dose toxicology studies in rats and dogs under the original IND submission (IND 106103). The summaries of these studies are based on and adapted from her review.

In a GLP-compliant 28-day toxicology study, Wistar rats received 3, 10, 30, or 90 mg/kg of tepotinib via oral gavage once daily for 4 weeks. Females in the 90 mg/kg group gained 30% more weight than other females, and males in this group gained 18% more than controls. Hematology changes consisted of mild inflammation in tepotinib-treated females, characterized by dose-dependent increases in WBCs, lymphocytes (HD), and neutrophils. Consistent with observations made in the 26-week study, male and female rats in the HD group had enlarged adrenal glands and reduced thyroid size. Females in the 90 mg/kg group had enlarged liver and spleen. Rats in the 90 mg/kg group exhibited microscopic lung pathology, including acute focal hemorrhage, mild alveolar macrophages, and mild multifocal foam cells. Other high-dose findings included mild decrease in liver glycogen deposition, numerous macrophages in the mesenteric lymph node, and moderate submucosal lymphoplasmacellular infiltrates in the trachea. Females had greater exposure (AUC) than males, and dose accumulation between Days 1 and 28 that was more pronounced at doses  $\geq 30$  mg/kg. Greater exposure in females generally correlated with greater toxicity in these animals; exposure in females at the highest dose in this study (despite the lower dose compared to the long-term toxicity study) was 11108 ng\*hr/mL, approximately half the human exposure at the recommended dose of 500 mg. In the 28-day dog study, tepotinib toxicity was more severe than in rats. Beagle dogs received 2.5, 10, or 40 mg/kg tepotinib via oral administration of a hard gelatin capsule once per day for

28 days. The target organs were liver and gallbladder. The primary clinical signs of toxicity were dose-dependent increases in vomiting and diarrhea. By Week 2, there were large increases in liver enzymes, including GLDH ( $\uparrow$ 2575%), ALT ( $\uparrow$ 1278%), and alkaline phosphatase ( $\uparrow$ 1091%). One female in the 40 mg/kg HD group had increased urine pH ( $\geq$ 9.0) at the end of the study, with several concomitant histopathological findings in the liver. Females in the HD group had macroscopic thickening of the gallbladder and mammary gland. Similarly to rats, females in the HD group had microscopic decreases in glycogen deposition. They also exhibited massive periductular fibrosis and bile duct epithelia hyperplasia. Males in the HD group had bile duct- and periportal hepatocyte necrosis. Males and females had moderate mixed periportal infiltrates. Males exposed to 10 or 40 mg/kg of tepotinib had minimal (focal) seminiferous tubule atrophy. Toxicokinetic analysis showed wide variability in pharmacokinetic (PK) parameters, especially in the high-dose group, and there was drug accumulation over the course of the main study. Exposure was dose-dependent and roughly dose-proportional (slightly high in males, slightly low in females). Tepotinib could be detected in tissues of recovery animals and was detected at higher concentrations in animals with liver histopathology.

Following a scale-up in tepotinib manufacturing that resulted in a potential for the presence of impurities at levels above the thresholds described in ICH Q3A/B, the Applicant conducted another GLP-compliant toxicology study in Wistar rats using once daily oral tepotinib doses of 30, 90, 450, or 2000 mg/kg that included spiked impurities (b) (4)

The study also included a toxicokinetic assessment of tepotinib and two of its metabolites, including the major human metabolite MSC2751109A (M506). One male in the 2000 mg/kg group was euthanized on Day 2 due to severe respiratory symptoms. All remaining animals in that group (including TK animals) were sacrificed prematurely on Day 5 due to clinical signs of body weight loss (-17%), reduced food consumption, abnormal feces (soft, yellow), increased salivation, eye and nostril discharge, and rooting in bedding material. Necropsy of these animals showed an extreme filling of the stomach and only mucous content in the intestines. At lower doses, changes in hematology and clinical chemistry values in rats from the 450 mg/kg group were consistent with dehydration. At doses  $\geq$  450 mg/kg, histopathological targets included the lung (alveolar foam cells with inflammation), liver (hepatocellular necrosis and mononuclear infiltrates), and large intestines (single cell necrosis in the epithelium and/ or lamina propria with granulocytic infiltrates). There was also mild hypertrophy of bile duct epithelium in several animals. The HNSTD was 450 mg/kg which resulted in exposures of 12700 and 27200 h\*ng/mL in males and females, respectively; in females the exposure was similar to exposures in humans at the 500 mg clinical dose. Exposure to the major human metabolite MSC2571109A was approximately 10% (females) to 20% (males) of the exposure to tepotinib. While present at lower exposures than in humans, this study shows that the major human metabolite was present in animals at levels sufficient to provide reasonable safety data. Finally, the toxicity of tepotinib at 90mg/kg in this

study matched that observed at the same dose in previous studies, suggesting that the elevated concentrations of impurities did not contribute to toxicity and providing qualification for the spiked impurities, though ultimately the levels of these impurities were below ICH thresholds and did not require nonclinical qualification.

**Table 5: Rat TK Data for Tepotinib and Metabolites**

<b>Tepotinib</b>								
<b>Day 28</b>								
Parameters	30 mg/kg/day		90 mg/kg/day		450 mg/kg/day		2000 mg/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female
N	4	4	4	4	4	4	4	4
C <sub>max</sub> (ng/mL)	218	467	257	684	810	1330	N.A.	N.A.
t <sub>max</sub> (h) <sup>a</sup>	3	3	3	3	6	3	N.A.	N.A.
AUC <sub>t</sub> (ng*h/mL)	2110	3630	2460	6570	12700	27200	N.A.	N.A.

<b>MSC2571109A (M506; major human metabolite)</b>								
<b>Day 28</b>								
Parameters	30 mg/kg/day <sup>b</sup>		90 mg/kg/day <sup>b</sup>		450 mg/kg/day <sup>b</sup>		2000 mg/kg/day <sup>b</sup>	
	Male	Female	Male	Female	Male	Female	Male	Female
N	4	4	4	4	4	4	4	4
C <sub>max</sub> (ng/mL)	40.3	46.7	49.8	76.2	158	171	N.A.	N.A.
t <sub>max</sub> (h) <sup>a</sup>	6	6	6	4.5	6	6	N.A.	N.A.
AUC <sub>t</sub> (ng*h/mL)	357	594	484	964	2300	3070	N.A.	N.A.

<b>MSC2571107A</b>								
<b>Day 28</b>								
Parameters	30 mg/kg/day <sup>b</sup>		90 mg/kg/day <sup>b</sup>		450 mg/kg/day <sup>b</sup>		2000 mg/kg/day <sup>b</sup>	
	Male	Female	Male	Female	Male	Female	Male	Female
N	4	4	4	4	4	4	4	4
C <sub>max</sub> (ng/mL)	33.2	28.4	38.8	55.3	129	119	N.A.	N.A.
t <sub>max</sub> (h) <sup>a</sup>	6	6	6	6	6	6	N.A.	N.A.
AUC <sub>t</sub> (ng*h/mL)	283	364	384	730	1950	2200	N.A.	N.A.

*(Applicant Tables Derived from Study DA-0061-0)*

## 5.5.2. Genetic Toxicology

### The Applicant's Position:

Tepotinib did not show any evidence of genotoxic activity in 2 in vitro studies in bacterial or mammalian cells, and in 1 in vivo micronucleus study in rats.

### The FDA's Assessment (data presented by FDA):

FDA agrees with the Applicant's assessment.

### In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

**Study title/ number: EMD 1214063 - Bacterial Mutagenicity Assay, Salmonella typhimurium and Escherichia coli/ # T17192**

Key Study Findings:

- Tepotinib was not mutagenic in strains tested, in the presence or absence of S9
- Standard positive controls confirmed the sensitivity and validity of the assay

GLP compliance: Yes

Test system: Test system: *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 and *Escherichia coli* strain WP2 *uvrA* +/- S9 metabolic activation; up to 5000 µg per plate

Study is valid: Yes

#### In Vitro Assays in Mammalian Cells

##### **Study title/ number: EMD 1214063 - In vitro mammalian cell gene mutation test (L5178Y/TK<sup>+</sup>)/ # T17188**

Key Study Findings:

- Tepotinib did not increase mutation frequency in absence of S9
- In the presence of S9, 1 of 2 experiments revealed 2.05x greater mutation frequency induced by 1.58 µg/mL than occurred spontaneously in the concurrent control. The slight trend toward increased mutation frequency was not >3x concurrent control and was within 1.5x historical control. The study is therefore considered negative.
- Standard positive and negative controls confirmed the validity and sensitivity of the assay

GLP compliance: Yes

Test system: Mouse lymphoma L5178Y cells; up to 50 µg/mL for 3 hours +/- S9 and up to 15.8 µg/mL for 24 hours -S9

Study is valid: Yes

#### In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

##### **Study title/ number: EMD 1414063 – Micronucleus test in rats after oral administration/ T17266**

Key Study Findings:

- Tepotinib did not increase the incidence of micronucleated, polychromatic erythrocytes (MN-PCE)
- Rats treated with 1333 or 2000 mg/kg tepotinib experienced diarrhea

GLP compliance: Yes

Test system: Male Wistar rats received one dose of tepotinib via oral gavage. Investigators harvested bone marrow 24-hours post-dose for low- and mid-dose groups (667 or 1333 mg/kg, respectively), and 24- or 48-hours post-dose for the 2000 mg/kg, high-dose group.

Study is valid: Yes

### 5.5.3. Carcinogenicity

#### The Applicant's Position:

Carcinogenicity studies were not conducted based on the current development of tepotinib in patients suffering from advanced cancer and in line with the ICH S9 guideline.

#### The FDA's Assessment:

FDA agrees. Consistent with the principles discussed in the ICH S9 guidance, carcinogenicity studies are not expected for the development of a drug intended for the treatment of patients with advanced cancer.

### 5.5.4. Reproductive and Developmental Toxicology

#### The Applicant's Position:

Two preliminary embryo-fetal development studies in rabbits revealed maternotoxic effects starting at a dose level of 50 mg/kg/day and a dose dependent increase in the number of skeletal malformations (teratogenicity) starting at a dose level of 5 mg/kg/day.

In line with the ICH S9 guideline, studies on fertility and early embryonic development and pre and postnatal development were not conducted based on the envisaged therapeutic indication of tepotinib for treatment of patients with advanced cancer. Histopathological examination of reproductive organs in general toxicology studies with tepotinib did not reveal any relevant effects. In addition, sperm analysis (i.e., morphology and motility) conducted at the end of the dosing period in the 26-week repeat-dose toxicity study in rats did not show any treatment-related change. Overall, the data indicate no risk for impairment of fertility.

#### The FDA's Assessment (data presented by FDA):

In general, FDA agrees that tepotinib showed malformations at doses  $\geq 5$  mg/kg and increased embryoletality at doses  $\geq 50$  mg/kg in rabbits. These doses all resulted in exposures lower than the human exposure (see details below). FDA also agrees that fertility and pre- and postnatal development studies are not warranted to support approval in the proposed indication in patients with advanced cancer.

#### **Study title / number: Preliminary embryo-fetal development study by oral route in rabbits/ MSC2156119J-RF5400**

##### Key Study Findings

- One fetus from the 0.5 mg/kg group was malformed with ectopic kidney; one from the 5 mg/kg group was malformed with spina bifida
- One fetus in each of the 5 and 25 mg/kg groups had malrotated hind limbs
- 5 fetuses and 3 fetuses from the 5 and 25 mg/kg groups, respectively, had hyperextension of the right hind limb

Conducting laboratory and location:



GLP compliance:

Yes

Methods

Dose and frequency of dosing: 0, 0.5, 5, or 25 mg/kg per day  
 Route of administration: Oral gavage  
 Formulation/Vehicle: Methocel K4M®  
 Species/Strain: New Zealand White Rabbit  
 Number/Sex/Group: 8 females per group  
 Satellite groups: TK groups  
 Study design: Treatment period = organogenesis period (GD)  
 Days 6-18; Does observed until Day 29  
 Deviation from study protocol affecting interpretation of results: None that affected study interpretation

**Observations and Results**

Parameters	Major findings																				
Mortality	There were no maternal deaths																				
Clinical Signs	<table border="1"> <thead> <tr> <th>Dose</th> <th>0 mg/kg</th> <th>0.5 mg/kg</th> <th>5 mg/kg</th> <th>25 mg/kg</th> </tr> </thead> <tbody> <tr> <td>Vaginal bleeding</td> <td>1 (14%)</td> <td>0</td> <td>1 (13%)</td> <td>0</td> </tr> <tr> <td>Appearing thin</td> <td>1 (14%)</td> <td>2 (25%)</td> <td>3 (38%)</td> <td>5 (63%)</td> </tr> <tr> <td>Soft stool/ diarrhea</td> <td>0</td> <td>0</td> <td>2 (25%)</td> <td>0</td> </tr> </tbody> </table>	Dose	0 mg/kg	0.5 mg/kg	5 mg/kg	25 mg/kg	Vaginal bleeding	1 (14%)	0	1 (13%)	0	Appearing thin	1 (14%)	2 (25%)	3 (38%)	5 (63%)	Soft stool/ diarrhea	0	0	2 (25%)	0
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Appearing thin	1 (14%)	2 (25%)	3 (38%)	5 (63%)																	
Soft stool/ diarrhea	0	0	2 (25%)	0																	
Body Weights and Feed Consumption	<ul style="list-style-type: none"> <li>Dams in the high dose (HD) group gained the least weight</li> <li>Dams in the mid-dose (MD) and HD groups showed trending toward consuming less food than controls, but group means were not significant</li> </ul>																				

	<p><b>Mean Doe Body Weight</b></p> <table border="1"> <caption>Estimated Mean Doe Body Weight (kg)</caption> <thead> <tr> <th>Gestation Day</th> <th>0 mg/kg</th> <th>0.5 mg/kg</th> <th>5 mg/kg</th> <th>25 mg/kg</th> </tr> </thead> <tbody> <tr><td>0</td><td>3.78</td><td>3.62</td><td>3.70</td><td>3.75</td></tr> <tr><td>5</td><td>3.95</td><td>3.82</td><td>3.85</td><td>3.88</td></tr> <tr><td>10</td><td>4.05</td><td>3.88</td><td>3.90</td><td>3.90</td></tr> <tr><td>15</td><td>4.12</td><td>3.92</td><td>3.98</td><td>3.90</td></tr> <tr><td>20</td><td>4.12</td><td>3.90</td><td>3.95</td><td>3.82</td></tr> <tr><td>25</td><td>4.18</td><td>3.95</td><td>3.98</td><td>3.90</td></tr> <tr><td>30</td><td>4.15</td><td>4.05</td><td>4.02</td><td>3.95</td></tr> </tbody> </table> <p><b>Mean Food Consumption</b></p> <table border="1"> <caption>Estimated Mean Food Consumption (g/doe/day)</caption> <thead> <tr> <th>Gestation Day</th> <th>0 mg/kg</th> <th>0.5 mg/kg</th> <th>5 mg/kg</th> <th>25 mg/kg</th> </tr> </thead> <tbody> <tr><td>0</td><td>175</td><td>170</td><td>170</td><td>175</td></tr> <tr><td>5</td><td>195</td><td>185</td><td>180</td><td>185</td></tr> <tr><td>10</td><td>190</td><td>175</td><td>170</td><td>170</td></tr> <tr><td>15</td><td>140</td><td>100</td><td>100</td><td>90</td></tr> <tr><td>20</td><td>150</td><td>110</td><td>90</td><td>90</td></tr> <tr><td>25</td><td>110</td><td>100</td><td>100</td><td>100</td></tr> <tr><td>30</td><td>90</td><td>100</td><td>120</td><td>100</td></tr> </tbody> </table>	Gestation Day	0 mg/kg	0.5 mg/kg	5 mg/kg	25 mg/kg	0	3.78	3.62	3.70	3.75	5	3.95	3.82	3.85	3.88	10	4.05	3.88	3.90	3.90	15	4.12	3.92	3.98	3.90	20	4.12	3.90	3.95	3.82	25	4.18	3.95	3.98	3.90	30	4.15	4.05	4.02	3.95	Gestation Day	0 mg/kg	0.5 mg/kg	5 mg/kg	25 mg/kg	0	175	170	170	175	5	195	185	180	185	10	190	175	170	170	15	140	100	100	90	20	150	110	90	90	25	110	100	100	100	30	90	100	120	100
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<b>Necropsy Findings: Maternal, Gross</b>	Unremarkable																																																																																
<b>Necropsy Findings: Cesarean Section Data</b>																																																																																	

Cesarean Section Data (EFD Study; Rabbits)				
mg/kg/day	0	0.5	5	25
Pregnancy index (%)	100%	100%	100%	100%
# Females w/ only viable fetuses (%)	4 (67%)	4 (50%)	5 (63%)	3 (38%)
Number pregnant	7	8	8	8
Number not pregnant	0	0	0	0
Gravid uterine weight (g)	484.12	506.79	457.23	496.69
Mean corpora lutea	10.86	11.25	11.88	11.88
Mean implantation sites	10.14	9.38	8.75	9.50
Mean % pre-implantation loss	6.35	16.42	26.64	20.30
Mean % post-implantation loss	19.98	6.01	15.21	7.05
Mean litter size	8.29	8.75	7.75	8.75
Mean early resorptions	1	4	1	3
Mean late resorptions	1	0	1	0
<b>Fetal weight changes relative to controls</b>				
Male		3%	3%	-3%
Female		11%	15%	9%

Toxicokinetic Parameters in Dams			
Dose mg/kg/day	0.5	5	25
<b>Gestational Day 6</b>			
T <sub>max</sub> (hr)	4	4	4
C <sub>max</sub> (ng/mL)	0.05	3.90	32.28
AUC <sub>(0-24)</sub> (ng*hr/mL)	6.1	49.0	319.8
<b>Gestational Day 18</b>			
T <sub>max</sub> (hr)	5	4	6
C <sub>max</sub> (ng/mL)	0.27	4.64	34.15
AUC <sub>(0-24)</sub> (ng*hr/mL)	3.1	56.7	365.5

**Table 6: Mean Fetal Malformations and Variations (EFD Study; Rabbits)**

Dose mg/kg/day	0	0.5	5	25
Number of Fetuses/(Litters Evaluated)	58/6	70/8	62/7	70/8
Gross malformations: # of fetuses affected, (% of litters)				
Skeletal anomalies	53 (8.83%)	63 (7.88%)	52 (7.43%)	55 (6.88%)
Spina bifida	0 (0%)	0 (0%)	1 (14.3%)	0 (0%)
Ectopic kidney	0	1 (12.5%)	0	0 (0%)
Bilateral hind limb malrotation	0 (0%)	0 (0%)	1 (14.3%)	1 (12.5%)
Hyperextension of hind limb	0 (0%)	0 (0%)	5 (71.4%)	3 (37.5%)
Cranium frontal, missing central ossification	22 (83.3%)	35 (100%)	35 (85.7%)*	7 (37.5%)**

Dose mg/kg/day	0	0.5	5	25
Number of Fetuses/(Litters Evaluated)	58/6	70/8	62/7	70/8
Cranium interparietal, missing central ossification (% of litters)	15 (100%)	27 (87.5%)	29 (85.7%)*	2 (25%)**
*p<0.05; **p<0.001				

**Study title / number: Preliminary embryo-fetal development study by oral route in rabbits/ MSC2156119J**

**Key Study Findings**

- In the 450 mg/kg group 4/11 animals were found dead; 3 additional animals died prematurely
- In the 150 mg/kg group, 2 animals aborted and 1 animal died prematurely
- Fetuses exposed to tepotinib had significant, dose-dependent increase in skeletal malformations: malrotation of paws, misshapen scapula, malpositioned clavicle and/or calcaneous/ talus

Conducting laboratory and location:



GLP compliance:

Yes

**Methods**

Dose and frequency of dosing: 0, 50, 150, 450 mg/kg/day  
 Route of administration: Oral gavage  
 Formulation/Vehicle: Methocel K4M®  
 Species/Strain: New Zealand White Rabbit  
 Number/Sex/Group: 8 females per group  
 Satellite groups: TK groups  
 Study design: Treatment period = organogenesis period (GD) Days 6-18; Does observed until Day 29, when they were sacrificed and subject to necropsy

Deviation from study protocol

affecting interpretation of results: Due to high toxicity and death, dosing stopped on Day 19 in 450 mg/kg group

Observations and Results

Parameters	Major findings
Mortality	<ul style="list-style-type: none"> <li>In the 450 mg/kg group 2 females were found dead (2 on Day 11, 2 on Day 12); 3 additional animals found dead after treatment withdrawal (~Day 15); 4 remaining animals (including TK animals) were prematurely sacrificed to limit inhumane suffering</li> <li>In the 150 mg/kg group, 1 animal died on Day 12</li> </ul>
Clinical Signs	Two animals in the 150 mg/kg group had spontaneous abortions.
Body Weights and Feed Consumption	<p>The figure contains two line graphs. The top graph, 'Mean Doe Body Weight', plots body weight in kg against Gestation Day (0 to 30). The 450 mg/kg group (purple) shows a sharp decline from ~3.35 kg at Day 0 to ~2.98 kg at Day 10. The 50 mg/kg group (red) shows the highest weight, reaching ~3.9 kg by Day 30. The 0 mg/kg (blue) and 150 mg/kg (green) groups follow similar trends, ending around 3.7 kg and 3.6 kg respectively. The bottom graph, 'Mean Food Consumption', plots consumption in g/animal/day against Gestation Day (0 to 35). All groups show a general downward trend from ~170-200 g/day at Day 5 to ~80-110 g/day by Day 30. The 50 mg/kg group (red) consistently consumes more than the other groups.</p>

Gravid Uterine Weights	<table border="1"> <thead> <tr> <th>Dose</th> <th>0 mg/kg</th> <th>50 mg/kg</th> <th>150 mg/kg</th> </tr> </thead> <tbody> <tr> <td>mean gravid uterine weight (g)</td> <td>464.08</td> <td>479.40</td> <td>387.53</td> </tr> </tbody> </table>				Dose	0 mg/kg	50 mg/kg	150 mg/kg	mean gravid uterine weight (g)	464.08	479.40	387.53																																								
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Mean Toxicokinetic Parameters in Dams			
Dose mg/kg/day	50	150	450
<b>Gestational Day 6</b>			
T <sub>max</sub> (hr)	6	4	6
C <sub>max</sub> (ng/mL)	68.23	139.67	807.44
AUC <sub>(0-24)</sub> (ng*hr/mL)	720	1593	16705
<b>Gestational Day 18</b>			
T <sub>max</sub> (hr)	4	6	N.E.
C <sub>max</sub> (ng/mL)	305.01	604.65	N.E.
AUC <sub>(0-24)</sub> (ng*hr/mL)	3898	11097	N.E.

N.E. = not evaluable

**Table 7: Fetal Malformations and Variations (EFD Study; Rabbits)**

Dose mg/kg/day		0	50	150
Number of Fetuses/(Litters Evaluated)		57/7	47/6	42/4
Skeletal anomalies # of fetuses/(% litters)		46/57	33/47	39/42
Fore paw	Misshapen scapula (bilat.)	0 (0%)	0 (0%)	29 (100%)***
	Malposition clavicle (bilat.)	0 (0%)	0 (0%)	16 (75%)***
	Malrotation (bilat.)	0 (0%)	7 (17%)**	42 (100%)***
	Unossified great tubercle (bilat.)	15 (71%)	10 (67%)	27 (100%)***
Hind paw	Malposition calcaneus (bilat.)	0 (0%)	0 (0%)	23 (100%)***
	Malposition talus (bilat.)	0 (0%)	0 (0%)	23 (100%)***
	Malrotation (bilat.)	0 (0%)	0 (0%)	28 (100%)***
Cranium	Missing central ossification, parietals	32 (100%)	17 (100%)*	14 (100%)*
Sternum	2 <sup>nd</sup> sternebra, bipartite	1 (14%)	0 (0%)	16 (75%)***
	5 <sup>th</sup> sternebra, unossified	9 (57%)	6 (50%)	18 (100%)**
	1 <sup>st</sup> sternebra, incomplete ossification	0 (0%)	0 (0%)	11 (50%)***
	2 <sup>nd</sup> sternebra, incomplete ossification	2 (29%)	2 (17%)	9 (75%)**

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001

### 5.5.5. Other Toxicology Studies

#### The Applicant's Position:

##### *Metabolites*

The major circulating human metabolite MSC2571109A has no genotoxic potential as assessed in a bacterial mutagenicity assay and a mouse lymphoma assay.

##### *Impurities*

The specified identified impurities (b) (4) were synthesized and tested in good laboratory practice

(GLP)-compliant, in vitro genotoxicity studies for point mutations and chromosomal aberrations. In addition, impurity (b) (4) was also tested in an in vivo Comet assay in rats. All studies were negative, indicating that none of the tested impurities has genotoxic potential. In addition, the same impurities were qualified in 2 GLP-compliant 4-week repeat-dose toxicity studies in rat using drug substance batches spiked with these impurities. Acceptance criteria for these specified impurities were set, taking into consideration the qualified levels at the NOAEL and the relation to the proposed clinical dose of 500 mg/patient/day.

*Phototoxicity*

The ultraviolet absorption bands and extinction coefficients, together with in vitro phototoxicity testing, provided initial evidence for a phototoxic potential of tepotinib. However, this was disproven by an in vivo phototoxicity study in pigmented rats after single oral administrations of tepotinib up to 1,500 mg/kg.

The FDA’s Assessment:

FDA agrees with the Applicant’s assessment of metabolites, impurities, and phototoxic potential of tepotinib.

*Metabolites*

Investigators conducted GLP-compliant in vitro mutation assays in Salmonella typhimurium and Escherichia coli bacterial cells (Study # 15-DA172-N0), and mouse lymphoma L5178 cells (Study # 15-DA192-N0). MSC2571109A, the major tepotinib metabolite, was not mutagenic in the presence or absence of S9 mix. Standard positive and negative controls confirmed the sensitivity and validity of these assays.

*Impurities*

Investigators conducted in vitro assays in bacterial and mammalian cells to determine whether tepotinib impurities were genotoxic. None of the tested impurities were genotoxic.

**Table 8: In Vitro Reverse Mutation Assay in Bacterial Cells (Ames Assay)**

Impurity	(b) (4)				
Study #	T17453	1892304	1892301	1892303	1892302
Bacterial strains	S. typhimurium (98, 100, 102, 1535, 1537) E. coli (WP2 uvrA)	S. typhimurium (98, 100, 1535, 1537) E. coli (WP2 uvrA)	S. typhimurium (98, 100, 1535, 1537) E. coli (WP2 uvrA)	S. typhimurium (98, 100, 1535, 1537) E. coli (WP2 uvrA)	S. typhimurium (98, 100, 1535, 1537) E. coli (WP2 uvrA)
Concentration	Up to 1580 µg/plate	Up to 5000 µg/plate	Up to 5000 µg/plate	Up to 5000 µg/plate	Up to 5000 µg/plate
Genotoxic	negative	negative	negative	negative	negative
S9 mix	+/-	+/-	+/-	+/-	+/-

Impurity	(b) (4)				
Study #	T17453	1892304	1892301	1892303	1892302
GLP-compliant	yes	yes	yes	yes	yes
Study valid	yes	yes	yes	yes	yes

**Table 9: In Vitro Genotoxicity Assays in Mammalian Cells**

Impurity	(b) (4)				
Study #	T17452	8384520	18-DA0064-0	8384519	18-DA0069-0
Cell type	V79 Chinese hamster	Fresh human lymphocytes	Fresh human lymphocytes	Fresh human lymphocytes	Fresh human lymphocytes
Concentration	Up to 50 µg/mL	Up to 30 µg/mL	Up to 15.6 µg/mL	Up to 5 µg/mL	Up to 62.5 µg/mL
Genotoxic	Negative for ↑ micronuclei	Negative for ↑ chromosome aberrations			
S9 mix	+/-	+/-	+/-	+/-	+/-
GLP-compliant	yes	yes	yes	yes	yes
Study valid	yes	yes	yes	yes	yes

Other Genetic Toxicity Studies

**Study title/ number: Comet Assay Analysis of DNA Damage Induced by In Vivo Exposure of Sprague Dawley Rats to (b) (4) / # HX303**

Key Study Findings:

- Tepotinib impurity, (b) (4) did not induce a dose-dependent increase in DNA migration or LMW DNA diffusion
- The impurity is negative for genotoxicity in the liver, duodenum, and glandular stomach of SD rats

GLP compliance: Yes

Test system: Male Sprague-Dawley rats received up to 1000 mg/kg (b) (4) orally once per day for 2 consecutive days; portions of the left liver lobe, duodenum, and glandular stomach were harvested 4 hours after last dose

Study is valid: Yes

**Study title/ number: Evaluation of in vitro phototoxicity on Balb-c 3T3 fibroblasts using the Neutral Red uptake assay/ # 70-484**

In a GLP-compliant neutral red phototoxicity experiment, investigators assessed the viability of BALB/c 3T3 murine fibroblasts by correlating tepotinib concentration with neutral red dye uptake in live cells following treatment with 5 J/cm<sup>2</sup> of UVA radiation. Tepotinib caused cytotoxicity (i.e. decrease in Neutral Red uptake) at the highest 2 (31.6 and 100 µg/mL) or 5 (1 to 100 µg/mL) concentrations in the absence or presence of UVA, respectively. The

photoirritancy factor (PIF, the  $IC_{50}$  in the absence of UVA divided by  $IC_{50}$  in the presence of UVA) was 16.3 indicating that tepotinib was potentially phototoxic.

**Study title/ number: Single Dose Phototoxicity Study to Determine the Effects of Oral Administration of MSC2156119J on Eyes and Skin in Pigmented Rats/ # 20017987**

Because the neural red phototoxicity experiment suggested propensity for tepotinib to be phototoxic, the Applicant conducted a GLP-compliant study in Long-Evans pigmented rats to determine whether the drug is phototoxic in vivo. Rats received 500, 1000, or 1500 mg/kg of tepotinib administered once via oral gavage, followed 3 hours later by a 10-minute exposure to simulated sunlight UV radiation. Microscopic analysis did not reveal evidence of skin or ocular toxicity in rats from any group. Tepotinib was not acutely phototoxic in vivo.

X Amy M. Skinner, PhD; Stephanie L. Aungst, PhD  
Primary Reviewers

X Whitney S. Helms, PhD  
Supervisor

## 6 Clinical Pharmacology

### 6.1. Executive Summary

#### The FDA's Assessment:

In the current Application, the proposed dosing regimen is 500 mg tepotinib hydrochloride hydrate (equivalent to 450 mg tepotinib free base) orally once daily (QD) with food. In the clinical pharmacology section of the Assessment Aid, the dosage will be expressed as tepotinib hydrochloride hydrate.

The proposed dosing regimen of 500 mg QD was initially selected based on results from dose finding study where the maximum tolerated dose (MTD) was not reached up to a dosage of 1400 mg QD, with dose-limiting toxicities (DLTs) observed at dose levels of 1000 mg and 1400 mg and no DLTs at 500 mg QD. Selection of 500 mg QD was further evaluated in additional dose selection studies, which showed an acceptable safety profile and numerically better preliminary efficacy compared to a lower dosage of 300 mg QD. In addition, PK/pharmacodynamic (PD) modeling and simulation suggested that a dosage of 500 mg QD is sufficient to achieve sustained inhibition of phospho-MET at a level > 95% in more than 90% patients with mixed solid tumors.

The effectiveness of the selected dosage was demonstrated in the single arm study (VISION), in which the overall response rate (ORR) was determined to be 43% and duration of response (DOR) was determined to be 11.1 months for the previously treated patient population; while the ORR was 43% and the DOR was 10.8 months for the treatment-naïve population. No apparent exposure-response relationship was observed for safety or efficacy endpoints at a dosage of 500 mg QD.

The clinical pharmacology review primarily focused on determining the drug-drug interaction potential for tepotinib as a victim. Metabolism and in vitro data suggested that tepotinib was a substrate of CYP3A4, CYP2C8 and P-gp. However, the fractions metabolized by individual major CYP isozymes could not be reliably quantified. The worst-case scenario for the tepotinib exposure change when CYP3A4, CYP2C8 and P-gp are induced or inhibited remains unknown. The potential reduction in tepotinib exposure may decrease tepotinib anti-tumor activity, while a potential increase in tepotinib exposure may increase the incidence and severity of tepotinib adverse reactions. Thus, a post-marketing commitment (PMC) study was issued to determine tepotinib exposure change with concomitant use of rifampin when P-gp, CYP3A4 and CYP2C8 are induced; and a post-marketing requirement (PMR) study was issued to determine tepotinib exposure change with concomitant use of itraconazole when CYP3A4 and P-gp are inhibited.

### 6.1.1. Recommendations:

The Clinical Pharmacology review team has reviewed the information contained in NDA 214096. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 10.

**Table 10: Key Clinical Pharmacology Review Issues**

Review Issue	Recommendations and Comments
<b>Pivotal and Supportive evidence of effectiveness</b>	The primary evidence of effectiveness comes from the pivotal study VISION in which ORR was determined to be 43% and DOR was determined to be 11.1 months for the previously treated patient population; ORR was 43% and DOR was 10.8 months for the treatment naïve population.
<b>General dosing instructions</b>	The proposed tepotinib dosing regimen of 500 mg QD (equivalent to 450 mg tepotinib free base QD) with food is acceptable for approval from a clinical pharmacology perspective: <ul style="list-style-type: none"> <li>• DLTs were observed at dose levels of 1000 mg and 1400 mg but not at the 500 mg dose during dose finding.</li> <li>• The preliminary efficacy was numerically better at 500 mg dose as compared to the 300 mg dose.</li> <li>• PK/PD modeling and simulation suggested that a tepotinib dose of 500 mg once daily is sufficient to achieve sustained inhibition of phospho-MET at a level &gt; 95% in &gt; 90% of mixed solid tumor population.</li> <li>• Exposure response analysis suggests no apparent association between tepotinib exposure and efficacy and safety at the 500 mg QD dosage</li> <li>• Tepotinib was administered immediately after breakfast in VISION. In the food effect study, a high-fat, high-calorie meal increased the mean tepotinib AUC<sub>0-∞</sub> by 1.6-fold and C<sub>max</sub> by 2-fold and shifted the median T<sub>max</sub> from 12 hours to 8 hours. The potential decreased exposure when tepotinib is taken without food may compromise the anti-tumor activity. In addition, administration of tepotinib with food is expected to mitigate the gastrointestinal toxicity, including diarrhea, which were among the most common adverse reactions.</li> </ul>
<b>Dosing in patient with organ impairment</b>	<ul style="list-style-type: none"> <li>• No dose adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh criteria).</li> <li>• No dose adjustment is needed for patients with mild or moderate renal impairment (CLcr &gt; 30 mL/min).</li> </ul>
<b>Drug-drug interactions</b>	<p><i>As victim</i></p> <ul style="list-style-type: none"> <li>• Avoid concomitant use of TEPMETKO with strong CYP3A4 inducers.</li> <li>• Avoid concomitant use of TEPMETKO with dual strong CYP3A inhibitors or P-gp inhibitors.</li> </ul> <p><i>As perpetrator</i></p>

Review Issue	Recommendations and Comments
	<ul style="list-style-type: none"> <li>Avoid coadministration of TEPMETKO with P-gp substrates where minimal concentration changes may lead to serious or life-threatening adverse reactions. If concomitant use is unavoidable, reduce the P-gp substrate dosage in accordance with its approved product labeling.</li> </ul>
<b>Labeling</b>	<p>The proposed labeling is acceptable upon the Applicant's agreement to FDA's revisions to the labeling. The FDA recommended adding the following dosage modifications to the labeling to avoid drug interactions:</p> <ul style="list-style-type: none"> <li>Avoid concomitant use of TEPMETKO with strong CYP3A4 inducers.</li> <li>Avoid concomitant use of TEPMETKO with dual strong CYP3A inhibitors or P-gp inhibitors.</li> </ul>

### 6.1.2. Post-Marketing Requirements and Commitments

The rationales and descriptions of post-marketing requirements (PMR) and commitments (PMC) are summarized in Table 11. The PMC and PMR are requested to address the drug interaction potential for tepotinib as a victim.

**Table 11: Summary of Post-Marketing Requirements and Commitments**

Post-Marketing Commitment	
PMC Rationale	Mass balance study results suggested that oxidative metabolites account for up to 48% of the total tepotinib dose. In vitro study results suggested that tepotinib was a substrate of CYP3A4, CYP2C8 and P-gp. However, the fractions metabolized by individual CYP enzymes could not be reliably quantified. The worst-case scenario for the tepotinib exposure reduction when P-gp, CYP3A4 and CYP2C8 are induced remains unknown. The potential reduction in tepotinib exposure may decrease TEPMETKO anti-tumor activity. Therefore, a clinical drug interaction study is needed to provide dosage recommendations when TEPMETKO (tepotinib) is administered concomitantly with P-gp inducers, strong CYP3A4 inducers and moderate CYP2C8 inducers to determine the worst-case scenario (there is no strong CYP2C8 inducer).
PMC Description	Conduct a drug interaction study to evaluate the effect of rifampin on the single dose pharmacokinetics of tepotinib to assess the magnitude of decreased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a P-gp inducer, and strong CYP3A4 inducer and moderate CYP2C8 inducer. Design and conduct the trial in accordance with the FDA Guidance for Industry titled " <a href="#">Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions</a> ".
Post-Marketing Requirement	
PMR Rationale	Mass balance study result suggested that oxidative metabolites account for up to 48% of the total tepotinib dose. In vitro study results suggested that

	tepotinib was a substrate of CYP3A4, CYP2C8 and P-gp. However, the fractions metabolized by individual CYP enzymes could not be reliably quantified. There is currently no medication known to be a strong inhibitor of both CYP2C8 and an inhibitor of P-gp; thus, the worst-case scenario for inhibition occurs when tepotinib is co-administrated with dual P-gp inhibitor and strong CYP3A4 inhibitor. The magnitude of tepotinib exposure change and the clinical effect when both P-gp and CYP3A4 are inhibited remains unknown. The potential tepotinib exposure increase may increase the incidence and severity of adverse reactions to TEPMETKO. As a result, a clinical drug interaction study is needed to support dosing recommendations when TEPMETKO (tepotinib) is administered concomitantly with strong CYP3A4 inhibitors and P-gp inhibitors.
PMR Description	Conduct a drug interaction study to evaluate the effect of itraconazole on the single dose pharmacokinetics of tepotinib to assess the magnitude of increased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 and P-gp inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled " <a href="#">Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions</a> ".

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

#### Data and Applicant's position:

A comprehensive clinical pharmacology program was conducted for tepotinib. The pharmacokinetic (PK) profile of tepotinib was characterized in cancer patients and healthy participants across a dose range from 30 mg to 1,400 mg per day and in different ethnic groups. On-treatment tumor biopsies from the first-in-human (FIH) multiple ascending dose (MAD) study (Study EMR200095-001) were used in a translational PK/Pd model to define the recommended clinical dose for the NSCLC indication.

Dedicated clinical studies were conducted to characterize the mass balance and metabolite profile of tepotinib; to support the development of different formulations; to investigate the influence of food and proton pump inhibition on the bioavailability of tepotinib; to investigate the interaction with CYP3A4 and P-glycoprotein (P-gp); and to investigate the effect of hepatic impairment on the PK of tepotinib. A population PK model was established and the influence of intrinsic and extrinsic factors was characterized.

The relationship between tepotinib exposure and efficacy endpoints (objective response [OR], duration of response [DOR], progression-free survival [PFS]) as well as safety endpoints was

evaluated to further confirm the proposed clinical dose and dose reduction level. Exposure-QTc analyses were conducted to characterize the potential of tepotinib for QT prolongation.

The totality of investigations is appropriate to inform the proper use of tepotinib in the target population and to support the proposed labeling.

**The FDA's Assessment:**

FDA agrees with the Applicant's position that the clinical pharmacology program in general supports tepotinib dose selection for the target population. However, the current submission provided insufficient data to evaluate the drug interaction potential for tepotinib as victim. As a result, FDA issued a PMC and PMR to evaluate the effect of rifampin (a strong CYP3A4 inducer, a moderate CYP2C8 inducer and a P-gp inducer) and the effect of itraconazole (a strong CYP3A4 inhibitor and a P-gp inhibitor) on tepotinib exposure, respectively.

The clinical pharmacology program in the current NDA submission includes the following assessments supported by a total of fourteen clinical trials with nine trials in healthy subjects and five trials in patients with cancer:

- Dose selection/Dose Confirmation
  - EMR200095-001: dose escalation first in human study to investigate the MET kinase inhibitor tepotinib under 3 different regimens in patients with advanced solid tumors.
  - EMR200095-003: Japanese dose escalation study of MET inhibitor tepotinib given orally as monotherapy to patients with solid tumors.
  - EMR200095-004: study to evaluate the efficacy, safety, and PK of tepotinib as monotherapy vs. sorafenib in Asian patients with MET+ advanced hepatocellular carcinoma and Child-Pugh Class A liver function.
  - EMR200095-005: study to evaluate efficacy, safety, and PK of tepotinib as monotherapy in patients with MET+ advanced hepatocellular carcinoma with Child-Pugh Class A liver function who have failed sorafenib treatment.
  - MS200095-0022: single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplification (VISION).
- Dedicated Hepatic Impairment
  - MS200095-0028: parallel group study to investigate the effect of various degrees of hepatic impairment on the PK, safety and tolerability of the MET kinase inhibitor tepotinib.
- Drug Interaction

- MS200095-0030: 2-period crossover study to evaluate the effect of tepotinib on CYP3A by investigating the PK of the CYP3A substrate midazolam in healthy subjects.
- MS200095-0032: single sequence, 2-period study to evaluate the effect of tepotinib on P-gp by investigating the PK of the P-gp probe substrate dabigatran etexilate in healthy subjects.
- MS200095-0039: 3-period crossover study to investigate the effect of a PPI (omeprazole) on the PK of tepotinib in healthy subjects.
- Food Effect, Relative BA/BE
  - EMR200095-002: crossover study to investigate the food effect and relative BA of tepotinib in 2 groups of healthy subjects.
  - MS200095-0044: study with crossover design in each part to investigate the BE of the tablet formulation of tepotinib TF3 compared to TF2, and to investigate the influence of food on the PK of each tablet formulation TF2 and TF3 of tepotinib in healthy subjects.
  - MS200095-0012: crossover study to investigate the relative BA of 2 tepotinib film-coated tablet formulations in healthy subjects.
  - MS200095-0038: 2-period, 2-sequence cross-over study to evaluate the bioequivalence of TF3 administered as 5 tablets of 100 mg vs 2 tablets of 250 mg dose in healthy subjects.
- Mass Balance, Absolute and Relative BA/BE
  - EMR200095-007: study to investigate the absolute and relative BA, mass balance, and metabolite profile of tepotinib in healthy male subjects.

The to-be-marketed formulation for tepotinib is TF3. Five tepotinib formulations (Capsule Formulations: CF1, CF2; Tablet Formulations: TF1, TF2 and TF3) were used in the clinical pharmacology studies. Dose finding/confirmation assessments were mainly conducted with the CF2 and TF1 formulation, while drug interaction and dedicated hepatic impairment assessments were conducted with TF2. Formulation TF2 was initially used in the ongoing VISION study and all patients were gradually switched to TF3 upon implementation of Protocol Amendment 6 (dated 26 March 2019) until March 10, 2020. CF1 was the formulation initially utilized in the FIH study. CF2 was developed due to the low tepotinib exposure with CF1 and was adopted in all subsequent cohorts.

FDA concludes that adequate bridging has been established across formulations, supported by the established bioequivalence between the TF3 and TF2 (Study MS200095-0044), relative bioavailability study between TF1 and TF2 (Study MS200095-0012), and relative bioavailability study between CF2 and TF1 (EMR200095-002).

Tepotinib concentrations in human plasma samples were analyzed via liquid chromatography coupled with tandem mass spectrometric detection (LC-MS/MS). All LC-MS/MS assays were validated or partially validated according to applicable guidances (Bioanalytical Method Validation, FDA Guidance for Industry; Guideline on Bioanalytical Method Validation, EMA) and fulfilled requirements with respect to linearity, selectivity, accuracy, and precision (Refer to section 19.4 for more details on bioanalytical methods).

Phospho-MET levels were used as a pharmacodynamic marker. Phospho-MET levels were determined using a Luminex based assay for analysis of phospho-MET (Y1234/Y1235 and Y1349) and total MET levels. The assay has been validated and is considered adequate to support PK/PD analysis and dose selection.

## 6.2.2. General Dosing and Therapeutic Individualization

### 6.2.2.1. General Dosing

#### Data:

Throughout the biopharmaceutical development program of tepotinib, different capsule and tablet formulations have been used. This includes an initial capsule formulation (CF) 1, containing (b) (4) drug substance; a further capsule formulation, CF2, containing (b) (4) drug substance; a first tablet formulation (TF), TF1; and further tablet formulations, TF2 and TF3 with (b) (4) drug substance.

TF2 was used in the ongoing pivotal VISION (MS200095-0022) study but all patients were gradually switched to TF3 upon implementation of Protocol Amendment 6. The proposed commercial formulation, TF3, was specifically developed to improve manufacturability and process robustness, and is provided as film-coated tablets containing (b) (4) drug substance at dose strengths of 100 mg and 250 mg (hydrochloride hydrate salt).

The bioequivalence of 2 tablets of the 250 mg TF3 dose strength compared with 1 tablet of 500 mg TF2 was confirmed under fasted conditions in Study MS200095-0044.

In the initial MAD study (EMR200095-001), a maximum tolerated dose was not reached up to the highest administered dose of 1,400 mg. The recommended Phase II dose (RP2D) of 500 mg was defined using Pd data from on-treatment tumor biopsies, analyzed in a translational PK/Pd model to achieve the target level of  $\geq 95\%$  MET inhibition in  $> 90\%$  of the patient population.

The safety, tolerability and clinical efficacy of the RP2D was confirmed in clinical studies and exposure-safety and exposure-efficacy analyses.

For the management of adverse events (AEs) at the proposed clinical dose of 500 mg, a dose reduction level of 250 mg once daily is recommended. This dose reduction level was selected

based on clinical experience with dose reductions to 300 mg and 200 mg in the VISION study, the translational PK/Pd model, and exposure-efficacy and exposure-safety analyses.

The Applicant's Position:

The proposed clinical dose of 500 mg once daily was selected in a Pd biomarker-driven approach and was confirmed by clinical data, including exposure-safety and exposure-efficacy analyses. This dose is associated with  $\geq 95\%$  MET inhibition in  $> 90\%$  of the patient population.

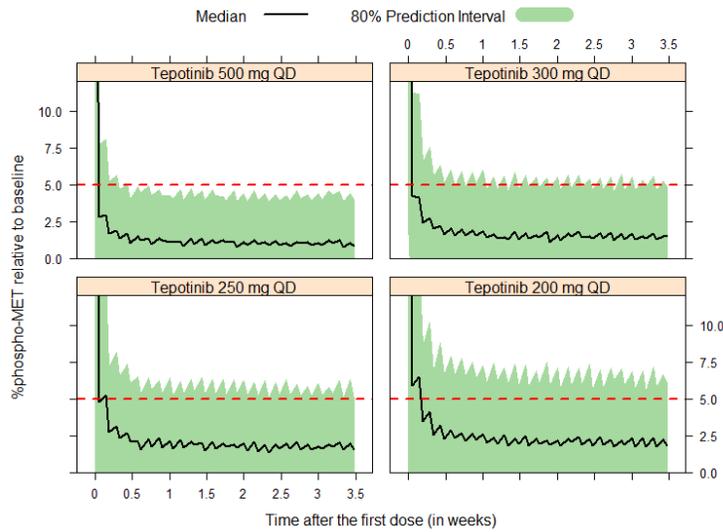
The FDA's Assessment:

FDA agrees with the Applicant's position.

The proposed dosing regimen of 500 mg QD was initially selected based on results from dose finding study EMR200095-001, in which a MTD was not reached up to the dose level tested of 1400 mg QD; DLTs were observed at dose levels of 1000 mg and 1400 mg QD. The selection of 500 mg QD was further confirmed with safety and observed preliminary antitumor activity data from studies EMR200095-003 and EMR200095-004, in which the median PFS of 2.7 months, and the median OS of 13.5 months were determined at the RP2D of 500 mg QD. Numerically lower median PFS of 1.3 months and OS of 8.4 months were determined at the lower dose of 300 mg QD. The preliminary efficacy was numerically better at higher dose of 1000 mg, with the median PFS of 3.45 months, while OS was not determined. Given the observed DLTs at dose levels  $\geq 1000$  mg, FDA considers the proposed 500 mg QD dosage acceptable.

The selection of the 500 mg QD dosing regimen was further supported by the PK/PD modeling and simulation, which shows that this dosing regimen with food could achieve  $\geq 95\%$  phospho-MET inhibition in tumors in greater than 90% of the population (Figure 17). The saturation of phospho-MET inhibition was consistent with the flat exposure-response for safety and efficacy endpoints from VISION following a dosage of 500 mg QD. Refer to the Appendix 19.4 for more details on Population PK and Exposure-Response analyses.

**Figure 17: Population Simulation of phospho-MET Inhibition in Mixed-Solid Tumor Population**



Source: Study EMR200095-001 PK-Pd Report, Figure 7.

There are five tepotinib formulations (Capsule Formulations: CF1, CF2; Tablet Formulations: TF1, TF2 and TF3) were used in the clinical pharmacology studies (Table 12). Adequate bridging has been established between the formulations.

**Table 12: Formulations of Tepotinib Used in Clinical Studies**

Formulation	Tepotinib	Dose Strength (mg)	Study Number
Tablet Formulation 3 (TF3)	(b) (4)	250	MS200095-0044
		100, 250	MS200095-0022 (VISION) <sup>a</sup>
		100, 250	MS200095-0038
Tablet Formulation 2 (TF2)	(b) (4)	500	MS200095-0044
		500	MS200095-0012
		100, 500	MS200095-0022 (VISION)
		500	MS200095-0028
		500	MS200095-0030
		500	MS200095-0032
		500	MS200095-0039
Tablet Formulation 1 (TF1)	(b) (4)	100	EMR200095-001
		30	EMR200095-002
		100	EMR200095-004
		25, 100	EMR200095-005
		25, 100	EMR200095-006
		100	EMR200095-007
		100	MS200095-0012
Capsule Formulation 2 (CF2)	(b) (4)	15, 100	EMR200095-001
		15	EMR200095-002
		15, 100	EMR200095-003
Capsule Formulation 1 (CF1)	(b) (4)	15, 100	EMR200095-001

The primary dose-finding and dose confirmation efforts were primarily conducted with the CF2 (EMR200095-001, EMR200095-003), TF1 (EMR200095-004, EMR200095-005 and EMR200095-006) formulations. CF1 was the formulation initially utilized in the first in human (FIH) study and was replaced by CF2 and TF1 formulations due to its relatively low bioavailability. Adequate bridge between CF2 and TF1 was established in the relative bioavailability study showing comparable tepotinib exposure with the two formulations (Table 13).

**Table 13: Relative Bioavailability between Tepotinib Formulations TF1 and CF2**

Parameter	Ratio (%)	90% Lower CL	90% Upper CL
AUC <sub>0-1</sub>	111.2	102.4	120.7
AUC <sub>0-∞</sub>	110.8	102.3	120.1
C <sub>max</sub>	114.9	105.5	125.2

Source: CSR of Study EMR200095-001, Table 11-7, page 49

The bridging between TF1 and TF2 was supported by the demonstration of bioequivalence between the two formulations in the relative bioavailability study EMR200095-0012 (Table 14).

**Table 14: Relative Bioavailability between TF1 and TF2**

Drug Substance	Parameter	Treatment	n	Geometric Least Squares Mean	Ratio Test / Reference (%)	90%CI of Ratio
Tepotinib	AUC <sub>0-t</sub> (ng*h/mL)	Test	23	25424.8	98.68	93.67, 103.96
		Reference	23	25764.8		
	AUC <sub>0-∞</sub> <sup>a</sup> (ng*h/mL)	Test	18	25783.9	95.71	88.43, 103.59
		Reference	17	26939.9		
	C <sub>max</sub> (ng/mL)	Test	23	466.3	96.88	90.80, 103.36
		Reference	23	481.3		

Source: CSR of Study EMR200095-0012, table 11-6, page 81.

Both tepotinib formulations TF2 and TF3 were used in VISION. Formulation TF2 was used initially and all patients were gradually switched to TF3 upon implementation of Protocol Amendment 6 (dated 26 March 2019) until 10 March 2020. The clinical outcomes were thus achieved based on a combination effect by treatment using both TF2 and TF3. Based on the relative bioavailability and food effect study MS200095-0044, the bioequivalence between TF3 and TF2 was established under fasted condition (Table 15).

**Table 15: Relative Bioavailability between TF3 and TF2**

Parameter	N <sup>b</sup>	Treatment/ Comparison between	Geometric LS-Mean	Ratio of Geometric LS-Mean (%)	90% CI <sup>a</sup> of Ratio (%)	Intra-subject CV (%)
AUC <sub>0-t</sub> (h*ng/mL)	38	T: TF3, fasted	18622	-	-	-
	38	R: TF2, fasted	16143	-	-	-
		T/R	-	115.35	108.55;122.58	15.77
AUC <sub>0-∞</sub> (h*ng/mL)	38	T: TF3, fasted	19295	-	-	-
	38	R: TF2, fasted	16728	-	-	-
		T/R	-	115.34	108.51;122.60	15.83
C <sub>max</sub> (ng/mL)	38	T: TF3, fasted	287	-	-	-
	38	R: TF2, fasted	253	-	-	-
		T/R	-	113.57	107.62;119.85	13.94

Source: CSR of Study MS200095-0044, table 11, page 67.

The exposure following TF2 under fed conditions was comparable to that for TF3 under fed conditions (Table 16). As a result, no clinically relevant effect is expected as a result from the switch from the TF2 to TF3 formulation.

**Table 16: Summary of Tepotinib PK for TF2 and TF3 under Fasted and Fed conditions**

Parameter	Statistics	Part B		Part C	
		TF2, fasted N = 12 <sup>b</sup>	TF2, fed N = 14	TF3, fasted N = 12	TF3, fed N = 12
AUC <sub>0-t</sub> (h*ng/mL)	GeoMean	12609	23457	17964	29307
	(GeoCV%)	(38.1)	(25.1)	(19.8)	(25.0)
	95% CI <sup>a</sup>	9978; 15932	20333; 27062	15859; 20348	25056; 34279
AUC <sub>0-∞</sub> (h*ng/mL)	GeoMean	13037	24443 <sup>c</sup>	18447	30118
	(GeoCV%)	(38.2)	(25.9) <sup>c</sup>	(20.0)	(25.5)
	95% CI <sup>a</sup>	10314; 16479	20956; 28510	16262; 20927	25674; 35331
C <sub>max</sub> (ng/mL)	GeoMean	199	476	280	559
	(GeoCV%)	(29.5)	(19.6)	(15.3)	(17.0)
	95% CI <sup>a</sup>	165; 239	426; 533	254; 309	503; 623

Source: CSR of MS200095-0044, Table 15, page 75

The TF3 formulation has two dose strengths: 100 mg and 250 mg. Although bioequivalence has been established between the two dose strengths (Table 17), the 100 mg dose strength is not included in the proposed USPI for marketing purposes. The decision may potentially be due to there only being one recommended dose adjustment level to that of 250 mg QD for adverse reactions. However, the additional dose strength may provide additional flexibility on dosage modification in future submissions.

**Table 17: Statistical Comparison of PK Parameters between Tepotinib TF3 100 mg and 250 mg**

Parameter	N	Treatment/ Comparison between	Geometric LS-Mean	Ratio of Geometric LS-Mean (%)	90% CI <sup>a</sup> of Ratio (%)	Intra- subject CV (%)
AUC <sub>0-t</sub> (h*ng/mL)	17 <sup>b</sup>	T: 5 x 100 mg TF3	15060	-	-	-
	18	R: 2 x 250 mg TF3	16523	-	-	-
		T/R	-	91.15	83.21; 99.84	15.26
AUC <sub>0-∞</sub> (h*ng/mL)	17 <sup>b</sup>	T: 5 x 100 mg TF3	15640	-	-	-
	18	R: 2 x 250 mg TF3	17201	-	-	-
		T/R	-	90.92	82.99; 99.61	15.29
C <sub>max</sub> (ng/mL)	18	T: 5 x 100 mg TF3	252	-	-	-
	18	R: 2 x 250 mg TF3	240	-	-	-
		T/R	-	104.62	95.17; 115.00	16.37

Source: CSR of MS200095\_0038, Table 9, page 48.

The recommendation that tepotinib is administered with food is supported by the food effect study showing the mean AUC<sub>0-INF</sub> of tepotinib increased by 1.6-fold and C<sub>max</sub> increased by 2-fold (Table 18), following administration of a high-fat, high-calorie meal (approximately 800 to 1,000 calories, 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat). The median T<sub>max</sub> shifted from 12 hours to 8 hours. In addition, taking tepotinib with food is expected to mitigate the gastrointestinal toxicities including diarrhea, which were among the most common adverse reactions. The food effect is considered clinically meaningful, as a reduction in exposure following administration of tepotinib without food may potentially reduce anti-tumor activity and tepotinib was administered with food in VISION.

**Table 18: Food Effect of Tepotinib with Formulation TF3**

Part C						
AUC <sub>0-t</sub> (h*ng/mL)	12	T: TF3, fed	29307	-	-	-
	12	R: TF3, fasted	17964	-	-	-
		T/R	-	163.15	146.17;182.10	14.93
AUC <sub>0-∞</sub> (h*ng/mL)	12	T: TF3, fed	30118	-	-	-
	12	R: TF3, fasted	18447	-	-	-
		T/R	-	163.26	146.09;182.46	15.10
C <sub>max</sub> (ng/mL)	12	T: TF3, fed	559	-	-	-
	12	R: TF3, fasted	280	-	-	-
		T/R	-	199.61	176.44;225.82	16.79

Source: CSR of MS200095-0044, Table 16, page 76

The clinical consequence for patients who take tepotinib without food was explored by using PK/PD modeling. The modeling and simulation suggested that the rate of patients who will not reach 95% phosphor-MET inhibition is numerically higher under fasting conditions (Table 19). Based on the results from the PK/PD modeling, FDA agrees with the Applicant's proposal of giving tepotinib with food considering that it may mitigate gastrointestinal toxicities.

**Table 19: Population PKPD Simulation for phosphor-MET inhibition**

Percentile of Patients not reached 95% Inhibition				
All Patients	Dose (mg)	Median	10 <sup>th</sup> – 90 <sup>th</sup> percentile	
FED	250	23.1	20.1	28.3
	500	9.6	8.81	10.6
FAST	250	29.1	24.5	34.8
	500	14.4	11.9	17.4

Source: Reviewer's independent analysis

### 6.2.2.2. Therapeutic Individualization

#### Data:

##### *Intrinsic factors*

In a population PK analysis, age, sex, race, body weight and disease status had no relevant influence on the PK of tepotinib, i.e., not resulting in exposures (median for categorical covariates or 10<sup>th</sup> to 90<sup>th</sup> percentile for continuous covariates) outside the 80% to 125% intervals of typical cancer patients.

Both the clinical study in patients with Child-Pugh Class A and B hepatic dysfunction, and the population PK analysis showed no clinically relevant effect of mild or moderate hepatic impairment on the PK of tepotinib. The total tepotinib exposure was 13% (AUC) and 29% (C<sub>max</sub>) lower in patients with moderate hepatic impairment compared to healthy participants. The observed mean free AUC was higher in patients with mild (13%) and moderate (24%) hepatic impairment compared with healthy participants. However, this is within the observed exposure variability and is not considered clinically relevant based on the favorable safety profile. The effect of severe hepatic impairment has not been studied.

In agreement with the low extent of renal elimination, the population PK analysis showed no evidence for clinically meaningful effects of mild or moderate renal impairment on the PK of tepotinib. The effect of severe renal impairment has not been studied.

##### *Extrinsic factors*

A food effect was shown for all formulations tested including the proposed commercial formulation, TF3. At the proposed clinical dose of 500 mg TF3, a standard high fat, high-calorie breakfast increased the AUC of tepotinib by approximately 1.6-fold and C<sub>max</sub> by approximately 2-fold. The effect of a normal breakfast was in a similar range as a standard high-fat, high-calorie breakfast. Tepotinib was administered in the clinical studies with a normal breakfast, and the proposed mode of administration in the labeling is that tepotinib should be taken with food.

Proton pump inhibition had no clinically relevant effect on the bioavailability of tepotinib.

Based on metabolite profiling in excreta, no single identified metabolic pathway comprises more than 25% of the administered dose. Therefore, the drug-drug interaction (DDI) potential with tepotinib as a victim of interactions with coadministered drugs that interact with drug-metabolizing enzymes is considered low.

Tepotinib is a P-gp substrate. However, P-gp inhibitors are not expected to alter tepotinib exposure to a clinically relevant extent (Section 6.3.1). Strong inducers of P-gp may have the potential to decrease tepotinib exposure, and the proposed labeling advises that concomitant use of strong P-gp inducers should be avoided.

#### The Applicant's Position:

No dose adjustment is recommended based on intrinsic factors in patient subpopulations. The PK and safety of tepotinib in patients with severe hepatic or renal impairment have not been studied.

Tepotinib is subject to a food effect and should be administered with food. Administration in the pivotal VISION study was also after a normal breakfast. The exposure and clinical data thus reflect individual and cultural differences in dietary habits.

Apart from strong P-gp inducers, tepotinib is not expected to be sensitive to the potential effects of other coadministered drugs.

#### The FDA's Assessment:

FDA agrees with the Applicant that no dosage adjustment is recommended based on intrinsic factors (i.e., mild or moderate renal impairment, mild or moderate hepatic impairment) in patient subpopulations.

FDA's conclusion that no dosage adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh classification) is based on the results from the dedicated hepatic impairment study, in which the exposure was similar in healthy subjects and patients with mild hepatic impairment (Child-Pugh Class A), with no clinically relevant decrease (13% decrease in AUC and 29% decrease in C<sub>max</sub>) in patients with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects (Table 20).

**Table 20: Comparison of Tepotinib PK Between Hepatic Function Groups Based on Child-Pugh Classification**

Parameter (unit)	Hepatic Function Group	n	Geometric LS Mean	95% CI of Geometric LS Mean (%)	Comparison to Healthy Control		
					Ratio (%)	90% CI of Ratio (%)	GeoCV%
AUC <sub>0-t</sub> (ng*h/mL)	Healthy Control	6	27000	(19300, 37800)			40.2
	Mild Impairment	6	25600	(18300, 35800)	94.81	(64.09, 140.26)	
	Moderate Impairment	6	23500	(16800, 33000)	87.20	(58.94, 129.00)	
AUC <sub>0-∞</sub> (ng*h/mL)	Healthy Control	6	27500	(19800, 38200)			39.3
	Mild Impairment	6	26100	(18800, 36300)	94.99	(64.75, 139.35)	
	Moderate Impairment	6	24200	(17400, 33600)	87.92	(59.93, 128.98)	
C <sub>max</sub> (ng/mL)	Healthy Control	6	406	(331, 497)			23.6
	Mild Impairment	6	416	(340, 510)	102.45	(80.90, 129.73)	
	Moderate Impairment	6	288	(235, 353)	71.02	(56.08, 89.93)	

Source: CSR of Study MS200095-0028, Table 16, Page 71

In response to FDA’s information request, the effect of hepatic impairment on tepotinib exposure was further evaluated after reclassification using ODWG criteria. The result also suggested that the difference in tepotinib exposure in both mild and moderate hepatic impairment cohorts as compared to that of healthy subjects were not clinically relevant (Table 21). The Applicant considered that decreased exposure may be explained by the mechanism of decreased plasma protein binding, due to diminished albumin synthesis by the liver, and this may lead to an increase in free fraction of the drug and an increase in the plasma clearance of total drug in the absence of alteration of free drug clearance (SDN 29, 10/8/2020).

**Table 21: Tepotinib Total Plasma Pharmacokinetic Parameters by ODWG Class**

NCI-ODWG	Statistic	CL/F (L/h)	V <sub>d</sub> /F (L)	T <sub>1/2</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng·h/mL)	AUC <sub>0-∞</sub> (ng·h/mL)
<b>Normal</b>	N	11	11	11	11	11	11
	Mean (SD)	15.7 (3.758)	892 (90.23)	41.1 (8.964)	437 (56.59)	29800 (7749)	30300 (7826)
	Min, Max	10.5, 20.6	798, 1050	31.3, 55.2	334, 510	21600, 42100	21800, 42700
	Median	16	915	37	419	27800	28200
	GeoMean (GeoCV%)	15.3 (25.5%)	888 (10.0%)	40.3 (21.4%)	433 (13.3%)	29000 (25.6%)	29400 (25.5%)
<b>Mild</b>	N	4	4	4	4	4	4
	Mean (SD)	28.7 (13.3)	1820 (456.6)	48 (15.67)	256 (33.68)	17400 (7192)	18100 (7443)
	Min, Max	16.3, 47.5	1510, 2500	36.4, 71.1	229, 304	8990, 26500	9460, 27600
	Median	25.5	1640	42.2	245	17100	17600
	GeoMean (GeoCV%)	26.7 (46.3%)	1780 (23.2%)	46.3 (30.1%)	254 (12.7%)	16200 (47.0%)	16900 (46.3%)
	Geo Mean Ratio to Normal (90% CI)	162.2% (118.2%; 222.4%)	205.7% (175.2%; 241.5%)	126.8% (105.0%; 153.2%)	58.9% (49.6%; 69.9%)	60.2% (43.8%; 82.9%)	61.7% (45.0%; 84.6%)
<b>Moderate</b>	N	2	2	2	2	2	2
	Mean (SD)	16.7 (2.994)	1110 (183.2)	46.1 (0.6554)	362 (121.6)	26900 (4828)	27300 (4881)
	Min, Max	14.6, 18.9	982, 1240	45.6, 46.5	276, 448	23500, 30300	23900, 30800
	Median	16.7	1110	46.1	362	26900	27300
	GeoMean (GeoCV%)	16.6 (18.1%)	1100 (16.7%)	46.1 (1.4%)	352 (35.3%)	26700 (18.2%)	27100 (18.1%)
	Geo Mean Ratio to Normal (90% CI)	111.2% (72.6%; 170.3%)	116.8% (94.0%; 145.0%)	105.0% (81.4%; 135.5%)	84.7% (67.2%; 106.9%)	90.0% (58.5%; 138.5%)	90.0% (58.7%; 137.8%)
<b>Severe</b>	N	1	1	1	1	1	1
	Mean (SD)	14.3 (NC)	1530 (NC)	74.4 (NC)	255 (NC)	31000 (NC)	31500 (NC)

Source: Response to FDA information request, SDN 29, 10/8/2020, Table 1, Page 5.

In addition, the Applicant considered that there is only a slight increase in the unbound drug exposure, which further supports the conclusion that mild and moderate hepatic impairment did not have a clinically relevant effect on the tepotinib exposure (Table 22). FDA considers the Applicant's rationale acceptable.

**Table 22: Tepotinib Unbound Plasma Pharmacokinetic Parameters by ODWG Class**

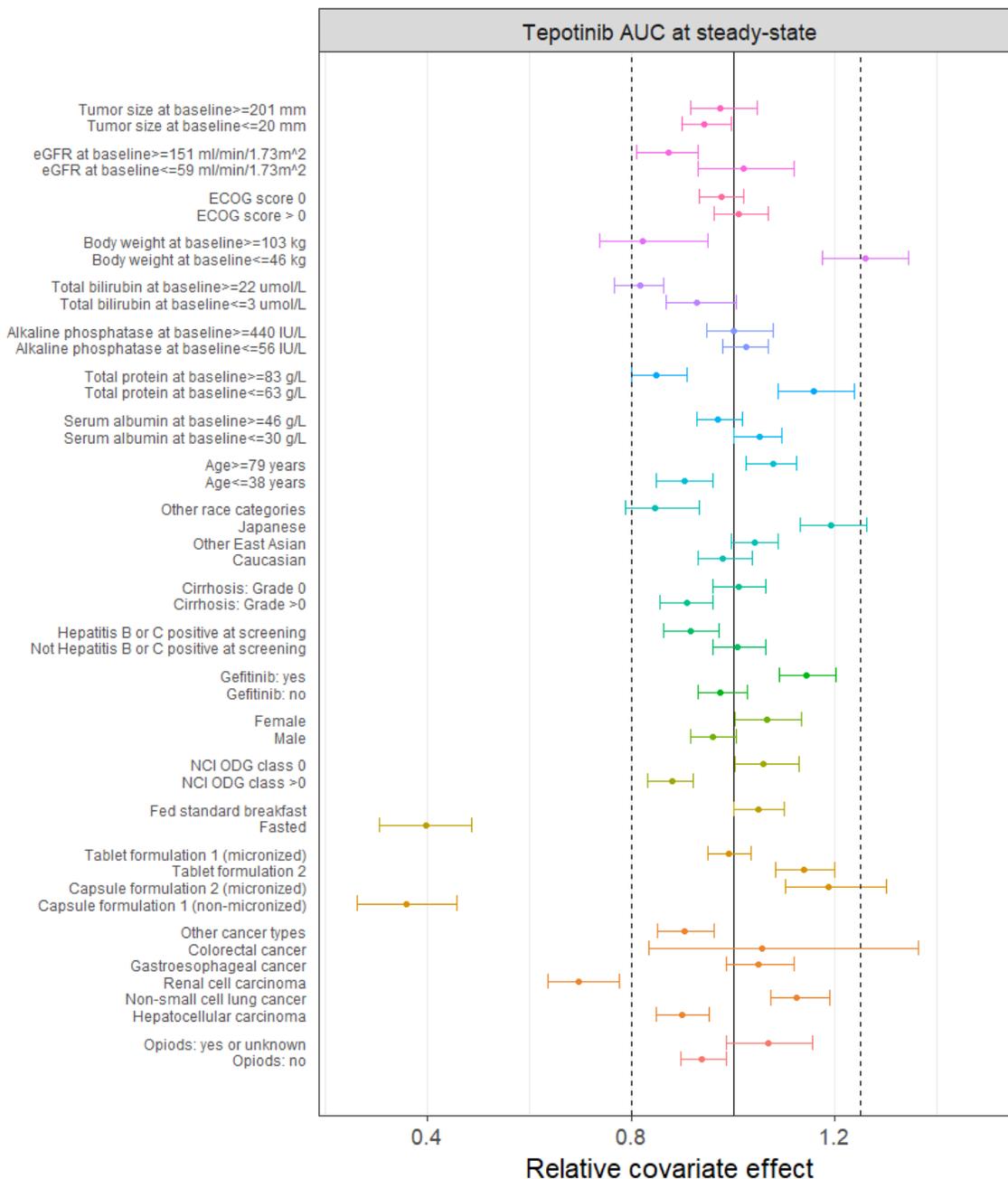
NCI-ODWG Classification	Statistic	CL/F <sub>tu</sub> (L/h)	C <sub>max, fu</sub> (ng/mL)	AUC <sub>0-∞, fu</sub> (ng·h/mL)
<b>Normal</b>	N	11	11	11
	Mean (SD)	786 (222.9)	8.95 (2.09)	609 (143.2)
	Min, Max	561, 1260	5.72, 12.5	356, 803
	Median	695	9.24	648
	GeoMean (GeoCV%)	761 (26.4%)	8.71 (25.1%)	591 (26.4%)
<b>Mild</b>	N	4	4	4
	Mean (SD)	1040 (380.2)	6.89 (0.8826)	476 (158)
	Min, Max	729, 1530	5.88, 7.98	293, 617
	Median	947	6.84	496
	GeoMean (GeoCV%)	990 (36.8%)	6.84 (12.9%)	454 (36.8%)
	Geo Mean Ratio to Normal (90% CI)	124.3% (90.7%; 170.3%)	76.8% (59.1%; 99.8%)	80.4% (58.7%; 110.2%)
<b>Moderate</b>	N	2	2	2
	Mean (SD)	636 (64.14)	9.36 (2.441)	711 (71.61)
	Min, Max	591, 682	7.64, 11.1	660, 761
	Median	636	9.36	711
	GeoMean (GeoCV%)	635 (10.1%)	9.2 (26.8%)	709 (10.1%)
	Geo Mean Ratio to Normal (90% CI)	84.8% (55.4%; 129.7%)	111.1% (78.0%; 158.2%)	117.9% (77.1%; 180.5%)
<b>Severe</b>	N	1	1	1
	Mean (SD)	424 (NC)	8.59 (NC)	1060 (NC)
	Min, Max	424, 424	8.59, 8.59	1060, 1060
	Median	424	8.59	1060
	GeoMean	424	8.59	1060
	Geo Mean Ratio to Normal (90% CI)	50.8% (29.2%; 88.4%)	99.3% (62.7%; 157.4%)	196.8% (113.2%; 342.3%)

Source: Response to FDA information request, SDN 29, 10/8/2020, Table 3, Page 7.

FDA agrees that no dose adjustment is necessary for patients with mild or moderate renal impairment. No dedicated renal impairment study was conducted to evaluate the effect of renal impairment on the PK of tepotinib. The population PK analysis of 591 participants (eGFR range 39.4 to 236 mL/min/1.73 m<sup>2</sup>, including 64 patients with moderate renal impairment from VISION Study) suggested that the apparent clearance of tepotinib did not show a clinically meaningful association with eGFR. FDA agrees a dedicated study to evaluate the effect of severe renal impairment on the PK of tepotinib is not required, given that renal excretion of tepotinib is identified as a minor route of elimination.

FDA also agrees with the Applicant that no clinically significant effects on tepotinib pharmacokinetics were observed based on subpopulation including sex, age (18 to 89 years), race/ethnicity (White, n = 362; Black, n = 17; Japanese, n = 28; Other East Asian, n = 145; Hispanic, n = 25; other, n=14) and body weight (35.5 to 136 kg) (Figure 18). Refer to the Population PK analyses in Appendix 19.4 for details.

**Figure 18: Forest Plot Showing the Association of the Predicted AUC<sub>ss</sub> and Covariates**



Source: Pharmacometrics Pooled Population PK Report, April 2020, Figure 36

In terms of extrinsic factors, FDA agrees with the Applicant that tepotinib should be given with food, given the observed increase in AUC by 1.6-fold and C<sub>max</sub> by 2-fold with high fat, high-calorie breakfast (refer to section 6.2.2.1 for more details). FDA also agrees that no clinically

significant differences in tepotinib pharmacokinetics were observed when co-administered with multiple daily doses (40 mg daily for 5 days) of omeprazole (proton pump inhibitor) under fed conditions, as supported by results from Study MS200095-0039 (Table 23).

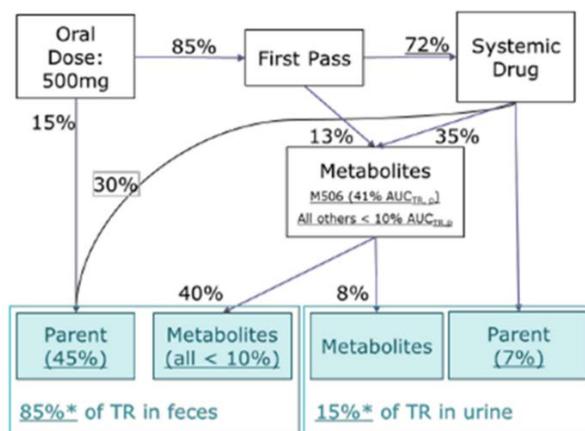
**Table 23: Statistical Comparisons of Primary PK Parameters of Tepotinib**

Parameter	Treatment/ Comparison Between	Geometric LS Mean	Ratio of Geometric LS Means (%)	90% CI <sup>a</sup> of Ratio (%)	Intrasubject CV (%)
AUC <sub>0-t</sub> (h*ng/mL)	A	21722	-	-	-
	B	16220	-	-	-
	C	23649	-	-	-
	C/A	-	108.87	101.20, 117.13	10.41
	C/B	-	145.80	135.52, 156.86	10.41
AUC <sub>0-∞</sub> (h*ng/mL)	A	23081	-	-	-
	B	17412	-	-	-
	C	25343	-	-	-
	C/A	-	109.80	101.69, 118.55	10.93
	C/B	-	145.55	134.80, 157.15	10.93
C <sub>max</sub> (ng/mL)	A	428	-	-	-
	B	227	-	-	-
	C	445	-	-	-
	C/A	-	104.10	92.93, 116.61	16.22
	C/B	-	196.34	175.28, 219.93	16.22

Source: CSR of MS200095-0039, Table 7, Page 45. A: single dose of 500 mg tepotinib with food; B: Five days of 40 mg omeprazole fasted, with tepotinib on day 5 fasted; C: Five days of 40 mg omeprazole fasted, with tepotinib on day 5 under fed condition.

However, FDA considers that there is insufficient evidence to support labeling recommendations to address the drug interaction potential for tepotinib as a victim. Mass balance and bioavailability study EMR200095-007 suggested that metabolites account for a substantial amount (48%) of recovered radioactivity (Figure 19).

**Figure 19. Major Routes of Excretion of <sup>14</sup>C-Labeled Tepotinib**



Source: Summary of Clinical Pharmacology Studies, Figure 19, page 81.

In vitro data from Study DMPK 87-08 and XT134049 suggested that tepotinib is a substrate of CYP2C8 and CYP3A4, with CYP3A4 having a higher contribution to the metabolism than CYP2C8. Although the Applicant acknowledges that fractions metabolized by individual CYP isozymes could not be reliably quantified (Response to FDA Information Request, sequence NO. 029, 10/8/2020), no in vivo study has been conducted to further evaluate the effect of CYP3A4 and CYP2C8 inhibitors or inducers on tepotinib exposure. In addition, tepotinib is a P-gp substrate in vitro and has moderate passive permeability. Although FDA agrees with the Applicant that the maximum increase in AUC through complete inhibition of biliary secretion (clearance reduction by 30%), would translate to a clinically irrelevant AUC increase of 1.4-fold, the additive effect of both CYP3A4/CYP2C8 and P-gp induction or inhibition has not been evaluated nor reliably predicted.

In response to FDA's information request (sequence NO. 029, 10/8/2020), the Applicant agreed with FDA's concern and proposed to conduct a dedicated post-marketing study (PMR) using the dual strong CYP3A4 inhibitor and P-gp inhibitor itraconazole to reflect a worst-case scenario of inhibition of both CYP3A4 and P-gp.

Although FDA agrees with the Applicant's proposal of avoiding the concomitant use of strong CYP3A4 inducers and P-gp inducers, FDA considered that the avoidance limits the treatment options for this patient population. FDA considered that the use of a PBPK modeling approach to estimate the magnitude of DDI resulting from P-gp/CYP3A inducers would be insufficient to support dosage recommendations. There are concerns about the development of a reliable PBPK model given the remaining uncertainties in the fraction of individual CYP enzymes and P-gp contribution to tepotinib clearance, and the limited experience using the PBPK approach to estimate P-gp induction effect and combined effect of simultaneous CYP and P-gp induction. As a result, FDA considers it is necessary for the Applicant to conduct a clinical trial as a PMC to evaluate the effect of a strong CYP3A4 inducer and P-gp inducer on tepotinib exposure, such as rifampin, which is a strong CYP3A4, moderate CYP2C8, and P-gp inducer.

In conclusion, FDA in general agrees with the Applicant regarding therapeutic individualization based on intrinsic and extrinsic factors. However, FDA considered that the drug interaction potential for tepotinib as a victim is not adequately evaluated. FDA thus issued a PMC using rifampin as strong CYP3A4, moderate CYP2C8 and P-gp inducer to determine the induction effect on tepotinib exposure, and a PMR using itraconazole as strong inhibition of CYP3A4 and P-gp inhibitor to determine the inhibition effect on tepotinib exposure.

### **6.2.2.3. Outstanding Issues**

#### Data and the Applicant's Position:

No outstanding issues.

#### The FDA's Assessment:

FDA agrees with the Applicant's position.

### **6.3. Comprehensive Clinical Pharmacology Review**

#### **6.3.1. General Pharmacology and Pharmacokinetic Characteristics**

##### Data:

An overview of the clinical PK of tepotinib is provided below.

##### *Absorption*

Despite the limited solubility profile, a mean absolute bioavailability of 71.6% (geometric mean; range 62% to 81%) was observed for a 500 mg dose of tepotinib TF1 administered after a high-fat, high-calorie breakfast.

The proposed commercial formulation TF3 (2 tablets of the 250 mg dose strength) was shown to be bioequivalent to TF2 (1 tablet of the 500 mg dose strength) under fasted conditions (Study MS200095-0044). TF2 was tested against TF1 in a relative bioavailability study under fed conditions and had very similar concentration-time profiles and bioavailability, with exposure ratios of TF2 vs. TF1 within the bioequivalence boundaries (Study MS200095-0012). Therefore, the absolute bioavailability of the proposed commercial formulation, TF3, is expected to be similar to that observed for TF1.

Tepotinib exposure increased in the presence of food (Section 6.2.2.2). Tepotinib was generally administered after a normal breakfast in studies with cancer patients, including the VISION study, and the proposed mode of administration in the labeling is that tepotinib should be taken with food.

Following administration of single oral doses of 500 mg TF3 in the fed state, the median time to  $C_{max}$  (median  $t_{max}$ ) was 8 h (range from 6 to 12 h).

Tepotinib exposure after administration of the TFs increased dose-proportionally over the clinically relevant dose range up to 500 mg. The PK of tepotinib does not change with time.

The proton pump inhibitor, omeprazole had no clinically relevant effect on the PK profile of tepotinib when administered under fed conditions.

##### *Distribution*

In human plasma, tepotinib is highly protein-bound (98%). Following a single iv dose of  $^{14}C$ -labeled tepotinib, the volume of distribution during the terminal phase ( $V_z$ ) was shown to be large, with a geometric mean (geometric CV%) of 574 L (14.4%).

Tepotinib was identified as a P-gp substrate. Considering the high fraction absorbed (85%) after oral administration, and based on a worst-case in which P-gp-mediated biliary secretion accounts

for 30% of the total clearance, P-gp inhibitors are not expected to alter tepotinib exposure to a clinically relevant extent.

#### *Metabolism*

Tepotinib is metabolized in humans with metabolites accounting for 48% of recovered tepotinib-related radioactivity in feces and urine. No single metabolic pathway accounted for > 25% of tepotinib elimination.

The contribution of the major circulating metabolite (MSC2571109A) to the overall efficacy of tepotinib in humans is estimated to be negligible.

#### *Excretion*

Tepotinib is mainly excreted via feces (approximately 85% of administered radioactivity, adjusted for total recovery), with urinary excretion being a minor excretion pathway. After a single oral administration of a radiolabeled dose of 500 mg tepotinib, the major circulating metabolite accounted for only about 3% of the total radioactivity in feces.

Following a single iv dose of tepotinib, the geometric mean (geometric CV%) clearance was estimated to be 12.8 L/h (7.8%).

The effective half-life for tepotinib was approximately 32 h based on the population PK analysis. After multiple daily administrations of 500 mg tepotinib TF1, median accumulation was 2.5-fold for  $C_{max}$  and 3.3-fold for  $AUC_{0-24h}$ .

#### The Applicant's Position:

The clinical PK and ADME properties of tepotinib have been well characterized.

#### The FDA's Assessment:

FDA generally agrees with the Applicant's position. However, FDA considers that fractions metabolized by each individual CYP isozyme could not be reliably quantified. Lack of such information will make the evaluation of the drug interaction potential for tepotinib as victim difficult without in vivo drug interaction data. Metabolism and in vitro data suggested that tepotinib is a substrate of CYP3A4, CYP2C8 and P-gp. The potential tepotinib exposure increase due to CYP3A4/2C8 and P-gp inhibition may increase the incidence and severity of adverse reactions of tepotinib, while the potential reduction in tepotinib exposure due to CYP3A4/2C8 and P-gp induction may decrease TEPMETKO anti-tumor activity. As a result, FDA issued a PMC and a PMR to address this drug interaction concerns. Refer to sections 6.1.2 and 6.2.2.2 for more details.

### 6.3.2. Clinical Pharmacology Questions

#### 6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

##### Data:

MET phosphorylation as a proximal target engagement biomarker was assessed in paired tumor biopsies from the FIH MAD study (Study EMR200095-001) at different dose levels and evaluated in a translational PK/Pd model. Efficacy and Pd profiling in KP-4 xenograft tumors suggested that near-complete inhibition of MET kinase activity ( $\geq 95\%$  reduction in phospho-MET) is required to achieve tumor regression. The human PK/Pd model simulations suggested that the proposed clinical tepotinib dose of 500 mg once daily is sufficient to achieve sustained inhibition of phospho-MET at a level  $> 95\%$  in more than 90% of a mixed solid tumor population.

The high degree of MET inhibition is confirmed by the exposure-efficacy analyses for the clinical endpoints OR, DOR and PFS. The clinically meaningful efficacy of tepotinib (Section 8.1.2) was associated with a flat exposure-response association across the clinically obtained exposure range in VISION.

##### The Applicant's Position:

The clinically meaningful efficacy of tepotinib is in agreement with the high degree of sustained target inhibition predicted from a translational PK/Pd model and confirmed by the exposure-efficacy analysis.

##### The FDA's Assessment:

FDA agrees with the Applicant's position that population PK/PD modeling and simulation provide supportive evidence for efficacy. Refer to sections 6.2.2.1 and 8.1 for more details on efficacy evaluation.

#### 6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

##### Data:

The proposed dosing regimen of 500 mg once daily was defined by a translational model-based approach, using nonclinical PK and Pd data (inhibition of the MET pathway), nonclinical efficacy data (inhibition of tumor growth) and clinical PK and Pd data. Efficacy and Pd profiling in KP-4 xenograft tumors suggested that near-complete inhibition of MET kinase activity ( $\geq 95\%$  reduction in phospho-MET) is required to achieve tumor regression. Therefore, this level of MET inhibition was used as the target to be achieved in humans.

Clinical PK and Pd data from the Phase I, FIH, MAD Study EMR200095-001 were used to adapt the nonclinical PK/Pd model to the human setting. The human PK/Pd model simulations suggested that a tepotinib dose of 500 mg once daily is sufficient to achieve sustained inhibition of phospho-MET at a level > 95% in more than 90% of a mixed solid tumor population. The safety and tolerability data from Study EMR200095-001 and from Study EMR200095-003 further supported the selection of 500 mg once daily for Phase II studies.

In the ongoing Phase II single-arm pivotal VISION study, daily doses of 500 mg tepotinib were administered and shown to be efficacious with a tolerable and manageable safety profile, as reflected in a high mean relative dose intensity of 90.3%, confirming the selected clinical dose and regimen.

The exposure-efficacy analysis for OR (primary endpoint), and DOR and PFS (secondary endpoints), showed similar efficacy across the exposure range observed in VISION. The observation of a flat exposure-efficacy relationship in the VISION study is in line with the simulation results from the translational PK/Pd model that predicted biologically meaningful target inhibition in a large proportion of the patient population at the proposed clinical dose of 500 mg.

The risk for the most frequent treatment-emergent adverse event (TEAE), peripheral edema, showed a flat exposure-response association at exposures beyond the first quartile achieved in the VISION study. Other safety endpoints, including serum lipase, serum amylase, AST and ALT did not show any association with tepotinib exposure. Exposure-QTc modeling showed no clinically relevant prolongation of the QTc interval.

No dose individualization based on intrinsic or extrinsic factors is recommended in the target patient population (Section 6.2.2.2). The PK and safety of tepotinib in patients with severe hepatic or renal impairment have not been studied.

#### The Applicant's Position:

The proposed clinical dose of 500 mg once daily was selected based on a biomarker-driven approach targeting a  $\geq 95\%$  reduction in phospho-MET. Exposure-response analysis for efficacy endpoints show that this dose is associated with clinically meaningful and exposure-independent clinical efficacy.

Clinical data and exposure-safety analysis show a manageable and exposure-independent safety profile. Analysis of intrinsic and extrinsic factors does not suggest dose modification for specific subpopulations.

The totality of data shows that the proposed clinical dose of 500 mg is adequately chosen for the treatment of the target patient population.

#### The FDA's Assessment:

FDA agrees with the Applicant's position that the proposed 500 mg QD dosage (equivalent to 450 mg tepotinib free base) with food is adequate for the treatment of the proposed patient population. Refer to section 6.2.2.1 for a more detailed evaluation.

### **6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

#### Data and Applicant's Position:

Based on the analysis of intrinsic and extrinsic factors, no alternative dosing regimen or management strategy is required for subpopulations (Section 6.2.2.2).

#### The FDA's Assessment:

FDA agrees with the Applicant's position that no alternative dosing regimen or risk management strategy is required for subpopulations such as age (18 to 89 years), race/ethnicity (White, Black, Asian, Japanese, and Hispanic), sex, body weight (35.5 to 136 kg), mild to moderate renal impairment (CL<sub>cr</sub> 30 to 89 mL/min), or mild to moderate hepatic impairment (Child-Pugh A and B). Refer to section 6.2.2.2 for more details regarding evaluation of dose individualization based on intrinsic factors.

### **6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

#### Data:

At the proposed clinical dose of 500 mg TF3, a standard high fat, high-calorie breakfast increased AUC of tepotinib by about 1.6-fold and C<sub>max</sub> by about 2-fold. The effect of a normal breakfast was in a similar range as a standard high-fat, high-calorie breakfast. Tepotinib was administered in clinical studies with a normal breakfast, and the proposed labeling recommends administration with food. Proton pump inhibition had no clinically relevant effect on the PK of tepotinib.

Owing to multiple metabolic pathways (no metabolic pathway accounting for > 25% of tepotinib elimination), tepotinib has low sensitivity toward inhibitors of drug-metabolizing enzymes.

Tepotinib is a substrate to P-gp. Strong P-gp inhibition is not expected to result in clinically relevant effects (Section 6.3.1). However, strong P-gp inducers have the potential to decrease tepotinib exposure and concomitant use of such drugs should be avoided.

Tepotinib had no clinically relevant effect on CYP3A4.

Tepotinib had a weak effect on the sensitive P-gp substrate dabigatran etexilate (increases in AUC<sub>0-∞</sub> and C<sub>max</sub> of 45% and 38%, respectively). Clinical effects of coadministered P-gp-dependent drugs with a narrow therapeutic index should be monitored. In vitro, tepotinib is an inhibitor of breast cancer resistance protein (BCRP). Based on a study in which the BCRP substrate gefitinib

was coadministered, strong effects on BCRP are not expected. However, interactions with sensitive BCRP substrates cannot be excluded, and the clinical effects of such drugs should be monitored.

Based on in vitro data, tepotinib and its metabolite may have the potential to increase the AUC of coadministered metformin through inhibition of its renal excretion mediated via organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporter (MATE) 2. The clinical effects of coadministered metformin should be monitored.

#### The Applicant's Position:

Tepotinib is subject to a positive food effect. However, the clinical efficacy and safety data have been obtained from clinical studies in which tepotinib was administered with a non-standardized breakfast, and thus reflect individual and cultural differences in dietary habits. In addition, the flat exposure-efficacy and exposure-safety profiles demonstrate that the benefit/risk profile of tepotinib is not expected to be sensitive to modest changes in exposure.

With the exception of strong P-gp inducers that may have the potential to decrease tepotinib exposure, tepotinib has a low potential for clinically relevant DDI, both as victim, and as perpetrator. Concomitant use of strong P-gp inducers should be avoided. During coadministration with tepotinib, the clinical effects of P gp-dependent substances with a narrow therapeutic index, of sensitive BCRP substrates and of metformin should be monitored.

#### The FDA's Assessment:

##### *Tepotinib as victim*

FDA considers that the drug interaction potential for tepotinib as victim was not adequately assessed. Mass balance study results suggested that oxidative metabolites account for up to 48% of the total tepotinib dose. In vitro study results suggested that tepotinib was a substrate of CYP3A4, CYP2C8 and P-gp. However, the fractions metabolized by these individual CYP enzymes could not be reliably quantified. The worst-case scenario for the tepotinib exposure change when P-gp, CYP3A4 and CYP2C8 are induced or inhibited remains unknown.

The potential reduction in tepotinib exposure may decrease tepotinib anti-tumor activity, while the potential tepotinib exposure increase may increase the incidence and severity of adverse reactions of tepotinib. Dose adjustments for when tepotinib is used concomitantly with strong CYP3A4 inducers, moderate CYP2C8 inducers, and P-gp inducers, as well as strong CYP3A4 inhibitors, strong CYP2C8 inhibitors and P-gp inhibitors was not determined. Therefore, FDA issued a PMC using rifampin as strong CYP3A4 and moderate CYP2C8 inducer and P-gp inducer to determine the induction effect on tepotinib exposure, and a PMR using itraconazole as strong

inhibition of CYP3A4 and P-gp inhibitor to determine the inhibition effect on tepotinib exposure. Refer to sections 6.2.2.2 and 6.1.2 for more details.

*Tepotinib as Perpetrator*

In human liver microsomes, tepotinib inhibited CYP3A4 with  $K_i$  of 12.5  $\mu\text{m}$ . The drug interaction potential was further evaluated in vivo, in which coadministration of multiple doses of tepotinib 500 mg QD had no clinically relevant significant effect on the PK of midazolam (Table 24).

**Table 24: Statistical Comparison of Primary Midazolam PK Parameters**

Parameter	Treatment	n	Geometric LS-Mean	Ratio of Geometric LS-Mean (%)	90% CI <sup>a</sup> of Ratio (%)	Intrasubject CV (%)
AUC <sub>0-t</sub> (h*pg/mL)	T: tepotinib + midazolam	12	109477	-	-	-
	R: midazolam	12	107969	-	-	-
	TR	-	-	101.40	89.35;115.06	17.37
AUC <sub>0-∞</sub> (h*pg/mL)	T: tepotinib + midazolam	12	110550	-	-	-
	R: midazolam	12	109285	-	-	-
	TR	-	-	101.16	89.24;114.66	17.22
C <sub>max</sub> (pg/mL)	T: tepotinib + midazolam	12	50954	-	-	-
	R: midazolam	12	49172	-	-	-
	TR	-	-	103.62	86.91;123.56	24.35

Source: CSR of Study MS200095-0030, Table 7, Page 50

The in vitro data suggests that tepotinib may inhibit P-gp, BCRP and MATE2 (Table 26). The drug interaction potential for tepotinib to inhibit P-gp was evaluated in Study MS200095-0032, in which 500 mg QD tepotinib for 8 days was shown to increase dabigatran C<sub>max</sub> by 40% and AUC<sub>0-∞</sub> by 50% (Table 25). As a result, FDA recommends avoiding coadministration of tepotinib with P-gp substrates where minimal concentration changes may lead to serious or life-threatening adverse reactions.

**Table 25: Statistical Comparisons of Primary Dabigatran PK Parameters**

Parameter	Treatment	n	Geometric LS-Mean	Ratio of Geometric LS-Mean	90% CI <sup>a</sup> of Ratio (%)	Intrasubject CV (%)
AUC <sub>0-t</sub> (h*ng/mL)	T: tepotinib + dabigatran	19 <sup>c</sup>	698	-	-	-
	R: dabigatran	20	461	-	-	-
	T/R	-	-	151.38	127.35;179.93	31.45
AUC <sub>0-∞</sub> (h*ng/mL)	T: tepotinib + dabigatran	19 <sup>c</sup>	717	-	-	-
	R: dabigatran	19 <sup>b</sup>	496	-	-	-
	T/R	-	-	144.70	122.89;170.39	28.74
C <sub>max</sub> (ng/mL)	T: tepotinib + dabigatran	19 <sup>c</sup>	75.5	-	-	-
	R: dabigatran	20	54.5	-	-	-
	T/R	-	-	138.45	121.59;157.65	23.39

Source: CSR of Study MS200095-0032, Table 8, Page 53

FDA agrees with the Applicant that tepotinib will unlikely have a clinically meaningful effect on the PK of a BCRP substrates. The effect of tepotinib on BCRP substrates has not been studied clinically. In vitro study shows an IC50 value of 1.9 μM for tepotinib on BCRP, which is 4.6-fold higher than that of P-gp. As a result, the magnitude of drug interaction for tepotinib on BCRP substrates is expected to be smaller than what has been observed with P-gp substrate dabigatran (40-50%). In addition, itraconazole, which also has a similar in vitro inhibitory profile (IC50 of 2 μM and 0.5 μM for BCRP and P-gp), causes a 30% to 40% increase in exposure of rosuvastatin (BCRP substrate) during coadministration (PMIDs: 12709722, 12709722, 27943276).

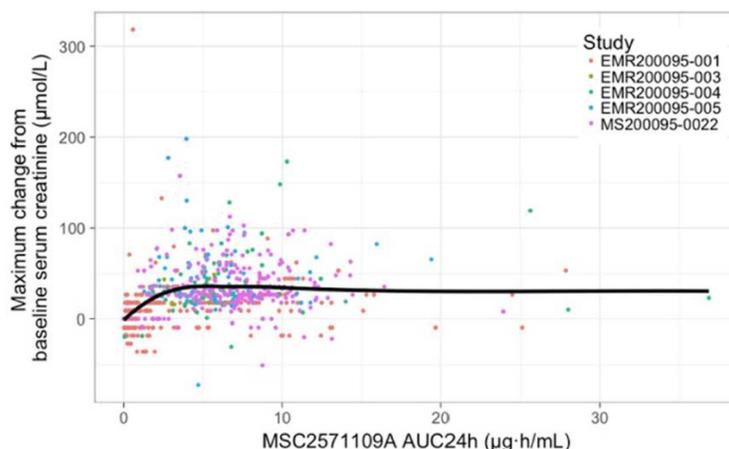
**Table 26: In Vitro Inhibition of Drug Transporters by Tepotinib and Clinical Relevance**

Transporter (Study Report)	Mean IC <sub>50</sub> (μM)	[I]/IC <sub>50</sub>	FDA Criteria	EMA Criteria	Assessment EMA/FDA (Potential Risk for Clinical DDI)
			In Vivo DDI Study not Needed if [I]/IC <sub>50</sub>	In vivo DDI Study not Needed if [I]/IC <sub>50</sub>	
P-gp (DMPK 57-09)	0.41	8917 (intestinal)	< 10 (intestinal)	< 5 (intestinal)	Yes
		0.39 (systemic)	< 0.1 (systemic)	< 0.01 (systemic)	Yes
BCRP (DMPK 55-11)	1.9	1924 (intestinal)	< 10 (intestinal)	< 5 (intestinal)	Yes
		0.084 (systemic)	< 0.1 (systemic)	< 0.01 (systemic)	Yes/No <sup>a</sup>
OCT1 (DMPK 24-12)	2.3	0.084	NA	< 0.02	Yes/NA <sup>b</sup>
OATP1B1 (PCT-114-18)	177	0.001	< 0.1	< 0.02	No
OATP1B3 (PCT-114-18)	35	0.006	< 0.1	< 0.02	No
OAT1 (PCT-114-18)	271	0.001	< 0.1	< 0.01	No
OAT3 (PCT-114-18)	> 300	< 0.001	< 0.1	< 0.01	No
BSEP (XS-0165)	> 12.8	< 0.013	NA	< 0.01	Remote/NA <sup>c</sup>
OCT2 (PCT-063-15)	67	0.002	< 0.1	< 0.01	No
MATE1 (PCT-064-15)	3.6	0.044	< 0.1	< 0.01	Yes/No <sup>a</sup>
MATE2 (PCT-064-15)	1.1	0.15	< 0.1	< 0.01	Yes

*Source: Summary of Clinical Pharmacology Studies, Table 31, Page 100*

FDA agrees that tepotinib will unlikely have a clinically meaningful effect on the PK of MATE2K or OCT2 substrates. MATE2 substrates include a variety of basic compounds with creatinine and metformin being of potential clinical relevance. Although exposure-response analysis showed that the effect of tepotinib or MSC2571109A exposure on the maximal creatinine increase (Figure 20), such observations were not associated with other clinical signs suggestive of acute or chronic renal damage. Grade 3 or 4 increased creatinine was reported in only 1 (0.6%) patient (Grade 3). The time course of the increase in serum creatinine following a single dose of 500 mg tepotinib in healthy subjects suggests that the effect appears to be reversible (Figure 21).

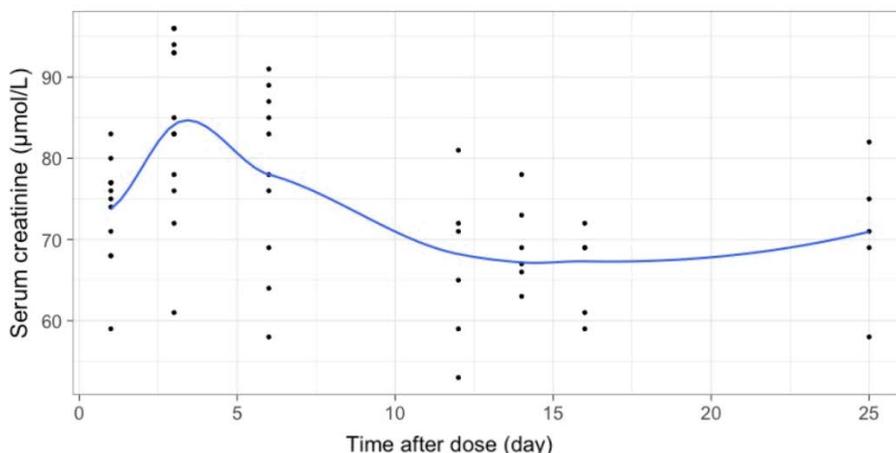
**Figure 20: Maximum Change from Baseline Serum Creatinine Concentration Versus MSC2571109A AUC<sub>24h</sub>**



Source: Pharmacometrics Exposure-Safety Report, April 2020, Figure 52.

Similar findings were reported for several other drugs, including selective and unselective MET inhibitors such as capmatinib and crizotinib, as well as other kinase inhibitors such as gefitinib, imatinib, nilotinib and tucatinib.

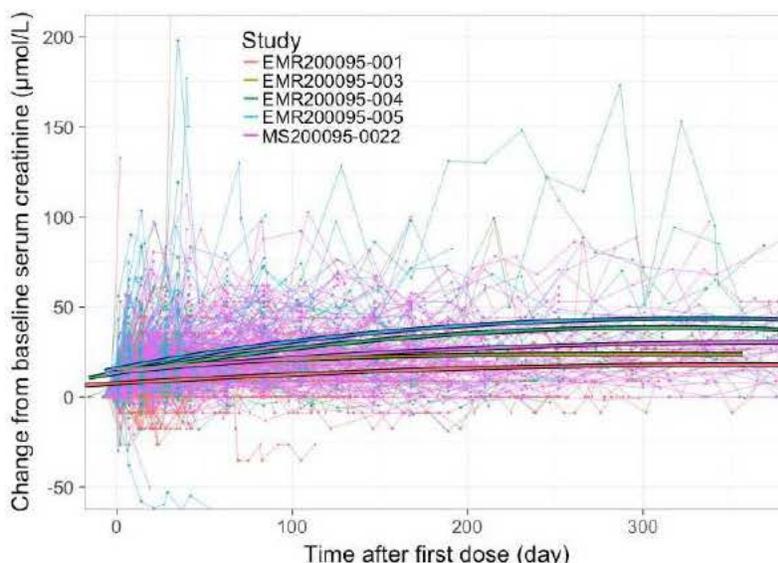
**Figure 21: Serum Creatinine over Time after a Single Tepotinib Dose of 500 mg in Healthy Subjects**



Source: Pharmacometrics Exposure-Safety Report, April 2020, Figure 53.

*Review note: The observed serum creatine increase appears to be attributed to the OCT2 inhibition by MSC2571109A, given the observed [I]/IC<sub>50</sub> of 0.6 and the exposure response shown in Figure 20. The maximum serum creatine change appears to occur on day 3, likely due to the effect of MSC2571109A, the T<sub>max</sub> of which occur after day 1. Median time to onset of increased creatinine in VISION Cohorts A + C was 3.14 weeks (Figure 22). The lag of time to onset may potentially attributed to the time for MSC2571109A to achieve steady state.*

**Figure 22: Observed Change from Baseline Serum Creatinine Concentration Versus Time**



*Source: Pharmacometrics Exposure-Safety Report, April 2020, Figure 44.*

Among the drugs known to be MATE2 substrates, metformin is clinically relevant in the current proposed patient population. Changes in its exposure due to concomitant use of tepotinib was evaluated as such changes may lead to clinically significant effects on blood glucose or relevant adverse effects including lactate acidosis. Across the clinical studies, 61 patients received concomitant metformin. However, none of the patients experienced adverse reactions clearly attributable to increases in metformin exposure. No systematic or consistent trends of blood glucose increases, or decreases, were observed following initiation of tepotinib treatment in patients taking metformin. Taken together, FDA concludes that a clinically meaningful drug interaction with MATE2K and OCT2 substrates is unlikely.

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Primary Reviewer

Team Leader



## **7 Sources of Clinical Data**

### **7.1. Table of Clinical Studies**

Data:

**Table 27: Listing of Clinical Trials Relevant to this NDA**

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<b>Pivotal study to Support Efficacy and Safety</b>								
MS200095-0022	NCT 02864992	Phase II, multicenter, open-label, single-arm study	Cohorts A, B: TF2: 1 x 500 mg QD Cohorts A, B, C: TF3: 2 x 250 mg QD	Efficacy (OR, DOR, PFS, OS), Safety, Tolerability, PK, and Pd	Until disease progression, intolerable toxicity, death, or withdrawal from treatment	Cohort A (METex14): 152 Cohort B (METamp): 23 Cohort C (METex14): 29	Patients with advanced or metastatic NSCLC with METex14 skipping alterations or METamp	128 centers across 12 countries
<b>Studies to Support Safety</b>								
EMR200095-001	NCT 01014936	Phase I, open-label, non- randomized dose- escalation, first-in-human study	Regimen 1 CF1: 30-230 mg, QD CF2: 30-400 mg, QD Regimen 2 CF1: 30-115 mg, QD CF2: 60-315 mg, QD Regimen 3 CF2: 300-1,400 mg, QD TF1: 5 x 100 mg, QD	MTD/RP2D, Safety, Tolerability, Efficacy, PK, and Pd	Until disease progression, unacceptable toxicity, or withdrawal from treatment	149	Patients with solid tumors, refractory to standard therapy or for which no effective standard therapy is available	4 centers across 2 countries
EMR200095-003	NCT 01832506	Phase I, open-label study	CF2: 215-500 mg QD	MTD/RP2D, Safety, Tolerability, Efficacy, PK, and Pd	Until disease progression, unacceptable toxicity, or withdrawal from treatment	12	Japanese patients with solid tumors	2 centers in Japan

NDA/BLA Multi-disciplinary Review and Evaluation NDA 214096  
TEPMETKO, Tepotinib

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
EMR200095-004	NCT 01988493	Phase Ib/II, randomized, active-controlled study	Phase Ib TF1: 300-1,000 mg, QD Phase II TF1: 5 x 100 mg, QD	RP2D (Ib), Efficacy (II), Safety, Tolerability, PK, and Pd	Until disease progression, intolerable toxicity, or withdrawal from treatment	Phase Ib: 27 Phase II: 89 (tepotinib: 45, active control: 44)	Asian patients with advanced HCC, 1L (sorafenib-naïve) MET+ tumors only	Phase Ib: 8 centers across 3 countries  Phase II: 43 centers across 3 countries
EMR200095-005	NCT 02115373	Phase Ib/II, single-arm study	Phase Ib TF1: 300-500 mg, QD Phase II TF1: 5 x 100 mg QD	RP2D (Ib), Efficacy (II), Safety, Tolerability, PK, and Pd	Until disease progression, intolerable toxicity, death, or withdrawal from treatment	Phase Ib: 17 Phase II: 49	Patients with advanced HCC, 2L (after failure of sorafenib treatment), MET+ tumors only	Phase Ib: 15 centers across 3 countries  Phase II: 30 centers across 6 countries
<b>Other studies</b>								
EMR200095-006	NCT 01982955	Phase Ib/II, randomized, active-controlled, open-label study	Phase Ib TF1: 300-500 mg QD in combination with gefitinib 250 mg QD Phase II (rand.) TF1: 5 x 100 mg QD in combination with gefitinib 250 mg QD Phase II (non-rand.) TF1: 5 x 100 mg QD in combination with gefitinib 250 mg QD	RP2D (Ib), Efficacy (II), Safety, Tolerability PK, and Pd	Until disease progression, intolerable toxicity, or withdrawal from treatment	Phase Ib: 18 Phase II (rand.): 54 (tepotinib: 31, active control: 23) Phase II (non-rand.): 15	Phase Ib: Patients with advanced NSCLC after failure of EGFR-TKI treatment, MET+ tumors only Phase II: Patients with advanced EGFRm+ NSCLC, 2L (after failure of 1L EGFR-TKI treatment), MET+ and EGFR T790M-	Phase Ib: 7 centers across 4 countries  Phase II: 51 centers across 10 countries

NDA/BLA Multi-disciplinary Review and Evaluation NDA 214096  
TEPMETKO, Tepotinib

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
							(rand.) or T790+ (non-rand.) tumors	
EMR200095-002	NA	Phase I, open-label, randomized, crossover study	Two single oral doses: CF2: 2 x 15 mg TF1: 1 x 30 mg	Relative BA (CF2/TF1), Food effect (TF1), Safety, Tolerability, PK, and Pd	Two single doses	28	Healthy participants	Single center in France
EMR200095-007	NA	Phase I, open label, 3-part study	Part A CF3: 5 x 100 mg single dose (labeled with <sup>14</sup> C) Part B TF1: 5 x 100 mg single dose followed by iv tracer bolus with <sup>14</sup> C-labeled tepotinib tracer Part C 1 x 100 mg as 100 mL oral solution single dose Either TF1* (b)(4) 1 x 100 mg or TF1 1 x 100 mg	Part A: Mass balance, metabolite profile, Safety, Tolerability, PK Part B: Absolute BA (TF1), Safety, Tolerability, PK Part C: Relative BA (Oral solution/ TF1) and (TF1/TF1*), Safety, Tolerability, PK	Single dose	27	Healthy participants	Single center in The Netherlands
MS200095-0012	NCT 03021642	Phase I, open-label, randomized, crossover study	Period 1, Period 2: Either TF1: 5 x 100 mg Or TF2: 1 x 500 mg	Relative BA (TF1/TF2), Safety, Tolerability, PK	Single dose (per period)	24	Healthy participants	Single center in the UK
MS200095-0028	NCT 03546608	Phase I, open-label, parallel-group study	TF2: 1 x 500 mg single dose	Relative BA (healthy participants/ patients with hepatic impairment), PK, Safety, Tolerability	Single dose	18	Healthy participants and patients with Child-Pugh A and B hepatic impairment	2 centers in the US

NDA/BLA Multi-disciplinary Review and Evaluation NDA 214096  
TEPMETKO, Tepotinib

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
MS200095-0030	NCT 03628339	Phase I, open-label, single sequence, 2 period crossover study	Period 1: Midazolam 1 x 7.5 mg one single dose Period 2: TF2: 1 x 500 mg QD over 11 days; Midazolam 1 x 7.5 mg one single dose in combination with 11th dose of tepotinib	DDI perpetrator potential toward CYP3A4, PK, Safety, Tolerability	11 doses of TF2 over 11 days	12	Healthy participants	Single center in Germany
MS200095-0032	NCT 03492437	Phase I, open-label, single- sequence, 2 period study	Period 1: Dabigatran etexilate 75 mg alone Period 2: TF2: 1 x 500 mg QD over 8 days Dabigatran etexilate 75 mg in combination with 8th dose of tepotinib	DDI perpetrator potential toward P-gp, PK, Safety, Tolerability	8 doses of TF2 over 8 days	20	Healthy participants	Single center in Germany
MS200095-0038	NCT 04204902	Phase I, open-label, single-dose, randomized, 2 period, 2 sequence crossover study	Period 1, Period 2: Fasted state: Either TF3 5 x 100 mg single oral dose followed by TF3 2 x 250 mg single oral dose Or TF3 2 x 250 mg single oral dose followed by TF3 5 x 100mg single oral dose	BE (TF3: 5 x 100 mg and 2 x 250 mg), PK, Safety, Tolerability	Single dose (per period)	18	Healthy participants	Single center in Germany

NDA/BLA Multi-disciplinary Review and Evaluation NDA 214096  
TEPMETKO, Tepotinib

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
MS200095-0039	NCT 03531762	Phase I, open-label, 3-period crossover study	Period 1: TF2: 1 x 500 mg single dose Period 2: Omeprazole 1 x 40 mg QD over 5 days TF2: 1 x 500 mg administered (fasted state) in combination with the 5th dose of Omeprazole Period 3: Omeprazole 1 x 40 mg daily over 5 days TF2: 1 x 500 mg administered (fed state) in combination with the 5th dose of Omeprazole	DDI victim potential toward PPI, PK, Safety, Tolerability	Single dose of TF2 (per period)	12	Healthy participants	Single center in Germany
MS200095-0044	NCT 03629223	Phase I, open-label, 3 part crossover study	Part A, Periods 1 and 2: Each period single dose of either TF2: 1 x 500 mg or TF3: 2 x250 mg Part B, Periods 1 and 2: Each period single dose of TF2: 1 x 500 mg Part C, Periods 1 and 2: Each period single dose of TF3: 2 x 250 mg	BE Between TF3 and TF2, Food Effect, PK, Safety, Tolerability	Single dose (per period)	66	Healthy participants	Single center in Germany

1L=first line, 2L=second line, BA=bioavailability, BE=bioequivalence, CF=capsule formulation, CYP3A4=cytochrome P450 3A4, DDI=drug-drug interaction, DOR=duration of response, EGFR TKI=epidermal growth factor receptor tyrosine kinase inhibitor, HCC=hepatocellular carcinoma, MET=mesenchymal-epithelial transition factor, METamp=MET amplification, METex14=MET gene MET exon 14, MTD=maximum tolerated dose, NA=not applicable, non-rand.=non-randomized, NSCLC=non small cell lung cancer, OR=objective response, OS=overall survival, Pd=pharmacodynamic, PFS=progression-free survival, P-gp=p-glycoprotein, PK=pharmacokinetic, PPI=proton pump inhibitors, QD=once daily, rand.=randomized, RP2D=Recommended Phase II Dose, TF=tablet formulation.

**Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.**

The Applicant's Position:

Table 27 provides a listing of clinical studies relevant to this application.

The FDA's Assessment:

FDA agrees with EMD Serono's list of clinical trials relevant to this NDA.

The efficacy analyses supporting this marketing application are based on Cohort A, which included 152 patients as of the data cut-off date of July 1, 2020. While patients with NSCLC harboring METex14 skipping alterations have also been enrolled to Cohort C (n=103), the duration of follow-up for this cohort was very limited at the time of NDA submission, limiting the utility of assessing efficacy in Cohort C at the time of review. Cohort B consists of 24 patients with metastatic NSCLC with MET amplification and was included in the pooled safety population used to inform Section 5 of labeling. Supportive safety data include results for patients who received tepotinib as a single agent at the recommended dose in four additional studies [Studies EMR-001 (n=42), EMR-003 (n=6), EMR-004 (n=59), EMR-005 (n=62)]. The pooled safety population used to inform Section 5 of labeling includes a total of 448 patients (from Cohorts A, B, and C of VISION and the four additional studies noted)).

## **8 Statistical and Clinical Evaluation**

### **8.1. Review of Relevant Individual Trials Used to Support Efficacy**

#### **8.1.1. Study MS200095-0022 (VISION)**

##### **Trial Design**

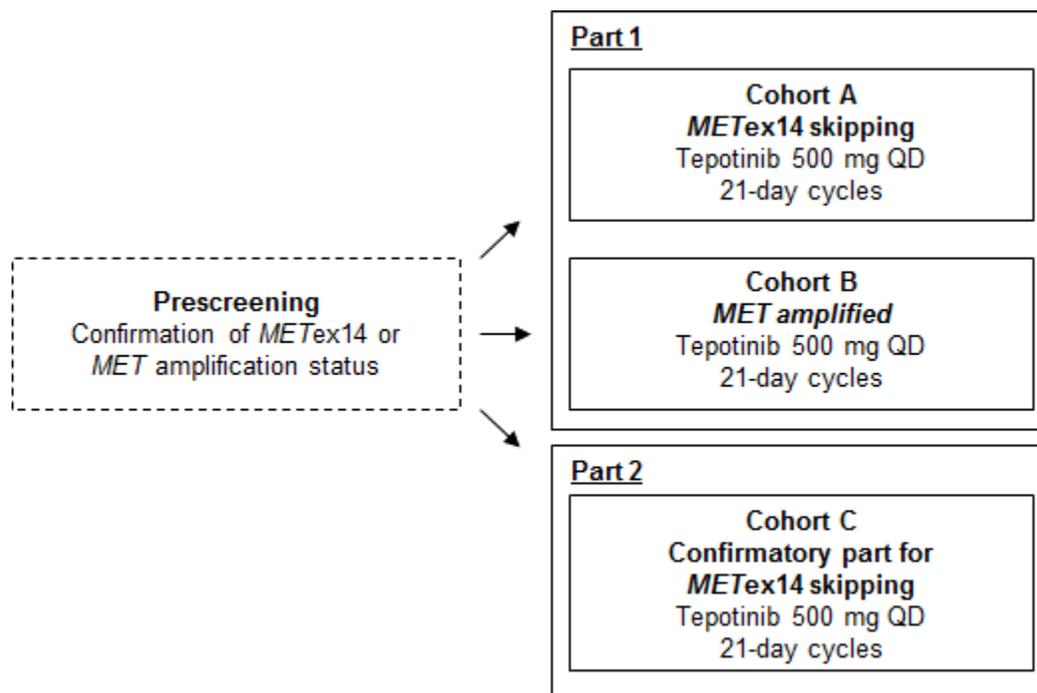
The Applicant's Description:

##### **Basic study design**

The pivotal MS200095-0022 study (referred to as VISION study hereafter) is an ongoing Phase II single-arm, open-label study that aims to investigate the antitumor activity and tolerability of tepotinib in patients with advanced NSCLC harboring METex14 skipping alterations or MET amplification for first to third line of systemic therapy.

Three cohorts were planned in the study (see Figure 23). Cohorts A and C include NSCLC patients who tested positive for METex14 skipping alterations; patients in these 2 cohorts are enrolled under the same inclusion criteria and undergo the same study procedures. Cohort B includes NSCLC patients who tested negative for METex14 but positive for MET amplification.

**Figure 23: VISION Study Design**



At the time of the data cutoff for this submission (01 January 2020), enrollment into cohort A was complete and enrollment into cohort C was ongoing. In this submission both these *METex14* cohorts form the basis of the safety evaluation, and only cohort A forms the basis of the efficacy evaluation.

Cohort B includes patients outside of the intended indication; no efficacy results from this cohort are included in this document and safety results are included in the pooled safety analyses.

#### **Trial location**

The study was conducted at 128 study centers in Belgium, France, Germany, Israel, Italy, Japan, Poland, South Korea, Spain, Taiwan, The Netherlands, and the US (27 study centers in the US).

#### **Diagnostic criteria**

Determination of patients' *METex14* skipping alteration or *MET* amplification status was conducted during the prescreening period.

Prospective testing of *METex14* skipping alterations was performed centrally by 2 independent methodologies: by evaluating circulating ctDNA obtained from plasma (liquid biopsy [LBx]) or by evaluating RNA obtained from fresh or archival (formalin-fixed, paraffin-embedded) tumor-biopsy [TBx] tissue. While contemporaneous testing with both methodologies was highly recommended, the use of both tests was not a strict requirement for enrollment.

Testing for *MET* amplification was performed by liquid biopsy.

### **Key inclusion/exclusion criteria**

The study included adult male and female patients  $\geq 18$  years of age with measurable disease according to response evaluation criteria in solid tumors (RECIST 1.1) and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. Patients were to have histologically or cytologically confirmed advanced NSCLC (all types including squamous and sarcomatoid) and be either treatment-naïve (for first-line therapy) or pretreated with no more than 2 lines of prior therapy. Patients needed to have *MET* alterations to be eligible, as described previously under “Diagnostic criteria”.

### **Dose selection**

The proposed clinical dose of 500 mg was determined based on the first-in-human study EMR200095-001 and translational modeling approach using clinical and nonclinical PK/Pd and tumor growth data (Sections 6.2.2 and 6.3.2.2).

### **Study treatment**

Patients received 500 mg tepotinib orally once daily during each 21-day cycle until progression of disease (as assessed according to RECIST 1.1), withdrawal of consent, AE leading to discontinuation, or death. Treatment was continuous with no interruption between cycles.

### **Assignment to treatment**

All patients were to receive tepotinib in this single-arm study.

### **Dose modification, dose discontinuation**

Dependent on circumstances, the Investigator could either temporarily interrupt tepotinib treatment, or continue tepotinib treatment at a lower dose level until an AE related to tepotinib recovered to  $\leq$  Grade 2 or to baseline values.

Regarding dose reduction, the dose was initially to be reduced to 300 mg once daily. Further dose reductions were made on a case-by-case basis in agreement with the Sponsor. Following the implementation of Clinical Study Protocol Version 8.0 (17 January 2020), the standard dose reduction was changed to 250 mg once daily (Section 6.2.2).

### **Administrative structure**

An Independent Review Committee (IRC) conducted a blinded review of tumor assessment images from all patients.

An Independent Data Monitoring Committee (IDMC) performed periodic reviews to evaluate the safety of patients participating in the study. In addition to the outputs on safety data prepared for this purpose, outputs on efficacy data for each of the interim analyses were also provided to the IDMC.

### **Procedures and schedule**

#### *Tumor response assessment*

Patients were to have tumor assessments according to RECIST 1.1 every 6 weeks following the Cycle 1, Day 1 Visit until 9 months and every 12 weeks thereafter, until disease progression, death, or withdrawal of consent.

#### *Survival Follow-up*

Patients were to be followed-up every 3 months ( $\pm 2$  weeks) to collect information about survival and anticancer treatments.

#### *Key Safety measurements*

Any AEs, whether observed by the Investigator or reported by the patient, were to be reported. The AE reporting period for safety surveillance began when a patient was initially included in the study (date of first signature of main informed consent before screening) and continued until the Safety Follow-Up Visit performed  $30 \pm 3$  days after the last dose of study treatment. Any serious adverse event (SAE) assessed as related to tepotinib was to be reported whenever it occurred, irrespective of the time elapsed since the last administration of tepotinib.

Vital signs, ECG measurements, and hematological and biochemical laboratory tests, were performed at screening, at the beginning of each cycle  $\pm 3$  days, at the End of Treatment Visit and the Safety Follow-Up Visit.

#### *PK sampling*

Sparse PK sampling was to be performed predose, at 1.5 h postdose, and at 4 h postdose on Cycle 1, Day 1 and on Cycle 2, Day 1.

#### *Patient Reported Outcomes*

All patients were required to complete 3 patient reported outcome (PRO) assessments: EuroQol Five Dimension Five Level Scale (EQ-5D-5L), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13).

The questionnaires were to be completed every 6 weeks from Cycle 1, Day 1 until 9 months and every 12 weeks thereafter until disease progression, death or withdrawal of consent.

### **Concurrent medications**

The following treatments were permitted with some prerequisites described in detail in the Study Protocol:

- Concomitant medications with a narrow therapeutic window and known to be transported by P-gp, BCRP, OCT2, MATE1, and MATE2 and OCT1 were permitted, but were to be used with caution;
- Symptomatic treatment of brain metastasis with anticonvulsants known to have a reduced risk for drug interactions;
- Localized radiation therapy to alleviate symptoms such as bone pain;
- Supportive treatment, if initiated prior to study entry, was allowed to continue.

The following treatments were prohibited during the study:

- Any other cancer therapy;
- Drug(s), for which the product labeling included a contraindication for P-gp, BCRP, OCT1, OCT2, MATE1, and MATE2 inhibiting drugs;
- Drug(s) that were known to induce P-gp and thereby may decrease efficacy of tepotinib.

### **Treatment compliance**

Each patient recorded the number of tablets and dosage of tepotinib taken daily on a diary card. On the days that PK samples were taken, patients were to record the actual time of taking tepotinib on the diary card. This diary card was to be returned to the Investigator/study center at each visit.

Tepotinib administration was recorded in the eCRF, as applicable.

### The FDA's Assessment:

FDA agrees with the Applicant's description of the VISION study (Study MS200095-0022).

### **Study Endpoints**

#### The Applicant's Description:

The primary efficacy endpoint of the study was ORR (confirmed complete response [CR] or partial response [PR]) as per IRC determined according to RECIST 1.1.

The secondary endpoints included ORR as per Investigator assessment according to RECIST 1.1, DOR and PFS as per IRC and Investigator, overall survival (OS), and PROs.

Other secondary study endpoints were TEAEs and deaths, abnormal clinical laboratory tests, markedly abnormal vital signs, ECG and physical examination, and PK.

Given the rarity of the investigated indication, the mechanism of action of tepotinib supported by strong scientific evidence, and the lack of satisfactory targeted therapy options for NSCLC harboring *MET* alterations, a single-arm design was considered appropriate for the pivotal VISION study. The primary endpoint is regarded as appropriate in the single-arm setting based on various guidelines and considering that OR inherently reflects clinical activity. DOR is considered important for further characterizing the responses.

The IRC was implemented to independently assess tumor response in line with RECIST 1.1 and was the key assessment defining the primary endpoint of the study.

#### The FDA's Assessment:

The study endpoints described above by EMD Serono are acceptable. The primary efficacy endpoint of the study is ORR per RECIST 1.1 as assessed by BIRC. The secondary endpoints include DOR, PFS, and OS. Time-to-event endpoints, such as PFS and OS, are difficult to interpret in single arm trials without a control arm and are analyzed in a descriptive manner for this review.

### **Statistical Analysis Plan and Amendments**

#### The Applicant's Description:

Details of statistical analyses were described in a statistical analysis plan, which was finalized prior to the conduct of the analyses. The statistical analysis plan was amended 3 times until the database lock for the presented analyses, mainly in order to reflect protocol amendments with regards to study design and populations, and to omit the per protocol analysis and to describe the analyses of PROs in more detail.

No formal statistical hypothesis was tested; data were analyzed in a descriptive manner.

The main analysis sets for which efficacy results are based on, are shown in Figure 24.

#### **Efficacy analysis**

The primary endpoint of OR was assessed by the ORR, which was defined as the proportion of patients with a best overall response (BOR) of confirmed CR or PR, as assessed per RECIST 1.1 by IRC. The study aims for an ORR (based on an IRC primary endpoint measure) in the range of 40% to 50%, with a lower limit of the corresponding exact 2-sided 95% CI (according to Clopper-Pearson) to be above 20%.

Kaplan–Meier methods were used to analyze the DOR, PFS, and OS.

#### **Safety analysis**

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1. The severity of AEs was graded using the National Cancer Institute–Common Terminology Criteria for Adverse Event (NCI-CTCAE; Version 4.03) toxicity grades.

Laboratory results were classified according to the NCI-CTCAE Version 4.03. Additional laboratory results that are not part of NCI-CTCAE were presented according to the categories: below normal limits, within normal limits and above normal limits (according to the respective local laboratory normal ranges). The worst on-treatment grades (i.e., on or after first study treatment administration and within 30 days after last study treatment administration) were summarized (considering only patients with post-baseline laboratory samples) using the following grades:  $\geq 3$ ,  $\geq 4$ .

For the Integrated Safety Summary (ISS) analyses, which included VISION safety data, see Section 8.2.

### **Patient reported outcomes**

Baseline, post-baseline and change from baseline values were summarized at each time point and visually presented using box and whiskers plots. Only on-treatment visits with available data for more than 10 patients are included in tables and plots.

A mixed-effect model repeated measures (MMRM) analysis was used in addition to evaluate the longitudinal change from baseline for the following PRO scores: Dyspnea (EORTC QLQ-LC13; items 3, 4, and 5); Cough (EORTC QLQ-LC13; item 1); and Chest pain (EORTC QLQ-LC13; item 10).

#### The FDA's Assessment:

FDA generally agrees with the Applicant's description of primary and secondary endpoints and statistical analysis plan. FDA does not abide by the target ORR selected by the applicant for efficacy assessment but allows it only as a guide to facilitate sample size calculation. Time-to-event endpoints such as PFS and OS are not interpretable in non-randomized open-label trials without a control arm.

The final versions of the protocol and statistical analysis plan were submitted to the IND for FDA review and were found to be acceptable.

### **Protocol Amendments**

#### The Applicant's Description:

The original clinical study protocol, dated 14 January 2016, underwent 7 global amendments. At the time of the 01 January 2020 data cutoff, VISION study protocol version 7.0 (dated 25 June 2019) was in place globally. Highlighting the most important protocol versions, it is worth mentioning that:

- The inclusion of tepotinib as first-line therapy for patients in the VISION study was introduced through protocol version 4.0 (dated 15 March 2017). Previous protocol versions only allowed the inclusion of patients with tepotinib as second or later therapy lines.

- Protocol version 5.0 (10 May 2018) introduced the evaluation of NSCLC patients with *MET* amplification who are negative for *MET*ex14 skipping alterations (cohort B); note that cohort B will not be described in this document as it is not part of the proposed indication.
- Version 6.0 (26 March 2019) introduced cohort C and version 7.0 (dated 25 June 2019) introduced new safety specifications (for patients with confirmed ILD, tepotinib treatment was to be permanently discontinued).
- Protocol version 8.0, approved after the data cutoff (dated 17 January 2020), has introduced the specification for an additional analysis with an extended follow-up time of 15 months for patients in cohort A, in line with advice from the US FDA. In addition, standard dose reduction was changed to 250 mg once daily.

The FDA's Assessment:

FDA agrees with the Applicant's summary of changes in the amendments listed above.

## 8.1.2. Study Results

### Compliance with Good Clinical Practices

#### Data:

The study was conducted in accordance with the ethical principles of the ICH guideline for Good Clinical Practice (GCP), and the Declaration of Helsinki, as well as with applicable local regulatory requirements.

#### The Applicant's Position:

The VISION study was GCP compliant.

#### The FDA's Assessment:

FDA agrees with the Applicant's position.

### Financial Disclosure

#### Data:

VISION study financial interests/arrangements with clinical investigators were tracked and disclosed. Details of financial disclosure are presented in Section 19.2.

#### The Applicant's Position:

The integrity of the VISION study data was not affected by the financial interest of the Investigators.

#### The FDA's Assessment:

FDA agrees with the Applicant's position. EMD Serono has adequately disclosed any financial interests/arrangements with clinical investigators in accordance with the guidance for industry. Details of financial disclosure are presented in Section 19.2.

### Patient Disposition

#### Data:

Efficacy results reported in this document are based on cohort A, including data from patients with confirmed *MET*ex14 skipping alterations treated until the data cutoff of 01 July 2020. The key analysis populations included in this document are provided in Figure 24.

The efficacy analyses in this document focus on the 146 patients who had their first dose of study treatment before 02 October 2019 (ITT-02 Oct 2019 population) with at least 9 months of follow-up from the start of treatment (expected to yield 6 months of follow-up post response in patients

with an objective response [OR]). In addition, data are presented for the 99 patients who had their first dose of study treatment before 02 April 2019 (ITT-02 Apr 2019 population) with a follow-up extended to at least 15 months from the start of treatment (expected to yield 12 months of follow-up after onset of response in patients with an OR).

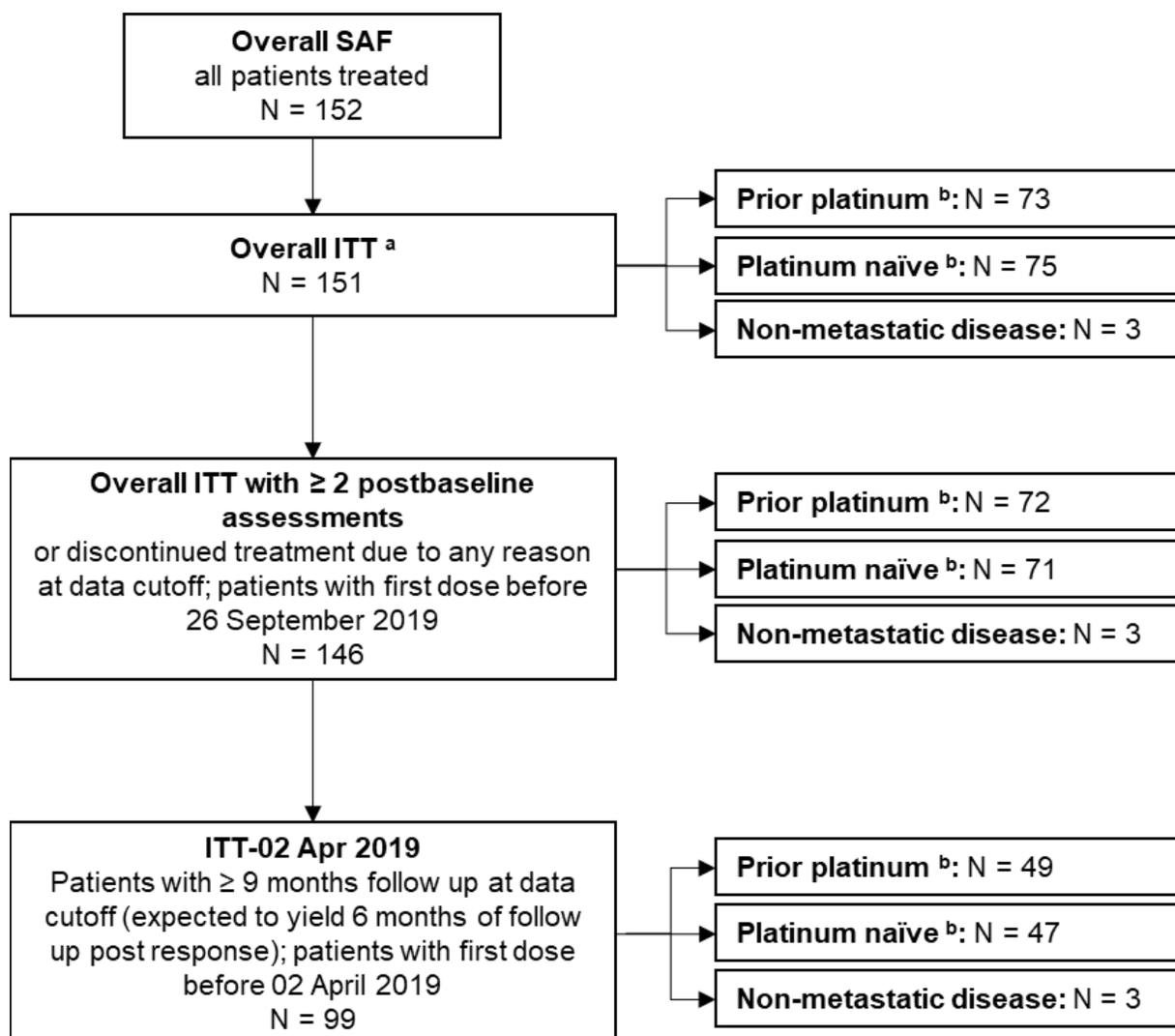
Efficacy analyses on the overall ITT population (N = 151) are provided in the VISION 01 July 2020 cutoff tables, figures, and listings, but are not discussed extensively in this document.

Results are presented for overall, as well as patients who received prior platinum-based therapy for metastatic disease (referred to as prior platinum-based therapy patients) or not (referred to as platinum-naïve patients).

In the ITT-02 Oct 2019 population, all responders had  $\geq 6$  months follow-up from the onset of response or event (progressive disease or death) or discontinued treatment  $< 6$  months after onset of response. Within the ITT-02 Apr 2019, all but 1 responders had  $\geq 12$  months follow-up from the onset of response or event (progressive disease or death) or discontinued treatment  $< 12$  months after onset of response.

Among the patients enrolled before 02 October 2019, 120 patients (81.6%) permanently discontinued treatment due to progressive disease (75 patients), AE (24 patients), death (12 patients), consent withdrawal (5 patients), other reasons (3 patients), or protocol noncompliance (1 patient). Treatment is ongoing in 27 patients. Refer to VISION 01 July 2020 cutoff, Table 15.1.1.1o.

**Figure 24: Key VISION Cohort A Study Populations Analyzed for Efficacy (01 January 2020 data cutoff)**



Source: VISION CSR, Table 15.1.1.1, 15.1.1.2, 15.1.1.2s, 15.2.1.1a, 15.2.1.17a, 15.2.1.17b, 15.2.1.17bs.

ITT=intention-to-treat, SAF=safety analysis set.

a One patient was excluded from all efficacy analyses due to insufficient *MET*ex14 skipping alteration data.

b Prior platinum is defined as use of prior platinum-based therapy for metastatic disease.

### The Applicant's Position:

The analysis populations are considered adequate to assess the clinical benefit of tepotinib in the proposed indication. Disease progression was the primary reason for treatment discontinuation.

**The FDA’s Assessment:**

FDA’s analysis of patient disposition (and all FDA analyses of the ITT population) is based on the data submitted by the Applicant corresponding to the July 1, 2020 data cut-off. There were 152 patients enrolled in Cohort A of the VISION study, including 83 patients who received prior lines of therapy (referred to as previously treated patients) and 69 patients who did not receive any prior lines of therapy (referred to as treatment-naïve patients). These two subpopulations of patients are the focus of FDA’s efficacy analyses. FDA’s rationale for assessing efficacy separately for treatment-naïve and previously treated is due to differences in available therapy for these patient populations. The previously treated population includes 3 patients with non-metastatic disease and 1 patient with insufficient METex14 skipping data (who was not included in the ITT population proposed by EMD Serono).

**Table 28: Patient Disposition – Cohort A of VISION Study**

	Previously Treated N=83	Treatment Naïve N=69	All Patients N=152
	n (%)	n (%)	n (%)
<b>Treatment Phase</b>			
Ongoing	13 (15.7)	15 (21.8)	28 (18.4)
Discontinued from treatment	70 (84.3)	54 (78.2)	124 (81.6)
Discontinued from study	47 (56.7)	39 (56.5)	86 (56.6)
<b>Primary Reason for discontinuation from treatment phase</b>			
Progressive Disease	54 (77.1)	23 (42.6)	77 (62.0)
Adverse Event	8 (11.4)	18 (33.3)	26 (21.0)
Death	4 (5.7)	8 (14.8)	12 (9.7)
Withdrew Consent	2 (2.9)	3 (5.5)	5 (4.0)
Protocol Non-compliance	0 (0)	1 (1.8)	1 (0.8)
Other	2 (2.9)	1 (1.8)	3 (2.4)
<b>Primary Reason for discontinuation from post-treatment follow-up</b>			

Death	41 (87.2)	35 (89.7)	76 (88.4)
Withdrew Consent	6 (12.8)	4 (10.3)	10 (11.6)

### **Protocol Violations/Deviations**

#### Data:

#### Protocol deviations

Important protocol deviations were defined as deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being. Important protocol deviations include dosing of patients despite not satisfying the inclusion/exclusion criteria, failure to withdraw upon fulfillment of withdrawal criteria, incorrect dose and/or exposure, receipt of prohibited medication, and GCP deviations. Each deviation was assessed for clinical importance, which was defined as a deviation potentially impacting efficacy.

Overall, only 1 patient in cohort A had an important protocol deviation that resulted in exclusion from the ITT analysis set. This patient was excluded from all efficacy analyses due to insufficient METex14 skipping alteration data.

For full details on the important protocol deviations in cohort A, refer to VISION clinical study report (CSR), Section 10.2.

#### The Applicant's Position:

There was only 1 important protocol deviation that resulted in exclusion of the patient from the efficacy analyses, with no impact on the integrity of study results and conclusions.

#### The FDA's Assessment:

FDA disagreed with EMD Serono's exclusion of one patient from the analysis population due to "insufficient METex14 skipping alteration data." This patient was included in FDA's assessments of efficacy.

Please refer to section 4.1 for additional discussion regarding a protocol deviation where source data (cytology reports) were being sent to (b) (4) after the data cutoff. From the initiation of the study in September 2016 through November 2018, cytology results were collected and sent (b) (4) for inclusion in the radiology review, as specified in the protocol. The process was mistakenly interrupted from November 13, 2018 until December 12, 2019. It was identified by the sponsor and the cytology reports were sent, but after the data cutoff. A total of 11 patients were affected. The inspection revealed that this deviation affected the assessments based on the source data for 3 of 11 patients. The changes in response based on the corrected data improved the outcome of the drug for Subject (b) (6) and worsened the outcome for Subjects

(b) (6) Based on the results of the OSI inspections (b) (4) the clinical data generated from these three investigator sites appear to be reliable and adequate in support of this NDA.

Review of the key protocol deviations in the Clinical Study Report (CSR) reveals that the two most common deviation categories are laboratory assessment criteria (which usually meant a missed lab or labs outside of window) and informed consent deviations. These protocol deviations are not expected to have materially altered the assessment of safety or effects on ORR and DOR.

### Table of Demographic Characteristics

#### Data:

Key demographic and baseline characteristics of cohort A are summarized in Table 29.

**Table 29: Demographics and Baseline Characteristics, VISION Cohort A – Overall SAF**

	Overall N = 152 (100%)	Prior Platinum-Based Therapy N = 74 (100%)	Platinum-Naïve N = 75 (100%)
<b>Sex, n (%)</b>			
Male	79 (52.0)	38 (51.4)	39 (52.0)
Female	73 (48.0)	36 (48.6)	36 (48.0)
<b>Race, n (%)</b>			
White	108 (71.1)	46 (62.2)	60 (80.0)
Asian	38 (25.0)	24 (32.4)	13 (17.3)
Not collected at site	4 (2.6)	3 (4.1)	1 (1.3)
Other	1 (0.7)	1 (1.4)	0 (0.0)
<b>Ethnicity, n (%)</b>			
Not Hispanic or Latino	148 (97.4)	71 (95.9)	74 (98.7)
Missing	3 (2.0)	3 (4.1)	0 (0.0)
<b>Age (years)</b>			
Mean (StD)	73.0 (± 8.97)	71.7 (± 9.89)	74.6 (± 7.69)
Median (Q1, Q3)	73.1 (68.1, 79.9)	72.8 (65.0, 79.8)	74.0 (68.9, 80.0)
Min, Max	41, 94	41, 88	56, 94
<b>Age groups, n (%)</b>			
< 65 years	27 (17.8)	18 (24.3)	8 (10.7)
≥ 65 years	125 (82.2)	56 (75.7)	67 (89.3)
65 to < 75 years	57 (37.5)	24 (32.4)	32 (42.7)
75 to < 85 years	58 (38.2)	28 (37.8)	29 (38.7)
≥ 85 years	10 (6.6)	4 (5.4)	6 (8.0)

	Overall N = 152 (100%)	Prior Platinum-Based Therapy N = 74 (100%)	Platinum-Naïve N = 75 (100%)
<b>Country, n (%)</b>			
United States	40 (26.3)	21 (28.4)	19 (25.3)
France	26 (17.1)	13 (17.6)	12 (16.0)
Japan	19 (12.5)	7 (9.5)	11 (14.7)
Spain	17 (11.2)	9 (12.2)	7 (9.3)
Germany	15 (9.9)	5 (6.8)	10 (13.3)
Italy	12 (7.9)	4 (5.4)	8 (10.7)
South Korea	10 (6.6)	9 (12.2)	1 (1.3)
Taiwan	5 (3.3)	5 (6.8)	0 (0.0)
Belgium	3 (2.0)	1 (1.4)	2 (2.7)
Poland	2 (1.3)	0 (0.0)	2 (2.7)
<b>Geographic region, n (%)</b>			
Europe	77 (50.7)	32 (43.2)	43 (57.3)
North America	40 (26.3)	21 (28.4)	19 (25.3)
Asia	35 (23.0)	21 (28.4)	13 (17.3)

Source: VISION CSR, Table 15.1.3.1a and 15.1.3.1c.

Max=maximum, Min=minimum, Q1=quartile 1, Q3=quartile 3, SAF=safety analysis set, StD=standard deviation.

### The Applicant's Position:

In the overall safety analysis set (SAF), 52.0% of patients were male, 71.1% of patients were White, and 26.3% of patients were from the US. Most patients (82.2%) were ≥ 65 years of age and 44.8% of patients were ≥ 75 years of age, which is typical for the *METex14* NSCLC population (Schrock 2016; Awad 2016). Similar patterns were observed in prior platinum-treated and platinum-naïve patients.

### The FDA's Assessment:

FDA's description of patient demographic and baseline characteristics for Cohort A of the VISION study are provided below.

**Table 30: Demographics and Baseline Characteristics, VISION Cohort A**

	Overall N = 152 (100%)	Previously Treated N = 83 (100%)	Treatment-Naïve N = 69 (100%)
<b>Sex, n (%)</b>			
Male	79 (52.0)	40 (48.2)	36 (52.2)

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	Overall N = 152 (100%)	Previously Treated N = 83 (100%)	Treatment-Naïve N = 69 (100%)
Female	73 (48.0)	43 (51.8)	33 (47.8)
<b>Race, n (%)</b>			
White	108 (71.1)	52 (62.7)	56 (81.2)
Asian	38 (25.0)	26 (31.3)	12 (17.4)
Not collected at site	4 (2.6)	4 (4.8)	1 (1.4)
Other	1 (0.7)	1 (1.2)	0 (0.0)
<b>Ethnicity, n (%)</b>			
Not Hispanic or Latino	148 (97.4)	80 (96.4)	68 (98.6)
Missing	3 (2.0)	3 (3.6)	0 (0.0)
<b>Age (years)</b>			
Mean (SD)	73.0 (± 8.97)	71.7 (± 9.89)	74.6 (± 7.92)
Median (Q1, Q3)	73.1 (68.1, 79.9)	72.8 (65.0, 79.8)	74.0 (68.9, 81.0)
Min, Max	41, 94	41, 88	56, 94
<b>Age groups, n (%)</b>			
< 65 years	27 (17.8)	19 (22.9)	8 (11.6)
≥ 65 years	125 (82.2)	64 (77.1)	61 (88.4)
65 to < 75 years	57 (37.5)	28 (33.7)	29 (42.0)
75 to < 85 years	58 (38.2)	32 (38.6)	26 (37.7)
≥ 85 years	10 (6.6)	4 (4.8)	6 (8.7)
<b>Country, n (%)</b>			
United States	40 (26.3)	23 (27.7)	17 (24.6)
France	26 (17.1)	15 (18.1)	11 (15.9)
Japan	19 (12.5)	9 (10.8)	10 (14.5)
Spain	17 (11.2)	10 (12.0)	7 (10.1)
Germany	15 (9.9)	6 (7.2)	9 (13.0)
Italy	12 (7.9)	5 (6.0)	7 (10.1)
South Korea	10 (6.6)	9 (10.8)	1 (1.4)
Taiwan	5 (3.3)	5 (6.0)	0 (0.0)
Belgium	3 (2.0)	1 (1.2)	2 (2.9)
Poland	2 (1.3)	0 (0.0)	2 (2.9)
<b>Geographic region, n (%)</b>			
Europe	77 (50.7)	37 (44.6)	40 (58.0)
North America	40 (26.3)	23 (27.7)	17 (24.6)
Asia	35 (23.0)	23 (27.7)	12 (17.4)
<b>ECOG PS, n (%)</b>			
0	41 (27.0)	16 (19.3)	25 (36.2)
1	111 (73.0)	67 (80.7)	44 (63.8)

Source: FDA reviewer-generated table based on Applicant submitted data (ADSL), DCO: July 1, 2020

Max=maximum, Min=minimum, Q1=quartile 1, Q3=quartile 3, SAF=safety analysis set, SD=standard deviation.

## Other Baseline Characteristics

### Data:

The disease history of cohort A is summarized in Table 31. A summary of prior therapies is provided in Table 32.

**Table 31: Disease Characteristics (Disease History), VISION Cohort A – Overall SAF**

	Overall N = 152 (100%)	Prior Platinum Based Therapy N = 74 (100%)	Platinum Naïve N = 75 (100%)
<b>Nicotine consumption, n (%)</b>			
Never used	65 (42.8)	36 (48.6)	28 (37.3)
Regular user	3 (2.0)	0 (0.0)	3 (4.0)
Occasional User	0 (0.0)	0 (0.0)	0 (0.0)
Former user	76 (50.0)	31 (41.9)	44 (58.7)
Missing	8 (5.3)	7 (9.5)	0 (0.0)
<b>Time since initial cancer diagnosis (years) <sup>a, b</sup></b>			
n (%)	152 (100.0)	74 (100.0)	75 (100.0)
Missing	0	0	0
Mean (SD)	1.04 (2.244)	1.12 (1.129)	0.94 (2.996)
Median	0.54	0.72	0.12
(Q1, Q3)	0.11, 1.24	0.34, 1.30	0.07, 0.88
Min, Max	-0.02, 25.26	0.02, 4.46	-0.02, 25.26
<b>Histopathological classification, n (%)</b>			
Adenocarcinoma	131 (86.2)	65 (87.8)	63 (84.0)
Squamous	14 (9.2)	8 (10.8)	6 (8.0)
Sarcomatoid	3 (2.0)	0 (0.0)	3 (4.0)
Adenosquamous	2 (1.3)	1 (1.4)	1 (1.3)
Other	2 (1.3)	0 (0.0)	2 (2.7)
NSCLC-NOS	1 (0.7)	0 (0.0)	1 (1.3)
Carcinoma	1 (0.7)	0 (0.0)	1 (1.3)
<b>Disease Stage at study entry, n (%)</b>			
Stage IIIB	3 (2.0)	0 (0.0)	0 (0.0)
Stage IV	149 (98.0)	74 (100.0)	75 (100.0)

Source: VISION CSR, Table 15.1.5.1a, 15.1.5.1c, 15.1.5.2, 15.1.5.2c.

Max=maximum, Min=minimum, NSCLC=non-small cell lung cancer, NOS=not otherwise specified, Q1=quartile 1, Q3=quartile 3, SAF=safety analysis set, SD=standard deviation.

- a Time since initial cancer diagnosis (years) = (date of informed consent for pre-screening/screening – date of initial cancer diagnosis+1)/ 365.25.  
b One patient, 6060055 has date of initial cancer diagnosis after pre-screening.

**Table 32: Prior Anticancer Therapy, VISION Cohort A – Overall SAF (Combined Set)**

	Overall N = 152 (100%)	Prior Platinum Based Therapy N = 74 (100%)	Platinum Naïve Therapy N = 75 (100%)
<b>Prior Anticancer Drug Therapy for Advanced NSCLC, n (%)</b>			
Yes	83 (54.6)	74 (100.0)	6 (8.0)
No	69 (45.4)	0 (0.0)	69 (92.0)
<b>Number of Prior Anticancer Drug Therapy Lines for Advanced NSCLC, n (%)</b>			
1	49 (32.2)	42 (56.8)	5 (6.7)
2	33 (21.7)	31 (41.9)	1 (1.3)
3 <sup>a</sup>	1 (0.7)	1 (1.4)	0 (0.0)
<b>Prior Anticancer Therapy for Metastatic Disease</b>			
n (%)	80 (52.6)	74 (100.0)	6 (8.0)

Source: VISION CSR, Tables 15.1.4.2 and 15.1.4.2c.

SAF=safety analysis set.

- a One patient was enrolled with 3 prior lines of therapy and is listed in protocol deviations.

**The Applicant’s Position:**

The overall study population, based on the reported disease history, was representative of the *METex14* NSCLC population as reported in the literature. Similar patterns were observed in prior platinum-treated and platinum-naïve patients.

**The FDA’s Assessment:**

FDA’s description of patient disease characteristics and prior anticancer therapy for Cohort A of the VISION study are provided below.

**Table 33: Disease Characteristics (Disease History), VISION Cohort A**

	Overall N = 152 (100%)	Previously Treated N = 83 (100%)	Treatment Naïve N = 69 (100%)
<b>Nicotine consumption, n (%)</b>			
Never used	65 (42.8)	39 (52.0)	26 (37.7)
Regular user	3 (2.0)	1 (1.3)	2 (2.9)
Occasional User	0 (0.0)	0 (0.0)	0 (0.0)
Former user	76 (50.0)	35 (46.7)	41 (59.4)
Missing	8 (5.3)	8 (9.6)	0 (0.0)
<b>Time since initial cancer diagnosis (years) <sup>a, b</sup></b>			
Mean (SD)	1.04 (2.244)	1.14 (1.089)	0.92 (3.119)
Median	0.54	0.77	0.11
Min, Max	-0.02, 25.26	0.02, 4.46	-0.02, 25.26
<b>Histopathological classification, n (%)</b>			
Adenocarcinoma	131 (86.2)	73 (87.9)	58 (84.0)
Squamous	15 (9.9)	9 (10.8)	6 (8.7)
Sarcomatoid	3 (2.0)	0 (0.0)	3 (4.3)
Adenosquamous	2 (1.3)	1 (1.2)	1 (1.4)
NSCLC-NOS	1 (0.7)	0 (0.0)	1 (1.4)
<b>Disease Stage at study entry, n (%)</b>			
Stage IIIB	3 (2.0)	3 (3.6)	0 (0.0)
Stage IV	149 (98.0)	80 (96.4)	69 (100.0)
<b>Brain Metastases, n (%)</b>			
Present	15 (9.9)	9 (10.8)	6 (8.7)
Absent	137 (90.1)	74 (89.2)	63 (91.3)

Source: FDA reviewer-generated table based on Applicant submitted data (ADSL), DCO: July 1, 2020

Max=maximum, Min=minimum, NSCLC=non-small cell lung cancer, NOS=not otherwise specified, SD=standard deviation.

a Time since initial cancer diagnosis (years) = (date of informed consent for pre-screening/screening – date of initial cancer diagnosis+1)/ 365.25.

b One patient, 6060055 has date of initial cancer diagnosis after pre-screening.

**Table 34: Prior Anticancer Therapy – VISION Cohort A**

	Overall N = 152 (100%)	Previously Treated N = 83 (100%)	Treatment Naïve N = 69 (100%)
<b>Prior Anticancer Drug Therapy for Advanced NSCLC, n (%)</b>			
Yes	83 (54.6)	83 (100.0)	0 (0)
No	69 (45.4)	0 (0.0)	69 (100.0)
<b>Number of Prior Anticancer Drug Therapy Lines for Advanced NSCLC, n (%)</b>			
1	49 (32.2)	49 (59.0)	0 (0)
2	33 (21.7)	33 (39.8)	0 (0)
3	1 (0.7)	1 (1.2)	0 (0.0)
<b>Prior Anticancer Therapy for Metastatic Disease</b>			
n (%)	80 (52.6)	80 (96.4)	0 (0)

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

#### Data:

In the overall SAF, the majority of patients (66.4%) were exposed to a relative dose intensity of 90% to 110%. The mean dose intensity (9,340.4 mg/3 weeks) corresponded to 89% of the target dose intensity (10,500 mg/3 weeks; refer to VISION CSR Table 15.1.7.3). No dose reduction was reported for the majority of patients (99 [65.1%] patients).

#### The Applicant’s Position:

The compliance and relative dose intensity were high in the VISION study.

#### The FDA’s Assessment:

FDA agrees with EMD Serono’s exposure analysis for patients enrolled in the VISION study. Please refer to section 8.2.2 further below for additional information.

### Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

#### Data:

In the ITT-02 Oct 2019, objective response was observed in 66 patients, yielding a clinically meaningful ORR of 45.2% (95% CI: 37.0, 53.6; Table 35). In addition, 24.7% of patients had a BOR of stable disease. A decrease in tumor size was observed for the majority of patients in this population (Figure 25). These efficacy results were consistent with the ITT-02 Apr 2019 analyses,

as well as between prior platinum-treated and platinum naïve patients.

Consistent ORR results were observed across the subgroups analyzed (Figure 26). In particular, clinically meaningful and highly consistent ORR was reported for the ITT-02 Oct 2019 and the ITT-02 April 2019 populations independent of prior therapy with regard to lines of therapy for advanced NSCLC (Table 36).

**Table 35: Best Overall Response and Objective Response Rate, Independent Evaluation, VISION Cohort A – ITT Analysis Set**

	Overall	Prior Platinum Based Therapy	Platinum Naïve
<b>Overall ITT <sup>a</sup>, N</b>	146	72	71
BOR, n (%) <sup>b</sup>			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	65 (44.5)	35 (48.6)	30 (42.3)
Stable disease	37 (25.3)	17 (23.6)	18 (25.4)
Progressive disease	23 (15.8)	9 (12.5)	14 (19.7)
Not Evaluable	21 (14.4)	11 (15.3)	9 (12.7)
ORR, n (%)	65 (44.5)	35 (48.6)	30 (42.3)
[95% CI] <sup>c</sup>	[36.3, 53.0]	[36.7, 60.7]	[30.6, 54.6]
<b>ITT-02 Apr 2019, N</b>	99	49	47
BOR, n (%) <sup>b</sup>			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	46 (46.5)	26 (53.1)	20 (42.6)
Stable disease	19 (19.2)	9 (18.4)	8 (17.0)
Progressive disease	19 (19.2)	7 (14.3)	12 (25.5)
Not Evaluable	15 (15.2)	7 (14.3)	7 (14.9)
ORR, n (%)	46 (46.5)	26 (53.1)	20 (42.6)
[95% CI] <sup>c</sup>	[36.4, 56.8]	[38.3, 67.5]	[28.3, 57.8]

Source: VISION CSR, Table 15.2.1.1a, 15.2.1.17a, 15.2.1.17b, 15.2.1.17bs.

BOR=best overall response, CI=confidence interval, ITT=intention-to-treat, ORR=objective response rate.

OR evaluated by the independent evaluation was the primary endpoint.

- a Only patients with at least 2 post-baseline assessments or who discontinued treatment for any reason are included.
- b Complete response and partial response must be confirmed, and stable disease must last at least 12 weeks.
- c 95% exact confidence interval using the Clopper-Pearson method.

**Figure 25: Percent Change in Sum of Longest Diameters Between Baseline and Best Post-Baseline Assessment, Independent Evaluation, VISION Cohort A – ITT-02 Oct 2019**



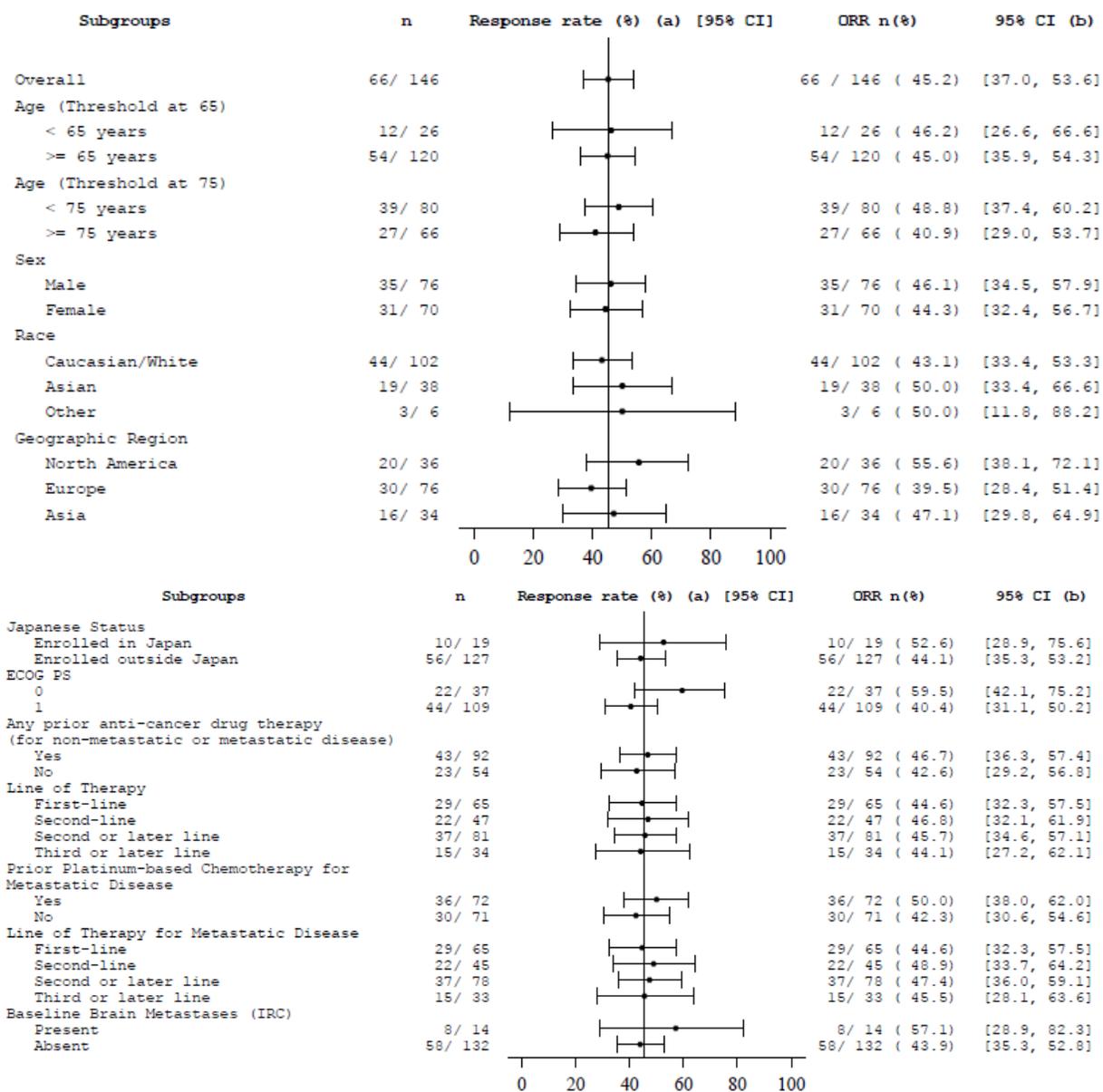
Source: VISION 01 July 2020 cutoff, Figure 15.2.1.14ao.

BOR=best overall response, CR=complete response, ITT=intention-to-treat, NE=not evaluable, PD=progressive disease, PR=partial response, SD=stable disease.  
3 patients excluded due to baseline/on-treatment measurement not being available.

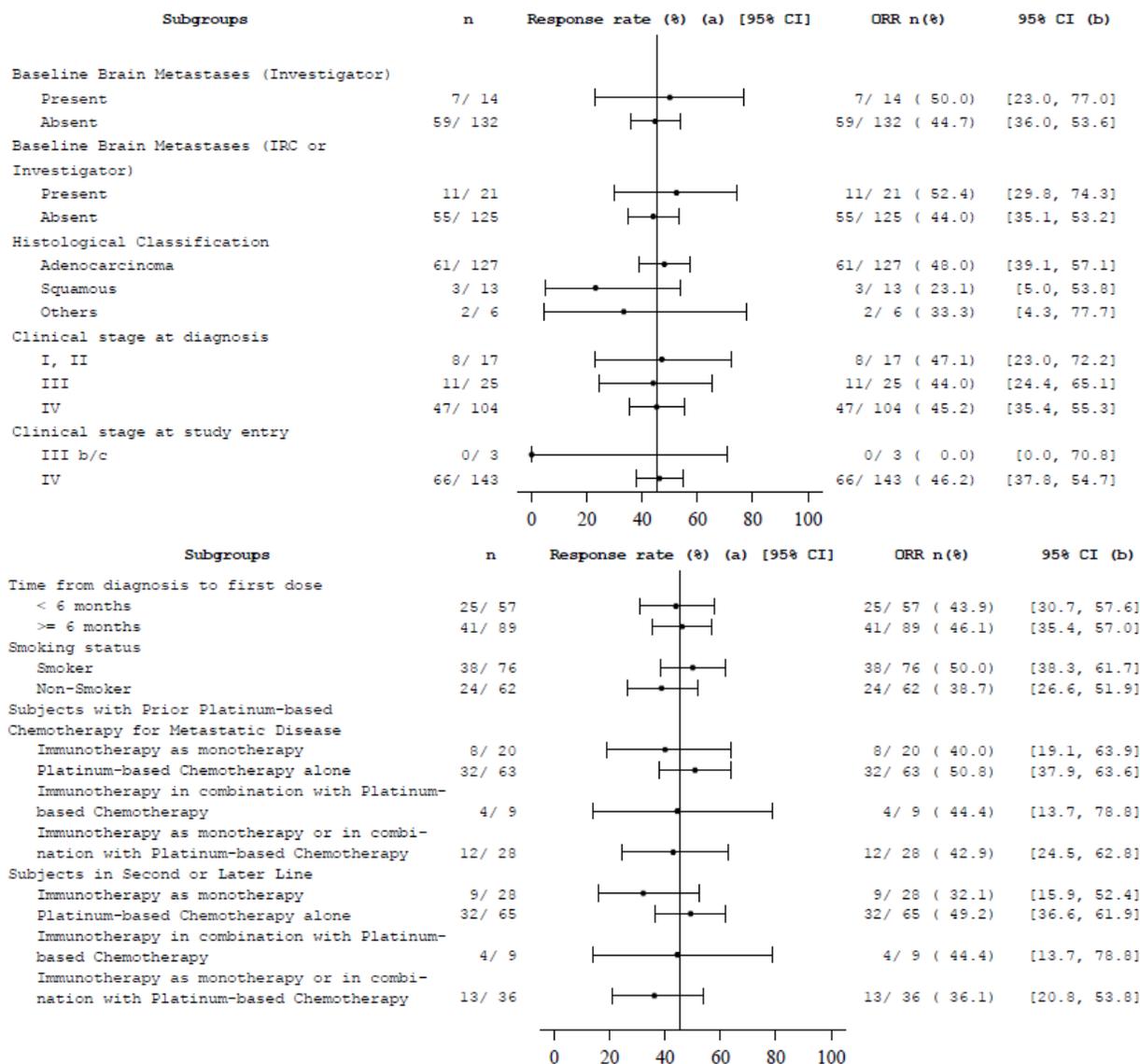
BOR: NE\* = BOR of NE where ongoing patient has not had two post-baseline tumor assessments.

**Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.**

**Figure 26: Forest Plot of Objective Response, Independent Evaluation, VISION Cohort A –ITT-02 Oct 2019**



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Source: VISION 01 July 2020 cutoff, Figure 15.2.1.6bo.

CI=confidence interval, ECOG PS= Eastern Cooperative Oncology Group Performance Score, IRC=independent review committee, ITT=intention-to-treat, OR=objective response, ORR=objective response rate.

a Number of patients with confirmed complete or partial response / number of patients in subgroup.

b 95% exact confidence interval using the Clopper-Pearson method.

**Table 36: Best Overall Response and Objective Response Rate by Line of Therapy, Independent Evaluation, VISION Cohort A – ITT-02 Oct 2019 Analysis Population**

	Overall	First line	Second line or later
<b>ITT-02 Oct 2019, N</b>	146	65	81
BOR, n (%) <sup>a</sup>			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	66 (45.2)	29 (44.6)	37 (45.7)
Stable disease	36 (24.7)	15 (23.1)	21 (25.9)
Progressive disease	25 (17.1)	12 (18.5)	13 (16.0)
Not Evaluable	19 (13.0)	9 (13.8)	10 (12.3)
ORR n (%)	66 (45.2)	29 (44.6)	37 (45.7)
[95% CI] <sup>b</sup>	[37.0, 53.6]	[32.3, 57.5]	[34.6, 57.1]
<b>ITT-02 April 2019, N</b>	99	43	56
BOR, n (%) <sup>a</sup>			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	45 (45.5)	19 (44.2)	26 (46.4)
Stable disease	20 (20.2)	8 (18.6)	12 (21.4)
Progressive disease	19 (19.2)	9 (20.9)	10 (17.9)
Not Evaluable	15 (15.2)	7 (16.3)	8 (14.3)
ORR n (%)	45 (45.5)	19 (44.2)	26 (46.4)
[95% CI] <sup>b</sup>	[35.4, 55.8]	[29.1, 60.1]	[33.0, 60.3]

Source: VISION 01 July 2020 cutoff, Tables 15.2.1.1bo, 15.2.1.1bs, 15.2.1.17bo, 15.2.1.17bs.

BOR=best overall response, CI=confidence interval, ITT=intention-to-treat, ORR=objective response rate.

a Complete response and partial response must be confirmed, and stable disease must last at least 12 weeks.

b 95% exact confidence interval using the Clopper-Pearson method.

### The Applicant's Position:

Treatment of METex14 NSCLC patients with tepotinib resulted in a high and clinically meaningful response rate. The ORR for patients who had at least 9 months of follow-up after start of treatment, yielding 6 months of follow-up post response (ITT-02 Oct 2019 population) was consistent with the ORR for patients who had at least 15 months of follow-up after start of treatment yielding 12 months of follow-up post response (ITT-02 Apr 2019 population), underscoring the robustness and stability of the tepotinib efficacy results. A consistent benefit with tepotinib was also observed independent of whether a patient received prior anticancer therapies, including platinum-based therapy for metastatic disease; this observation supports the scientific concept of METex14 as an oncogenic driver for NSCLC. Furthermore, benefit was consistent between elderly and younger patients, supporting the suitability of tepotinib for METex14 NSCLC, which typically manifests in the elderly. Overall, results were consistent across the subgroups analyzed, underscoring the robustness of the tepotinib efficacy results shown in the overall population.

The FDA's Assessment:

FDA's analyses of the primary and key secondary endpoints per the clinically relevant subpopulations are presented in Table 37. In the population of previously treated patients, the observed ORR was 43% (95% CI: 33, 55). In the treatment-naïve population, the observed ORR was 43% (95% CI: 32, 56). All observed responses were partial responses. Refer to Data Quality and Integrity section of this document for more information regarding FDA's estimation of ORR, in particular with respect to updated efficacy data submitted by the Applicant.

As of the July 1, 2020 data cut-off date, the duration of response data for each patient population of clinical interest was mature, with median duration of response reached for both the previously treated patient population and the treatment-naïve patient population. The DOR follow-up range was 3.6 to 37.8 months for the previously treated population and 1.3 to 29.9 months) for the treatment-naïve population. In the previously treated population, 27 (75%) patients were followed for more than 6 months (13 censored) and 9 (25%) patients were followed for more than 12 months (4 censored). In the treatment-naïve population, 20 (67%) patients were followed for more than 6 months (6 censored) and 4 (13%) patients were followed for more than 12 months (0 censored).

**Table 37: Overall Response Rate and Duration of Response per Independent Evaluation, VISION Cohort A**

	Previously Treated N=83	Treatment Naïve N=69
<b>Overall Response Rate (ORR)</b>		
Observed Responses, n	36	30
ORR, % (95% CI) <sup>a</sup>	43 (33,55)	43 (32,56)
<b>Duration of Response (DOR)</b>		
Median DOR, months <sup>b</sup> (95% CI) <sup>c</sup>	11.1 (9.5, 18.5)	10.8 (6.9, NE)
Responders with DOR ≥ 6 months, n (%) <sup>d</sup>	27 (75)	20 (67)
Responders with DOR ≥ 9 months, n (%) <sup>d</sup>	18 (50)	9 (30)
Responders with DOR ≥ 12 months, n (%) <sup>d</sup>	9 (25)	4 (13)

Source: FDA reviewer-generated table using Applicant provided data (ADRS), DCO: July 1, 2020

CI=confidence interval, NE=not estimable

- a 95% exact confidence interval (CI) using the Clopper-Pearson method.
- b Product-limit (Kaplan-Meier) estimates
- c 95% confidence interval (CI) using the Brookmeyer and Crowley method
- d Observed proportion of responders with duration of response longer than landmark time

## Data Quality and Integrity

### Data:

The study was monitored in accordance with ICH GCP (ICH Topic E6, 1996) and any other applicable regulations.

Investigator site audits were conducted in the US (Site 104 and 152), Spain (Site 601 and 606), France (Site 302), and Japan (Site 804). No concerns regarding data integrity were reported following the completion of these audits.

### The Applicant's Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data or change the conclusions drawn.

### The FDA's Assessment:

During the review of the 90-day efficacy update information, FDA identified that some of the patients with responses reported in the 90-day efficacy update (July 2020 data cut-off) differed from some of the patients identified as responders in the original efficacy data (January 2020

data cut-off). Sixty-five patients were identified as responders in the initial efficacy data, but two patients previously reported as having response were not included in the updated efficacy data and instead five new responders were included (including at least three patients with a duration of response start date before the initial data cut-off date who were not identified as having a response in the initial efficacy data), for a total of 68 responders in the updated efficacy data. In addition, it appeared that the date of onset of response had been changed for several patients, impacting the duration of response.

Additional details were obtained through information requests (IR) as outlined further below (Section 19.5). A teleconference was scheduled to discuss the responses to IR. During a teleconference with EMD Serono on December 4, 2020, FDA requested clarifications regarding the details of the study charter and EMD Serono reported that the way the charter is written, at every IRC assessment point the response assessment for an individual patient could potentially change.

FDA recommended that EMD Serono obtain details regarding the reason for change in independent radiology assessments for each patient for whom the response assessment and/or onset of response date had changed between the data cut-off for the initial submission and the data cut-off for the efficacy update and submit this information for FDA review. On December 9, 2020, EMD Serono provided this information (please refer to Section 19.5) along with clarification of the independent imaging review process and its application in the conduct of the VISION study. On December 23, 2020, FDA requested additional information. Please refer to section 19.5 for additional details of FDA's request to EMD Serono sent on December 23, 2020. EMD Serono provided responses on December 31, 2020. On January 8, 2021, FDA sent an additional IR to request a listing of timepoints with dates of the scan for each timepoint for the patients under review and to indicate the location in their December 31, 2020 submission of pathology reports which led to changes in IRC reads or to provide copies of these reports. EMD Serono provided responses on January 11, and 12, 2021

A teleconference between FDA and EMD Serono was held on January 13, 2021. At the conclusion of the teleconference, it was agreed that FDA will not accept the reported change in response assessment to partial response for Subject (b) (6). FDA indicated that the cytology report that led to the change in response assessment was too far out (over 1 year) from the time points of the real-time assessments which were read as progression of disease. FDA expressed concerns that the cytology was not obtained contemporaneously and indicated this patient will not be considered a responder and the progressive disease assessment at timepoint (TP) 2 will be maintained. In addition, it was agreed that FDA will not accept the reported change in response assessment to partial response for Subject (b) (6). The histology report that led to the change in assessment to partial response for Reviewer 1 did not result in a similar change in assessment for Reviewer 2. It remains unclear why Reviewer 2 did not change the assessment at TP2 with a histology report indicating granuloma. This suggests that

Reviewer 2 either based assessment of progression on other imaging findings or did not believe the histology report was adequate evidence that the new lung nodule was not due to lung cancer. FDA's assessment is that the histology results alone are not enough evidence to definitively conclude that cancer progression could be excluded. FDA agreed with the assessments provided by EMD Serono for the remaining patients, and therefore, this patient would not be considered a responder. FDA agreed with assessments provided by EMD Serono for the remaining patients; please refer to Section 19.5 for detailed information on the remaining patients.

### **Efficacy Results – Secondary and other relevant endpoints**

#### Data:

The median DOR (mDOR) was 11.1 months (95% CI: 8.4, 18.5) in the ITT-02 Oct 2019 (Table 38 and Figure 27). Most of the responses to tepotinib occurred early (within 3 months of first dose) and were deep and durable, up to 37.7 months after start of response. Of note, among the 66 patients with a confirmed complete or partial response, all had a duration of follow-up of at least 6 months after the onset of response and the majority (84.8%) had (at the time of cutoff) an ongoing response of  $\geq 12$  months or event (progressive disease or death) or treatment discontinuation due to any reason  $< 12$  months past onset of response.

Consistent results for DOR were observed in the ITT-02 Apr 2019 analyses (Table 38). Within the ITT-02 Apr 2019, all but 1 patient had a duration of follow-up of at least 12 months after the onset of response.

The durable responses to tepotinib were further reflected by the clinically meaningful mPFS of 8.9 months [95% CI: 8.2, 11.0] and a median overall survival (mOS) of 17.6 months (95% CI: 15.0, 21.0) in the ITT-02 Oct 2019 (Table 38). Consistent results were observed in the ITT-02 Apr 2019 analyses.

Overall, efficacy results were consistent between prior platinum-treated patients and platinum naïve patients within both ITT populations (Table 38 and Figure 28). Consistent results were also observed independent of lines of therapy for advanced NSCLC (refer to VISION 01 July 2020 cutoff, Tables 15.2.2.3co, 15.2.2.3cs, 15.2.2.4o, 15.2.2.4s, 15.2.3.9o, 15.2.3.9s, 15.2.4.4o, and 15.2.4.4s).

**Table 38: Efficacy Results, Independent Evaluation VISION Cohort A, ITT-02 Oct 2019 and ITT-02 Apr 2019 Analysis Populations**

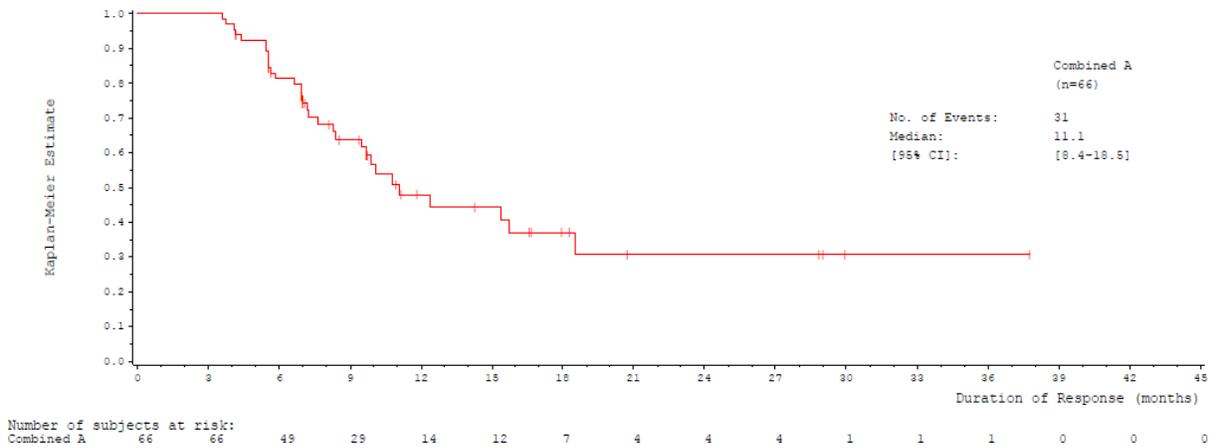
	Overall	Prior Platinum Based Therapy	Platinum Naïve
<b>ITT-02 Oct 2019, N</b>	146	72	71
ORR <sup>a</sup> n (%)	66 (45.2)	36 (50.0)	30 (42.3)
[95% CI] <sup>b</sup>	[37.0, 53.6]	[38.0, 62.0]	[30.6, 54.6]
mDOR, months <sup>c</sup> [95% CI] <sup>d</sup>	11.1 [8.4, 18.5]	12.4 [9.5, 18.5]	10.8 [6.9, ne]
DOR ≥ 6 months, n (% of responders)	49 (74.2)	27 (75.0)	22 (73.3)
DOR ≥ 9 months, n (% of responders)	29 (43.9)	18 (50.0)	11 (36.7)
DOR ≥ 12 months, n (% of responders)	14 (21.2)	9 (25.0)	5 (16.7)
mPFS, months <sup>c</sup> [95% CI] <sup>d</sup>	8.9 [8.2, 11.0]	11.0 [8.2, 13.7]	8.5 [6.8, 10.8]
Patients with event (PD/Death), n (%)	86 (58.9)	41 (56.9)	43 (60.6)
mOS time <sup>c</sup> , months [95% CI] <sup>d</sup>	17.6 [15.0, 21.0]	19.8 [15.2, 24.9]	15.8 [9.3, 22.1]
Patients with event, n (%)	75 (51.4)	32 (44.4)	40 (56.3)
<b>ITT-02 April 2019, N</b>	99	49	47
ORR <sup>a</sup> n (%)	45 (45.5)	25 (51.0)	20 (42.6)
[95% CI] <sup>b</sup>	[35.4, 55.8]	[36.3, 65.6]	[28.3, 57.8]
mDOR, months <sup>c</sup> [95% CI] <sup>d</sup>	11.1 [8.4, 18.5]	12.4 [8.4, 18.5]	10.8 [3.7, 29.9]
DOR ≥ 6 months, n (% of responders)	34 (75.6)	19 (76.0)	15 (75.0)
DOR ≥ 9 months, n (% of responders)	25 (55.6)	15 (60.0)	10 (50.0)
DOR ≥ 12 months, n (% of responders)	14 (31.1)	9 (36.0)	5 (25.0)
mPFS, months <sup>c</sup> [95% CI] <sup>d</sup>	8.5 [6.8, 11.0]	11.0 [6.7, 13.7]	7.8 [3.8, 10.8]
Patients with event (PD/Death), n (%)	67 (67.7)	32 (65.3)	33 (70.2)
mOS time <sup>c</sup> , months [95% CI] <sup>d</sup>	17.0 [12.0, 20.4]	19.7 [12.8, 24.9]	15.3 [8.0, 22.1]
Patients with event, n (%)	63 (63.6)	28 (57.1)	32 (68.1)

Source: VISION 01 July 2020, Table 15.2.1.1bo, 15.2.1.17bo, 15.2.1.1bs, 15.2.1.17bs, 15.2.2.1o, 15.2.2.3ao, 15.2.2.3bo, 15.2.2.4o, 15.2.2.1s, 15.2.2.3as, 15.2.2.3bs, 15.2.2.4s, 15.2.3.1o, 15.2.3.9o, 15.2.3.1s, 15.2.3.9s, 15.2.4.1o, 15.2.4.4o, 15.2.4.1s, 15.2.4.4s.

CI=confidence interval, DOR=duration of response, ITT=intention-to-treat, mDOR=median duration of response, mOS=median overall survival, mPFS=median progression-free survival, ne=not estimable, ORR=objective response rate, PD=progressive disease.

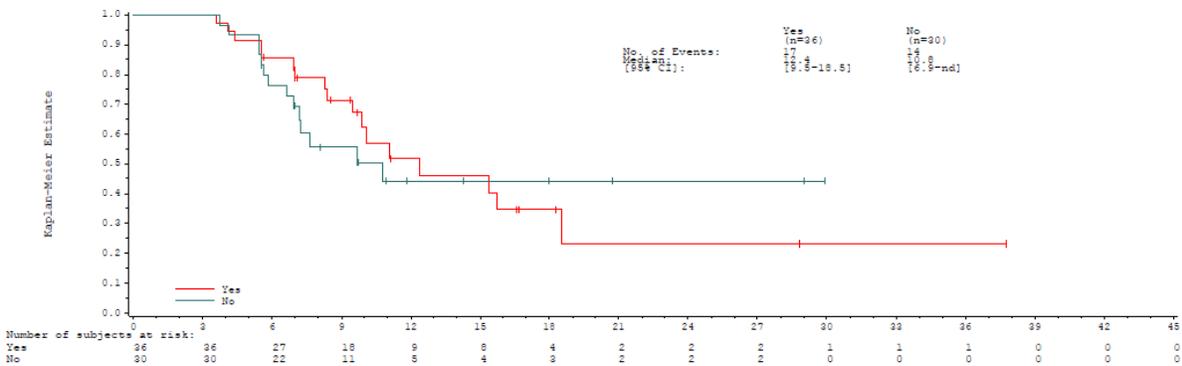
- a Confirmed complete response/partial response.
- b 95% exact CI using the Clopper-Pearson method.
- c Product-limit (Kaplan-Meier) estimates.
- d 95% CI for the median using the Brookmeyer and Crowley method.

**Figure 27: Kaplan-Meier Curve Showing Duration of Response, Independent Evaluation, VISION Cohort A – ITT-02 Oct 2019**



Source: VISION 01 July 2020, Figure 15.2.2.2o.  
CI=confidence interval, ITT=intention-to-treat, nd=not determined.

**Figure 28: Kaplan-Meier Curve Showing Duration of Response by Prior Platinum-based Chemotherapy for Metastatic Disease, Independent Evaluation, VISION Cohort A – ITT-02 Oct 2019**



Source: VISION 01 July 2020, Figure 15.2.2.5o.  
CI=confidence interval, ITT=intention-to-treat, nd=not determined.

Results determined by independent evaluation are supported by the Investigator assessment, with a tendency for higher ORRs and a longer DOR in the Investigator assessment (Table 39). Three patients in the ITT-02 Oct 2019 population were identified with complete responses by Investigator assessment (refer to VISION 01 July 2020, Table 15.2.1.9bo).

**Table 39: Efficacy Results, Investigator Assessment, VISION Cohort A – ITT-02 Oct 2019 and ITT-02 Apr 2019 Analysis Populations**

	Overall	Prior Platinum Based Therapy	Platinum Naïve
<b>ITT-02 Oct 2019, N</b>	146	72	71
ORR <sup>a</sup> n (%)	79 (54.1)	42 (58.3)	35 (49.3)
[95% CI] <sup>b</sup>	[45.7, 62.4]	[46.1, 69.8]	[37.2, 61.4]
mDOR, months <sup>c</sup> [95% CI] <sup>d</sup>	12.7 [9.7, 18.3]	14.0 [9.8, 17.1]	10.9 [7.2, ne]
DOR ≥ 6 months, n (% of responders)	56 (70.9)	31 (73.8)	25 (71.4)
DOR ≥ 9 months, n (% of responders)	40 (50.6)	23 (54.8)	17 (48.6)
DOR ≥ 12 months, n (% of responders)	27 (34.2)	17 (40.5)	10 (28.6)
mPFS, months <sup>c</sup> [95% CI] <sup>d</sup>	8.6 [6.9, 11.0]	9.6 [6.7, 13.8]	8.6 [6.8, 11.0]
Patients with event (PD/Death), n (%)	95 (65.1)	48 (66.7)	45 (63.4)
<b>ITT-02 April 2019, N</b>	99	49	47
ORR <sup>a</sup> n (%)	55 (55.6)	29 (59.2)	24 (51.1)
[95% CI] <sup>b</sup>	[45.2, 65.5]	[44.2, 73.0]	[36.1, 65.9]
mDOR, months <sup>c</sup> [95% CI] <sup>d</sup>	14.0 [9.7, ne]	14.3 [9.8, ne]	10.9 [7.1, ne]
DOR ≥ 6 months, n (% of responders)	38 (69.1)	20 (69.0)	18 (75.0)
DOR ≥ 9 months, n (% of responders)	32 (58.2)	19 (65.5)	13 (54.2)
DOR ≥ 12 months, n (% of responders)	27 (49.1)	17 (58.6)	10 (41.7)
mPFS, months <sup>c</sup> [95% CI] <sup>d</sup>	8.6 [6.7, 12.2]	9.9 [5.5, 15.8]	8.6 [6.0, 12.2]
Patients with event (PD/Death), n (%)	68 (68.7)	34 (69.4)	32 (68.1)

Source: VISION 01 July 2020 cutoff, Tables 15.2.1.9bo, 15.2.1.9bs, 15.2.1.18bo, 15.2.1.18bs, 15.2.2.11o, 15.2.2.11s, 15.2.2.13o, 15.2.2.13s, 15.2.2.14o, 15.2.2.14s, 15.2.2.15o, 15.2.2.15s, 15.2.3.12o, 15.2.3.12s, 15.2.3.16o, 15.2.3.16s.

CI=confidence interval, DOR=duration of response, ITT=intention-to-treat, mDOR=median duration of response, mOS=median overall survival, mPFS=median progression-free survival, ne=not estimable, ORR=objective response rate, PD=progressive disease.

a Confirmed complete response/partial response.

b 95% exact CI using the Clopper-Pearson method.

c Product-limit (Kaplan-Meier) estimates.

d 95% CI for the median using the Brookmeyer and Crowley method.

### The Applicant's Position:

The efficacy analyses provided evidence of clinically meaningful response rates, deep and durable responses, and rapid onset of responses. The mDOR strongly supports the clinical benefit of tepotinib treatment. PFS and OS analyses provided additional supportive evidence. Efficacy was consistent between the ITT-02 Oct 2019 and the ITT-02 Apr 2019 populations, comprising patients with at least 6 months and 12 months of follow-up post response, respectively. Consistency in the efficacy of tepotinib was also shown between prior platinum-treated patients and platinum-naïve patients as well as across lines of therapy for advanced NSCLC. The results by

independent evaluation were supported by the results based on Investigator assessment, with a tendency for higher ORRs and a longer DOR in the Investigator assessment compared with the independent evaluation.

**The FDA's Assessment:**

FDA analysis of DOR is presented in Table 37 and are described in the context of overall response rate in the section above.

FDA considered the potential role for concurrent genomic alterations harbored by patients with MET exon 14 splice mutations (e.g., MET amplification (MET-amp), murine double minute gene (MDM2) amplification, cyclin-dependent kinase 4 gene (CDK4) amplification, and EGFR amplification) regarding the evaluation of efficacy. FDA reasoned that given the prevalence of MET exon 14 skipping, the overlap of genetic alterations is low. In the literature, MET amplification/mutation prevalence is about 5% (close to 2.5% for each). MDM2 is amplified in about 5% and CDK4 is amplified in about 4% of NSCLC patients. Furthermore, there is little overlap between MET mutations and amplifications of these genes in the literature.

Regarding the smoking status subgroup results, though it seems like a significant difference, FDA believes it is hard to make inference regarding a subgroup from a small trial. The smoking status subgroup confidence intervals are wide and overlap, so given the relatively small sample sizes no definitive conclusions can be drawn.

FDA's analyses of efficacy per investigator assessment are provided below. FDA agrees with the Applicant's assessment that these analyses are supportive of the primary analysis per independent assessment.

FDA's analyses of efficacy in patients who tested positive in tumor tissue and patients who tested positive in plasma ctDNA are presented separately in Table 41 below. Some of the sample sizes are quite small and the results are considered to be exploratory.

As described in FDA's Assessment of Study Endpoints, PFS and OS results are difficult to interpret in a non-randomized, open-label trial without a control, and therefore are considered exploratory in the VISION study. FDA did not independently confirm the results of these endpoints.

**Table 40: Efficacy Results per Investigator Assessment, VISION Cohort A**

	Previously Treated N=83	Treatment Naïve N=69
<b>Overall Response Rate (ORR)</b>		
Observed Responses, n	45	34
ORR, % (95% CI) <sup>a</sup>	54 (43,65)	49 (37,62)
<b>Duration of Response (DOR)</b>		
Median DOR, months <sup>b</sup> (95% CI) <sup>c</sup>	12.7 (9.7, 17.1)	10.9 (7.1, NE)
Responders with DOR ≥ 6 months, n (%) <sup>d</sup>	31 (69)	23 (68)
Responders with DOR ≥ 12 months, n (%) <sup>d</sup>	17 (38)	9 (26)

Source: FDA reviewer-generated table using Applicant provided data (ADRS), DCO: July 1, 2020

CI=confidence interval, NE=not estimable

a 95% exact confidence interval (CI) using the Clopper-Pearson method.

b Product-limit (Kaplan-Meier) estimates

c 95% confidence interval (CI) using the Brookmeyer and Crowley method

d Observed proportion of responders with duration of response longer than landmark time

**Table 41: Efficacy Results per BIRC for the Tumor Positive and Plasma Positive Subgroups, VISION Cohort A**

	Tumor Tissue Positive		Plasma ctDNA Positive	
	Previously Treated N=46	Treatment Naïve N=42	Previously Treated N=55	Treatment Naïve N=44
<b>Overall Response Rate (ORR)</b>				
Observed Responses, n	22	16	24	22
ORR, % (95% CI) <sup>a</sup>	48 (33, 63)	38 (24, 54)	44 (30, 58)	50 (35, 65)
<b>Duration of Response (DOR)</b>				
Median DOR, months <sup>b</sup> (95% CI) <sup>c</sup>	12.4 (9.7, NE)	NE (5.7, NE)	11.1 (8.4, 18.5)	7.6 (6.6, NE)
Responders with DOR ≥ 6 months, n (%) <sup>d</sup>	15 (68)	10 (62)	19 (79)	15 (68)
Responders with DOR ≥ 9 months, n (%) <sup>d</sup>	12 (54)	6 (37)	13 (54)	7 (32)
Responders with DOR ≥ 12 months, n (%) <sup>d</sup>	6 (27)	3 (19)	7 (29)	3 (14)

Source: FDA reviewer-generated table using Applicant provided data (ADRS), DCO: July 1, 2020

CI=confidence interval, NE=not estimable

a 95% exact confidence interval (CI) using the Clopper-Pearson method.

b Product-limit (Kaplan-Meier) estimates

c 95% confidence interval (CI) using the Brookmeyer and Crowley method

d Observed proportion of responders with duration of response longer than landmark time

## **Dose/Dose Response**

### Data and the Applicant's Position:

A tepotinib dose of 500 mg once daily was administered in the VISION study. To assess the relationship between tepotinib exposure and efficacy, exposure-response analyses were conducted (Section 6.3.2).

### The FDA's Assessment:

Please refer to FDA comments in Section 6.3.2

## **Durability of Response**

### Data:

See discussion of DOR in "Efficacy Results – Secondary and other relevant endpoints".

### The Applicant's Position:

Responses were shown to be deep and durable. See discussion of DOR in "Efficacy Results – Secondary and other relevant endpoints".

### The FDA's Assessment:

FDA's analyses of DOR are provided in Table 37.

## **Persistence of Effect**

### Data:

See discussion of PFS and OS in "Efficacy Results – Secondary and other relevant endpoints".

### The Applicant's Position:

Clinically meaningful mPFS of 8.9 months (95% CI: 8.2, 11.0) and mOS of 17.6 months (95% CI: 15.0, 21.0) were observed in the ITT-02 Oct 2019.

### The FDA's Assessment:

FDA considers PFS, a time-to-event endpoint, to be exploratory in the context of a single arm trial; therefore, these results were not verified. FDA's analyses of DOR are provided in Table 37.

## **Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

### Data:

All patients were asked to take part in all PRO assessments: EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13. Overall, the completion rate for PROs in this study was very high, approximating 90% per visit, and remained high up to Cycle 21 (refer to VISION 01 July 2020 cutoff, Tables 15.2.6).

Results in the ITT-02 Oct 2019 (N=146) were consistent across the 3 PRO tools and suggested that health-related quality of life (HRQoL) remains stable over time. For EORTC QLQ-LC13, an improvement in the symptom scale of coughing was observed at Week 12 and remained stable. For dyspnea and pain in chest, symptom intensity remained stable over time.

Overall, the results observed in patients who received their first dose before 02 April 2019 were consistent with the ITT-02 Oct 2019. A clinically meaningful improvement (i.e., prespecified reduction of > 10 points from baseline) in the coughing symptom scale was observed in the ITT-02 Apr 2019 patients.

The Applicant's Position:

The stability observed in the assessment of HRQoL for patients treated with tepotinib indicates control of the symptoms in this population, as a worsening is to be expected in the case of ineffective and/or toxic therapies.

The FDA's Assessment:

FDA considers the analyses of patient-reported outcome (PRO) endpoints to be exploratory in this study as PROs are difficult to interpret in non-randomized, open-label trials. Additionally, the Applicant did not have a pre-specified analysis plan for these endpoints, and no threshold for a clinically meaningful effect was specified.

**Additional Analyses Conducted on the Individual Trial**

Data and the Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

**8.1.3. Integrated Review of Effectiveness**

The FDA's Assessment:

This application is primarily supported by the results of the VISION study. As of the July 1, 2020 data cut-off, median DOR was 11.1 months for previously treated patients and 10.8 months for treatment-naïve patients. The responses were durable with 75% of the previously treated and

67% of the treatment-naïve responders achieving six months or longer of response. Duration of response was more than 9 months for 50% of previously treated and 30% of treatment-naïve patients who achieved a response. Subgroup analyses demonstrated the consistency of results across various prespecified subgroups.

#### 8.1.4. Assessment of Efficacy Across Trials

##### Data and The Applicant's Position:

While the efficacy assessment in this submission is based solely on the VISION study, it was possible to place the VISION efficacy results in the context of data from available therapies to help further substantiate the clinical activity of tepotinib. This includes:

- the outcomes of patients under prior anticancer treatments for advanced NSCLC before their entry in the VISION study (VISION pre-study anticancer therapy) and,
- the results from published evidence on patients with NSCLC harboring *MET*ex14 skipping alterations who have received available therapies and did not receive any prior MET therapy.

Both comparisons support the clinical benefit with tepotinib treatment in *MET*ex14 NSCLC patients (Table 42). A substantially higher and clinically relevant benefit with tepotinib was seen across all endpoints, i.e., ORR, DOR, PFS, and OS, when compared with the respective results with available therapies, including chemotherapy and immune checkpoint inhibitors.

Results were consistent across both comparisons. The ORR with tepotinib was 44.5% (95% CI: 36.3, 53.0) by independent evaluation and 54.8% (95% CI: 46.4, 63.0) by Investigator assessment. The lower bounds of the 95% CIs around the ORR point estimates with tepotinib were higher than:

- the ORR of 31.3% reported with available therapies patients received prior to the VISION study and,
- the ORR ranging from 17% to 33% observed with available therapies as reported in the literature for *MET*ex14 NSCLC patients ([Sabari 2018](#); [Pruis 2020](#); [Landi 2019](#)).

These observations were supported by consistently higher DOR, PFS and OS results with tepotinib compared with available, non-targeted therapies.

Known limitations of these approaches are the selection bias of patients enrolled in VISION and contributing data to the pre-study anticancer therapy, or the differences in study population and design between VISION and studies contributing to the literature-derived data. However, these

approaches are regarded as useful in placing the VISION study results in the context of current knowledge and the limited therapy standards that are available for this *METex14* selected elderly population with high unmet need.

**Table 42: Efficacy in the Pivotal VISION Study Relative to Available Therapies in Patients with Advanced NSCLC Harboring METex14 Skipping Alterations**

Population/line of Therapy	VISION, Cohort A, upon Therapy with Tepotinib 500 mg once daily, Combined Set (Overall ITT) <sup>a</sup>		Any Pre-study Anticancer Therapy for Patients Enrolled in VISION Cohort A, Combined Set <sup>b</sup>	Literature, Advanced METex14 NSCLC, No MET/HGF inhibitor <sup>c</sup>
	IRC	Investigator		
<b>Overall</b>				
ORR, n/N (%) [95% CI]	65/146 (44.5) [36.3, 53.0]	80/146 (54.8) [46.4, 63.0]	26/83 (31.3) [21.6, 42.4]	4/24 (17) [6, 36] <sup>1</sup> 2/6 (33) <sup>2</sup> 3/13 (23) <sup>2</sup> 2/9 (22, first line) <sup>6</sup>
mDOR, months [95% CI] (min/max)	9.9 [7.2, ne]	14.0 [9.7, 18.3]	7.0 (1, 17)	NA
mPFS, months [95% CI] (min/max)	8.6 [8.0, 11.0]	9.7 [7.0, 12.2]	4.0 (0, 26)	1.9 [1.7, 2.7] <sup>1</sup> 10.9 [7.4, 16.9] <sup>3</sup>
mOS, months [95% CI]		19.1 [12.3, 26.8]	NA	8.1 [5.3, ne] <sup>4</sup> 6.7 <sup>5</sup>
<b>Prior platinum-based therapy</b>				
ORR, n/N (%) [95% CI]	35/72 (48.6) [36.7, 60.7]	42/72 (58.3) [46.1, 69.8]	25/74 (33.8) [23.2, 45.7]	NA
mDOR, months [95% CI] (min/max)	11.1 [8.3, ne]	16.4 [9.8, ne]	6.5 (1, 17)	NA
mPFS, months [95% CI] (min/max)	11.0 [8.2, 13.7]	11.0 [5.8, 17.1]	4.0 (0, 26)	NA
mOS, months [95% CI]		19.7 [12.8, ne]	NA	NA

Source: Table 7 and Table 8, and refer to VISION CSR Tables 15.1.4.2 and 15.1.4.2c.

Literature references: 1. Sabari 2018; 2. Pruis 2020; 3. Wolf 2018; 4. Awad 2019; 5. Gow 2017; 6. Landi 2019.

CI=confidence interval, HGF=hepatocyte growth factor, IRC=independent review committee, ITT=intention-to-treat, MET=mesenchymal-epithelial transition factor, METex14=MET exon 14, Max=maximum, Min=minimum, mDOR=median duration of response, mOS=median overall survival, mPFS=median progression-free survival, NA=not available, ne=not estimable, NSCLC=non-small cell lung cancer, ORR=objective response rate.

a For ORR, complete response/partial response were confirmed and only patients with at least 2 post-baseline assessments or who discontinued treatment for any reason are included. The 95% exact CI for the ORR was calculated using the Clopper-Pearson method. For the analysis of mPFS and mOS, all patients in the overall ITT were included (Overall, N = 151; Prior platinum-based therapy, N = 73). mDOR, mPFS, and mOS are product-limit (Kaplan-Meier) estimates; 95% CI using the Brookmeyer and Crowley method.

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- b ORR was determined as the sum of the complete response and the partial response (based on the best response across all prior drug therapies) divided by the number of patients with available data. The 95% exact CI for the ORR was calculated using the Clopper-Pearson method. The median presented for DOR and PFS is based on the longest value recorded across all prior drug therapies.
- c ORR was determined as the sum of the complete response and the partial response. Overall survival reported for patients who have never received a MET inhibitor.

Note: the majority of platinum-naïve patients did not receive any pre-study anticancer therapy and they are therefore not included in this analysis.

### Additional Efficacy Considerations

#### The FDA's Assessment:

No additional efficacy data were considered by FDA other than the data described in Section 8.1.2. Given the limited nature of the data regarding response to other anticancer therapies for patients with NSCLC harboring METex14 skipping alterations and the limitations of the approaches used to collect this data as described by the Applicant, FDA does not consider the comparisons presented above by the Applicant informative for the assessment of efficacy.

### 8.1.5. Integrated Assessment of Effectiveness

#### Data:

The study met the primary endpoint by demonstrating a clinically meaningful ORR based on independent review in the range of 40% to 50% with a lower limit of the corresponding exact 2-sided 95% CI exceeding 20%.

- Tepotinib treatment of METex14 NSCLC patients resulted in a high and clinically meaningful rate of response: ORR of 44.5% (95% CI: 36.3, 53.0) in the overall ITT (N = 146) and ORR of 46.5% (95% CI: 36.4, 56.8) in the ITT-02 Apr 2019 (N = 99).
- Among the 65 patients with confirmed response in the overall ITT, 67.7% had (at the time of cutoff 01 January 2020) an ongoing response of  $\geq 6$  months or event (progressive disease or death) or treatment discontinuation due to any reason  $< 6$  months past onset of response.
- Responses were shown to be deep and durable, with a rapid onset, with most patients achieving a response within the first 3 months of their first dose.
- The Kaplan-Meier estimate of mDOR of 9.9 months (95% CI: 7.2, ne) in the overall ITT and 11.1 months (95% CI: 7.2, ne) in the ITT-02 Apr 2019, strongly supports the clinical benefit of treatment with tepotinib.
- Clinically meaningful outcomes were observed in PFS (median of 8.6 months [95% CI: 8.0, 11.0]) and OS (median of 19.1 months [95% CI: 12.3, 26.8]) analyses in the overall ITT (N = 151), supporting the overall highly efficacious profile of tepotinib.
- The results by Investigator assessment support the efficacy results as provided by independent evaluation, with a tendency for a higher ORR (54.8% [95% CI: 46.4, 63.0]; overall ITT) and a longer mDOR (14.0 months [95% CI: 9.7, 18.3]; overall ITT) in the Investigator assessment.
- The results of the overall ITT were consistent with the efficacy results for patients who received their first dose before 02 April 2019, i.e., had at least 6 months of follow-up of

response, underscoring the robustness and stability of tepotinib efficacy.

- Consistent benefit with tepotinib across all endpoints was also observed between prior platinum-treated and platinum-naïve patients, supporting the scientific concept of *METex14* being an oncogenic driver for NSCLC.
- Benefit was consistent between elderly and younger patients, supporting the suitability of tepotinib for *METex14* NSCLC, which typically manifests in the elderly.
- Consistent benefit was observed across all other analyzed subpopulations, such as sex, race, line of therapy, baseline brain metastases, clinical stage at study entry, time from diagnosis to first dose, and smoking status within the ITT population. This substantiates the robustness of the efficacy with tepotinib.
- Results were consistent across the 3 PRO tools (EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13), suggesting a stability in HRQoL over time. In EORTC QLQ-LC13, favorable effects with regard to stability of symptom intensities for dyspnea and pain in chest, and an improvement in the coughing symptom scale were observed.
- The clinical benefit with tepotinib in *METex14* NSCLC from the VISION study was further substantiated when put in the context of available non-targeted therapies, with higher ORR, DOR, PFS and OS being observed with tepotinib.

#### The Applicant's Position:

The efficacy results from the VISION study indicate that tepotinib provides a substantial and clinically meaningful benefit for patients with metastatic NSCLC harboring *METex14* skipping alterations. The unsatisfactory efficacy of available non-targeted therapies and their associated toxicity, together with the advanced age and poor prognosis of the *METex14* NSCLC population, limiting the tolerability and effectiveness of available therapies, further corroborate the clinical significance of tepotinib as an efficacious therapeutic option independent of prior therapy for this population with a high unmet medical need.

#### The FDA's Assessment:

The primary results from the VISION study (ORR of 43% in both populations of patients with previously treated and treatment-naïve disease) show evidence of durable antitumor response of tepotinib in patients with metastatic NSCLC harboring *METex14* skipping alterations, irrespective of the line of therapy. While the ORR in the treatment-naïve population did not exceed that observed with available therapy of anti-PD-(L)1 antibody in combination with chemotherapy, it is in the range of ORR observed with FDA-approved available therapies, and the differing safety profile and option for treatment with a single agent administered orally make this a valuable treatment option for treatment-naïve patients. When considered in this context, the ORR and durable responses observed with tepotinib are reasonably likely to

predict clinical benefit indicating tepotinib provides a meaningful therapeutic benefit over existing treatments, even for treatment-naïve patients. Progression-free survival and overall survival results are not interpretable in a single-arm study.

## 8.2. Review of Safety

### Data:

The safety analyses forming the basis of the safety profile of tepotinib are presented in Sections 8.2.4 and 8.2.5.

### The Applicant's Position:

Tepotinib was associated with a tolerable and manageable safety profile in patients with advanced NSCLC harboring *MET*ex14 skipping alterations, when administered as monotherapy at a dose of 500 mg once daily in the pivotal VISION study. The AEs observed were typical of the underlying NSCLC or were linked to the mode of action of tepotinib. The risks associated with tepotinib can be managed with dose modifications, routine care and guidance provided in the labeling.

### The FDA's Assessment:

FDA assessments in this review will refer to the recommended dose as 450 mg QD (based on tepotinib free base, equivalent to 500 mg tepotinib hydrochloride hydrate), as this is the convention which will be used in the US prescribing information (USPI). For a description of the safety populations used to inform the USPI, see FDA's assessment in Section 8.2.1. For FDA's integrated assessment of safety, see Section 8.2.11.

### 8.2.1. Safety Review Approach

#### Data and the Applicant's Position:

The safety analyses focus on the data from 181 patients with advanced NSCLC harboring *MET*ex14 skipping alterations in cohorts A and C of the pivotal VISION study treated with tepotinib up to the cutoff date of 01 January 2020. The SAF of VISION cohorts A + C comprises the totality of the safety data available for tepotinib in the intended population of *MET*ex14 NSCLC and intended dosage and allows for a comprehensive analysis. As *MET*ex14 NSCLC is a rare and life-threatening disease with a high unmet medical need, this is considered adequate to characterize the safety profile of tepotinib at the intended dose.

To further characterize the safety profile of tepotinib, safety data from all 373 patients with cancer treated at the proposed dose of 500 mg once daily monotherapy were pooled from the following studies:

- Ongoing pivotal VISION study (cutoff date 01 January 2020)
  - cohort A (N = 152 patients) and cohort C (N = 29 patients); NSCLC patients harboring *MET*ex14 skipping alterations
  - cohort B (N = 23 patients); NSCLC patients with *MET* amplification.
- 2 completed Phase I single-arm studies of patients with advanced solid tumors
  - Study EMR200095-001 (N = 42 patients) and
  - Study EMR200095-003 (N = 6 patients).
- 2 completed Phase II studies of patients with hepatocellular carcinoma (HCC)
  - Study EMR200095-004 (N = 59 patients) and
  - Study EMR200095-005 (N = 62 patients).

While the pooled safety set (referred to as POOL) includes patients treated for different types of cancers, the increased number of exposed patients (compared with VISION cohorts A + C) allows for a more comprehensive view of the safety profile of tepotinib across all clinical studies involving the proposed dose of tepotinib. The pooling strategy is supported by the fact that the safety profile across the tepotinib studies has been generally consistent. This renders the POOL relevant for the description of the safety profile of tepotinib 500 mg monotherapy in the proposed indication.

No additional safety signals have been identified in the POOL, confirming that the observed safety profile in VISION cohorts A + C is supported by the profile of the POOL. Differences observed between VISION cohorts A + C and the POOL are considered as either due to the underlying populations included in the different studies, differences in the severity of the disease, or due to the longer treatment duration in VISION cohorts A + C. Data from the POOL are described mainly to place the VISION study in context and to provide a comprehensive overview of the tepotinib safety profile.

Patients dosed at a lower or higher dose than 500 mg daily continuously or with intermittent dosing have been excluded from the POOL. Patients treated with tepotinib in combination with gefitinib (Study EMR200095-006) were also excluded from the POOL. For completeness, separate tables for patients who received lower or higher doses than 500 mg as well as patients from the EMR200095-006 study are included in the ISS of this submission.

Safety data were collected at regular intervals and in accordance with best clinical practice for the patient population under study (Section 8.2.3). The safety analyses supporting this application were comprehensive and included all grades and Grade  $\geq 3$  all-causality and

treatment-related TEAEs, TEAEs leading to permanent discontinuation, temporary discontinuation or dose modifications, serious TEAEs, and deaths. Analyses on hematology and biochemistry parameters, vital signs and ECG were also performed. Identified risks, potential risks and AEs of clinical interest were analyzed using the search strategies described in Table 43.

**Table 43: Categories and Preferred Terms for Identified and Potential Risks and AEs of Clinical Interest**

Category	MedDRA Terms
Interstitial lung disease (ILD)	SMQs: Interstitial lung disease – narrow PTs: Acute respiratory distress syndrome, Atypical pneumonia, Organising pneumonia, Pulmonary alveolar haemorrhage, Acute respiratory failure, Respiratory failure
Edema	PTs: Face oedema, Oedema, Oedema peripheral, Localised oedema, Oedema genital, Periorbital oedema, Scrotal oedema, Peripheral swelling, Abdominal wall oedema
Increased creatinine	PTs: Hypercreatininaemia, Blood creatinine increased, Blood creatinine abnormal
Hypoalbuminemia	PTs: Blood albumin abnormal, Blood albumin decreased, Hypoalbuminaemia
Amylase and lipase increased	PTs: Amylase abnormal, Amylase increased, Hyperamylasaemia Lipase abnormal, Lipase increased, Hyperlipasaemia Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, Pancreatic enzymes increased
Transaminases increased	PTs: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Transaminases increased, Transaminases abnormal, Hypertransaminasaemia, AST/ALT ratio abnormal
Hepatobiliary toxicity	SMQ: Drug related hepatic disorders – comprehensive search
Renal failure acute	SMQ: Acute renal failure – narrow
Renal failure chronic	SMQ: Chronic kidney disease – narrow
Fluid retention	SMQ: Haemodynamic oedema, effusions and fluid overload – narrow
Generalized edema	PT: Generalized edema
Pleural effusion	PT: Pleural effusion
QT prolongation	SMQ: Torsade de pointes/QT prolongation – broad search PTs: Seizure, Tonic convulsion, Clonic convulsion, Generalised tonic-clonic seizure

ALT=alanine transaminase, AST=aspartate transaminase, MedDRA=Medical Dictionary for Regulatory Activities, PT=preferred term, SMQ=standardised MedDRA query.

The safety review approach implemented in this submission is considered appropriate to support the use of tepotinib in patients with metastatic NSCLC harboring *MET*ex14 skipping alterations.

**The FDA’s Assessment:**

FDA’s clinical safety assessment of tepotinib is based primarily on data from the VISION study

and a pooled safety population of 448 patients treated with tepotinib as a single agent at the recommended dose of 450 mg once daily. The safety review included review and analysis of the clinical study report (CSR), EMD Serono's risk:benefit assessment, case report forms, selected narratives, the integrated summary of safety (ISS), and the primary datasets submitted by EMD Serono. The reviewers analyzed key safety datasets using several safety analysis queries and MedDRA based Adverse Events Diagnostics tool. Subgroup analyses were performed as necessary to further characterize the safety profile of tepotinib including specific safety issues for tepotinib.

The safety population used to inform the Adverse Reactions section (Section 6) of the USPI includes 255 patients with metastatic NSCLC harboring METex14 skipping alterations treated across Cohorts A and C of VISION, all of whom received tepotinib at a starting dose of 450 mg QD.

The pooled safety data used to inform the Warning and Precautions section of the USPI is based on a total population of 448 patients treated with tepotinib at the recommended dose of 450 mg once daily. Based on the data cutoff date of July 1, 2020, this includes 255 patients with NSCLC with METex14 skipping alterations from Cohort A (n=152) and Cohort C (n=103) of VISION; 24 patients with metastatic NSCLC with MET amplification from Cohort B of VISION; and 169 patients from four additional studies of tepotinib in patients with various solid tumors [Studies EMR-001 (n=42), EMR-003 (n=6), EMR-004 (n=59), EMR-005 (n=62)]. Two of the four additional studies (EMR-001 and EMR-003) are completed dose finding, single arm studies in patients with metastatic solid tumors; the other two studies (EMR-004 and EMR-005) are completed dose expansion studies in patients with hepatocellular carcinoma.

The data cut-off dates were January 1, 2020 for the initial SCS and July 1, 2020 for the 90-day safety update. The results presented in this review are based on the 90-day safety update data unless otherwise noted.

The Grouped Terms (GT) used in this review are listed below:

**Abdominal Pain** (GT) includes: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain, and Hepatic pain.

**Acute Kidney Injury** (GT) includes: Acute kidney injury, Azotemia, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal failure, Renal impairment, and Renal injury.

**Arrhythmia** (GT) includes: Atrioventricular block, Electrocardiogram QT prolonged, and Long QT syndrome.

**Cough** (GT) includes: Cough, Productive cough, and Upper-airway cough syndrome.

**Diarrhea** (GT) includes: Colitis, and Diarrhea.

**Dizziness** (GT) includes: Dizziness, Dizziness postural, and Vertigo.

**Dysgeusia** (GT) includes: Dysgeusia.

**Dyspnea** (GT) includes: Dyspnea, Dyspnea at rest, and Dyspnea exertional.

**Fatigue** (GT) includes: Asthenia, and Fatigue.

**Hemorrhage** (GT) includes: Conjunctival hemorrhage, Duodenal ulcer hemorrhage, Epistaxis, Gastrointestinal hemorrhage, Hematuria, Hemoptysis, Hemorrhage intracranial, Hemorrhoidal hemorrhage, Laryngeal hemorrhage, Procedural hemorrhage, Pulmonary hemorrhage, Subdural hemorrhage, Tongue hemorrhage, Upper gastrointestinal hemorrhage, and Vaginal hemorrhage.

**Headache** (GT) includes: Headache.

**Hypertension** (GT) includes: Hypertension.

**Hypotension** (GT) includes: Hypotension.

**Hypothyroidism** (GT) includes: Hypothyroidism.

**Musculoskeletal Pain** (GT) includes: Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, and Spinal pain.

**Neuropathy Peripheral** (GT) includes: Hypoesthesia, Neuralgia, Neuropathy peripheral, Paranesthesia, and Peripheral sensory neuropathy.

**Edema** (GT) includes: Eye edema, Face edema, Generalized edema, Localized edema, Edema, Edema genital, Edema peripheral, Periorbital edema, and Scrotal edema.

**Pneumonia** (GT) includes: Pneumonia, Pneumonia aspiration, and Pneumonia bacterial.

**Pneumonitis** (GT) includes: Interstitial lung disease, and Pneumonitis.

**Pyrexia** (GT) includes: Pyrexia.

**Rash** (GT) includes: Dermatitis acneiform, Dermatitis bullous, Drug eruption, Eczema, Palmar-plantar erythrodysesthesia syndrome, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Skin exfoliation, and Toxic skin eruption.

**Stomatitis** (GT) includes: Aphthous ulcer, Mouth ulceration, Mucosal inflammation, and Stomatitis.

**Urinary Tract Infection** (GT) includes: Cystitis, Escherichia urinary tract infection, Pyelonephritis acute, Urinary tract infection, and Urinary tract infection bacterial.

**Vomiting** (GT) includes: Retching, and Vomiting.

## 8.2.2. Review of the Safety Database

### Overall Exposure

#### Data:

All analyses considered patients as treated, i.e., patients were allocated to the study treatment that they received. The pooling strategy approach is described in Section 0 and has been agreed with the FDA at the pre-NDA interactions.

As of 01 January 2020, the median duration of exposure in VISION cohorts A + C was 21.9 weeks (range 0 to 159 weeks; Table 44). The median number of cycles received was 7.3, with approximately 52% (94/181) of patients having received 7 or more cycles (refer to ISS Table 12.5.1.1). The mean dose intensity (9,485.3 mg/3 weeks) corresponded to 90.3% of the target dose intensity (10,500 mg/3 weeks). Eighty-six (47.5%) patients in VISION cohorts A + C remain on treatment (refer to ISS Table 12.1.1.1).

The median duration of exposure in the POOL was 13.1 weeks, and the median number of cycles was 4.4, with approximately 37% (137/373) of patients having received 7 or more cycles (Table 44 and refer to ISS Table 12.5.1.1). Patients in VISION cohorts A + C stayed on treatment longer compared to patients enrolled in other studies in the POOL. This difference is attributable to the different phases and design of the studies included in the POOL, which were conducted in various highly advanced-stage cancer indications.

**Table 44: Summary of Drug Exposure**

	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181)	POOL (N=373)
Duration of therapy (weeks)		
Mean ± Std	29.5 ± 27.93	22.1 ± 23.54
Median	21.9	13.1
Q1; Q3	9.3; 38.3	6.0; 29.1
Min; Max	0; 159	0; 159
Cumulative dose (mg)		
Mean ± Std	88147.0 ± 83947.05	67585.5 ± 70863.80
Median	67500.0	43000.0
Q1; Q3	31500.0; 104700.0	21000.0; 87700.0
Min; Max	500; 553800	500; 553800
Dose intensity (mg/3 weeks)		
Mean ± Std	9485.3 ± 1540.31	9667.3 ± 1422.53
Median	10425.0	10500.0
Q1; Q3	8700.0; 10500.0	9383.5; 10500.0
Min; Max	4677; 10739	500; 10739
Relative dose intensity (%) category, n (%)		
< 60	10 (5.5)	13 (3.5)
≥ 60 – <80	31 (17.1)	52 (13.9)
≥ 80 – <90	13 (7.2)	30 (8.0)
≥ 90 – <110	127 (70.2)	278 (74.5)
≥ 110	0 (0.0)	0 (0.0)

Source: ISS Table 12.5.1.1.

Q1=25% Quartile, Q3=75% Quartile, SAF=safety analysis set, Std=standard deviation.

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Duration of therapy (days) is calculated as: (date of last dose – date of first dose + 1). Relative dose intensity (%) is defined as the actual dose intensity divided by the planned dose per cycle. Each cycle is defined by a 3 week period.

Most patients in VISION cohorts A + C received 500 mg tepotinib without any dose reduction (127 patients, 70.2%). For 41 (22.7%) patients, the dose was reduced to 300 mg; 26 of these patients stayed on 300 mg treatment for more than 84 days (refer to ISS Table 12.5.2.1). Of the 41 patients who were dose reduced to 300 mg, 13 patients were further reduced to 200 mg. In the POOL, most patients received 500 mg tepotinib without any dose reduction (288 patients, 77.2%). For 65 (17.4%) patients, the dose was reduced to 300 mg. A total of 32 (8.6%) patients were able to stay on 300 mg treatment for more than 84 days. Of the 65 patients who were dose reduced to 300 mg, 17 patients were further reduced to 200 mg.

The Applicant’s Position:

The overall exposure duration was sufficient to assess the safety of tepotinib. Relative dose intensity in the VISION study was high (mean dose intensity of 90.3% of the target dose intensity) and the majority of patients in VISION and the POOL had no dose reductions.

The FDA’s Assessment:

FDA agrees that the overall exposure duration was sufficient to assess the safety of tepotinib. Results are presented below for safety populations assessed by FDA. In Cohort A and C, 255 patients with MET exon 14 skipping alterations NSCLC received at least one dose of tepotinib. As shown in the table below, the median duration of treatment for patients in Cohorts A and C is 22 weeks (range 0–188).

**Table 45: Summary of exposure, safety population**

Exposure	Trial Arm		
	VISION A+C N = 255 n (%)	VISION A+B+C N = 279 n (%)	Pooled N = 448 n (%)
<b>Exposure duration (weeks) (AVAL)</b>			
Mean (SD)	31 (29)	30 (29)	24 (25)
Median (Range)	22 (0–188)	22 (0–188)	17 (0–188)
<b>Cumulative Dose</b>			
Mean (SD)	91295 (85271)	88286 (83369)	73672 (74996)
Median (Min - Max)	70000 (500 - 655300)	66500 (500 - 655300)	48900 (500 - 655300)
<b>Actual Dose Intensity</b>			

Mean (SD)	9421 (1690)	9406 (1747)	9593 (1548)
Median (Min - Max)	10456 (1050 - 10739)	10458 (500 - 10739)	10472 (500 - 10739)
<b>Relative Dose Intensity</b>			
Mean (SD)	90 (16)	90 (17)	91 (15)
Median (Min - Max)	100 (10 - 102)	100 (5 - 102)	100 (5 - 102)

Source: ADSL (Subject-Level Analysis Dataset) - 2020-09-03, ADEX

Among 448 patients who received TEPMETKO, 32% were exposed for 6 months or longer and 12% were exposed for greater than one year as shown in the table below.

**Table 46: Treatment exposure, safety population in VISION Study**

Exposure	Trial Arm		
	VISION A+C N = 255 n (%)	VISION A,B,C N=279 n (%)	Pooled N = 448 n (%)
<b>Treatment exposure (weeks)</b>			
< 26	147 (58)	164 (58)	304 (68)
26 – 52	63 (25)	68 (24)	89 (20)
> 52 – 104	36 (14)	38 (14)	46 (10)
>= 104	9 (3.5)	9 (3.2)	9 (2.0)
Less than 26 weeks (6 months)	147 (58)	164 (58)	304 (68)
At least 26 weeks (6 months)	108 (42)	115 (41)	144 (32)
At least 52 weeks (1 year)	45 (18)	47 (17)	55 (12)
At least 104 weeks (2 years)	9 (3.5)	9 (3.2)	9 (2.0)

### Relevant Characteristics of the Safety Population:

#### Data:

Demographic characteristics in VISION cohorts A + C were as expected for the study population based on the VISION inclusion criteria (median age of 72.6 years with the youngest patient being 41 years old) and geographical spread of study sites (refer to ISS Table 12.2.1.1). The patient sex in VISION cohorts A + C was balanced (female 51.4%) and a majority of patients were White (67.4%); approximately one-quarter were Asian (50 patients; 27.6%).

In the POOL, 64.6% of patients were male, reflecting a higher proportion of males in the HCC studies (EMR200095-004 and EMR200095-005). The majority of patients were White (56.3%), consistent with VISION cohorts A + C. The median age in the POOL was 68.0 years, reflecting the lower age observed in the Phase I and HCC studies. Accordingly, patients  $\geq 65$  years of age were more common in VISION cohorts A + C than the POOL (82.3% and 61.7%, respectively).

Medical history, prior and concomitant medications in VISION cohorts A + C were reflective of the predominantly elderly population with advanced cancer (refer to ISS Tables 12.3.1.1, 12.4.1.1, 12.4.2.1). Similarly, the profile in the POOL and the few differences to the VISION cohorts A + C were driven by the features of the population included in the pooled studies.

#### The Applicant's Position:

The patient characteristics in VISION cohorts A + C were as expected for the study population, i.e., predominantly elderly patients with advanced disease. Differences observed compared with the POOL were due to the variety of patient populations within the pooled studies.

#### The FDA's Assessment:

FDA agrees with EMD Serono analysis of demographics of the safety population. The characteristics of the safety population of the VISION Study are consistent with the epidemiology and natural history of patients with metastatic non-squamous NSCLC. Patients with NSCLC with MET exon 14 skipping alterations (Cohorts A and C) were older (median age: 72 years) compared to the pooled safety population (n=448, median age: 68 years).

#### **Adequacy of the Safety Database:**

##### Data:

The safety profile of tepotinib was evaluated based on the data from 373 cancer patients in the clinical program who were treated with 500 mg tepotinib once daily, with a specific focus on the 181 METex14 NSCLC patients in cohorts A + C of the VISION study. The VISION cohorts A + C SAF comprises the totality of the safety data available for tepotinib in the intended population of METex14 NSCLC and intended dosage. See Section 0 for further details.

##### The Applicant's Position:

As METex14 NSCLC is a rare and life-threatening disease with a high unmet medical need, the VISION study design, the pooling strategy, the number of patients treated with tepotinib, and the corresponding exposure are considered adequate to characterize the safety profile of tepotinib at the proposed clinical dose and provide guidance on the management of risks.

##### The FDA's Assessment:

The safety database evaluated by FDA of 255 tepotinib-treated patients with NSCLC harboring MET exon 14 skipping alterations and a pooled safety population of 448 patients is adequate to

evaluate the safety of tepotinib.

### **8.2.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **Issues Regarding Data Integrity and Submission Quality**

##### Data:

No issues were identified regarding the integrity and quality of the safety data included in this application.

##### The Applicant's Position:

The Applicant had a comprehensive quality management system in place for monitoring safety data quality across all clinical studies included in the safety assessment. Quality management methods included site audits, safety data review by qualified experts, management of data quality (site collection, site-to-Sponsor data transmission, data analysis and data summarization), and management of regulatory document quality. No issues were identified that could potentially impact data integrity, prevent adequate assessment of the data, or change the conclusions drawn.

##### The FDA's Assessment:

The data submitted was organized and adequate to perform a complete review of the safety of tepotinib. To assess the reliability and quality of the data, the clinical reviewer conducted random cross-validation of datasets with CRFs from the VISION Study; this assessment raised no concerns regarding data integrity. Overall, FDA agrees that there were no significant data quality or reporting issues identified during the review of this NDA. FDA did issue several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the NDA.

#### **Categorization of Adverse Event**

##### Data:

All analyses considered patients as treated, i.e., patients were allocated to the study treatment that they received. The analysis of AE data was based on TEAEs only, defined as AEs which emerged or worsened during the on-treatment period. In all studies, the overall on-treatment period was defined from the first dose (Day 1) of tepotinib, up to and including 30 days after the last dose of study treatment, or death, whichever occurred earlier. Deaths were captured as part of the survival follow-up after the 30-day period following the last dose. In all studies, a cycle was defined as 21 days.

AEs were coded using version 22.1 of MedDRA. The severity of the AEs (coding and grading), including laboratory/vital sign changes reported as AEs, were graded using NCI-CTCAE; the NCI-CTCAE version depended on the time of the study conduct (Version 4.0 or 4.03). Per the ISS, laboratory values were graded according to NCI-CTCAE Version 4.03.

Detailed information collected for each AE included a description of the event, duration, whether the AE was serious, severity, relationship to study drug per the Investigator, action taken with study drug, and clinical outcome. TEAEs leading to permanent discontinuation of treatment, TEAEs leading to temporary discontinuation of treatment, and TEAEs leading to dose reduction, were also summarized.

Identified risks, potential risks and AEs of clinical interest were analyzed using the search strategies described in Table 43.

The Applicant's Position:

The overall approach to evaluate the safety data in this application is considered adequate.

The FDA's Assessment:

FDA agrees with EMD Serono description of adverse events categorization. All AEs regardless of causality were collected up to 30 days after the last dose. EMD Serono's AEs were coded using MedDRA version 23.0 and were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 or 4.03.

**Routine Clinical Tests**

Data:

Clinical safety tests carried out in the VISION Study are summarized in Table 47.

**Table 47: Schedule of Safety Tests in the VISION study**

Day	Prescreening	Screening/ Baseline	Treatment Period				EoT	30 Day Safety Follow-up Visit ± 3d
			Cycle 1 Day	Cycle 2 Day ± 3d	Cycle 3, 5, 7, 9, 11, 13, etc Day ± 3d	Cycle 4, 6, 8, 10 and 12 Day ± 3d		
		-28 to -1	1	1	1	1	≤ 14d of the Last Dose	
Mandatory Written Informed Consent	X	X						
Medical and Disease History		X						
Serum Pregnancy Test (if applicable)		X						
Urine Pregnancy Test (if applicable)			X	X	X	X	X	X
Chest X-Ray		X						
Physical Examination		X	X				X	X
Weight	X	X	X		X		X	X
ECOG PS		X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X
Adverse Events Assessment <sup>a</sup>		X	X	X	X	X	X	X
Concomitant Medication/Procedure		X	X	X	X	X	X	X
12-lead ECG		X	X	X	X	X	X	X
Echocardiography		X						
Hematology and Coagulation		X	X	X	X	X	X	X
Biochemistry		X	X	X	X	X	X	X
Urinalysis		X	X					X

Source: VISION Study Protocol Version 7.0, Table 1.

ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EoT=End of Treatment.

a The AE reporting period for safety surveillance begins when the patient is initially included in the study (date of first signature of main informed consent before screening) and continues until the 30-day safety follow-up visit. Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period will be reported on an ongoing basis in the appropriate section of the eCRF. Any SAE assessed as related to tepotinib must be reported whenever it occurs, irrespective of the time elapsed since the last administration of tepotinib.

Hematology, blood chemistry, and urinalysis consisted of laboratory tests processed at local laboratories.

The Applicant’s Position:

The clinical safety tests carried out in VISION study were appropriate for the safety monitoring of the population under study, based on the known safety profile of tepotinib.

The FDA’s Assessment:

FDA agrees that the schedule of assessments in the VISION Study was adequate to monitor and assess the safety of tepotinib.

**8.2.4. Safety Results**

**Deaths**

Data:

Disease progression was the most frequent reason for death in VISION cohorts A + C and the POOL (Table 48).

**Table 48: Primary Cause of Death**

Primary Cause of Death	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
All deaths	60 (33.1)	187 (50.1)
Disease Progression	47 (26.0)	141 (37.8)
Related AE <sup>a</sup>	1 (0.6)	3 (0.8)
Unrelated AE	9 (5.0)	16 (4.3)
Other	0 (0.0)	1 (0.3)
Unknown	2 (1.1)	25 (6.7)
Missing <sup>b</sup>	1 (0.6)	1 (0.3)
Deaths up to 30 days of last dose	24 (13.3)	60 (16.1)
Disease Progression	13 (7.2)	39 (10.5)
Related AE	1 (0.6)	3 (0.8)
Unrelated AE	8 (4.4)	13 (3.5)
Unknown	1 (0.6)	4 (1.1)
Missing	1 (0.6)	1 (0.3)
Deaths up to 60 days of first dose	9 (5.0)	31 (8.3)
Disease Progression	4 (2.2)	17 (4.6)

Primary Cause of Death	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Related AE	1 (0.6)	2 (0.5)
Unrelated AE	3 (1.7)	8 (2.1)
Unknown	0 (0.0)	3 (0.8)
Missing	1 (0.6)	1 (0.3)

Source: ISS Table 12.6.19.1.1 and Listing 12.6.21.1.

SAF=Safety analysis set.

- a Patients (b) (6)
- b Patient (b) (6) had a TEAE of acute hepatic failure leading to death after the patient had withdrawn consent. Therefore, the reason for death in the eCRF is recorded as “missing”. In the absence of a reported Investigator-assessed causality and other information, a possible relationship between the event and tepotinib cannot be ruled out.

Approximately 13% of patients in VISION cohorts A + C and in the POOL had a TEAE that led to death (Table 49). In VISION cohorts A + C and the POOL, the most frequent TEAEs leading to death were in the system organ class (SOC) General disorders and administration site conditions, with disease progression and general physical health deterioration as the most frequent preferred terms (PTs; refer to the VISION CSR Section 15.3.5 for narratives on deaths due to general physical health deterioration). In VISION cohorts A + C and the POOL, TEAEs leading to death were also frequently associated with the SOCs Respiratory, thoracic and mediastinal disorders and Infections and infestations, which is in keeping with the underlying NSCLC (refer to ISS Table 12.6.17.1).

**Table 49: TEAEs Leading to Death by SOC and PT**

SOC PT	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Patients with at least one TEAE leading to death	23 (12.7)	47 (12.6)
General disorders and administration site conditions	12 (6.6)	23 (6.2)
Disease progression	7 (3.9)	17 (4.6)
General physical health deterioration	4 (2.2)	5 (1.3)
Death	1 (0.6) <sup>a</sup>	5 (1.3)
Respiratory, thoracic and mediastinal disorders	5 (2.8)	8 (2.1)
Acute respiratory distress syndrome	1 (0.6)	1 (0.3)
Acute respiratory failure	1 (0.6)	1 (0.3)
Dyspnoea	1 (0.6)	2 (0.5)
Pneumonia aspiration	1 (0.6)	1 (0.3)
Pulmonary embolism	1 (0.6)	1 (0.3)
Pulmonary haemorrhage	1 (0.6)	1 (0.3)

SOC PT	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Respiratory failure	0 (0.0)	2 (0.5)
Infections and infestations	4 (2.2)	8 (2.1)
Bacterial infection	1 (0.6)	1 (0.3)
Pneumonia	1 (0.6)	2 (0.5)
Respiratory tract infection	1 (0.6)	1 (0.3)
Sepsis	1 (0.6)	3 (0.8)
Septic shock	0 (0.0)	1 (0.3)
Systemic infection	0 (0.0)	1 (0.3)
Cardiac disorders	1 (0.6)	1 (0.3)
Cardiac failure	1 (0.6)	1 (0.3)
Gastrointestinal disorders	1 (0.6)	3 (0.8)
Ileus	1 (0.6)	1 (0.3)
Gastrointestinal haemorrhage	0 (0.0)	1 (0.3)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (0.3)
Injury, poisoning and procedural complications	1 (0.6)	1 (0.3)
Spinal fracture	1 (0.6)	1 (0.3)
Hepatobiliary disorders	0 (0.0)	2 (0.5)
Hepatic failure	0 (0.0)	2 (0.5)
Nervous system disorders	0 (0.0)	2 (0.5)
Coma	0 (0.0)	1 (0.3)
Hypoglycaemic coma	0 (0.0)	1 (0.3)
Psychiatric disorders	0 (0.0)	1 (0.3)
Assisted suicide	0 (0.0)	1 (0.3)

Source: ISS Table 12.6.17.1

PT=preferred term; SAF=Safety analysis set; SOC=System Organ Class; TEAE=Treatment Emergent Adverse Event.

a Cause of death unknown.

As of the data cutoff date of 01 January 2020, 4 patients in the POOL (2 patients in VISION and 2 patients in other studies) died due to TEAEs that were considered treatment-related.

For 1 of these patients ( (b) (6) VISION cohort A), a TEAE leading to death was not recorded in the clinical database because it occurred after the patient withdrew informed consent; the reason for death was recorded as “missing”. In the absence of a reported Investigator-assessed causality and other information, a possible relationship between the event and tepotinib cannot be ruled out.

Asymptomatic elevation in hepatic transaminases in this patient started 2.5 weeks after the start of tepotinib treatment, eventually progressing to fatal acute hepatic failure. The course is

characteristic of acute hepatitis. Negative serology excluded chronic hepatitis B, C, and HIV, but no information is available on any other investigations that might have been performed to rule out other potential causes of liver failure. This makes a proper causality assessment difficult. The negative de-challenge does not suggest a causal association between the event and tepotinib treatment.

The second VISION patient with a treatment-related, fatal TEAE was a case of acute respiratory failure and is further discussed in Section 8.2.5.1.

For a listing of all TEAEs leading to death, refer to ISS Listing 12.6.20.1. For narratives on deaths in the VISION study, refer to the VISION CSR, Section 15.3.5.

The Applicant’s Position:

Events with a fatal outcome considered related to tepotinib were infrequent, with no specific pattern. Most of the reported deaths were related to the underlying cancer disease or its progression.

The FDA’s Assessment:

**Table 50: Causes of Death in Safety Population in VISION Study and Pooled Population**

	<b>VISION A+C N=255</b>	<b>Pooled N=448</b>
	Grade 5 N (%)	Grade 5 N (%)
<b>Total Deaths</b>	87 (34)	216 (48)
Progressive disease	66 (26)	162 (36)
AE not related to treatment	14 (5)	22 (4.7)
Primary cause unknown	4 (1.6)	28 (6)
AE related to treatment	3 (1.2)	5 (0.9)
<b>Within 30 days after last dose</b>	30 (12)	66 (15)
<b>Beyond 30 days after last dose</b>	57 (22)	150 (33)

Source: ADSL (Subject-Level Analysis Dataset) - 2020-09-03

From the pooled population, 28 patients have unknown cause of death, including 19 patients from Study EMR200095-001, two from Study EMR200095-004, two from Study EMR200095-005, four from VISION Cohort A, and one from VISION Cohort B. Five of the 28 patients died in the treatment-emergent adverse event reporting period of up to 30 days after last exposure and the remaining 23 died outside of this period. Four of the five patients who died within 30 days of last exposure (Study EMR200095-001; Patients (b) (6) Study

EMR200095-004 Patient (b) (6) and VISION; Patients (b) (6) had discontinued study drug due to disease progression. The fifth patient (VISION Patient (b) (6)) died while still on treatment but cause of death was reported as unknown.

Patient (b) (6) died at home and an autopsy was not performed. The patient died one day after the most recent administration and 153 days after the first administration of tepotinib. It was noted that (b) (6) (6 days prior to death), the patient experienced increased fatigue and an increased requirement of supplemental oxygen. On the same day, a chest X ray revealed edema and furosemide was prescribed. The patient was contacted by the site and reported feeling better. Three days later the patient died at home with no further investigations or information regarding the cause of death. The Investigator reported that probable cause of death might have been an acute cardiac, cerebrovascular, or thromboembolic event. The Investigator and the Sponsor assessed the event death as not related to tepotinib.

**Table 51: Deaths within 30 Days of Last Dose**

	<b>VISION A+C N = 255</b>
<b>Adverse Events</b>	<b>30 (12)</b>
Disease progression	16 (6)
Dyspnea	1 (0.4)
Pneumonia	2 (0.8)
Spinal fracture	1 (0.4)
Electrolyte imbalance	1 (0.4)
Pulmonary embolism	1 (0.4)
Acute respiratory failure	1 (0.4)
Pneumonia aspiration	1 (0.4)
Cardio-respiratory arrest	1 (0.4)
Pulmonary hemorrhage	1 (0.4)
Respiratory tract infection	1 (0.4)
Cardiac failure	1 (0.4)
Bacterial infection	1 (0.4)
Ileus	1 (0.4)

Death within 30 days of last dose of study drug (excluding deaths due to disease progression) was reported in 14 patients in Cohorts A and C of VISION. Among the deaths in VISION Cohorts A and C, investigators and the sponsor considered three were considered due to adverse reaction, with the other deaths attributed to disease progression or underlying disease. Fatal adverse reactions occurred in one patient (b) (6) due to pneumonitis (within 30 days of the last treatment dose), one patient (b) (6) due to hepatic failure (after 30 days of the last

treatment dose), and one patient (b) (6) due to dyspnea from fluid overload (within 30 days of the last treatment dose).

FDA reviewed data from the pooled population experiencing a treatment-emergent adverse event (TEAE) leading to death along with information on the study number, study duration, date of death, end date of treatment, and reason of death with narratives from the data cut-off of July 1, 2020. FDA agrees with Applicant's assessment of three fatal adverse reactions in Cohorts A and C of VISION. Dyspnea and acute respiratory failure (due to pneumonitis) are fatal adverse reactions that occurred within 30 days of the last treatment dose. For the other 12 deaths occurring within 30 days of last dose of tepotinib reported as due to TEAE in the tables above, the reviewer concluded based on review of the narratives that these were due to either progression of disease or underlying disease / comorbidities, and these were not included in labeling as fatal adverse reactions.

A brief narrative of these 12 fatal adverse events are presented below:

**Patient** (b) (6) a 76-year-old female, diagnosed with stage 4B NSCLC (b) (6). She received first dose of tepotinib (b) (6) and on day 252, she was hospitalized after an accidental fall. She suffered a cervical vertebral luxation with spinal cord compression. On (b) (6) she became tetraparetic and underwent C4-T2 vertebral decompression and destabilization with nails and screws. On (b) (6) she went into shock and her condition deteriorated due to multiorgan failure. The patient died (b) (6).

**Patient** (b) (6) an 89-year-old female, diagnosed with stage 4 NSCLC (b) (6). On (b) (6) the patient signed the informed consent form, but on the same day, the subject was diagnosed with pulmonary embolism (Grade 2). On (b) (6) the patient was noted with new lesion in the bone and (b) (6) she was hospitalized due to cardiac failure (Grade 3). On (b) (6) the patient was discharged on the hospital and (b) (6) she was noted with a new lung lesion CT scan during an evaluation visit. On day 465, she was taken to the hospital for dyspnea with suspected pulmonary embolism. On (b) (6) 466 days after the first administration of tepotinib, the patient died. No autopsy was performed.

**Patient** (b) (6) an 87-year-old male with a history of myelodysplastic syndrome, peripheral edema, and diverticulum intestinal who was diagnosed with stage 4 NSCLC (b) (6). Day 1 of tepotinib was on (b) (6). On (b) (6) he was hospitalized for vomiting and was diagnosed with ileus, pneumonia, and sepsis. Hospitalization course is unavailable, and the patient died (b) (6). An autopsy was performed. The autopsy report provided the following results: florid and purulent pneumonia on the right with status post partial resection of right lung with adenocarcinoma. Septic parietal thrombus in the thoracic aorta. Status post laparotomy with small intestine ileus with evidence of metastasis of the pulmonary carcinoma clogging the lumen of small intestine.

**Patient** (b) (6) an 84-year-old female with a history of atrial fibrillation and breast cancer (2011) was diagnosed with stage 4 NSCLC (b) (6). She underwent breast surgery and radiation (b) (6). The patient first dose of tepotinib was (b) (6) and (b) (6) a chest X-ray revealed right lung consolidation consistent with pneumonia. She received treatment with antibiotics, but (b) (6) she presented to the hospital with a fever and was admitted for acute respiratory insufficiency secondary to bilateral severe extensive pneumonia. Chest X-ray showed extensive conflating densifications in the entire right lung field as well as in the left mid and lower field which indicated worsened pneumonia, some pleural fluid in basal fields on the right, evident bronchovascular markings accentuated in hili, atheromatous aortic knob, borderline normal width of the upper mediastinum, and thickened pleura apical on the right. the patient was given antibiotics and maximum supportive care, however no resuscitation or intensive care with ventilation was requested by the patient. On (b) (6) the patient died due to pneumonia and an autopsy was not performed.

**Patient** (b) (6) a 78-year-old male with a history of pulmonary embolism, chest tube insertion and right metastatic pleural effusion was diagnosed with stage 1A NSCLC on (b) (6). He underwent surgery and chemo-radiation (b) (6). The patient was stage 4 at the time of study entry and at screening (b) (6) a CT scan showed target lesions at right pleuropulmonary paramediastinal region and nontarget lesions at supraclavicular, mediastinal lymph nodes, right pleural pulmonary thickening, peritoneal carcinomatosis, and subcapsular liver lesions. On day 504 of tepotinib, the patient was reported with generalized edema and was treated with diuretic medications. On the same day, the edema peripheral was reported as resolved. On (b) (6) day 518 after the first administration of tepotinib, the patient visited the emergency room due to dyspnea and was diagnosed with cardiac failure (cardiac insufficiency; Grade 4) and urinary tract infection (Grade 3). The subject died (b) (6) and an autopsy was not performed.

**Patient** (b) (6) a 71-year-old female, diagnosed with stage 4B NSCLC (b) (6). Radiotherapy was administered at the brain (b) (6) without any prior chemotherapy nor surgery. At the time of screening (b) (6) a CT scan revealed metastasis in brain. On (b) (6) the patient experienced serious adverse event of dyspnea and (b) (6) she received the first dose of tepotinib. A CT scan (b) (6) showed new lesions in abdominal wall and (b) (6) showed new lesions in bone respectively. On (b) (6) day 234 days after the first dose of tepotinib, she was diagnosed with respiratory tract infection with weakness and disorientation. CT scan (b) (6) showed postsurgical changes of the left front temporal craniotomy due to metastasis resection with a reduction of the pneumocephalus at the surgical site and postsurgical edema, leaving an area of encephalomalacia which led to a minimal retractile dilation of the frontal horn of the left lateral ventricle. Minimal hematic was present at the site of the resection. On (b) (6) she presented with reduced level of consciousness, with GCS 10. An emergency cranial CT scan was performed which revealed hemorrhage at the surgical site. On (b) (6) the patient was noted with rapid respiratory deterioration and hypoxemic respiratory failure and was given oxygen therapy. Due

to respiratory deterioration and poor level of consciousness it was decided to start palliative sedation. The patient died (b) (6)

**Patient** (b) (6) a 68-year-old male with history of diabetes was diagnosed (b) (6) (b) (6) with stage 4 NSCLC with primary tumor at the upper lobe of the lung with subsite at bone [C4-C5 vertebrae]. He received the first tepotinib dose (b) (6). On (b) (6) the subject was hospitalized for traumatologic programmed surgery and underwent placement of halo brace for pathological fracture and placement of halo cervical traction. On (b) (6) the patient was noted with broncho-aspiration and pneumonia. On (b) (6) 106 days after the first dose of tepotinib, a microculture was performed which was positive for Morganella Morganii. The site of the infection was unknown. On (b) (6) the patient developed sepsis and pyrexia and respiratory failure due to the complications associated with the surgery (cervical halo placement). A tracheostomy was placed, and his clinical condition worsened. The patient died (b) (6) and an autopsy was not performed.

**Patient** (b) (6) a 73-year-old male subject with a history of aortic stenosis and hypertension was diagnosed with stage 3A NSCLC (b) (6) and underwent chemoradiation. He received his first tepotinib dose (b) (6) and (b) (6) the patient developed grade 3 pulmonary hemorrhage. A CT scan showed left lung cavity due to the underlying disease and abnormal blood vessels around the cavity of the upper lobe at the tip of the bronchial arteries. On (b) (6) transcatheter arterial embolization was performed under local anesthesia due to pulmonary hemorrhage. On (b) (6) the patient was developed a second pulmonary hemorrhage with bleeding (approximately 200 mL). The patient's general condition further deteriorated, and oxygen saturation dropped to 80%. The patient died (b) (6) and an autopsy was not performed.

**Patient** (b) (6), an 85-year-old male with history of hypertension and Parkinson's disease was diagnosed with stage 4A NSCLC at the time of study entry. The patient received the first dose of tepotinib (b) (6). On (b) (6) he complained of dyspnea and was noted with tachycardia. A CT scan showed pneumonia aspiration in right lung. The patient was treated with antibiotics, but it was reported that due to subject's decision, cardiopulmonary resuscitation was not performed, and do-not-resuscitate order was signed. On (b) (6) pneumonia aspiration was fatal, and the subject died. An autopsy was not performed.

**Patient** (b) (6), a 77-year-old female diagnosed with stage 4 NSCLC (b) (6). She received the first dose of tepotinib on (b) (6). On (b) (6) the patient experienced fatigue, weakness, and chest pain. Dehydration was reported and poor oral intake was considered as a cause of dehydration. On day 50, the patient was diagnosed with serious electrolyte imbalance. It was reported that the event electrolyte imbalance was considered as secondary to dehydration. On (b) (6) the patient died at home and an autopsy was not performed.

**Patient** (b) (6), a 64-year-old male diagnosed with stage 4B NSCLC. The patient received his first dose of tepotinib on (b) (6). On (b) (6) he experienced pneumonia that required hospitalization and treatment with antibiotics. CT scan on (b) (6) confirmed the diagnosis of pneumonia. On (b) (6) the patient died, and an autopsy was not performed.

**Patient** (b) (6), a 77-year-old male with a history of atrial fibrillation, obesity, hypertension, dyslipidemia, and diabetes mellitus was diagnosed with stage 4A NSCLC (b) (6). He received his first dose of tepotinib on (b) (6). On (b) (6) it was reported that patient's general condition deteriorated with dyspnea and loss of consciousness leading to fall. The medical emergency team was called, and cardio-respiratory arrest was reported. On (b) (6) the patient died, and an autopsy was not performed.

### **Serious Adverse Events**

#### Data:

At least 1 serious TEAE was reported for 44.2% of patients in VISION cohorts A + C, and for 43.7% of patients in the POOL (Table 52).

In VISION cohorts A + C, the most common serious TEAEs were pleural effusion (7.2%), pneumonia and disease progression (each in 4.4%), and general physical health deterioration (3.9%), which are typical of the underlying disease. Serious TEAEs assessed as treatment-related by the Investigator in  $\geq 2\%$  of patients were pleural effusion (2.8%), generalized edema (2.2%) and peripheral edema (2.2%).

In the POOL, disease progression was the most common serious TEAE (6.7%), driven by VISION cohorts A + C. Ascites occurred exclusively in the POOL (2.7%) and can be explained by the underlying disease in the HCC studies.

**Table 52: Serious TEAEs and Treatment-related Serious TEAEs by SOC and PT in ≥ 2% of Patients**

SOC PT	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
<b>Any Serious TEAEs</b>		
Patients with at least one serious TEAE	80 (44.2)	163 (43.7)
General disorders and administration site conditions	31 (17.1)	55 (14.7)
Disease progression	8 (4.4)	25 (6.7)
General physical health deterioration	7 (3.9)	9 (2.4)
Generalised oedema	5 (2.8)	5 (1.3)
Oedema peripheral	4 (2.2)	9 (2.4)
Respiratory, thoracic and mediastinal disorders	30 (16.6)	36 (9.7)
Pleural effusion	13 (7.2)	13 (3.5)
Dyspnoea	6 (3.3)	9 (2.4)
Pulmonary embolism	4 (2.2)	4 (1.1)
Infections and infestations	20 (11.0)	34 (9.1)
Pneumonia	8 (4.4)	11 (2.9)
Gastrointestinal disorders	7 (3.9)	35 (9.4)
Abdominal pain	2 (1.1)	8 (2.1)
Ascites	0 (0.0)	10 (2.7)
Renal and urinary disorders	6 (3.3)	12 (3.2)
Acute kidney injury	5 (2.8)	9 (2.4)
<b>Treatment-related Serious TEAEs</b>		
Patients with at least one treatment-related serious TEAE	24 (13.3)	40 (10.7)
General disorders and administration site conditions	10 (5.5)	15 (4.0)
Generalised oedema	4 (2.2)	4 (1.1)
Oedema peripheral	4 (2.2)	8 (2.1)
Respiratory, thoracic and mediastinal disorders	9 (5.0)	9 (2.4)
Pleural effusion	5 (2.8)	5 (1.3)

Source: ISS Tables 12.6.15.1 and 12.6.16.1.

PT=preferred term; SAF=Safety analysis set; SOC=System Organ Class; TEAE=Treatment Emergent Adverse Event.

TEAEs meeting the 2% threshold in either VISION or POOL have been included.

### The Applicant's Position:

The SAE profile mostly reflected the severity of the underlying disease.

### The FDA's Assessment:

Serious adverse reactions occurred in 45% of the 255 patients in Cohorts A and C of VISION.

Serious adverse reactions in  $\geq 2\%$  of patients included pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), general physical health deterioration (3.5%), pulmonary embolism (2%), and musculoskeletal pain (2%). The table below summarizes the SAEs reported in  $\geq 2\%$  of patients in Cohorts A and C, all cohorts in VISION, and all solid tumor populations.

**Table 53: SAEs occurring in  $>$  or  $= 2\%$  of patients**

	Cohort A+C N=255 (%)	Cohort A+B+C N=279 (%)	Pooled N=448 (%)
<b>Total pts with at least one SAE</b>	45	46	44
<b>Pleural effusion</b>	7	6	3.8
<b>Pneumonia (GT)</b>	5	6	4
<b>Edema (GT)</b>	3.9	3.9	3.6
<b>Dyspnea (GT)</b>	3.9	3.9	2.9
<b>General health deterioration</b>	3.5	3.2	2.5
<b>Pulmonary embolism</b>	2	1.8	1.1
<b>Musculoskeletal pain (GT)</b>	2	1.8	1.3

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, TRTAG, TRTEMFL, AEDECOD, AEBODSYS, ATOXGRN, AESER.

Dyspnea (GT) includes: Dyspnea.

Musculoskeletal Pain (GT) includes: Back pain, Bone pain, Musculoskeletal chest pain, and Musculoskeletal pain.

Edema (GT) includes: Generalized edema, Localized edema, and peripheral edema.

Pneumonia (GT) includes: Pneumonia, Pneumonia aspiration, and Pneumonia bacterial.

### Dropouts and/or Discontinuations Due to Adverse Effects

#### Data:

At the cutoff date of 01 January 2020, 86 (47.5%) patients in VISION cohorts A + C were still on treatment (Table 54). Other studies included in the POOL were completed by the time of the data cutoff.

Permanent treatment discontinuation was reported for 52.5% of patients in VISION cohorts A + C and for 74.5% of patients in the POOL. The proportions of patients with death and TEAEs as reasons for permanent treatment discontinuation were generally consistent between VISION cohorts A + C and the POOL. Treatment discontinuation due to disease progression was reported for 28.2% of patients in VISION cohorts A + C and 47.7% of patients in the POOL.

Study discontinuation was reported for 37.0% of patients in VISION cohorts A + C and for 63.0% of patients in the POOL, and was mainly due to death. In VISION cohorts A + C, there were no

study discontinuations due to AEs; in the POOL, 6 (1.6%) patients discontinued the study due to AEs.

**Table 54: Patient Disposition**

Characteristic	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Safety Analysis Set	181 (100.0)	373 (100.0)
Still on Treatment	86 (47.5)	95 (25.5)
Off treatment but still in follow-up	28 (15.5)	43 (11.5)
Reason Off Treatment		
All	95 (52.5)	278 (74.5)
Disease Progression	51 (28.2)	178 (47.7)
Adverse Event <sup>a</sup>	25 (13.8)	53 (14.2)
Death	13 (7.2)	17 (4.6)
Withdrew Consent	3 (1.7)	12 (3.2)
Protocol Non-Compliance	1 (0.6)	1 (0.3)
Lost to Follow-Up	0 (0.0)	1 (0.3)
Other	2 (1.1)	16 (4.3)
Reason Off Study		
All	67 (37.0)	235 (63.0)
Death	59 (32.6)	130 (34.9)
Withdrew Consent	7 (3.9)	17 (4.6)
Disease Progression	0 (0.0)	56 (15.0)
Adverse Event	0 (0.0)	6 (1.6)
Lost to Follow-Up	0 (0.0)	1 (0.3)
Other	1 (0.6)	18 (4.8)
Missing	0 (0.0)	7 (1.9)

Source: ISS Table 12.1.1.1.

SAF=safety analyses set.

a The number reflects the primary reason for discontinuation recorded on the Disposition eCRF, resulting in a difference to the number presented in Table 54, which is based on the adverse event eCRF.

The incidence of TEAEs leading to permanent discontinuation of treatment was 21.0% (38 patients). The TEAEs leading to permanent discontinuation in  $\geq 2\%$  of patients were peripheral edema (3.9%) and disease progression (2.2%; Table 55). The pattern of TEAEs leading to permanent discontinuation was similar in VISION cohorts A + C and the POOL.

Peripheral edema was the most frequently reported treatment-related TEAE leading to permanent treatment discontinuation. All cases of peripheral edema were considered treatment-related by the Investigator.

**Table 55: TEAEs Leading to Permanent Treatment Discontinuation by SOC and PT in ≥ 1% of Patients in Any Group**

SOC PT	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
<b>Any TEAEs</b>		
Patients with at least 1 TEAE leading to permanent treatment discontinuation	38 (21.0)	81 (21.7)
General disorders and administration site conditions	18 (9.9)	35 (9.4)
Oedema peripheral	7 (3.9)	14 (3.8)
Disease progression	4 (2.2)	9 (2.4)
General physical health deterioration	3 (1.7)	4 (1.1)
Respiratory, thoracic and mediastinal disorders	11 (6.1)	13 (3.5)
Dyspnoea	3 (1.7)	3 (0.8)
Pleural effusion	2 (1.1)	2 (0.5)
Pneumonitis	2 (1.1)	2 (0.5)
Infections and infestations	3 (1.7)	7 (1.9)
Pneumonia	2 (1.1)	3 (0.8)
Injury, poisoning and procedural complications	3 (1.7)	3 (0.8)
Spinal fracture	2 (1.1)	2 (0.5)
Reproductive system and breast disorders	3 (1.7)	3 (0.8)
Oedema genital	3 (1.7)	3 (0.8)
Cardiac disorders	2 (1.1)	2 (0.5)
Gastrointestinal disorders	2 (1.1)	13 (3.5)
Ascites	0 (0.0)	6 (1.6)
<b>Treatment-related TEAEs</b>		
Patients with at least 1 treatment-related TEAE leading to permanent treatment discontinuation	19 (10.5)	33 (8.8)
General disorders and administration site conditions	10 (5.5)	18 (4.8)
Oedema peripheral	7 (3.9)	14 (3.8)
Respiratory, thoracic and mediastinal disorders	7 (3.9)	7 (1.9)
Dyspnoea	2 (1.1)	2 (0.5)
Pneumonitis	2 (1.1)	2 (0.5)

Source: ISS Tables 12.6.13.1 and 12.6.14.1.

SAF=Safety analysis set; TEAE=Treatment Emergent Adverse Event.

**The Applicant’s Position:**

In VISION cohorts A + C and in the POOL, the incidence of TEAEs leading to permanent discontinuation was low – no PT had an incidence > 4%.

The most frequent TEAEs leading to permanent discontinuation were either among those already identified as tepotinib adverse reactions or consistent with the underlying diseases; no new safety signal was identified.

The FDA’s Assessment:

The table below summarizes the adverse reactions leading to tepotinib discontinuation. Adverse reactions leading to discontinuation of tepotinib occurred in 20% of patients in Cohorts A and C of VISION; the most common (>1%) were edema (5%), pleural effusion (2%), dyspnea (1.6%), general health deterioration (1.6%), and pneumonitis (1.2%).

**Table 56: AEs leading to Treatment Withdrawal > 1%**

	Cohort A+C N=255 (%)	Cohort A+B+C N=279 (%)	Pooled N=448 (%)
<b>Total pts with at least one AE leading to treatment withdrawal</b>	20	20	21
<b>Edema (GT)</b>	5	4.7	4.5
<b>Pleural effusion</b>	2	1.8	1.1
<b>Dyspnea (GT)</b>	1.6	1.4	1.1
<b>General health deterioration</b>	1.6	1.4	1.1
<b>Pneumonitis (GT)</b>	1.2	1.2	0.6

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, TRTAG, TRTEMFL, AEDECOD, AEBODSYS, ATOXGRN, AACN.

Dyspnea (GT) includes: Dyspnea.

Edema (GT) includes: Face edema, Localized edema, Edema, Edema genital, Peripheral edema, and Scrotal edema.

Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.

**Dose Interruption/Reduction Due to Adverse Effects**

Data:

The incidence of TEAEs that led to temporary treatment discontinuation was 44.2% in VISION cohorts A + C and 37.3% in the POOL (Table 57).

In VISION cohorts A + C, the most commonly reported TEAE leading to temporary discontinuation was peripheral edema, followed by blood creatinine increased and pleural effusion. No other TEAE leading to temporary discontinuation was reported in > 5% of patients in VISION cohorts A + C.

The pattern was similar between VISION cohorts A + C and the POOL, and slight imbalances in incidences could be explained by the different underlying cancer diseases.

Per protocol, temporary discontinuation of treatment was allowed for ≤ 21 days.

**Table 57: TEAEs Leading to Temporary Discontinuation by SOC and PT in ≥ 2% of Patients**

SOC PT	Tepotinib 500 mg QD – SAF	
	VISION cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
<b>TEAEs in ≥ 2% of Patients</b>		
Patients with at least 1 TEAE leading to temporary discontinuation	80 (44.2)	139 (37.3)
General disorders and administration site conditions	46 (25.4)	68 (18.2)
Oedema peripheral	32 (17.7)	41 (11.0)
Generalised oedema	7 (3.9)	8 (2.1)
Investigations	27 (14.9)	40 (10.7)
Blood creatinine increased	13 (7.2)	17 (4.6)
Alanine aminotransferase increased	6 (3.3)	9 (2.4)
Amylase increased	4 (2.2)	4 (1.1)
Aspartate aminotransferase increased	3 (1.7)	8 (2.1)
Respiratory, thoracic and mediastinal disorders	16 (8.8)	17 (4.6)
Pleural effusion	9 (5.0)	9 (2.4)
Gastrointestinal disorders	13 (7.2)	30 (8.0)
Diarrhoea	6 (3.3)	7 (1.9)
Nausea	4 (2.2)	6 (1.6)
Infections and infestations	8 (4.4)	13 (3.5)
Metabolism and nutrition disorders	6 (3.3)	14 (3.8)
Renal and urinary disorders	5 (2.8)	8 (2.1)
Nervous system disorders	4 (2.2)	6 (1.6)
Hepatobiliary disorders	1 (0.6)	8 (2.1)
<b>Treatment-related TEAEs in ≥ 2% of Patients</b>		
Patients with at least 1 treatment-related TEAE leading to temporary discontinuation	64 (35.4)	100 (26.8)
General disorders and administration site conditions	40 (22.1)	57 (15.3)
Oedema peripheral	30 (16.6)	38 (10.2)
Generalised oedema	7 (3.9)	8 (2.1)
Investigations	25 (13.8)	36 (9.7)
Blood creatinine increased	13 (7.2)	17 (4.6)
Alanine aminotransferase increased	6 (3.3)	7 (1.9)
Respiratory, thoracic and mediastinal disorders	12 (6.6)	12 (3.2)

SOC PT	Tepotinib 500 mg QD – SAF	
	VISION cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Pleural effusion	9 (5.0)	9 (2.4)
Gastrointestinal disorders	9 (5.0)	16 (4.3)
Diarrhoea	6 (3.3)	7 (1.9)
Metabolism and nutrition disorders	6 (3.3)	11 (2.9)
Renal and urinary disorders	4 (2.2)	6 (1.6)

Source: ISS Tables 12.6.11.1 and 12.6.12.1.

SAF=Safety analysis set; TEAE=Treatment Emergent Adverse Event.

TEAEs meeting the threshold in either VISION or POOL have been included.

The incidence of TEAEs requiring a dose reduction was 28.7% in VISION cohorts A + C and 21.2% in the POOL (Table 58).

Peripheral edema most often led to dose reductions in both VISION cohorts A + C (14.4%) and the POOL (9.1%), and these TEAEs were considered treatment related by the Investigator. The pattern of TEAEs leading to dose reduction was similar in VISION cohorts A + C and the POOL.

**Table 58: TEAEs Leading to Dose Reduction by SOC and PT in ≥ 2% of Patients**

SOC PT	Tepotinib 500 mg QD – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
<b>TEAEs</b>		
Patients with at least 1 TEAE leading to dose reduction	52 (28.7)	79 (21.2)
General disorders and administration site conditions	32 (17.7)	45 (12.1)
Oedema peripheral	26 (14.4)	34 (9.1)
Generalised oedema	5 (2.8)	6 (1.6)
Investigations	12 (6.6)	18 (4.8)
Blood creatinine increased	6 (3.3)	8 (2.1)
Respiratory, thoracic and mediastinal disorders	7 (3.9)	7 (1.9)
Pleural effusion	6 (3.3)	6 (1.6)
Gastrointestinal disorders	3 (1.7)	8 (2.1)
<b>Treatment-Related TEAEs</b>		
Patients with at least 1 treatment-related TEAE leading to dose reduction	51 (28.2)	75 (20.1)
General disorders and administration site conditions	32 (17.7)	44 (11.8)
Oedema peripheral	26 (14.4)	34 (9.1)
Generalised oedema	5 (2.8)	6 (1.6)
Investigations	11 (6.1)	15 (4.0)
Blood creatinine increased	6 (3.3)	8 (2.1)
Respiratory, thoracic and mediastinal disorders	6 (3.3)	6 (1.6)
Pleural effusion	5 (2.8)	5 (1.3)

Source: ISS Tables 12.6.9.1 and 12.6.10.1.

SAF=Safety analysis set; TEAE=Treatment Emergent Adverse Event.

Note: TEAEs meeting the threshold in either VISION or POOL have been included.

### The Applicant's Position:

In VISION cohorts A + C and in the POOL, TEAEs leading to temporary discontinuation or dose modification of tepotinib were either among those already identified as the most frequent tepotinib adverse reactions or were consistent with the underlying diseases; no new safety signal was identified.

### The FDA's Assessment:

Dose interruptions due to an adverse reaction occurred in 44% of patients who received tepotinib in Cohorts A and C, 44% in all patients in the VISION Study and 39% in the all pooled population. Adverse reactions requiring dosage interruption in > 2% of patients in Cohorts A and C of VISION included edema, increased blood creatinine, pleural effusion, and pneumonia as presented in the table below.

**Table 59: Adverse events requiring dose interruption by preferred term (> 2 %)**

	Cohort A+C N=255 (%)	Cohort A+B+C N=279 (%)	Pooled N=448 (%)
<b>Total patients with at least one event (%)</b>	44	44	39
<b>Edema</b>	23	22	16
<b>Increased blood creatinine</b>	6	6	4.5
<b>Pleural effusion</b>	4.3	3.9	2.5
<b>Increased ALT</b>	3.1	3.2	2.5
<b>Pneumonia</b>	2.4	2.5	1.6

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, TRTAG, TRTEMFL, AEDECOD, AEBODSYS, ATOXGRN, AACN.

Dyspnea (GT) includes: Dyspnea.

Edema (GT) includes: Face edema, generalized edema, localized edema, Edema, Edema genital, peripheral edema, and Scrotal edema.

Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.

Dose reductions due to an adverse reaction occurred in 30% of patients in Cohorts A and B of VISION. Adverse reactions requiring dosage reductions in > 2% of patients included edema, pleural effusion, and increased blood creatinine as presented in the table below.

**Table 60: Adverse events requiring dose reduction by preferred term (> 2 %)**

	Cohort A+C N=255 (%)	Cohort A+B+C N=279 (%)	Pooled N=448 (%)
<b>Total patients with at least one event (%)</b>	30	29	23
<b>Edema (GT)</b>	19	18	13
<b>Pleural effusion</b>	2.7	2.5	1.6
<b>Increased Blood Creatinine</b>	2.7	2.5	2

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, TRTAG, TRTEMFL, AEDECOD, AEBODSYS, ATOXGRN, AACN.

Edema (GT) includes: face edema, generalized edema, localized edema, edema, genital edema, and peripheral edema.

### Significant Adverse Events

#### Data and the Applicant's Position:

For adverse reactions and other important safety aspects, see following subsection.

**The FDA's Assessment:**

FDA agrees that significant AEs are described in other sections.

**Treatment Emergent Adverse Events and Adverse Reactions**

Data:

*Overview of TEAEs*

The overall incidences of TEAE categories were generally consistent between VISION cohorts A + C and the POOL (Table 61).

In VISION cohorts A + C, 96.1% of patients had  $\geq 1$  TEAE, 49.7% had Grade  $\geq 3$  TEAEs, and 44.2% had serious TEAEs. Although most patients (86.7%) had treatment-related TEAEs, treatment-related Grade  $\geq 3$  TEAEs and treatment-related serious TEAEs were reported with lower incidences of 24.3% and 13.3%, respectively.

Most of the TEAEs leading to tepotinib dose reduction or temporary treatment discontinuation were considered treatment-related. The incidence of treatment-related TEAEs leading to permanent treatment discontinuation was 10.5%. Twenty-three patients died due to a TEAE, including 1 which was considered treatment-related by the Investigator. There was an additional treatment-related TEAE leading to death by the cutoff date, which was not recorded in the clinical database (see earlier subsection on "Deaths").

**Table 61: Overview of TEAEs and Exposure-Adjusted TEAE Incidence Rates**

Event	Tepotinib 500 mg QD – SAF					
	VISION Cohorts A + C (N=181) n (%)			POOL (N=373) n (%)		
	Patients with Events n (%)	PY	Incidence Rate per 100 PY	Patients with Events n (%)	PY	Incidence Rate per 100 PY
Any TEAE	174 (96.1)	8.7	1990.4	357 (95.7)	16.4	2181.6
TEAE, NCI CTCAE Grade $\geq 3$	90 (49.7)	77.7	115.8	197 (52.8)	124.7	158.0
Related TEAE	157 (86.7)	18.9	829.5	299 (80.2)	36.5	819.3
Related TEAE, NCI CTCAE Grade $\geq 3$	44 (24.3)	93.5	47.0	92 (24.7)	148.9	61.8
TEAE leading to treatment dose reduction	52 (28.7)	81.0	64.2	79 (21.2)	138.7	57.0
Related TEAE leading to treatment dose reduction	51 (28.2)	81.6	62.5	75 (20.1)	139.9	53.6
TEAE leading to temporary treatment discontinuation	80 (44.2)	70.8	113.0	139 (37.3)	121.5	114.4

Event	Tepotinib 500 mg QD – SAF					
	VISION Cohorts A + C (N=181) n (%)			POOL (N=373) n (%)		
	Patients with Events n (%)	PY	Incidence Rate per 100 PY	Patients with Events n (%)	PY	Incidence Rate per 100 PY
Related TEAE leading to temporary treatment discontinuation	64 (35.4)	74.7	85.7	100 (26.8)	130.0	76.9
TEAE leading to permanent treatment discontinuation	38 (21.0)	110.3	34.4	81 (21.7)	176.8	45.8
Related TEAE leading to permanent treatment discontinuation	19 (10.5)	111.1	17.1	33 (8.8)	179.1	18.4
Serious TEAE	80 (44.2)	90.2	88.7	163 (43.7)	147.7	110.4
Related serious TEAE	24 (13.3)	107.8	22.3	40 (10.7)	174.4	22.9
TEAE leading to death	23 (12.7)	115.3	19.9	47 (12.6)	184.6	25.5
Related TEAE leading to death	1 (0.6)	115.7	0.9	3 (0.8)	185.5	1.6

Source: ISS Table 12.6.1.2.1.

NCI CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; PY=patient years; SAF=safety analyses set; TEAE=treatment-emergent adverse event.

Exposure adjusted incident rate is calculated as number of patients experiencing AEs divided by the sum of the individual time of all patients in the safety analysis set from start of treatment to first onset of AE or to end of treatment period for patients without AE.

Incidence rates give the number of AEs expected in 100 patients within 1 year of treatment.

### Most common TEAEs

In VISION cohorts A + C, patients had TEAEs belonging most often to the following SOCs, with incidences of  $\geq 50\%$  (Table 62):

- General disorders and administration site conditions, driven by peripheral edema.
- Gastrointestinal disorders, driven by nausea and diarrhea.
- Investigations, driven by increases of creatinine.
- Respiratory, thoracic and mediastinal disorders, driven by dyspnea.

In VISION cohorts A + C, TEAEs reported in  $\geq 20\%$  of patients on the PT level were peripheral edema, diarrhea, nausea, blood creatinine increased, dyspnea and hypoalbuminemia.

The most commonly observed TEAEs in the POOL were consistent with those in VISION cohorts A + C.

In VISION cohorts A + C, a higher incidence ( $\geq 5\%$ ) of some PTs (peripheral edema, nausea, blood creatinine increased and dyspnea) was observed compared with the POOL. The observed incidence of dyspnea may be explained by NSCLC, the underlying disease studied in VISION.

In the POOL, the higher incidence of some PTs (ascites and abdominal pain) may be explained by the high proportion of HCC patient cohorts who contributed to the POOL.

The pattern of Grade  $\geq 3$  TEAEs differs from that of the most common TEAEs, because the latter were mainly mild to moderate in severity. The most common Grade  $\geq 3$  TEAEs were peripheral edema (7.2%), pleural effusion (5.5%), disease progression and hypoalbuminemia (4.4% each; refer to ISS Table 12.6.6.1); they were typical of the advanced NSCLC population, except for peripheral edema.

**Table 62: TEAEs by SOC and PT in  $\geq 10\%$  of Patients – All Grades and Grade  $\geq 3$**

SOC PT	Tepotinib 500 mg QD – SAF			
	VISION Cohorts A + C (N=181) n (%)		POOL (N=373) n (%)	
	All Grades	Grade $\geq 3$	All Grades	Grade $\geq 3$
Patients with at least one TEAE	<b>174 (96.1)</b>	<b>90 (49.7)</b>	<b>357 (95.7)</b>	<b>197 (52.8)</b>
General disorders and administration site conditions	144 (79.6)	35 (19.3)	292 (78.3)	76 (20.4)
Oedema peripheral	112 (61.9)	13 (7.2)	204 (54.7)	21 (5.6)
Fatigue	27 (14.9)	1 (0.6)	72 (19.3)	9 (2.4)
Asthenia	25 (13.8)	3 (1.7)	47 (12.6)	8 (2.1)
Gastrointestinal disorders	115 (63.5)	10 (5.5)	260 (69.7)	45 (12.1)
Nausea	58 (32.0)	2 (1.1)	95 (25.5)	5 (1.3)
Diarrhoea	50 (27.6)	1 (0.6)	101 (27.1)	6 (1.6)
Constipation	30 (16.6)	0	71 (19.0)	2 (0.5)
Vomiting	26 (14.4)	2 (1.1)	54 (14.5)	6 (1.6)
Abdominal pain	15 (8.3)	2 (1.1)	51 (13.7)	9 (2.4)
Ascites	2 (1.1)	1 (0.6)	44 (11.8)	11 (2.9)
Investigations	96 (53.0)	23 (12.7)	183 (49.1)	62 (16.6)
Blood creatinine increased	49 (27.1)	1 (0.6)	73 (19.6)	3 (0.8)
Amylase increased	19 (10.5)	7 (3.9)	27 (7.2)	10 (2.7)
Aspartate aminotransferase increased	15 (8.3)	3 (1.7)	40 (10.7)	14 (3.8)
Respiratory, thoracic and mediastinal disorders	95 (52.5)	25 (13.8)	139 (37.3)	35 (9.4)
Dyspnoea	37 (20.4)	4 (2.2)	56 (15.0)	8 (2.1)
Pleural effusion	25 (13.8)	10 (5.5)	38 (10.2)	11 (2.9)
Cough	22 (12.2)	1 (0.6)	30 (8.0)	1 (0.3)
Metabolism and nutrition disorders	77 (42.5)	14 (7.7)	178 (47.7)	47 (12.6)

Tepotinib 500 mg QD – SAF				
SOC	VISION Cohorts A + C (N=181) n (%)		POOL (N=373) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Hypoalbuminaemia	39 (21.5)	8 (4.4)	79 (21.2)	13 (3.5)
Decreased appetite	30 (16.6)	2 (1.1)	79 (21.2)	6 (1.6)

Source: ISS Tables 12.6.2.1.1 and 12.6.6.1.

PT = preferred term; SAF=Safety analysis set; SOC=System Organ Class; TEAE=Treatment Emergent Adverse Event.

Note: TEAEs of all grades meeting the threshold in either VISION or POOL have been included.

### Adverse Reactions

The incidence of adverse reactions in VISION cohorts A + C and the POOL by any grade and by Grade ≥ 3 is presented in Table 63. The product labeling only includes the incidence of adverse reactions in VISION cohorts A + C.

The assessment of adverse reactions is provided in Section 8.2.5.

**Table 63: Adverse Reactions – All Grades and Grade ≥ 3**

Tepotinib 500 mg QD – SAF				
	VISION Cohorts A + C (N=181) n (%)		POOL (N=373) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Respiratory, thoracic and mediastinal disorders				
ILD-like events <sup>a</sup>	7 (3.9)	2 (1.1)	9 (2.4)	2 (0.5)
General disorders and administration site conditions				
Edema <sup>b</sup>	123 (68)	13 (7.2)	227 (60.9)	21 (5.6)
Generalised edema	11 (6.1)	5 (2.8)	17 (4.6)	6 (1.6)
Gastrointestinal disorders				
Diarrhoea	50 (27.6)	1 (0.6)	101 (27.1)	6 (1.6)
Metabolism and nutrition disorders				
Hypoalbuminaemia <sup>c</sup>	41 (22.7)	8 (4.4)	83 (22.3)	13 (3.5)
Hepatobiliary disorders				
ALT increase	18 (9.9)	6 (3.3)	37 (9.9)	12 (3.2)
AST increase	15 (8.3)	3 (1.7)	40 (10.7)	14 (3.8)
Investigations				

	Tepotinib 500 mg QD – SAF			
	VISION Cohorts A + C (N=181) n (%)		POOL (N=373) n (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Creatinine increase <sup>d</sup>	51 (28.2)	1 (0.6)	77 (20.6)	4 (1.1)
Amylase increase <sup>e</sup>	19 (10.5)	7 (3.9)	27 (7.2)	10 (2.7)
Lipase increase <sup>f</sup>	13 (7.2)	4 (2.2)	29 (7.8)	16 (4.3)

Source: ISS Tables 12.6.25.2.6.1, 12.6.25.2.1.1, 12.6.25.2.3.1, 12.6.2.1.1 and 12.6.6.1.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, ILD=interstitial lung disease, SAF=Safety analysis set.

- a Based on composite term search and subsequent Sponsor Assessment (refer to ISS Table 12.6.25.2.6.1, excluding 1 patient for whom information received after data cutoff does not indicate an ILD-like event).
- b Includes terms localized edema, edema peripheral, edema, edema genital, face edema, periorbital edema.
- c Includes terms hypoalbuminemia, blood albumin decreased.
- d Includes terms blood creatinine increased, hypercreatininemia.
- e Includes terms amylase increased, hyperamylasemia.
- f Includes term lipase increased for VISION and terms lipase increased, hyperlipasemia for the POOL.

#### The Applicant's Position:

The most frequently affected SOCs or PTs in VISION cohorts A + C and in the POOL are consistent with AEs reported with other MET inhibitors or with the underlying diseases.

For adverse reactions, see Section 8.2.5.

The FDA's Assessment: Overall, the incidence of Grade 3 to 4 AEs, SAEs, AEs leading to withdrawal, and AEs leading to dose modification/interruption was similar between the VISION Study and the pooled safety population.

**Table 64:** Overview of Adverse Events

	Tepotinib		
	Vision A+C N = 255 (%)	Vision A+B+C N = 279 (%)	Pooled N = 448 (%)
All-Grade AEs	246 (96)	269 (96)	433 (97)
Grade 3-5 AEs	135 (53)	150 (54)	245 (55)
Grade 1-4 AEs	216 (85)	233 (84)	380 (85)
Grade 3-4 AEs	105 (41)	114 (41)	192 (43)
Grade 3	94 (37)	102 (37)	170 (38)
Grade 4	11 (4.3)	12 (4.3)	22 (4.9)
Grade 5 AEs	30 (12)	36 (13)	53 (12)
SAEs	115 (45)	127 (46)	199 (44)
Treatment discontinuation due to AEs	52 (20)	57 (20)	93 (21)
Dose modifications (interruption and reduction) due to AEs	123 (48)	135 (48)	191 (43)
Dose interruption due to AEs	112 (44)	123 (44)	174 (39)
Dose reduction due to AEs	76 (30)	82 (29)	104 (23)

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, TRTAG, TRTEMFL, AEDECOD, AEBODSYS, ATOXGRN, AESER, AACN, AESDTH, DTHFL.

Adverse reactions reported in >10% of patients in Cohorts A and C of the VISION Study, along with Grade 3-4 incidence are presented in the table below. The most common adverse events, reported with an incidence of  $\geq 20\%$ , in patients treated with tepotinib were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea.

**Table 65: Adverse Reactions (≥ 10%) in Patients Who Received Tepotinib in VISION Study**

Adverse Reactions	TEPMETKO (N = 255)	
	All Grades (%)	Grades 3 to 4 (%)
<b>General disorders and administration-site conditions</b>		
Edema <sup>a</sup>	70	9
Fatigue <sup>b</sup>	27	1.6
<b>Gastrointestinal disorders</b>		
Nausea	27	0.8
Diarrhea	26	0.4
Abdominal Pain <sup>c</sup>	16	0.8
Constipation	16	0
Vomiting <sup>d</sup>	13	1.2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Musculoskeletal Pain <sup>e</sup>	24	2.4
<b>Respiratory, thoracic, and mediastinal disorders</b>		
Dyspnea <sup>f</sup>	20	2
Cough <sup>g</sup>	15	0.4
Pleural effusion	13	5
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	16	1.2
<b>Infections and Infestations</b>		
Pneumonia <sup>h</sup>	11	3.9

<sup>a</sup> Edema includes eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, peripheral swelling, periorbital edema, and scrotal edema.

<sup>b</sup> Fatigue includes asthenia and fatigue.

<sup>c</sup> Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, and hepatic pain.

<sup>d</sup> Vomiting includes retching and vomiting.

<sup>e</sup> Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, non-cardiac chest pain, pain in extremity, and spinal pain.

<sup>f</sup> Dyspnea includes dyspnea, dyspnea at rest, and dyspnea exertional.

<sup>g</sup> Cough includes cough, and productive cough.

<sup>h</sup> Pneumonia includes pneumonia, pneumonia aspiration, and pneumonia bacterial.

## Laboratory Findings

### Data:

A summary of laboratory analyses by worst on-treatment NCI-CTCAE toxicity grade is presented in Table 66. This table only presents patients who had a worsening of the NCI-CTCAE Toxicity Grade on treatment.

**Table 66: Laboratory Analyses - Summary by Worst On-treatment NCI-CTCAE Toxicity Grade - Only Worsening from Baseline (≥ 10% Patients in Either Group)**

Laboratory abnormalities	Tepotinib 500 mg QD – SAF							
	VISION Cohorts A + C (N=181) n (%)				POOL (N=373) n (%)			
	Sample size	Grade ≥ 1	Grade 3	Grade 4	Sample size	Grade ≥ 1	Grade 3	Grade 4
<b>Hematology</b>								
Hemoglobin (g/L) Low	172	37 (21.5)	3 (1.7)	0	358	103 (28.8)	8 (2.2)	0
Leukocytes (10 <sup>9</sup> /L) Low	172	40 (23.3)	2 (1.2)	0	358	82 (22.9)	2 (0.6)	0
Lymphocyte (10 <sup>9</sup> /L) Low	147	76 (51.7)	13 (8.8)	4 (2.7)	322	162 (50.3)	30 (9.3)	6 (1.9)
Neutrophils (10 <sup>9</sup> /L) Low	161	26 (16.1)	1 (0.6)	0	337	47 (13.9)	2 (0.6)	1 (0.3)
Platelets (10 <sup>9</sup> /L) Low	172	30 (17.4)	0	0	358	80 (22.3)	1 (0.3)	0
<b>Biochemistry</b>								
Albumin (g/L) Low	170	129 (75.9)	15 (8.8)	0	356	285 (80.1)	28 (7.9)	0
Creatinine clearance Low	170	111 (65.3)	13 (7.6)	1 (0.6)	351	250 (71.2)	25 (7.1)	3 (0.9)
Creatinine (umol/L) High	172	96 (55.8)	1 (0.6)	0	358	191 (53.4)	3 (0.8)	0
Electrolytes								
Sodium (mmol/L) Low	172	51 (29.7)	13 (7.6)	0	358	129 (36.0)	34 (9.5)	1 (0.3)
Potassium (mmol/L) Low	172	33 (19.2)	5 (2.9)	0	358	52 (14.5)	7 (2.0)	0
Potassium (mmol/L) High	172	37 (21.5)	3 (1.7)	0	358	90 (25.1)	6 (1.7)	0
Corr. Serum Calcium (mmol/L) Low	167	24 (14.4)	1 (0.6)	0	352	49 (13.9)	1 (0.3)	0
Magnesium (mmol/L) Low	169	30 (17.8)	0	0	305	45 (14.8)	1 (0.3)	0
Liver tests								
Alanine Aminotransferase (U/L) High	173	69 (39.9)	4 (2.3)	1 (0.6)	359	174 (48.5)	15 (4.2)	1 (0.3)
Aspartate Aminotransferase (U/L) High	173	57 (32.9)	3 (1.7)	1 (0.6)	359	159 (44.3)	27 (7.5)	1 (0.3)
Total Bilirubin (umol/L) High	172	9 (5.2)	1 (0.6)	0	358	75 (20.9)	13 (3.6)	2 (0.6)

Laboratory abnormalities	Tepotinib 500 mg QD – SAF							
	VISION Cohorts A + C (N=181) n (%)				POOL (N=373) n (%)			
	Sample size	Grade ≥ 1	Grade 3	Grade 4	Sample size	Grade ≥ 1	Grade 3	Grade 4
Alkaline phosphatase (U/L) High	173	83 (48.0)	2 (1.2)	0	358	169 (47.2)	15 (4.2)	0
Gamma Glutamyl Transferase (U/L) High	172	39 (22.7)	8 (4.7)	0	354	80 (22.6)	21 (5.9)	3 (0.8)
Pancreatic Enzymes								
Lipase (U/L) High	169	33 (19.5)	7 (4.1)	0	348	66 (19.0)	15 (4.3)	4 (1.1)
Amylase (U/L) High	167	43 (25.7)	10 (6.0)	1 (0.6)	348	79 (22.9)	14 (4.1)	1 (0.3)

Source: ISS Tables 12.7.2b.1.1, 12.7.2b.2.1, 12.7.6b.1.1, and 12.7.6b.2.1.

NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events, SAF=safety analysis set.

Note: The denominators in the laboratory analyses presented in this table are based on patients with a baseline and at least one on-study value. Patients who had at least one grade worsening on study are included.

### Hematology

As per the Study Protocol, patients were able to enter the VISION study with NCI-CTCAE Grade 1 hematology abnormalities. The only on-treatment hematology parameter with worst on-treatment values of Grade ≥ 3 at an incidence ≥ 5% was low lymphocytes: 8.8% of patients with Grade 3 and 2.7% of patients with Grade 4 in VISION cohorts A + C and 9.3% of patients with Grade 3 and 1.9% of patients with Grade 4 in the POOL (refer to ISS Table 12.7.2b.1.1).

Most patients with on-treatment worsening had a shift of 1 grade. No more than 4% of patients had a 2-grade shift in any hematology parameter, except for low lymphocytes (10.5% in VISION cohorts A + C). It is of note that approximately one-third of patients had a reduced lymphocyte count at baseline (63/181 in VISION cohorts A + C and 130/373 in the POOL). Refer to ISS Tables 12.7.3.1.1 and 12.7.4.1.1.

Changes in hematology parameters were mainly laboratory findings and were infrequently reported as a TEAE. Irrespective of the incidence of Grade ≥ 3 events for low lymphocytes, the incidence of TEAEs of lymphopenia and lymphocyte count decreased was very low in VISION cohorts A + C (1.1% for each PT). One patient had a Grade 3 treatment-related TEAE of lymphopenia alongside shifts in lymphocyte count decrease. TEAE data from the POOL were consistent with VISION cohorts A + C (lymphopenia: 3 patients, 0.8%; lymphocyte count decreased: 2 patients, 0.5%). Refer to ISS Tables 12.6.2.1.1 and 12.6.7.1.

### Biochemistry

Adverse events that are based on laboratory parameter increases such as increases in liver enzymes, creatinine, and amylase/lipase, or decreases such as decrease in albumin are discussed in detail in Section 8.2.5.

Biochemistry parameters with on-treatment values of Grade 3 at an incidence of  $\geq 5\%$  in either VISION cohorts A + C or the POOL were low creatinine clearance (7.6% and 7.1%, respectively), low albumin (8.8% and 7.9%, respectively), low sodium (7.6% and 9.5%, respectively), high AST (1.7% and 7.5%, respectively), high glucose (2.4% and 5.6%, respectively), high amylase (6.0% and 4.1%, respectively) and high gamma-glutamyl transferase (4.7% and 5.9%, respectively; refer to ISS Tables 12.7.6b.1.1 and 12.7.6b.2.1). Grade 4 abnormalities were infrequent.

The most frequent 1-grade shifts on treatment were not considered clinically meaningful. Two-grade shifts on treatment were observed most frequently for low albumin (34.3% in VISION cohorts A + C and 37.0% in POOL) followed by low creatinine clearance (10.5% in VISION cohorts A + C and 10.2% in POOL). Low sodium was the most frequent 3-grade shift on treatment (5.5% in VISION cohorts A + C and 7.0% in POOL). Refer to ISS Tables 12.7.8.1.1 and 12.7.8.2.1.

Regarding the observation for low sodium, there were no shifts to Grade 4 low sodium in VISION cohorts A + C and 1 such shift in the POOL. Adverse events related to sodium decrease were infrequent. Grade 3 TEAEs of hyponatremia and blood sodium decreased were reported in 4 (2.2%) and 1 (0.6%) patients, respectively. Among VISION cohorts A + C patients who experienced Grade 3 low sodium on treatment, all except 1 had a clear alternative cause (e.g., concomitant medication or a relevant concurrent condition), and only 1 event (0.6%) was considered as treatment-related. Data from the POOL were consistent with the data from VISION cohorts A + C. Refer to ISS Tables 12.6.2.1.1, 12.6.6.1, and 12.6.7.1.

#### The Applicant's Position:

No clinically meaningful changes in hematology parameters were observed with tepotinib. The lymphocyte count decreases observed are not uncommon in patients with pretreated advanced solid tumors and may also be explained by progression of the underlying disease.

Apart from the adverse reactions that are based on biochemistry parameters (Section 8.2.5), no other clinically meaningful changes in biochemistry parameters were observed in VISION cohorts A + C.

#### The FDA's Assessment:

Laboratory abnormalities were analyzed using the laboratory datasets. The table below summarizes laboratory abnormalities worsening from baseline that occurred in  $\geq 20\%$  of patients who received tepotinib in Cohorts A and C of VISION.

**Table 67: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients Who Received TEPMETKO in VISION**

Laboratory Abnormalities	TEPMETKO <sup>1</sup>	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
<b>Chemistry</b>		
Decreased albumin	76	9
Increased creatinine	55	0.4
Increased alkaline phosphatase	50	1.6
Increased alanine aminotransferase	44	4.1
Increased aspartate aminotransferase	35	2.5
Decreased sodium	31	8
Increased potassium	25	1.6
Increased gamma-glutamyltransferase	24	5
Increased amylase	23	4.6
<b>Hematology</b>		
Decreased lymphocytes	48	11
Decreased hemoglobin	27	2
Decreased leukocytes	23	0.8

<sup>1</sup> The denominator used to calculate the rate varied from 207 to 246 based on the number of patients with a baseline value and at least one post-treatment value.

### Vital Signs

#### Data:

No specific pattern in change of blood pressure and no significant changes in weight and BMI were observed in patients treated with tepotinib.

#### The Applicant's Position:

Review of vital signs did not reveal any new safety observation.

#### The FDA's Assessment:

FDA review of the Applicant's submitted ISS section 12.8 with vital signs, weight, BMI, systolic and diastolic blood pressure revealed no specific pattern in the change of blood pressure and no significant changes in weight and BMI in patients treated with tepotinib.

### Electrocardiograms (ECGs) / QT

#### Data:

In VISION cohorts A + C, based on the safety ECG recordings, a QTcF > 500 ms was recorded in 4 (2.2%) patients; 3 had an alternative explanation (i.e. pre-existing rhythm abnormalities or electrolyte abnormalities) and baseline QTcF was missing in 1 patient. A QTcF increase of at least 60 ms from baseline was noted in 10 (5.5%) patients (Table 68). For 7 of the 10 patients, the QT prolongation observed had alternative explanations, i.e., atrial fibrillation, renal function impairment or pulmonary embolism. Three patients did not have notable alternative explanations for QT prolongation other than mild electrolyte abnormalities, which may not be sufficient to account for these QTc findings.

**Table 68: Summary of On-treatment QT Prolongation Findings**

QT Prolongation Findings	Tepotinib 500 mg qd – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Any on-treatment QTcF > 500 ms	4 (2.2)	9 (2.4)
On-treatment QTcF > 500 ms (baseline ≤ 450 ms)	2 (1.1)	2 (0.5)
On-treatment QTcF > 500 ms (baseline > 450 ms - ≤ 480 ms)	0	1 (0.3) <sup>a</sup>
On-treatment QTcF > 500 ms (baseline > 480 ms - ≤ 500 ms)	0	1 (0.3) <sup>a</sup>
On-treatment QTcF > 500 ms (baseline > 500 ms)	1 (0.6) <sup>b</sup>	4 (1.1) <sup>b</sup>
On-treatment QTcF > 500 ms (baseline unknown)	1 (1.1)	1 (0.3)
On-treatment QTcF prolonged by > 60 ms	10 (5.5)	14 (3.8)

Source: ISS Tables 12.8.2.1.2.1. and 12.8.2.1.1.1.

SAF = Safety Analysis Set. Footnotes are derived from a review of the patient level data.

a 1 had baseline QTcF of > 480 ms and a single on-treatment reading that was > 500 ms; the other had relevant concurrent events and concomitant medication that provided a clear alternative cause.

b No on-treatment worsening

Nine (5.0%) patients in VISION cohorts A + C had a TEAE identified in a broad search for events of QT prolongation (Table 69): 6 cases involved the PT of ‘electrocardiogram QT prolonged’ and 1 case each involved the PTs ‘long QT syndrome’, ‘syncope’ or ‘loss of consciousness’. Case review showed that the reports of syncope and loss of consciousness did not involve QT prolongation. At the AE level, 3 patients reported multiple episodes of QT prolongation without conclusive alternative explanations for the QTc effects, but the ECGs recorded at time of these events are not available. These isolated events/findings were of a low grade, nonserious, and asymptomatic.

**Table 69: Treatment Emergent Adverse Events Related to QTc Prolongation**

Primary SOC PT	Tepotinib 500 mg qd – SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
<b>Patients with at least one event</b>	9 (5.0)	16 (4.3)
Investigations	6 (3.3)	10 (2.7)
Electrocardiogram QT Prolonged	6 (3.3)	10 (2.7)
Nervous system disorders	2 (1.1)	5 (1.3)
Syncope	1 (0.6)	3 (0.8)
Generalised tonic-clonic seizure	0	1 (0.3)
Loss of consciousness	1 (0.6)	1 (0.3)
Cardiac disorders	1 (0.6)	1 (0.3)
Long QT syndrome	1 (0.6)	1 (0.3)

Source: ISS Table 12.8.2.3.1.

PT=preferred term, SOC=system organ class.

#### The Applicant's Position:

The possible effects of tepotinib on QT prolongation have been analyzed based on multiple sources. In vitro and in vivo nonclinical data have not indicated a risk of QT prolongation with tepotinib (Section 0). Exposure-QTc analyses (integrated across studies and in VISION) did not show any evidence of a significant prolongation effect on the QTcF interval in cancer patients; the upper bound of the 90% CI of the estimated population mean  $\Delta$ QTcF at the mean  $C_{max}$  did not exceed the threshold of 10 msec at the proposed clinical dose of 500 mg tepotinib or the highest administered dose of 1,400 mg.

In VISION cohorts A + C, there were 3 TEAE cases which describe multiple episodes of QT prolongation occurring on-treatment and without conclusive alternative explanations for these QT effects. QT prolongation events in these patients were nonserious and no ECG information (QT value) at time of the events is available. In addition, 3 other patients experienced a single episode of worst shift in QTcF from baseline of > 60 ms each as an ECG finding. These cases did not involve notable alternative explanations for QT prolongation. All events were clinically asymptomatic. No events of arrhythmia (including Torsade de Pointe) secondary to the prolongation of the QTc was reported. No pattern is observed regarding time to occurrence and some events had a late onset. Cancer patients have increased susceptibility to QT prolongation.

This condition will continue to be monitored as an important potential risk for tepotinib.

#### The FDA's Assessment:

FDA concurs with EMD Serono's analysis. Exposure-QTc modeling showed no clinically relevant prolongation of the QTc interval (see Section 6.3.2.2).

## **Immunogenicity**

### Data and the Applicant's Position:

Not applicable.

### The FDA's Assessment:

FDA agrees.

## **8.2.5. Analysis of Submission-Specific Safety Issues**

### Data:

The description of the identified risks associated with tepotinib includes a comprehensive analysis based on predefined medical concepts (for definitions, see Table 43), as well as nonclinical safety observations, published literature, epidemiological data, mode of action of tepotinib and class effects, in addition to information derived from the routine pharmacovigilance monitoring and assessment of AEs.

This section focuses on VISION cohorts A + C as the relevant dataset for the proposed labeling.

All TEAE analyses for the risks presented in this section can be found under the ISS Sections 12.6.25 and 12.6.26.

### **8.2.5.1. ILD**

#### Data:

ILD-like events are considered an important identified risk for tepotinib in NSCLC patients.

ILD-like events were identified by medical review of the cases within the composite term ILD, (see Table 43). This process initially identified 8 cases in VISION cohorts A + C (refer to ISS Table 12.6.25.2.6.1). For 1 of these cases, i.e., a fatal acute respiratory distress syndrome case in cohort C (patient 302-0026), additional information was received after the data cutoff date, indicating that this is not an ILD-like event. All findings regarding this patient were consistent with disease progression and the Investigator identified the disease under study to be the cause of the AE. This case is not discussed in this document in the context of ILD.

In VISION cohorts A + C, 7 (3.9%) patients had ILD-like events (Table 63). Of the 7 cases, 4 were reported as pneumonitis, 2 as ILD (PT), and 1 as acute respiratory failure. The event of acute respiratory failure, reported as secondary to ILD in a patient enrolled in cohort A, was fatal. In this patient, tepotinib treatment was permanently discontinued upon presentation of respiratory distress. Treatment with oxygen and multiple antibiotics were administered, but high dose steroids were not. The patient had a history of radiation pneumonitis requiring steroid treatment

that was resolved at the time of inclusion in the VISION study. The event of acute respiratory failure was considered related to tepotinib by the Investigator.

Out of the 7 ILD-like cases, 3 were serious, 2 were severe (Grade  $\geq 3$ ), and 6 were considered to be treatment-related by the Investigator. Three patients recovered from their ILD-like event. The time between treatment start and the onset of the event for the 7 patients ranged from 21 to 336 days. Tepotinib treatment was discontinued permanently in 4 patients and temporarily in 3 patients due to the ILD like events.

NSCLC and advanced age are known risk factors for ILD ([Skeoch 2018](#)). Other risk factors are pre-existing ILD, prior radiation of the lung, smoking, prior exposure to anticancer therapies like taxanes or any immune checkpoint inhibitor, and male sex. All VISION cohorts A + C patients with ILD-like events had at least one of these risk factors. The patient who experienced the fatal acute respiratory failure previously had radiation pneumonitis that resolved on steroids before being enrolled into cohort A of the VISION study.

#### The Applicant's Position:

ILD has been reported with several TKIs including MET inhibitors ([Skeoch 2018](#); [crizotinib US PI](#); [brigatinib US PI](#); [osimertinib US PI](#); [capmatinib US PI](#)) with comparable incidence. The potential mechanism of MET/HGF in tissue repair and protection from fibrosis is the modulation of myofibroblasts. Myofibroblasts are a primary source of many pro-apoptotic factors that induce epithelial and endothelial cell death in lung fibrosis. It has been proposed that HGF promotes normal tissue regeneration and prevents fibrotic remodeling in the lung, heart, kidney, and liver ([Panganiban 2011](#)). In nonclinical studies, reversible alveolar macrophage aggregates in rats were observed. However, the relevance of this finding to the identified risk of ILD in patients is unclear. There was no evidence of respiratory distress or other lung alterations in any repeat-dose toxicity studies in rat and dog.

The oncologist community is well familiar with the diagnosis and management of this risk. Mitigation measures are described in the Warnings and Precautions section of the proposed labeling, and include careful monitoring in case of symptoms, treatment interruption when ILD is suspected, and treatment discontinuation and appropriate treatment (e.g., with steroids) upon ILD diagnosis.

#### The FDA's Assessment:

In the pooled safety population of 448 patients, ILD/pneumonitis occurred in 2.2% of patients. This included one fatal event of pneumonitis, which was the only Grade 3 or higher event. Four patients (0.9%) discontinued tepotinib due to ILD/pneumonitis. The incidence of ILD/pneumonitis among the 255 patients in Cohorts A and C of VISION was 3.1%.

### 8.2.5.2. Edema

#### Data:

Events of edema, excluding generalized edema, were reported at a high frequency, in 123 (68%) patients in VISION cohorts A + C (Table 63). Among those, the most frequently reported TEAE was peripheral edema (112 [61.9%] patients). Generalized edema is discussed in the following subsection.

Edema was mostly mild to moderate in severity (Grade 1 to 2), and nonserious. Median time to onset of any-grade edema was approximately 7 weeks and the median time to resolution was approximately 67 weeks; 25 (13%) patients with edema fully recovered. Importantly, edema events were managed with temporary treatment discontinuations and/or dose reductions and only infrequently led to permanent treatment discontinuation. Eight (4.4%) patients had edema events leading to permanent treatment discontinuation, of whom 7 (3.9%) had peripheral edema. Overall, 35 (19.3%) patients had temporary treatment discontinuations and 29 (16.0%) patients had dose reductions due to edema; the most frequent PT was peripheral edema (17.7% and 14.4%, respectively).

In exposure-safety analyses, no apparent relationship was found between tepotinib exposure and time to first peripheral edema event and peripheral edema severity grade. The exposure-peripheral edema analysis suggested that the risk of developing edema may have reached the plateau at very low exposure levels of tepotinib.

#### The Applicant's Position:

Edema events have been commonly reported for MET inhibitors across several indications ([Hack 2014](#); [Garajova 2015](#)) and other selective MET inhibitors ([capmatinib US PI](#); [Gan 2019](#)). Therefore, edema events may be a potential class effect for drugs that inhibit the MET pathway, although the mechanism that leads to edema during treatment with tepotinib is unclear. A possible explanation is the role of MET in vascular and lymphatic endothelial tissue. HGF and VEGF synergistically improve the function of the endothelial barrier ([Shojaei 2010](#); [You 2008](#); [Hack 2014](#)) and MET inhibition may counteract this effect. Edema events were managed within routine clinical practice with temporary treatment discontinuations and/or dose reductions; permanent treatment discontinuations were infrequent. Safety-exposure analyses indicate that temporary treatment discontinuation could be the recommended mitigation measure for edema events.

#### The FDA's Assessment:

FDA grouped terms for edema include eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, periorbital edema, and scrotal edema. In the pooled safety population of 448 patients, edema occurred in 63% of patients (Grade 3-4 edema 8%). Within Cohorts A and C of VISION (n=255), edema occurred in 70% of patients (Grade 3-4 edema 9%). Edema led to interruption of tepotinib dosing in 23% of patients, dose reduction in

19% of patients, and permanent discontinuation of tepotinib in 5%. The incidence of edema as a serious adverse reaction was 4%.

### 8.2.5.3. Generalized Edema

#### Data:

In VISION cohorts A + C, 11 (6.1%) patients had generalized edema (Table 63), which was considered related to tepotinib in 10 patients. About half of patients with generalized edema had a Grade 3 event (5/11 patients) or a serious event (5/11 patients). All but 1 of the severe or serious events, respectively, were considered treatment-related by the Investigator. Generalized edema events led to a dose reduction in 5/11 patients and to temporary treatment discontinuation in 7/11 patients. No events led to permanent discontinuation. Generalized edema resolved in 3 of the 11 patients affected; median time to resolution was 42 days.

#### The Applicant's Position:

Generalized edema had a much lower frequency than peripheral edema, but often develops in patients who already have peripheral edema. Like peripheral edema, the mechanism that leads to generalized edema during treatment with tepotinib is unclear; however, generalized edema has been reported for several MET inhibitors ([crizotinib US PI](#)). Generalized edema events were managed within routine clinical practice with temporary treatment discontinuations and/or dose reductions.

#### The FDA's Assessment:

Generalized edema was included in the grouped terms for edema in FDA's assessment; see FDA's assessment in Section 8.2.5.3.

### 8.2.5.4. Hypoalbuminemia

TEAEs of hypoalbuminemia were common in VISION cohorts A + C (41 [22.7%] patients; Table 63). Most of these events were non-severe (Grade < 3) and non-serious. Hypoalbuminemia appeared to be long-lasting but did not lead to permanent treatment discontinuation. Dose reductions or temporary discontinuations were infrequent (1.7% each). Median time to onset of any grade hypoalbuminemia was approximately 9 weeks and the median time to resolution was approximately 24 weeks. Hypoalbuminemia resolved in 10 of the 41 patients affected.

On treatment, 15 (8.8%) patients had Grade 3 low albumin as a laboratory finding. A 2-grade on-treatment shift for low albumin was observed in 62 (34.3%) patients and a 3-grade shift in 5 (2.8%) patients. See Table 66 and refer to ISS Tables 12.7.8.1.1 and 12.7.8.2.1.

The severity of hypoalbuminemia had no clear effect on the incidence of edema. Overall, a broad overlap between hypoalbuminemia and edema was observed. Due to the high proportion of patients with hypoalbuminemia at baseline (34.3%; refer to ISS Table 12.7.7.1.1) and on

treatment (85.1%), hypoalbuminemia could not be ruled out as a potentially contributing factor for edema, even though edema was also reported in 7 (3.9%) patients without hypoalbuminemia (refer to ISS Table 12.6.25.5.3.1).

There was no evidence that hypoalbuminemia is secondary to renal loss of albumin, because hypoalbuminemia was not associated with proteinuria or albuminuria. Exposure-safety analyses showed that tepotinib exposure was associated with an approximate 25% decrease in serum albumin.

#### The Applicant's Position:

Hypoalbuminemia has been reported for other MET inhibitors ([capmatinib US PI](#); [Spigel 2017](#); [Wu 2018](#)) and may represent a potential class effect. The underlying mechanism of albumin decreases under treatment with MET inhibitors is not fully understood. Hypoalbuminemia appeared to be long-lasting but did not lead to permanent treatment discontinuation. Dose reductions or temporary discontinuations were infrequent.

#### The FDA's Assessment:

The incidence of hypoalbuminemia in the 90-day safety update pooled population (n=448) is 22% (grade 3 to 4 hypoalbuminemia 4.2%). No patients permanently discontinued tepotinib due to hypoalbuminemia.

### **8.2.5.5. Increased Creatinine**

#### Data:

TEAEs of increased creatinine were common in VISION cohorts A + C (51 [28.2%] patients; Table 63). These events were mostly mild or moderate (Grade 1 or 2) and nonserious. Only 1 patient discontinued treatment permanently due to creatinine increased. Thirteen (7.2%) patients temporarily discontinued treatment and for 6 (3.3%), a dose reduction was required due to increased creatinine. Median time to onset of increased creatinine was approximately 3 weeks and the median time to resolution was approximately 10 weeks. Increased creatinine completely resolved in approximately half of the patients (23/51).

In VISION cohorts A + C, most patients had normal creatinine levels at baseline (83.4%; refer to ISS Table 12.7.7.2.1) in laboratory measurements. Only 1 patient (0.6%) had a worst on-treatment Grade 3 value for increased creatinine; no patient had a worst on-treatment Grade 4 value. Worsening on-treatment shifts of 2 grades were documented for 12 (6.6%) patients; no shifts of 3 grades were documented. See Table 66 and refer to ISS Tables 12.7.8.1.1 and 12.7.8.2.1.

In exposure-safety analyses, graphical analysis showed that treatment with tepotinib was associated with an approximate 30 µmol/L mean increase in serum creatinine in all clinical studies.

In addition, a comprehensive assessment of TEAEs linked to renal toxicity was performed by investigating the SMQs of “Acute renal failure – narrow” and “Chronic kidney disease – narrow”. These analyses did not indicate a renal toxicity risk associated with tepotinib and the events identified seemed to be confounded by other AEs, the medical history of the patients, underlying disease or concomitant medications.

#### The Applicant’s Position:

Impairment of hemodynamic stability with concurrent TEAEs of edema and low levels of albumin may explain the changes in renal function tests, without suggesting a direct kidney toxicity of tepotinib. Furthermore, the observed increases in serum creatinine are likely to be the result of the inhibition of active tubular creatinine secretion, rather than being caused by any potential drug-induced renal injury. Several drugs (e.g., crizotinib, gefitinib, imatinib, pazopanib, sorafenib, and sunitinib) have been shown to increase serum creatinine level by inhibiting OCT2 (Arakawa 2017) and MATE1 transporters (Omote 2018; Shen 2018). Tepotinib (via its metabolite) has been identified as an inhibitor of the OCT2 transporter proteins, for which creatinine is a substrate. The effects on creatinine are likely due a secondary rise in serum creatinine, attributable to the inhibition of the renal active tubular secretion component of creatinine clearance mediated by OCT2 (Mathialagan 2017). Increased creatinine infrequently led to any tepotinib treatment modifications.

#### The FDA’s Assessment:

Across Cohorts A and C of VISION, increased creatinine (all grades) occurred in 55% of patients, with grades 3 to 4 increased creatinine in only 0.4% of patients. Given the high incidence of edema, the possibility that this might be contributing to a pre-renal effect on the kidney was considered. However, this would be expected to be a potential issue primarily for patients with generalized edema, which in the 90-day safety update was reported in only 13 (6.1%) of 255 patients in Cohorts A and C of VISION, with Grade 3-4 events in 2.0% of patients. Given the relatively low incidence of generalized edema compared to the 55% incidence of increased creatinine, this was not considered to be a contributing factor for most cases of increased creatinine.

Nonclinical studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins OCT2 and MATE2, and as creatinine is a substrate of these transporters, one component of the observed increases in creatinine may be the inhibition of active tubular secretion. As discussed in FDA’s assessment in Section 6.3.2.4 of the Clinical Pharmacology portion of this review, although exposure-response analysis showed an effect of tepotinib or MSC2571109A exposure on the maximal creatinine increase (Figure 20), such observations were not associated with other clinical signs suggestive of acute or chronic renal damage.

A median increase in serum creatinine of 31% was observed 21 days after initiation of treatment with tepotinib. The serum creatinine increases persisted throughout treatment and

were reversible upon treatment completion. This information will be included in the USPI in Section 6 under the laboratory abnormalities table.

#### **8.2.5.6. Amylase and Lipase Increased**

Data:

TEAEs of amylase and lipase increases were generally asymptomatic and there were no reports of pancreatitis. In VISION cohorts A + C, 24 (13.3%) patients had increases in amylase/lipase (composite term). The incidence of amylase increased and lipase increased was 10.5% and 7.2%, respectively (Table 63); no event was serious or led to treatment discontinuation or dose modification.

On-treatment worsening to Grade 3 of increased amylase and lipase levels were documented in 10 (6.0%) and 7 (4.1%) patients, respectively. One patient (0.6%) had a Grade 4 increase in amylase. Worsening on-treatment shifts of 2 grades were documented for 10 (5.5%) patients for amylase and 5 (2.8%) patients for lipase. Worsening on-treatment shifts of 3 grades were documented for 5 (2.8%) patients for amylase and 6 (3.3%) patients for lipase. See Table 66 and refer to ISS Tables 12.7.8.1.1 and 12.7.8.2.1.

In exposure-safety analyses, no apparent relationship was found between tepotinib exposure and serum lipase, or amylase levels.

The Applicant's Position:

Increase in pancreatic enzymes have been reported with other TKIs or MET inhibitors and may represent a potential class effect (Pezzilli 2011; brigatinib US PI; capmatinib US PI). There were no permanent discontinuations of tepotinib due to amylase/lipase increases and dose modifications were infrequent.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding pancreatic enzymes. In the 90-day safety update pooled population, patients treated with tepotinib had no permanent discontinuations due to increases in amylase or lipase. Dose modifications in the pooled population for increased amylase is 1.1% and 0.7% for increase lipase.

complete this section.]

#### **8.2.5.7. ALT and AST Increase**

Data:

In VISION cohorts A + C, 20 (11.0%) had TEAEs within the composite term transaminases increased. Of those, 18 (9.9%) and 15 (8.3%) patients had TEAEs of ALT increased and AST increased, respectively (Table 63). The events were mostly non-severe and nonserious. Two patients (1.1%) patients had dose reductions and 7 patients (3.9%) discontinued temporarily due to transaminases elevation; no patient discontinued treatment permanently due to transaminases increase. Median time to first onset for ALT and AST increase of any grade was approximately 3 weeks and the median time to resolution was approximately 4 weeks. Events resolved in most patients who reported the event (15 out of 20 patients).

On-treatment worsening to Grade 3 of increased ALT and AST levels were documented for 4 (2.3%) patients and 3 (1.7%) patients, respectively, in laboratory measurements. Grade 4 abnormalities were reported in 1 (0.6%) patient for each parameter. For most patients who had ALT and AST increases in laboratory measurements, the increases were mild or moderate (Grade 1 or 2). Worsening on-treatment shifts of 2 grades were documented for 9 (5.0%) patients for ALT and 6 (3.3%) patients for AST; shifts of 3 grades were documented for 1 (0.6%) patient for ALT and 2 (1.1%) patients for AST. See Table 66 and refer to ISS Tables 12.7.8.1.1 and 12.7.8.2.1.

One patient (fatal acute hepatic failure case) had on-treatment ALT and AST increases to Grade 4 in laboratory measurements. This patient met the Hy's Law criteria as defined by findings of ALT or AST  $\geq 3 \times$  ULN and total bilirubin  $\geq 2 \times$  ULN without concurrently elevated alkaline phosphatase  $\geq 2 \times$  ULN (ALP: 1.9 ULN). The patient withdrew informed consent and died thereafter from acute hepatic failure. Details on this patient are provided in the subsection "Deaths" of Section 8.2.4.

Overall, across the clinical program, there is no evidence that tepotinib causes severe drug-induced liver injury.

In exposure-safety analyses, no evidence of an association was found between tepotinib exposure and ALT or AST levels.

In addition, an assessment of TEAEs linked to hepatobiliary toxicity was performed by investigating the SMQ of "Drug-related hepatic disorders - comprehensive search". This analysis did not reveal any additional safety findings and contributes to the conclusion that there is no indication of a risk of severe hepatotoxicity with tepotinib.

#### The Applicant's Position:

The liver/hepatobiliary system was identified as the main target organ in tepotinib repeat-dose toxicity studies (in rat and dog). However, the comprehensive analysis of TEAEs and liver function parameters do not indicate a risk of severe hepatotoxicity in patients treated with tepotinib. Increase in transaminases is frequently observed with TKIs, including the MET inhibitor capmatinib ([capmatinib US PI](#)).

#### The FDA's Assessment:

Increased ALT/AST occurred in 13% of patients treated with tepotinib in the pooled population

(n=448). Grade 3 or 4 increased ALT/AST occurred in 4.2% of patients; the median time-to-onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178). A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). Three patients (0.7%) discontinued tepotinib due to increased ALT/AST. Given the incidence of AST/ALT elevations and the occurrence of a fatal adverse reaction, hepatotoxicity will be included in the USPI for tepotinib.

#### **8.2.5.8. Diarrhea**

##### Data:

In VISION cohorts A + C, diarrhea was one of the most frequent TEAEs; diarrhea occurred in 50 (27.6%) patients (Table 63) and considered related to tepotinib in 36 (19.9%) patients. Diarrhea was mostly mild to moderate in severity and nonserious and led to permanent treatment discontinuation in 1 (0.6%) patient.

##### The Applicant's Position:

Diarrhea is also observed with other TKIs and MET inhibitors ([crizotinib US PI](#); [capmatinib US PI](#)). Tepotinib dose modifications due to diarrhea were infrequent.

##### The FDA's Assessment:

In the 90-day safety update, diarrhea occurred in 27% of patients in VISION Cohorts A and C. Grades 3 to 4 diarrhea occurred 0.4% of patients and permanent discontinuation due to diarrhea occurred in 1 (0.4%) patient.

#### **8.2.5.9. Pleural Effusion**

##### Data:

In VISION cohorts A + C, pleural effusion was reported in 25 patients (13.8%) and considered related to tepotinib in about half of the patients (13 out of 25 patients). Grade  $\geq 3$  events and serious events were reported in 10 and 13 patients, respectively, and 2 patients permanently discontinued tepotinib.

##### The Applicant's Position:

Pleural effusion is a known comorbidity in patients with NSCLC. However, it is unclear whether the high incidence of pleural effusion is related to the underlying population with NSCLC harboring *MET*ex14 skipping alterations or part of a fluid retention syndrome, as edema (mainly peripheral but also generalized edema) is associated with tepotinib. Therefore, pleural effusion was classified as an important potential risk.

##### The FDA's Assessment:

In the 90-day safety update, pleural effusion occurred in 13% of patients in VISION Cohorts A and C. Grades 3 to 4 pleural effusion occurred 5% of patients. Pleural effusion was categorized as a serious adverse reaction in 7% of patients and led to permanent discontinuation of tepotinib in 2% of patients. Dosage interruptions and dose reductions due to pleural effusion occurred in 4.3% and 2.7% of patients, respectively. The incidences of pleural effusion as a serious adverse reaction and as an adverse reaction leading to discontinuation, dose interruption, or dose reduction of tepotinib are presented in the Adverse Reactions section of the USPI for tepotinib.

#### **8.2.5.10. QT Prolongation**

See subsections ECG / QT under Section 8.2.4.

#### **8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

##### Data and the Applicant's Position:

Patient reported outcomes are described in Section 8.1.2.

##### The FDA's Assessment:

Refer to section 8.1.2 further above. These clinical outcome assessments were not designed to inform safety/tolerability.

#### **8.2.7. Safety Analyses by Demographic Subgroups**

##### Data:

Tepotinib safety data were examined for effects of:

- intrinsic factors of age, sex, race, BMI, ECOG status, renal function and hypertension, and
- extrinsic factors of prior platinum-based chemotherapy for metastatic disease, line of therapy, prior immunotherapy, and nicotine consumption.

The number of patients per subgroup was limited and no definite conclusion can be made. However, overall, there were no clinically relevant differences observed in the safety of tepotinib across the defined subgroups.

The median age of the population enrolled in VISION cohorts A + C was 72.6 years, with the following breakdown by age for the subgroup analysis: < 65 years old (N=32), ≥ 65 to < 75 years old (N=70), ≥ 75 to < 85 years old (N=65), and ≥ 85 years old (N=14). Overall, no difference in safety was reported between elderly patients and younger patients.

The safety profile of tepotinib in patients treated with prior platinum-based chemotherapy for metastatic disease was consistent with the safety profile derived from all patients in VISION cohorts A + C, including all identified and potential risks. No additional safety findings were identified.

Potential DDIs involving tepotinib are discussed in Section 6. The safety aspect of potential DDIs between tepotinib and drugs which are substrates or inhibitors of dedicated drug transporters were evaluated by reviewing relevant AEs known to be associated with these drugs and assessed in patients having received one of these drugs vs. those who did not. These analyses showed that the safety profile of transporter substrates was not affected by coadministration of tepotinib, and concomitant use of P-gp inhibitors had no impact on the tepotinib safety profile.

Subgroup analyses are provided in ISS Section 12.6.27.

The Applicant's Position:

Overall, there were no clinically relevant differences observed in the safety of tepotinib across the defined subgroups.

The FDA's Assessment:

The median age of the 90-day safety update population (n=255) enrolled in VISION Cohorts A and C was 72 years, with 79% of patients 65 years or older and 43% of patients 75 years or older. The following is a breakdown by age VISION Cohorts A and C: < 65 years old (N=53), ≥ 65 to < 75 years old (N=93), ≥ 75 to < 85 years old (N=89), and ≥ 85 years old (N=20). An overview of AEs by age for the subgroups of patients < 75 years of age and ≥ 75 years of age is presented in Table 70. The incidences of Grade 3-4 AEs, SAEs, and AEs leading to dose interruption, dose reduction and treatment discontinuation were higher in the subgroup of patients ≥ 75 years old. The majority of Grade 3-4 AEs in both subgroups were Grade 3 events.

**Table 70: Adverse Events by Age in VISION Cohorts A and C**

	Subgroups by Age	
	<75 years (n=146)	≥75 years (n=109)
All Grade AEs, %	98	94
Grade 3-4 AEs, %	35	50
Grade 3, %	32	44
Grade 4, %	3.4	5.5
SAEs, %	38	54
Dose interruption due to AEs, %	38	52
Dose reduction due to AEs, %	25	37
Treatment discontinuation due to	16	27

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, AAGEGR1, TRTEMFL, AEDECOD, AEBODSYS, ATOXGRN, AESER, AACN, AESDTH, DTHFL

### 8.2.8. Specific Safety Studies/Clinical Trials

#### Data and the Applicant's Position:

There was no specific study or clinical trial that was conducted to evaluate a specific safety concern.

#### The FDA's Assessment:

Not applicable.

### 8.2.9. Additional Safety Explorations

#### **Human Carcinogenicity or Tumor Development**

##### Data:

For tepotinib, human carcinogenicity or tumor development studies were not conducted per ICH S6, ICH S1, and ICH S9.

##### The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

**Human Reproduction and Pregnancy**

Data:

There are no clinical data on the use of tepotinib in pregnant women. Studies in animals have shown teratogenicity (Section 5). Based on the mechanism of action and findings in animals, tepotinib can cause fetal harm when administered to pregnant women.

No data are available showing a secretion of tepotinib or its metabolites in human milk or an effect on the breast-fed infant or milk production.

The Applicant's Position:

The proposed labeling includes a statement that females of reproductive potential or male patients with female partners of reproductive potential should be advised of the potential risk to a fetus, and breastfeeding should be discontinued during treatment with tepotinib and for at least 1 week following the final dose. The proposed labeling also advises females of reproductive potential to use effective contraception and males with female partners of reproductive potential to use a barrier method for contraception during tepotinib treatment and for at least 1 week following the final tepotinib dose.

The FDA's Assessment:

Females of reproductive potential or males with female partners of reproductive potential are advised to use effective contraception during treatment with TEPMETKO and for one week after the final dose.

**Pediatrics and Assessment of Effects on Growth**

Data and the Applicant's Position:

Not applicable. See Section 10.

The FDA's Assessment:

Not applicable.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Data:

One potential overdose was reported in VISION cohorts A + C. There were no associated AEs with this observation.

No studies have been conducted to evaluate the abuse potential of tepotinib. There is no evidence that suggests a risk of dependence on tepotinib and given the nature of the drug, no potential for abuse is expected.

No studies have been conducted to evaluate the withdrawal and rebound potential of tepotinib. There is no evidence that suggests a risk for withdrawal or rebound with tepotinib.

The Applicant's Position:

No AEs related to overdose, abuse or withdrawal of tepotinib were reported. Due to its mechanism of action, the potential for abuse, withdrawal and rebound of tepotinib is considered very low.

The FDA's Assessment:

FDA agrees with EMD Serono's position.

### **8.2.10. Safety in the Postmarket Setting**

#### **Safety Concerns Identified Through Postmarket Experience**

Data and the Applicant's Position:

Tepotinib received regulatory approval in Japan for the treatment of patients with unresectable, advanced or recurrent NSCLC with *MET*ex14 skipping alterations in March 2020. Tepotinib is not yet approved anywhere else in the world.

Tepotinib was launched in Japan on 01 June 2020. Up to 09 June 2020, no spontaneous AE in the postmarketing setting has been received.

The FDA's Assessment:

Postmarket safety information is limited as tepotinib has been marketed only in Japan with launch in June 2020.

#### **Expectations on Safety in the Postmarket Setting**

Data:

Not applicable.

The Applicant's Position:

The safety assessment of tepotinib is considered adequate in the context of the proposed indication comprising a rare disease with high unmet need.

The FDA's Assessment:

The review team determined that a REMS is not required to ensure safe and effective use of tepotinib. Tepotinib will be prescribed by oncologists who are trained on how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance

with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

### 8.2.11. Integrated Assessment of Safety

#### Data:

Adverse reactions of tepotinib include ILD (as an important identified risk); edema, generalized edema, increased creatinine, hypoalbuminemia, increase in ALT and AST, diarrhea, increase in amylase and lipase. Important potential risks for which no causal relationship with tepotinib has been established include pleural effusion and QT prolongation.

In summary, the following AEs and laboratory parameter findings were observed in VISION cohorts A + C:

- Peripheral edema was the most frequently reported TEAE (61.9%). Edema has been consistently reported with other MET inhibitors and may be considered a class effect.
- TEAEs and treatment-related TEAEs were primarily Grade 1 or 2 in severity.
- A total of 60 (33.1%) patients died. Most deaths were due to progression of the disease; 23 (12.7%) patients had TEAEs leading to death, including 1 treatment-related acute respiratory failure, secondary to ILD. One additional patient (not included in the 23) had a TEAE of acute hepatic failure leading to death.
- The most common serious TEAEs were pleural effusion (7.2%), pneumonia and disease progression (each in 4.4%), and general physical health deterioration (3.9%). These events are typical for the underlying disease.
- The incidence of TEAEs leading to permanent discontinuation of treatment (21.0%) indicates a good tolerability for tepotinib. The most common TEAEs leading to permanent discontinuation were peripheral edema (3.9%) and disease progression (2.2%).
- The most common TEAEs leading to temporary discontinuation were peripheral edema (17.7%), blood creatinine increased (7.2%), and pleural effusion (5.0%). Those leading to dose reduction were peripheral edema (14.4%), pleural effusion (3.3%), and blood creatinine increased (3.3%).
- Review of clinical laboratory values, and vital signs did not reveal any additional safety findings.
- The safety of tepotinib was consistent across the subgroups analyzed.

#### The Applicant's Position:

Tepotinib, administered as monotherapy at a dose of 500 mg once daily in the pivotal VISION study, was associated with a tolerable and manageable safety profile in patients with advanced NSCLC harboring *MET*ex14 skipping alterations. The risks associated with tepotinib are mostly linked to the pharmacological class and have been reported with other MET inhibitors or with TKIs. The Sponsor considers that the risks can be managed with dose modifications, routine care and guidance provided in the labeling, and that no further mitigation measures are needed.

The FDA's Assessment:

The safety database for this NDA includes 448 patients with solid tumors who were treated with tepotinib at the recommended dose of 450 mg once daily, including 255 patients with NSCLC harboring *MET*ex14 skipping alterations from the VISION study. Among the 255 patients in Cohorts A and C of VISION, permanent discontinuation of tepotinib due to adverse reactions occurred in 20% of patients, 44% of patients had tepotinib dosing interrupted for adverse reaction, and dose reductions due to adverse reactions occurred in 30% of patients. The most common adverse reactions (incidence  $\geq 20\%$ ) were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea. The safety issues considered significant and serious enough to warrant inclusion in the Warnings and Precautions section of the USPI for tepotinib are interstitial lung disease/pneumonitis and hepatotoxicity.

## SUMMARY AND CONCLUSIONS

### 8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues in the application. While the Applicant sought approval for patients who received prior-platinum therapy and patients who were platinum-naïve, FDA considered approval in the previously treated and treatment-naïve populations, as these populations were considered most clinically relevant. The indication of tepotinib for the treatment of adult patients with metastatic NSCLC harboring *MET* exon 14 skipping alterations is mainly supported by non-randomized cohorts with 83 patients in the previously treated group and 69 patients in the treatment-naïve group of the VISION study.

### 8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the data in the VISION study, for patients with NSCLC harboring *MET* exon 14 skipping alterations (69 patients in the treatment-naïve setting and 83 patients in the previously treated setting), tepotinib demonstrates a clinically meaningful ORR and duration of response. The estimated ORR as assessed by BICR in the treatment-naïve setting was 43% (95% CI: 32, 56) and

in the previously treated setting was 43% (95% CI: 33, 55). The median duration of response is 10.8 (6.9, NE) months in the treatment-naïve population and 11.1 (9.5, 18.5) months in the previously treated population.

While the ORR in the treatment-naïve population did not exceed that observed with available therapy of anti-PD-(L)1 antibody in combination with chemotherapy, the differing safety profile and option for treatment with a single agent administered orally make this a valuable treatment option for treatment-naïve patients. When considered in this context, the ORR and durable responses observed with tepotinib are reasonably likely to predict clinical benefit indicating tepotinib provides a meaningful therapeutic benefit, even for treatment-naïve patients.

To obtain additional efficacy data to confirm the clinical benefit of tepotinib in treatment-naïve and previously treated patients with NSCLC harboring MET exon 14 skipping alterations, FDA recommends that EMD Serono submit reports, including datasets, that further characterize the clinical benefit of capmatinib in at least 130 patients who are treatment-naïve after all responders have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first) and from at least 143 patients who have been previously treated with systemic therapy after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first) to provide a more precise estimation of the BICR-assessed ORR and DOR. These patient populations will include the patients comprising the primary efficacy analysis population for this review.

The safety data set included 448 patients with solid tumors who were treated with tepotinib at the recommended dose, and this includes 255 patients from Cohorts A and C from the VISION study. The most common adverse events associated with tepotinib treatment were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea. Most adverse events were grade 1 or 2 and managed by study drug reduction and/or interruption. Serious adverse reactions occurred in 45% of patients who received tepotinib; however, the serious risks are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of tepotinib product labeling. Most discontinuations were attributed to disease progression from the underlying cancer and the rate of permanent discontinuation of tepotinib due to adverse events was 20%. The adverse reaction profile is acceptable when assessed in the context of clinical benefit observed and the life-threatening nature of metastatic NSCLC.

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for accelerated approval and provides evidence of the effectiveness of tepotinib as a single agent in patients with NSCLC harboring MET exon 14 skipping alteration in the treatment-naïve and previously treated settings. The reviewers recommend granting accelerated approval of tepotinib for the following indication: "TEPMETKO is indicated for the

treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.”

X

X

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Primary Statistical Reviewer

Statistical Team Leader

X

X

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Primary Clinical Reviewer

Clinical Team Leader

## 9 Advisory Committee Meeting and Other External Consultations

### The FDA's Assessment:

The division did not refer this application to an advisory committee because the application did not raise significant public health questions on the role of tepotinib in the proposed indication. The application also did not raise significant safety or efficacy issues.

## 10 Pediatrics

### The Applicant's Position:

On August 5, 2016 EMD Serono submitted the initial pediatric study plans for tepotinib. FDA issued a letter of agreement to the initial Pediatric Study Plan (iPSP-1) on September 2, 2016 for both proposed indications included in the iPSP. On November 8, 2019, EMD Serono submitted an amendment to the agreed iPSP (Amended Agreed iPSP-2) for tepotinib for the treatment of patients with advanced NSCLC whose tumors harbor *MET*ex14 skipping alterations. This amended iPSP-2 informed FDA of EMD Serono's intent to request a full pediatric waiver of the PREA requirement to provide data from pediatric studies for ages 0 through 17 years old (neonates, infants, children, adolescents). This is based on tepotinib having an extremely limited applicability to pediatrics due to the pathophysiology of the disease occurring, for the most part, in the adult population. The NSCLC indication is included in the FDA Guidance list of adult-related conditions that may be candidates for a disease specific waiver. FDA issued an Amended Agreed iPSP Agreement on December 17, 2019.

### The FDA's Assessment:

The FDA granted tepotinib orphan designation for treatment of NSCLC with MET genomic tumor aberrations in October 26, 2020. Because tepotinib has orphan drug designation for NSCLC it is exempt from the PREA requirement to conduct a pediatric assessment [PREA section 505B(a)(a)(A)] and no pediatric studies have been conducted in NSCLC.

## 11 Labeling Recommendations

Data:

This is an original application. Please see annotated label in Module 1.14.1.2 for proposed labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
1 INDICATIONS AND USAGE	(b) (4)	Reworded the indication to "adult patients with metastatic NSCLC harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.  Removed the statement, (b) (4)
2. DOSAGE AND ADMINISTRATION 2.1 Patient Selection for METex14 Skipping Alterations	--	Based on very limited data for T-L+ patients, added the following statements: Testing for the presence of MET exon 14 skipping alterations in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If an alteration is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.  Added the statement, An FDA-approved test for

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
		detection of MET exon 14 skipping alterations in NSCLC for selecting patients for treatment with TEPMETKO is not available.
2.2 Recommended Dosage	450 mg TEPMETKO once daily with food.	Removed the (b) (4) statement as it is not required or recommended in section 2.  Added instructions to take TEPMETKO approximately the same time every day and not to make up a missed dose within 8 hours of next scheduled dose.  Added instructions for patients to take the next dose of TEPMETKO at the scheduled time if vomiting occurs after taking a dose of TEPMETKO and permanently discontinue TEPMETKO in patients who are unable to tolerate 225 mg orally once daily.
2.3 (b) (4)	Dose reduction to 225 mg tepotinib and management table for any adverse reactions grade $\geq$ (b) (4) and ILD, respectively.	Modified Table 1 (recommended dose modifications) to include dose modification recommendations for increased ALT and/or AST without increased total bilirubin, for increased ALT and/or AST with increased

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
		total bilirubin in the absence of cholestasis or hemolysis, and for increased total bilirubin without concurrent increased ALT and/or AST. Also modified other adverse reactions to provide more specific guidance.
3. DOSAGE FORMS AND STRENGTHS	--	Deleted the (b) (4) statement as it is not required in section 3.
4 CONTRAINDICATIONS	--	--
5 WARNINGS AND PRECAUTIONS 5.1 Interstitial Lung Disease/Pneumonitis	Based on clinical findings in the VISION study EMD Serono proposes a warning and precautions on the AR ILD.	Modified to reflect data for a pooled safety population of 448 patients (see below). Added number of patients who required permanent discontinuation for this adverse reaction and deleted information (b) (4)
5.2 Hepatotoxicity	...	Added hepatotoxicity as an adverse reaction along with a description of the risk mitigation strategies.
5.3 Embryo-Fetal Toxicity	Embryo-fetal development studies revealed embryo-fetal toxicity (malformations).	Revised wording to be precise regarding the timing of contraception following the final dose of TEPMETKO.
(b) (4)		

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
		(b) (4)
6 ADVERSE REACTIONS	--	<p>Modified the pooled safety population used to inform Warnings &amp; Precautions (Section 5) to include 448 patients with solid tumors who received tepotinib 450 mg QD (in place of (b) (4) (b) (4) initially proposed by the Applicant). Included a description of TEPMETKO exposure in 448 patients treated with TEPMETKO.</p> <p>Modified safety population for the data presented in Section 6 to include all 255 patients with metastatic NSCLC with METex14 alterations who received tepotinib 450 mg QD in VISION (in place of (b) (4) (b) (4) initially proposed by the Applicant).</p> <p>Modified tables to include grades 1-4 and grades 3-4 adverse reactions and list</p>

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
		<p>categories in decreasing order.</p> <p>Included a description of serious adverse reactions, permanent discontinuation, dosage interruptions, and dose reductions.</p> <p>(b) (4)</p> <p>created a separate laboratory abnormalities table (Table 3).</p>
<p>7 DRUG INTERACTIONS</p> <p>7.1 Effect of Other Drugs on TEPMETKO</p>	--	<p>Added a description of strong CYP3A Inhibitors based on safety risk and PMR.</p> <p>Added a description of strong CYP3A inducers based on potential reduction on efficacy and PMC.</p> <p>Removed (b) (4)</p>
<p>7.2 Effect of TEPMETKO on Other Drugs</p>	--	<p>Revised P-gp substrates information to be consistent with current labeling practice.</p>

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
(b) (4)		
8 USE IN SPECIFIC POPULATIONS	Advise of the potential risk to a fetus.	--
8.1 Pregnancy		
8.2 Lactation and 8.3 Females and Males of Reproductive Potential	Instructions to use contraception during treatment and not breastfeed for at least one week following the final dose.	Minor revision to wording to be consistent with recently approved labeling.
8.4 Pediatric Use	--	--
8.5 Geriatric Use	--	Revised to include percentage of patients 75 years or older to be consistent with the regulation and most other labeling.
8.6 Hepatic Impairment	--	--
8.7 Renal impairment	--	--
(b) (4)	--	--
11. DESCRIPTION	--	--
12 CLINICAL PHARMACOLOGY	--	Removed information that can be considered

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
12.1 Mechanism of Action		promotional and not assessed.
12.2 Pharmacodynamics	Clinical findings and results of an exposure-QTc analysis are provided.	Removed statements that appear promotional.
12.3 Pharmacokinetics	--	Modified text per recent food effect guidance.
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	--	Removed redundant information.
(b) (4)		
14 CLINICAL STUDIES	The efficacy results by IRC of the primary endpoint and the main secondary endpoints (duration of response) are given for the ITT.	<p>Added a description of TEPMETKO administration with major (ORR) and additional efficacy outcome measure (DoR) and edited study description in format consistent with usual labeling practice.</p> <p>Revised the efficacy population analysis to consist of 69 treatment-naïve patients and 83 previously treated patients.</p> <p>Removed the (b) (4) information as this information is not required in Section 14.</p>

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
SECTION	Applicant's Proposed Labeling	FDA's proposed Labeling
		Removed statements <span style="float: right;">(b) (4)</span>  Modified the description regarding how MET exon 14 skipping alterations were prospectively determined (using central laboratories employing either a PCR-based or next-generation sequencing-based clinical trial assay using tissue (58%) and/or plasma (65%) samples).

The Applicant's Position:

The Applicant considers that the proposed labeling adequately reflects the posology, as well as the pharmacological, efficacy and safety profile of tepotinib and includes all the necessary advice for the use of the drug.

The FDA's Assessment:

The agreed upon labeling adequately reflects the pharmacological, efficacy, and safety profile of tepotinib and includes all the necessary advice for use of the drug.

## 12 Risk Evaluation and Mitigation Strategies (REMS)

### The FDA's Assessment:

The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of tepotinib for the indicated population. Recommendations for the safe and effective use of tepotinib are made in labeling and a Patient Package Insert. There are no additional risk management strategies required beyond the recommended labeling. Although tepotinib can cause severe/serious toxicity, it will be prescribed by oncologists who, by training, understand how to monitor and manage such serious toxicities.

## 13 Postmarketing Requirements and Commitment

### The FDA's Assessment:

EMD Serono has agreed to the following post marketing requirements (PMR) and post-marketing commitments (PMC):

#### **Clinical PMR:**

Submit the final reports including datasets from clinical studies to confirm and further characterize the clinical benefit of tepotinib for the treatment of patients with non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping alterations who are treatment-naïve and who have previously received systemic therapy, by providing a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response. This report will contain data from patients with NSCLC harboring MET exon 14 skipping alterations; data from at least 130 patients who are treatment naïve, after all responders have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first); and from at least 143 patients who have been previously treated with systemic therapy, after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first).

Final Report Submission: 04/2023

#### **Clinical Pharmacology PMR:**

Conduct a drug interaction study to evaluate the effect of itraconazole on the single dose pharmacokinetics of tepotinib to assess the magnitude of increased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 and P-gp inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions."

Draft Protocol Submission: 07/2021

Final Protocol Submission: 09/2021

Study Completion: 03/2022

Final Report Submission: 09/2022

#### **Clinical Pharmacology PMC:**

Conduct a drug interaction study to evaluate the effect of rifampin on the single dose pharmacokinetics of tepotinib to assess the magnitude of decreased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 inducer and moderate CYP2C8 inducer. Design and conduct the trial in

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accordance with the FDA Guidance for Industry titled “Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.”

Final Report Submission: 07/2022

**Clinical PMC:**

Submit a summary of the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of tepotinib for patients diagnosed with non-small cell lung cancer, whose tumors harbor MET exon 14 skipping. The results of the validation study may inform product labeling.

**Final Report Submission: 01/2022**

**14 Division Director (DHOT) (NME ONLY)**

**X**

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**15 Division Director (OCP)**

**X**

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**16 Division Director (OB)**

**X**

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**17 Division Director (Clinical)**

**X**

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**18 Office Director (or designated signatory authority)**

*This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.*

X

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## 19 Appendices

### 19.1. References

#### The Applicant's References:

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The FDA's References:

Not applicable.

## **19.2. Financial Disclosure**

The Applicant's Position:

In accordance with 21 CFR 54, EMD Serono, Inc. submitted a financial disclosure certification document in Module 1.3.4. The document includes a table listing all investigators who

participated in the covered study supporting NDA 214096; the table indicates for each investigator whether they have provided a Certification (FORM 3454), a Disclosure Statement (FORM 3455) or if the financial disclosure information is missing. For investigators where the financial disclosure information is missing, a certification was submitted documenting the Applicant acted with due diligence but was unable to obtain the missing information; the certification also included documentation as to why the information was not obtained.

**The FDA’s Assessment:**

EMD Serono reported that a total of 1381 out of 1391 (99%) principal investigators and sub-investigators responded and provided study-specific financial disclosure forms. For 10 sub-investigators in VISION from whom a signed financial disclosure was not obtained, this was reportedly due to the fact that the sub-investigators were not available to sign the form despite multiple attempts.

Disclosable financial interests were recorded by one sub-investigator participating in the VISION study. (b) (6) submitted a financial disclosure form and he is one of (b) (6) sub-investigators who participated in the VISION study from Site (b) (6) where (b) (6) patients were enrolled. The Applicant reports that (b) (6) was not the primary investigator at Site (b) (6) and his involvement with the study was limited. The Applicant also reports (b) (6) (b) (6) however, (b) (6) has no proprietary interest in tepotinib, nor does he have any equity interest in the compound. EMD Serono reports that it strictly follows guidelines related to minimizing bias from all investigators who participate in clinical research. Given the small number of patients potentially enrolled (b) (6) (b) (6) from Site (b) (6) it would not be expected to significantly influence the overall safety results. Efficacy results for the VISION study were also based on IRC review.

**Covered Clinical Study (Name and/or Number):\* VISION Study**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 1391		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: <u>1</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>10</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

\*The table above should be filled by the applicant, and confirmed/edited by the FDA.

### 19.3. Nonclinical Pharmacology/Toxicology

Data:

Not applicable

The Applicant's Position:

Not applicable

The FDA's Assessment:

### 19.4. **Not applicable.** OCP Appendices (Technical documents supporting OCP recommendations)

#### 19.4.1. Bioanalytical Methods

In human plasma, tepotinib was stable for  $\geq 24$  h at ambient temperature, for  $\geq 4$  freeze/thaw cycles and for  $\geq 1,099$  days at both  $-20^{\circ}\text{C}$  and  $-70^{\circ}\text{C}$ .

Table 71 shows an overview of the bioanalytical methods applied in the clinical studies.

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**Table 71: Summary of Bioanalytical Methods**

Study ID	Bioanalytical Report ID (in Appendix of Study Report)	Method Validation Report ID	Analyte	Matrix	Concentration Range (LLOQ is lower end of the concentration range)	Validation Status
EMR200095-001	(b) (4) R09-156	(b) (4) S09-155	Tepotinib	Plasma	0.186 – 93.0 ng/mL	Fully validated, non-GLP
	R09-156	S12-130	Tepotinib	Plasma	20.0 – 10,000 ng/mL	Partially validated, non-GLP
EMR200095-002	DMPK 82-13	(b) (4) S09-155	Tepotinib	Plasma	0.186 – 93.0 ng/mL	Fully validated, non-GLP
EMR200095-003	DMPK 83-13	S12-130	Tepotinib	Plasma	20.0 – 10,000 ng/mL	Partially validated, non-GLP
EMR200095-004	14-BJ001-P0	13NCD002	Tepotinib	Plasma	5.00 – 2,500 ng/mL	Partially validated, non-GLP
	8326-206	8324-380	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Partially validated, non-GLP
EMR200095-005	131021/150789	130811 (tepotinib) 150494 (metabolites)	Tepotinib	Plasma	5.00 – 2,500 ng/mL	Partially validated, non-GLP
			MSC2571107A MSC2571109A		0.100 – 100 ng/mL 0.500 – 500 ng/mL	Fully validated, GLP
EMR200095-006	13NCD006	13NCD002	Tepotinib	Plasma	5.00 – 2,500 ng/mL	Partially validated, non-GLP
	15-GR082-C0	8324-380	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Partially validated, non-GLP
	15-GR082-C0	8324-379	Gefitinib	Plasma	5.00 – 3,000 ng/mL	Partially validated, GLP
	13NCD006	13NCD005	Gefitinib	Plasma	5.00 – 3,000 ng/mL	fully validated, non-GLP
EMR200095-007	13-GR026-C0	130811	Tepotinib	Plasma	5.00 – 2,500 ng/mL	Partially validated, non-GLP
	14-GR002-P0	Internal procedure	<sup>14</sup> C-tepotinib	Plasma, whole blood, urine, feces	N/A	N/A
	14-GR014-C0	VS13014	<sup>14</sup> C-tepotinib	Plasma	0.025 – 15.0 dpm/mL	Fully validated, non-GLP
	14-GR004-C0	Internal procedure	Metabolite pattern	Plasma, urine, feces	N/A	N/A

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Study ID	Bioanalytical Report ID (in Appendix of Study Report)	Method Validation Report ID	Analyte	Matrix	Concentration Range (LLOQ is lower end of the concentration range)	Validation Status
MS200095-0012	16-GR001-C0	150494	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Fully validated, GLP
MS200095-0022 (VISION)	161024	150494	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Fully validated, GLP
MS200095-0028	N-U (b)(4)17-043A	N-A (b)(4)16-131	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Partially validated, non-GLP
	N-U (b)(4)17-043B	18-DA0606-0	Free fraction of Tepotinib	Plasma	2.50 – 10,000 ng/mL	Qualified, non-GLP
MS200095-0030	18-DA0607-0	150494	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Fully validated, GLP
	18-DA0608-0	N-X (b)(4)18-003	Midazolam and 1-hydromidazolam	Plasma	50.0 – 50,000 pg/mL	Fully validated, non-GLP
MS200095-0032	18-DA0364-0	N-A (b)(4)16-131	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Partial validation of method 150494, non-GLP
	18-DA0363-0	N-X (b)(4)17-008	Dabigatran	Plasma	1.00 – 1,000 ng/mL	Fully validated, non-GLP
MS200095-0038	N-A (b)(4)19-133	N-A (b)(4)16-131	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Partial validation of method 150494, non-GLP
MS200095-0039	N-A (b)(4)17-127	N-A (b)(4)16-131	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Partial validation of method 150494, non-GLP
MS200095-0044	N-A (b)(4)18-017	N-A (b)(4)16-131	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Partial validation of method 150494, non-GLP
Cross validation	N/A	130812	Tepotinib	Plasma	5.00 – 2,500 ng/mL	Non-GLP
Cross validation	N/A	130813	Tepotinib	Plasma	5.00 – 2,500 ng/mL	Non-GLP
Cross validation	N/A	150791	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Non-GLP
Cross validation	N/A	150793	Tepotinib MSC2571107A MSC2571109A	Plasma	5.00 – 2,500 ng/mL 0.100 – 100 ng/mL 0.500 – 500 ng/mL	Non-GLP
Cross validation	N/A	150250	Gefitinib	Plasma	5.00 – 3,000 ng/mL	Non-GLP
Cross validation	N/A	150794	Gefitinib	Plasma	5.00 – 3,000 ng/mL	Non-GLP

## 19.4.2. Population PK Analysis

The applicant conducted a population PK analysis to characterize the PK of tepotinib and its metabolite MSC2571109A, to identify covariate factors that could affect tepotinib and MSC2571109A disposition and compare the individual exposure estimates for subsequent exposure-response analyses. Data were collected from 11 completed studies and one ongoing study (MS200095-0022). The studies included in the population PK analysis are shown in Table 72 and the summary of number of subjects and observations in the tepotinib and MSC2571109A analysis data sets is shown in Table 73.

**Table 72: Overview of studies for PK analysis.**

Study ID	Dosing	PK assessments in current modeling project	Number of Subjects
EMR200095-001	Tepotinib CF1 Regimen 1: 30 to 230 mg; Regimen 2: 30 to 115 mg Tepotinib CF2 Regimen 1: 30 to 400 mg; Regimen 2: 60 to 315 mg; Regimen 3: 300 to 1400 mg Tepotinib TF1 Regimen 3: 500 mg	Rich blood sampling (predose and up to 72 hours post last dose) for determination of tepotinib and MSC2571109A concentrations	149 treated, 129 completed
EMR200095-002	Tepotinib TF1 30 mg single dose fed or fasted Tepotinib TF1 or CF2 30 mg single dose fed	Rich blood sampling (predose and up to 3 weeks postdose) for determination of tepotinib and MSC2571109A concentrations	28 treated, 27 completed
EMR200095-003	Tepotinib 215, 300 or 500 mg/day	Rich blood sampling (predose and up to 24 hours postdose) for determination of tepotinib and MSC2571109A concentrations	12 treated
EMR200095-004	Tepotinib 300, 500, 1000 mg/day	Phase Ib: rich blood sampling (predose and up to 24 hours postdose) Phase II: sparse blood sampling for determination of tepotinib and MSC2571109A concentrations	Phase Ib: 27 treated Phase II: 45 treated with tepotinib
EMR200095-005	Tepotinib 300 or 500 mg/day	Phase Ib: rich blood sampling (predose and up to 24 hours postdose) Phase II: sparse blood sampling (predose and up to 24 hours postdose) for determination of tepotinib and MSC2571109A concentrations	Phase Ib: 17 treated, 12 completed Phase II: 49 treated, 31 completed
EMR200095-006	Tepotinib 300 or 500 mg/day with gefitinib	Phase Ib: rich blood sampling (predose and up to 24 hours postdose) Phase II: sparse blood sampling for determination of tepotinib and MSC2571109A concentrations	Phase Ib: 21 planned Phase II: 171 planned, 70 enrolled (status June 2017)
EMR200095-007	- Mass balance and absolute bioavailability: tepotinib 500 mg single dose - Relative bioavailability: tepotinib 100 mg single dose	Rich blood sampling for determination of tepotinib and MSC2571109A concentrations (- Mass balance: predose and up to 3.5 weeks postdose - Absolute bioavailability: predose and up to 2 weeks postdose - Relative bioavailability: predose and up to 3 weeks postdose)	27 treated, 26 completed
EMR200095-0012	Tepotinib 500 mg single dose	Rich blood sampling (predose and up to 3 weeks postdose) for determination of tepotinib and MSC2571109A concentrations	24 treated, 22 completed
MS200095-0022	Tepotinib 500 mg/day	Sparse blood sampling (predose and up to 4 hours postdose) for determination of tepotinib and MSC2571109A concentrations	Cohort A (MET exon 14 skipping alterations): 70 to 90; Cohort B (MET

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			amplification): 80
MS200095-0028	Part 1: tepotinib 500 mg single dose Part 2: tepotinib up to 1000 mg single dose	Rich blood sampling (predose and up to 2 and 3 weeks postdose in healthy subjects and subjects with hepatic impairment, respectively) for determination of tepotinib and MSC2571109A concentrations	18 (Part 1) + 6 (Part 2, optional) planned
MS200095-0039	Tepotinib 500 mg single dose	Rich blood sampling (predose and up to 144 hours postdose) for determination of tepotinib and MSC2571109A concentrations	12 treated and completed
MS200095-0044	Part A: tepotinib TF2 or TF3 500 mg single dose fasted Part B: tepotinib TF2 500 mg single dose fed or fasted Part C: tepotinib TF3 500 mg single dose fed or fasted	Rich blood sampling (predose and up to 168 hours postdose) for determination of tepotinib and MSC2571109A concentrations	64 or more planned

Source: Summarized from PMAR – Population PK (18 February 2019 cut-off) Page 29-34 Table 1-6.

**Table 73: Number of subjects with observations and number of tepotinib and MSC2571109A observations in the analysis data sets stratified by study and dose range.**

Study / Dose <sup>a</sup>	Tepotinib		MSC2571109A	
	Number of subjects	Number of observations	Number of subjects	Number of observations
<b>EMR200095-001</b>				
30-200 mg	71	1345	0	0
215-400 mg	19	417	9	183
500 mg	42	798	39	750
700-1400 mg	17	335	7	131
All	149	2895	55	1064
<b>EMR200095-002</b>				
30-200 mg	28	1161	0	0
<b>EMR200095-003</b>				
215-400 mg	6	115	6	115
500 mg	6	114	6	114
All	12	229	12	229
<b>EMR200095-004</b>				
215-400 mg	7	99	7	92
500 mg	59	310	59	294
700-1400 mg	6	86	6	82
All	72	495	72	468
<b>EMR200095-005</b>				
215-400 mg	4	54	4	50
500 mg	62	329	62	316
All	66	383	66	366
<b>EMR200095-006</b>				
215-400 mg	6	93	6	89
500 mg	58	338	58	314
All	64	431	64	403
<b>EMR200095-007</b>				
30-200 mg	15	491	0	0
500 mg	12	230	0	0
All	27	721	0	0
<b>EMR200095-0012</b>				
500 mg	24	966	24	1047
<b>MS200095-0022</b>				
215-400 mg		2		2
500 mg	75	312	75	306
All	75	314	75	308
<b>MS200095-0028</b>				
500 mg	18	385	18	390
<b>MS200095-0039</b>				
500 mg	12	591	12	685
<b>MS200095-0044</b>				
500 mg	66	2217	66	2237
All				
All	613	10788	464	7197

<sup>a</sup> Dose level (mg/day) recorded at first occasion for each subject.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 37, Table 7.

The primary patient population were Caucasian (59.1%) and East Asian other than Japanese (23.7%). The median age of all patients was 58 years old (range: 18 - 89), 71.6% were males and the median body weight were 72.0 kg (range: 35.5 - 136 kg). The majority (n=448, 73.1%) of the 613 patients were of normal liver function, 146 patients (23.8%) with mild hepatic impairment, 16 (2.6%) with moderate hepatic impairment and 3 (0.5%) with severe hepatic impairment based on NCI hepatic impairment classification. Baseline covariates for the subjects in the tepotinib analysis data set were summarized in Table 74 and Table 75.

**Table 74: Summary of baseline continuous covariates**

Covariate	N <sup>a</sup>	Mean	sd <sup>b</sup>	Median	Min	Max
Age (years)	613	55.8	15.7	58.0	18.0	89.0
AGP (mg/dL)	18	63.9	26.9	62.0	29.0	124
ALP (IU/L)	613	134	133	90.0	20.0	1310
BILI (μmol/L)	613	10.5	6.70	9.00	2.00	66.0
eGFR (mL/min/1.73m <sup>2</sup> )	591	99.8	26.2	97.4	39.4	236
INR	578	1.09	0.172	1.05	0.870	2.90
Total protein (g/L)	535	71.7	6.16	71.0	50.0	93.0
S-Albumin (g/L)	511	39.3	5.36	40.0	23.0	72.0
Sum of longest diameters (mm) <sup>c</sup>	425	84.8	55.5	72.0	10.0	368
WT (kg)	613	72.9	15.8	72.0	35.5	136

<sup>a</sup>Number of subjects with non-missing values

<sup>b</sup>Standard deviation

<sup>c</sup>Sum of the longest diameters for target lesion at baseline, assessed by investigator

Values are rounded to 3 significant digits.

AGP: alpha-1 acid glycoprotein; ALP: alkaline phosphatase; BILI: total bilirubin;

eGFR: estimated glomerular filtration rate; INR: international normalized ratio;

WT: body weight

Source: PMAR – Population PK (18 February 2019 cut-off) Page 38, Table 8.

**Table 75: Summary of baseline categorical covariates**

Covariate		N	%
Sex	Male	439	71.6
	Female	174	28.4
Tumor type	Subject without cancer	175	28.5
	Hepatocellular carcinoma	144	23.5
	Non-small cell lung cancer	157	25.6
	Renal cell carcinoma	5	0.8
	Head and neck cancer	20	3.3
	Gastroesophageal cancer	31	5.1
	Colorectal cancer	29	4.7
	Breast cancer	10	1.6
	Prostate cancer	6	1.0
	Pancreatic cancer	3	0.5
	Other solid tumor	33	5.4
Food intake <sup>a</sup>	Fasted	93	15.2
	Fed standard breakfast	455	74.2
	Fed high fat breakfast	65	10.6
Formulation <sup>a</sup>	CF1	41	6.7
	CF2	111	18.1
	TF1	273	44.5
	TF1*	5	0.8
	TF2	151	24.6
	TF3	32	5.2
ECOG	ECOG 0	130	21.2
	ECOG 1	299	48.8
	ECOG 2	8	1.3
	ECOG 3	1	0.2
	(Missing)	175	28.5
Race	Caucasian	362	59.1
	African Origin	17	2.8
	Japanese	28	4.6
	Other East Asian	145	23.7
	Hispanic	25	4.1
	Other	14	2.3
	(Missing)	22	3.6
Cirrhosis	Grade0	560	91.4
	Grade1	33	5.4
	Grade2	18	2.9
	Grade3	1	0.2
	(Missing)	1	0.2
HBV/HCV	HBV/HCV-	445	72.6
	HBV/HCV+	55	9.0
	(Missing)	113	18.4
NCI ODG class	NCI 0	448	73.1
	NCI 1	146	23.8
	NCI 2	16	2.6
	NCI 3	3	0.5

Source: PMAR – Population PK (18 February 2019 cut-off) Page 39, Table 9.

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.30 using first-order conditional estimation with INTERACTION option (FOCE+I). Observations below the lower limit of quantification (LLOQ), observations after intake of tepotinib oral solution, observations from samples with extreme values for time since

last dose were excluded from the PK analysis. The plasma concentrations of tepotinib were described by a two-compartment disposition model with sequential zero- and first-order absorption and first-order elimination from the central compartment. The model included inter-individual variability (IIV) for  $CL_{par}$ ,  $k_a$ ,  $D1$ , central volume of distribution of parent drug ( $V_{c,par}$ ) and peripheral volume of distribution of parent drug ( $V_{p,par}$ ), inter-compartmental clearance of parent drug ( $Q_{par}$ ) and  $F_{par}$ . The residual error model is additive on the log-scale. Covariates included sex, race, age, WT, disease status, tumor type, NCI ODG classification of liver impairment, HBV/HCV+, baseline tumor burden, serum albumin, total bilirubin, alkaline phosphatase, international normalized ratio, total protein, co-administration of opioid analgesics, co-administration of gefitinib, estimated glomerular filtration rate (MDRD formula) and dose.

The final population PK parameter estimates for tepotinib are presented in Table 76. Estimated fixed and random effect parameters were estimated with good precision (%RSE < 23%). The magnitude of the interindividual variability was moderate for  $k_a$ ,  $D1$  and  $F_{par}$  for CF1. Residual variability was moderate.

**Table 76: Parameter estimates of the final tepotinib population PK model.**

Final model for tepotinib				
Run		80		
OFV		-8891.44		
Condition number		56.93		
Final model for tepotinib				
	Unit	Value	RSE (%)	SHR (%)
CL <sub>par</sub> <sup>a</sup>	L/h	20.4	2.07	
V <sub>c, par</sub> <sup>a</sup>	L	1020	2.00	
k <sub>a</sub>	h <sup>-1</sup>	0.278	6.16	
Q <sub>par</sub> <sup>a</sup>	L/h	1.32	4.22	
V <sub>p, par</sub> <sup>a</sup>	L	1180	16.6	
D1	h	4.09	5.34	
F <sub>par</sub>	(CV)	1.00	(FIX)	
Fasting state covariate on D1		-0.370	5.19	
DOSE covariate on F <sub>par</sub> (/100 mg)		-0.0412	9.71	
Fasting state covariate on F <sub>par</sub>		-0.209	4.94	
High fat meal covariate on F <sub>par</sub>		0.320	5.96	
CF1 covariate on F <sub>par</sub>		-0.656	7.67	
TF3 covariate on F <sub>par</sub>		0.154	7.08	
Fasting state covariate on k <sub>a</sub>		-0.561	2.63	
CF1 covariate on k <sub>a</sub>		-0.442	15.1	
TF1 covariate on k <sub>a</sub>		0.305	6.35	
TF1* covariate on k <sub>a</sub>		0.674	10.2	
eGFR at baseline covariate on CL <sub>par</sub>		0.199	23.5	
Hepatocellular carcinoma covariate on CL <sub>par</sub>		0.130	44.2	
Colorectal cancer covariate on CL <sub>par</sub>		-0.281	16.4	
μ-opioids covariate on CL <sub>par</sub>		-0.167	10.1	
NCI ODG class > 0 covariate on D1		-0.332	6.09	
Body weight at baseline covariate on F <sub>par</sub>		-0.475	15.4	
NCI ODG class > 0 covariate on F <sub>par</sub>		-0.0729	16.7	
INR at baseline covariate on Q <sub>par</sub>		3.81	10.5	
Serum albumin at baseline covariate on Q <sub>par</sub>		4.14	10.9	
Age covariate on V <sub>c, par</sub>		0.219	14.7	
Non-small cell lung cancer covariate on V <sub>c, par</sub>		-0.232	13.2	
Patient subject covariate on V <sub>p, par</sub>		-0.810	4.52	
Study 0028 covariate on CL <sub>par</sub>		-0.115	22.4	
IIV CL <sub>par</sub>	(CV)	0.335	4.57	36.4
IIV k <sub>a</sub>	(CV)	0.653	5.86	31.2
IIV D1	(CV)	0.652	4.98	26.1
IIV F <sub>par</sub>	(CV)	0.283	5.78	44.0
IIV F <sub>par</sub> for CF1	(CV)	0.713	10.8	75.7
IIV CL <sub>par</sub> for healthy subject	(CV)	0.128	7.64	54.6
IIV F <sub>par</sub> for healthy subject	(CV)	0.188	6.38	54.7
Prop. RUV	(CV)	0.337	0.351	6.39

<sup>a</sup> Multiplied by a conversion factor of 0.9.

The SEs were obtained from the \$COV step in NONMEM using the MATRIX=S option. The RSE for IIV and RUV parameters are reported on the approximate SD scale. Values are rounded to three significant digits.

The equations for the covariate effects on each parameter are provided in Appendix 10.1.

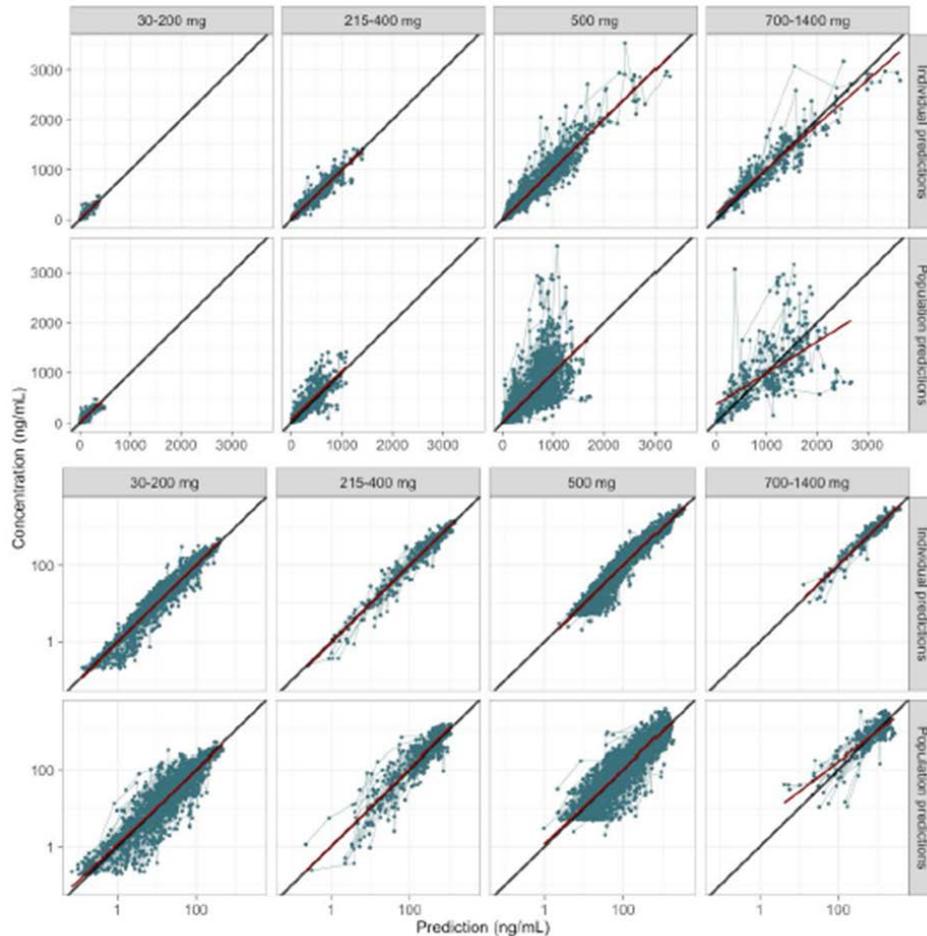
See List of Abbreviations and Definition of Terms for definitions.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 67, Table 15.

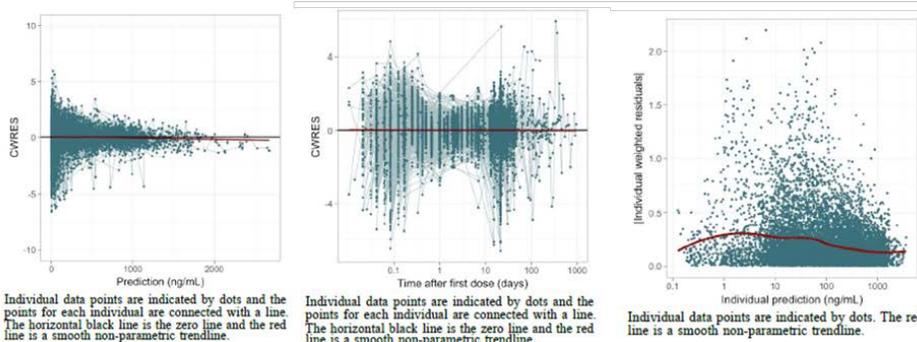
The diagnostic plots for the final PK model are shown in Figure 29 and the pcVPC (prediction corrected visual predictive check) on the final PK model is shown in Figure 30. The pcVPC stratified by study and by formulation are shown in Figure 31 and Figure 32. The model

described the observed data well, while the variability in the data seems slightly over- or under predicted for some data.

Figure 29. Diagnostic plots for the final population PK model for tepotinib



Individual data points are indicated by dots and the points for each individual are connected with a line. Top set of panels using linear scales and the bottom set of panels use logarithmic scales. The black line is the line of unity and the red line is a smooth non-parametric trendline.



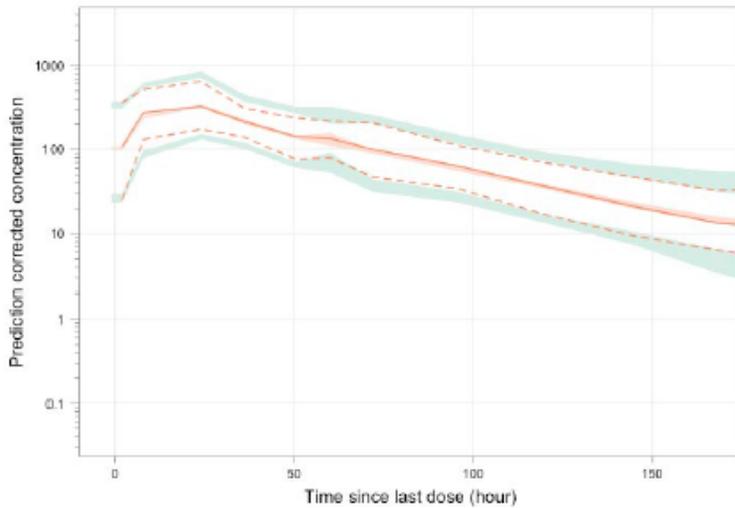
Individual data points are indicated by dots and the points for each individual are connected with a line. The horizontal black line is the zero line and the red line is a smooth non-parametric trendline.

Individual data points are indicated by dots and the points for each individual are connected with a line. The horizontal black line is the zero line and the red line is a smooth non-parametric trendline.

Individual data points are indicated by dots. The red line is a smooth non-parametric trendline.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 69-71, Figure 17-20.

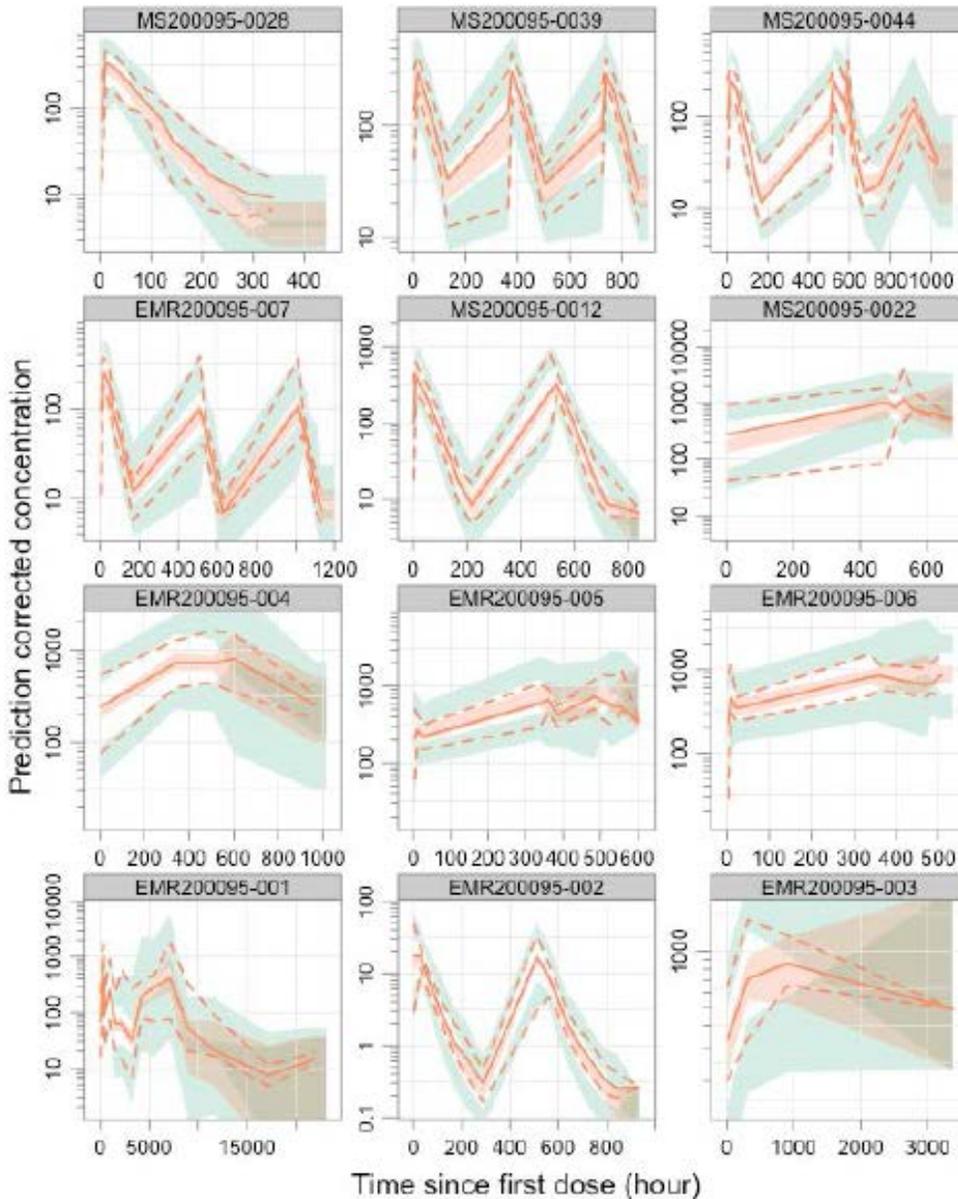
**Figure 30: pcVPC of tepotinib concentrations vs time since last dose.**



The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles, based on 100 simulated data sets. The x-axis was cut at 175 hours.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 72, Figure 21.

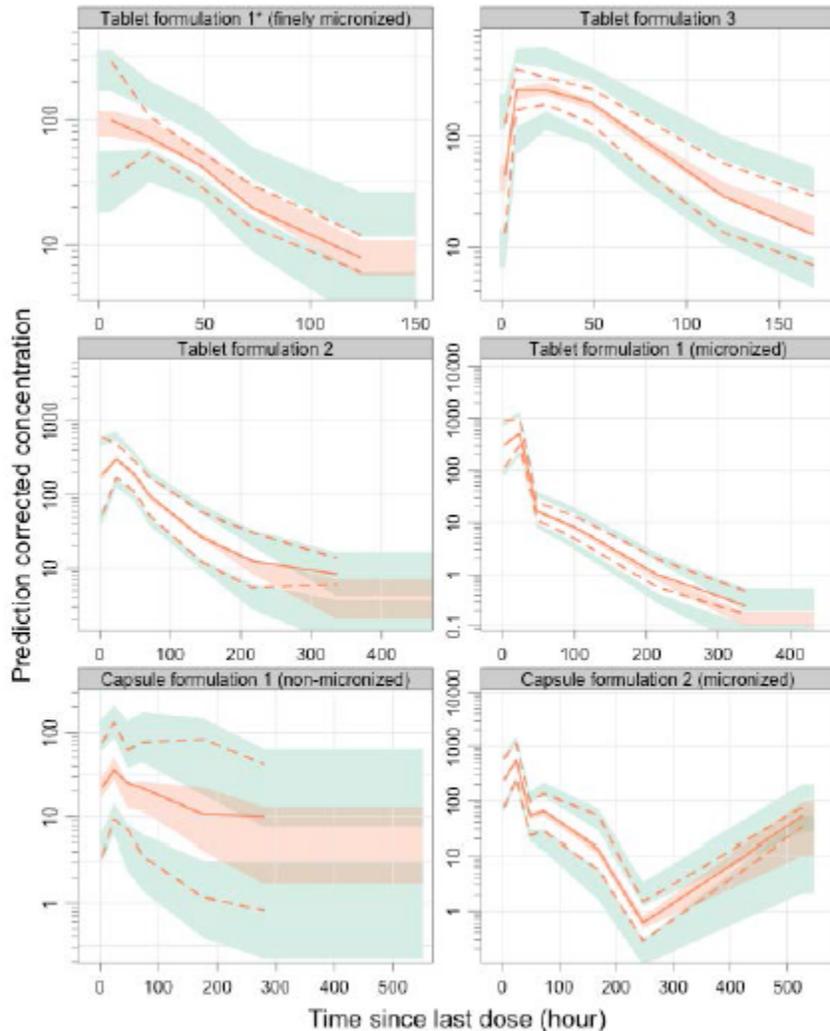
Figure 31: pcVPC of tepotinib concentrations vs time since first dose stratified by study



The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles, based on 100 simulated data sets.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 73, Figure 22.

Figure 32: pcVPC of tepotinib concentrations vs time since last dose stratified by formulation

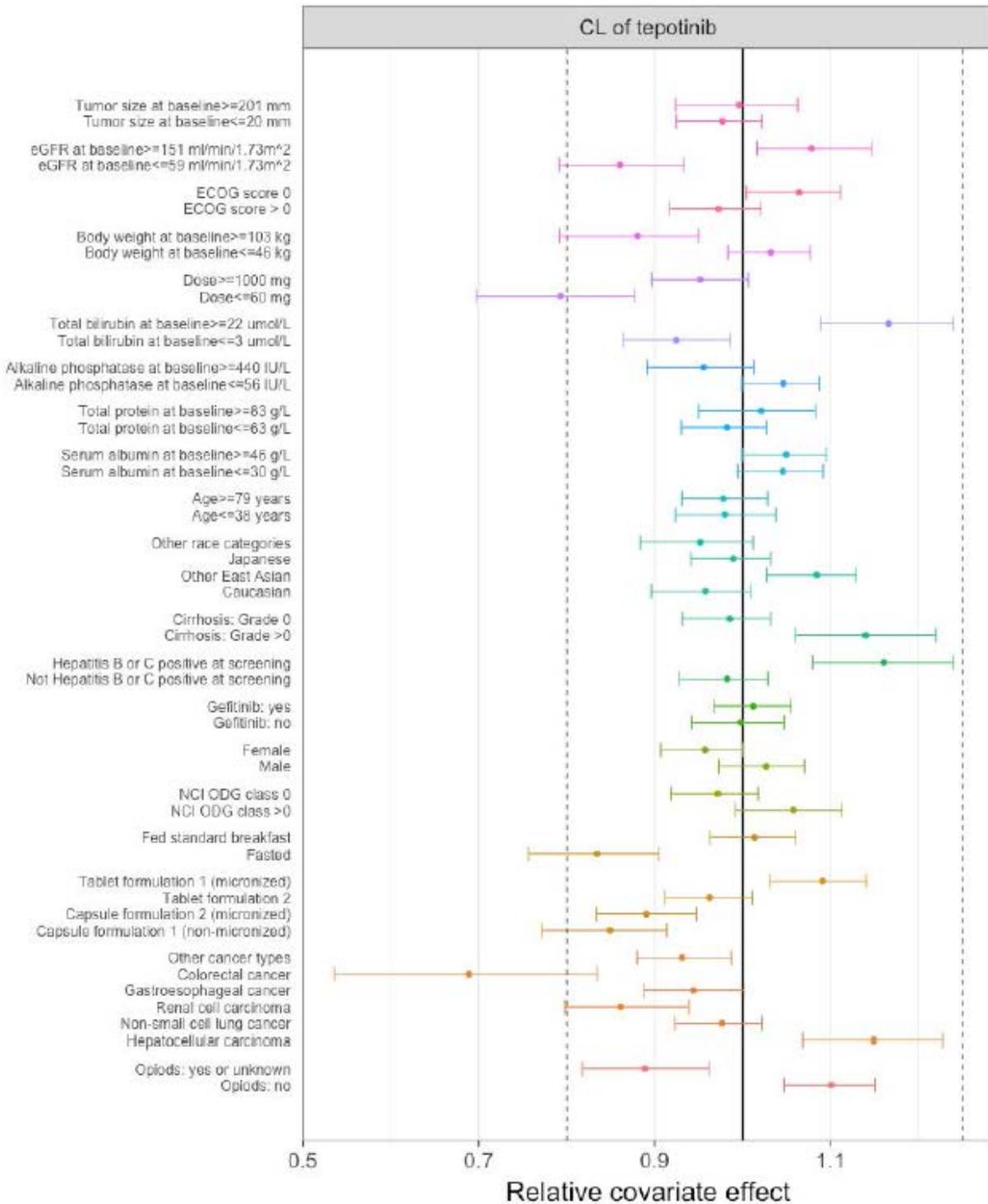


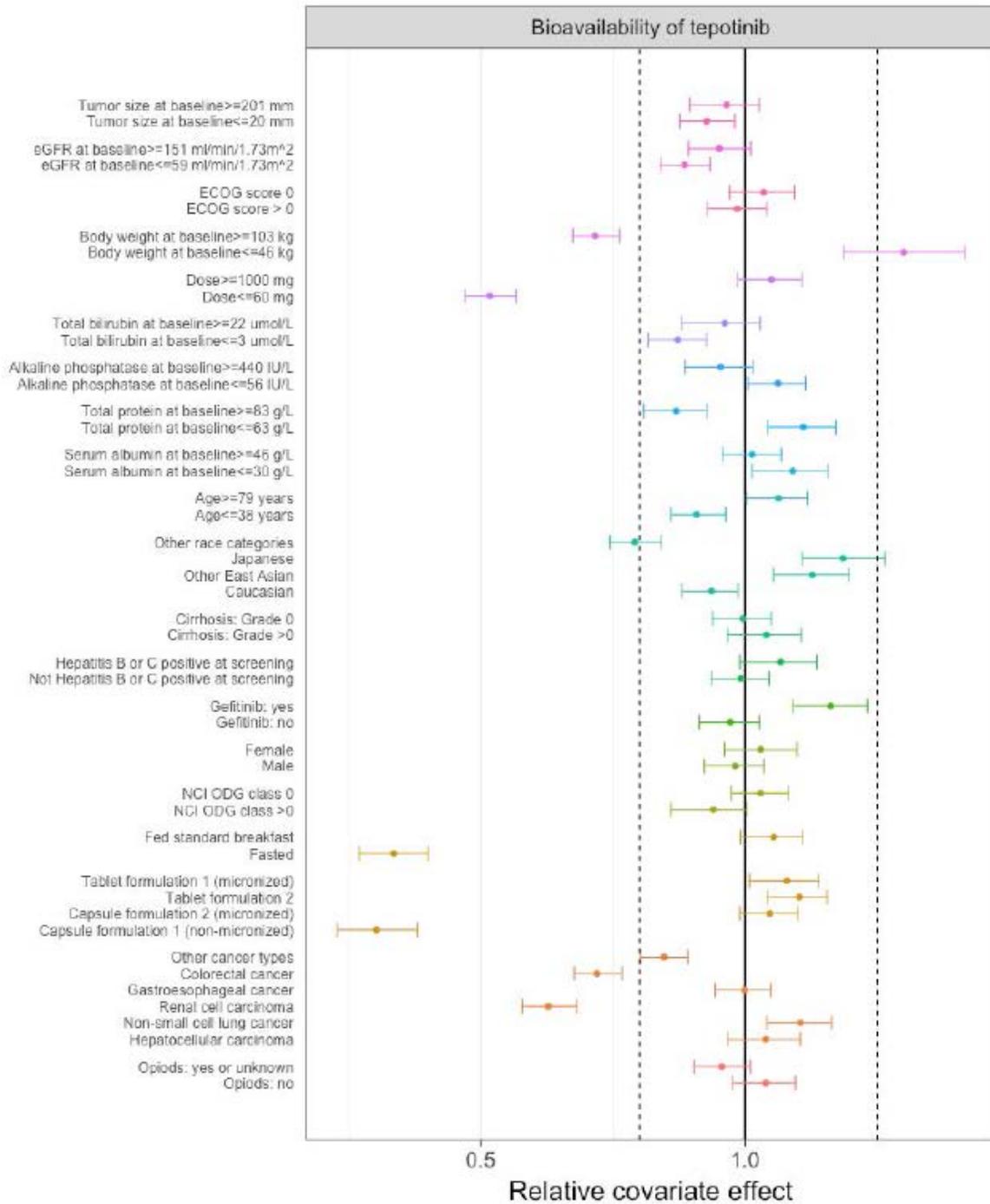
The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles, based on 100 simulated data sets.

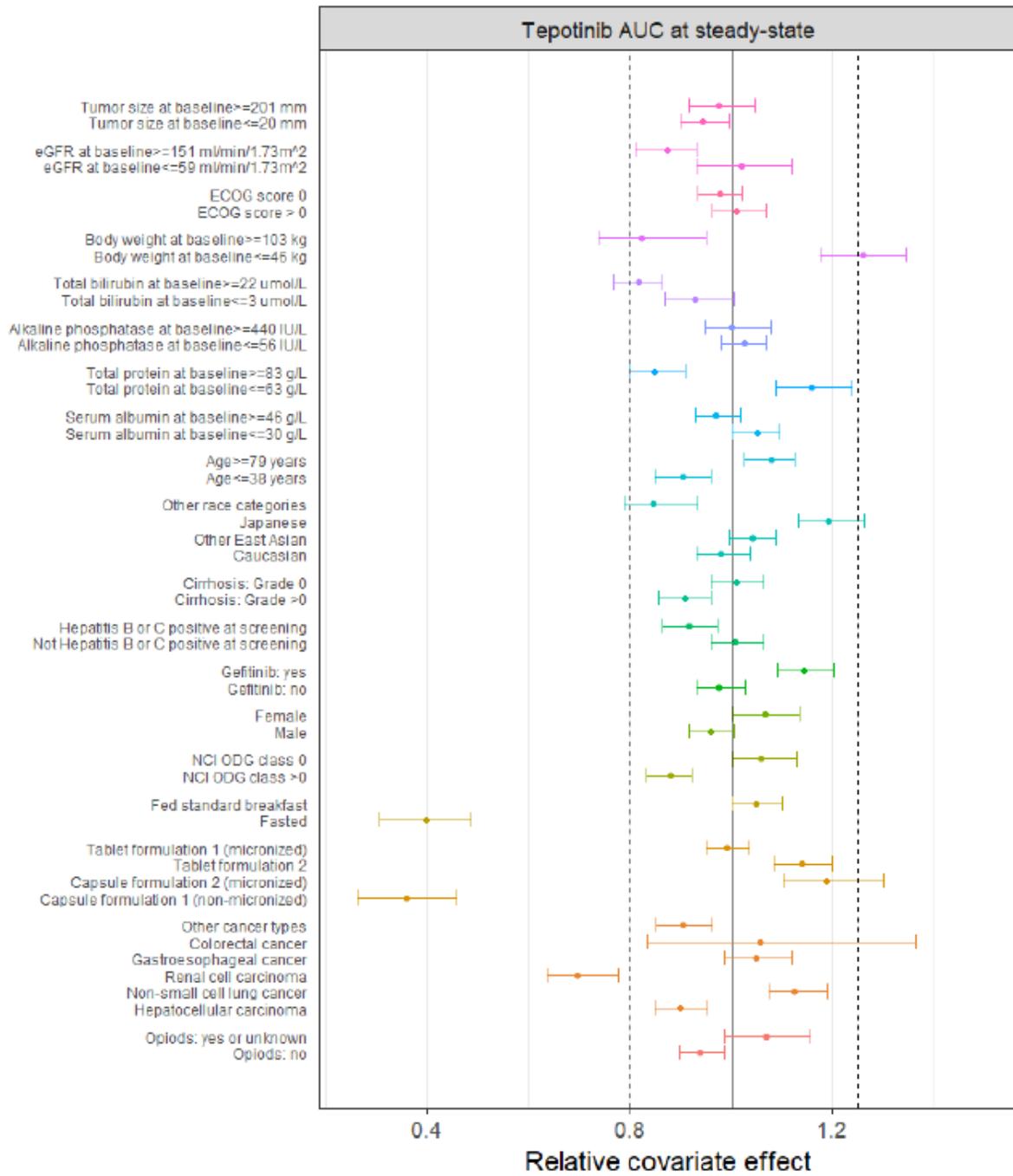
Source: PMAR – Population PK (18 February 2019 cut-off) Page 74, Figure 23.

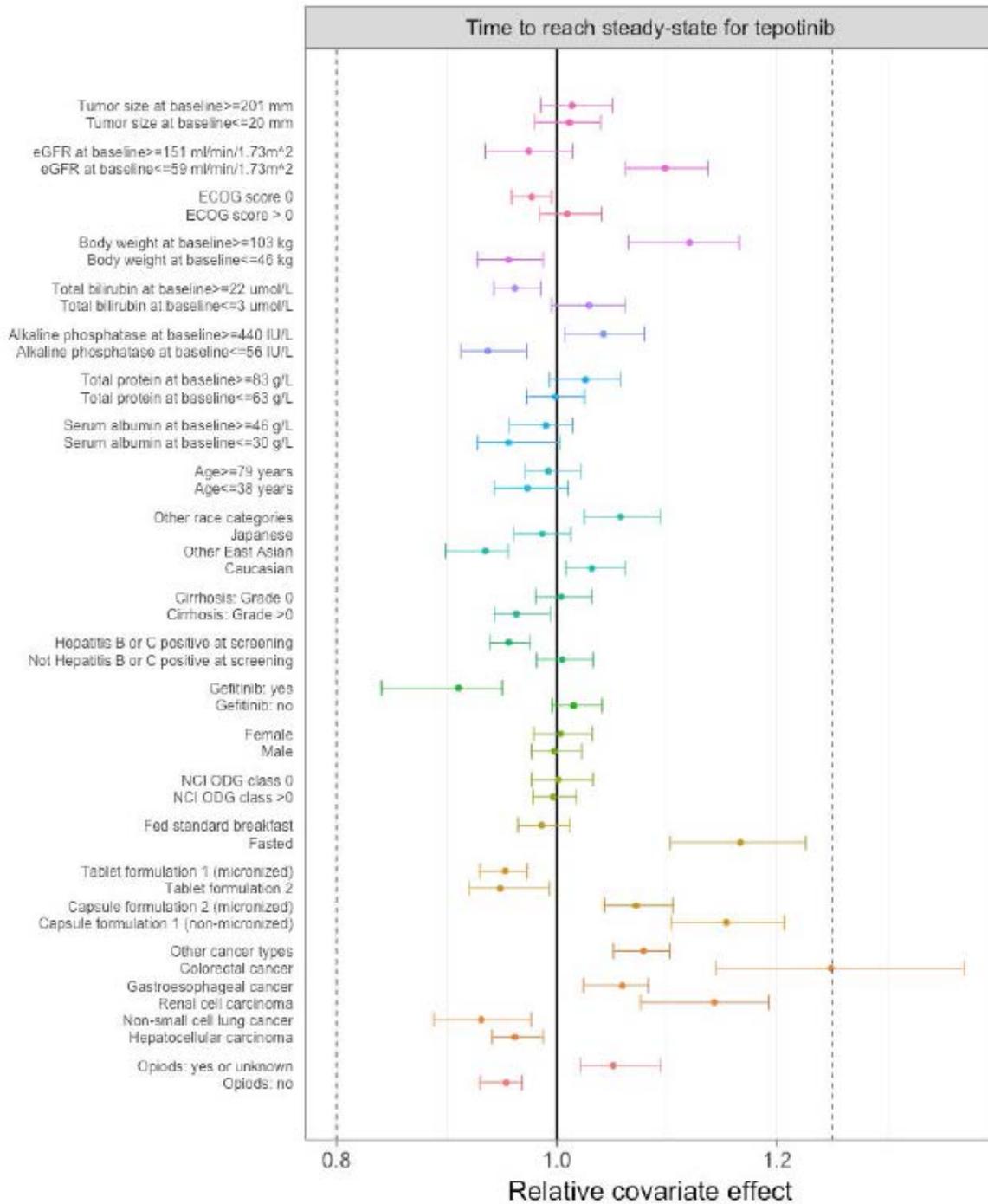
The influence of covariates on tepotinib primary and secondary PK parameters were checked and dose, formulation, food intake status can be expected to influence tepotinib PK in a substantial way. (Figure 33)

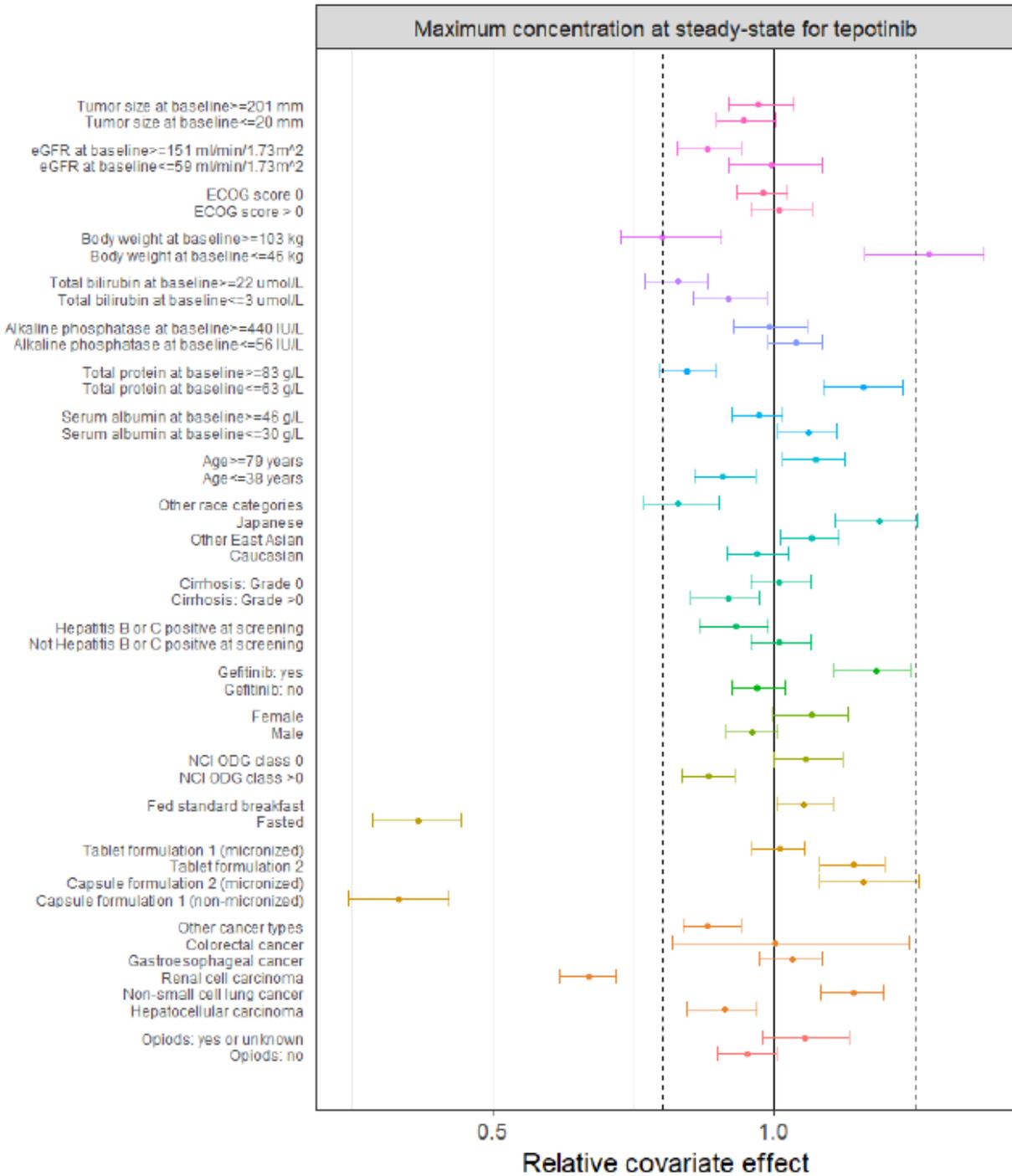
**Figure 33: Forest plot showing the association of the primary and secondary PK parameters and covariates, assuming a dosing regimen of 500 mg daily, based on the final tepotinib population PK model, for cancer patients in the analysis data set.**

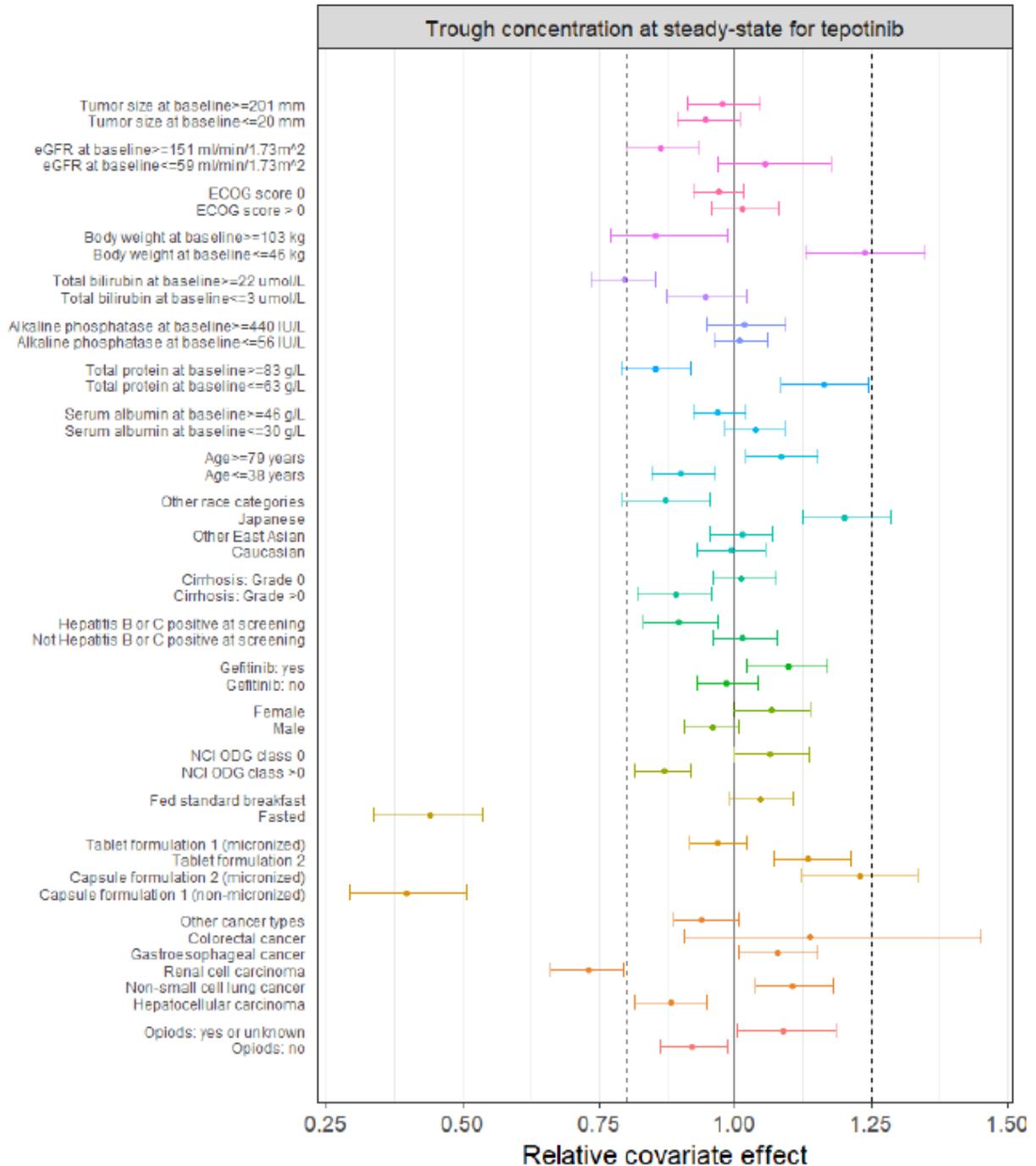












Source: PMAR – Population PK (18 February 2019 cut-off) Page 86-91, Figure 34-39.

The structural model for MSC2571109A was added to the parent model with fixed individual and population parameter estimates of the tepotinib model. The tepotinib concentrations were not included in the analysis of MSC2571109A data. The concentration of MSC2571109A were

described by a two-compartment model with first-order elimination from the centration compartment. The fraction of tepotinib metabolized to MSC2571109A was fixed to 1, which assumed that all eliminated tepotinib formed MSC2571109A. The model included inter-individual variability (IIV) for  $CL_{met}$ , central volume of distribution of parent drug ( $V_{c,met}$ ) and peripheral volume of distribution of parent drug ( $V_{p,met}$ ), and inter-compartmental clearance of parent drug ( $Q_{met}$ ). The residual error model is additive on the log-scale. Covariates included sex, race, age, WT, disease status, tumor type, NCI ODG classification of liver impairment, HBV/HCV+, baseline tumor burden, serum albumin, total bilirubin, alkaline phosphatase, international normalized ratio, total protein, co-administration of opioid analgesics, co-administration of gefitinib, estimated glomerular filtration rate (MDRD formula) and dose. The final population PK parameter estimates for MSC2571109A are presented in Table 77. Estimated fixed and random effect parameters were estimated with good precision (%RSE < 25%). The magnitude of the interindividual variability was moderate for  $V_{c,met}$  and  $Q_{met}$ . Residual variability was moderate.

**Table 77: Parameter estimates of the final tepotinib population PK model.**

Final model for MSC2571109A				
Run		51		
OFV		-7823.36		
Condition number		8.44		
Final model for MSC2571109A				
	Unit	Value	RSE (%)	SHR (%)
$CL_{met}^a$	L/h	40.2	2.40	
$V_{c,met}^a$	L	131	5.04	
$Q_{met}^a$	L/h	106	5.98	
$V_{p,met}^a$	L	152	2.90	
eGFR at baseline covariate on $CL_{met}$		0.311	24.2	
Body weight at baseline covariate on $CL_{met}$		-0.696	11.7	
Non-small cell lung cancer covariate on $CL_{met}$		0.498	17.2	
Hepatocellular carcinoma covariate on FM		-0.398	5.77	
East Asian on $Q_{met}$		1.40	35.5	
Patient subject covariate on $V_{p,met}$		2.31	2.17	
NCI ODG class > 0 covariate on $V_{c,met}$		0.520	9.46	
IIV $CL_{met}$	(CV)	0.536	2.30	27.0
IIV $V_{c,met}$	(CV)	0.859	4.11	23.0
IIV $Q_{met}$	(CV)	0.791	13.6	62.6
IIV $V_{p,met}$	(CV)	0.248	14.1	62.9
IIV $CL_{met}$ for healthy volunteers	(CV)	0.255	6.25	54.2
Prop. RUV	(CV)	0.298	0.419	4.17

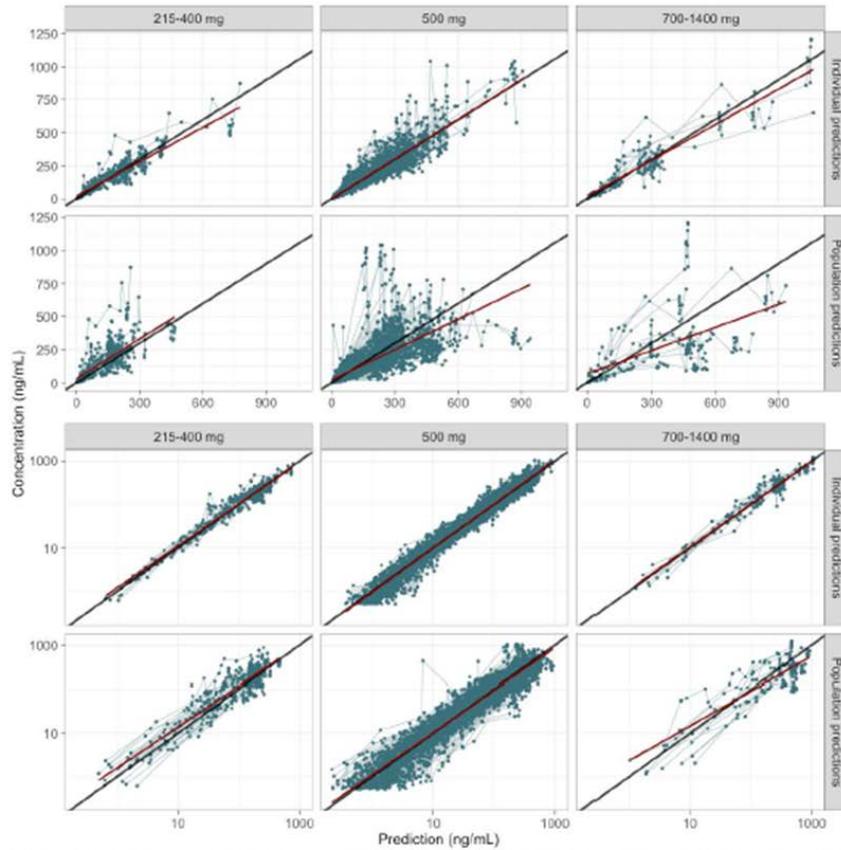
<sup>a</sup> Multiplied by a conversion factor of 0.9.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 96, Table 19.

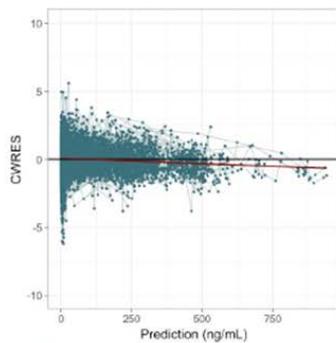
The diagnostic plots for the final PK model are shown in Figure 34. The pcVPC (prediction corrected visual predictive check) on the final PK model is shown in Figure 35. The pcVPC stratified by study is shown in Figure 36. In general, the final MSC2571109A population PK model describes the data well pcVPC plots generally showed a good agreement for the

observed median concentrations. While an under-prediction of the observations in study EMR200095-001 was observed.

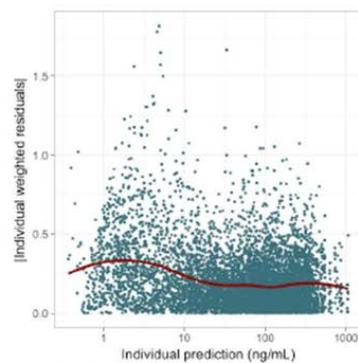
**Figure 34: Diagnostic plots for the final population PK model for MSC2571109A**



Individual data points are indicated by dots and the points for each individual are connected with a line. Top set of panels using linear scales and the bottom set of panels use logarithmic scales. The black line is the line of unity and the red line is a smooth non-parametric trendline.



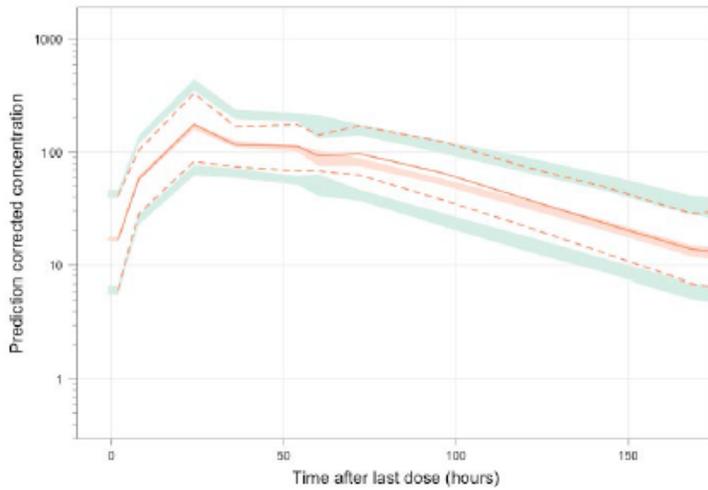
Individual data points are indicated by dots and the points for each individual are connected with a line. The horizontal black line is the zero line and the red line is a smooth non-parametric trendline.



Individual data points are indicated by dots. The red line is a smooth (loess).

Source: PMAR – Population PK (18 February 2019 cut-off) Page 97-99, Figure 43-45.

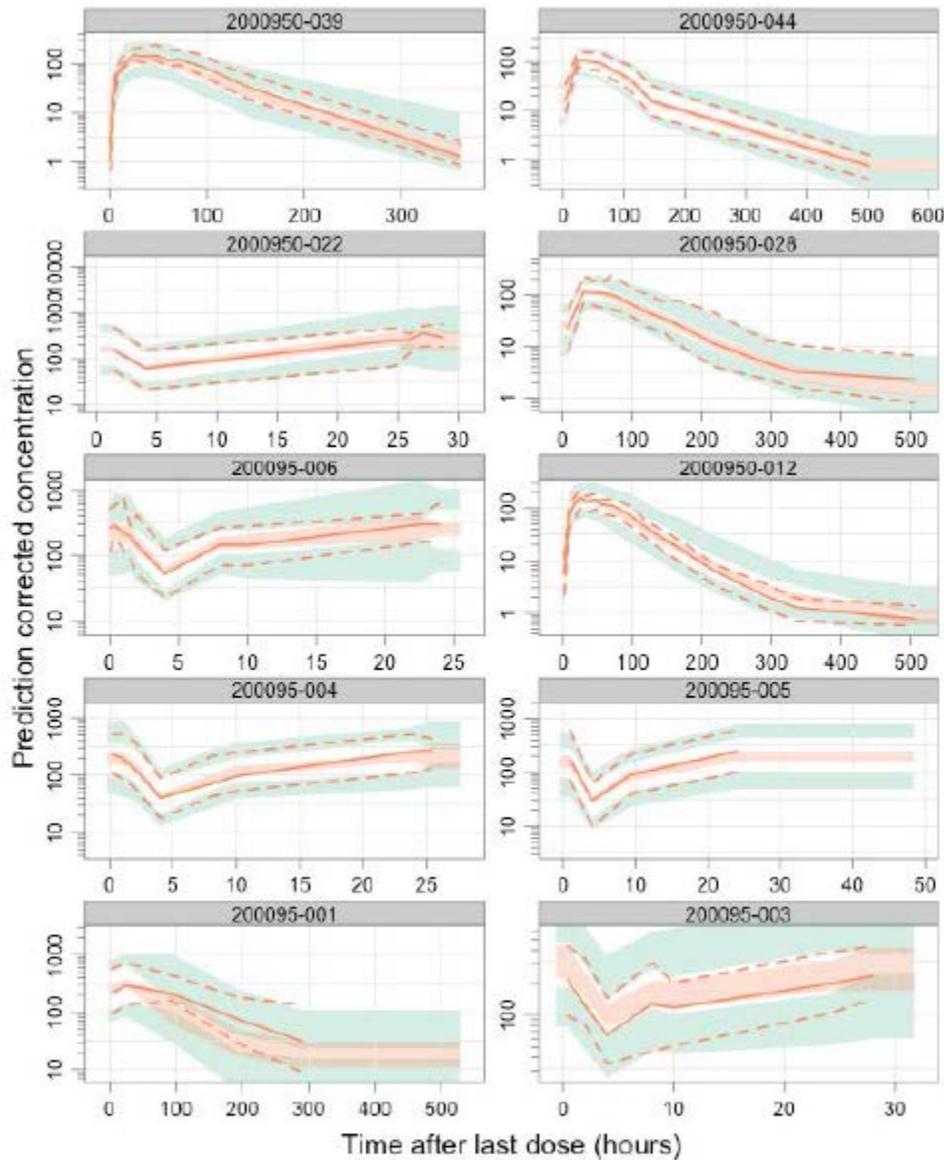
**Figure 35: pcVPC of MSC2571109A concentrations versus time since last dose**



The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles, based on 100 simulated data sets. The x-axis was cut at 175 hours.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 100, Figure 46.

Figure 36: pcVPC of MSC2571109A concentrations vs time since last dose stratified by study



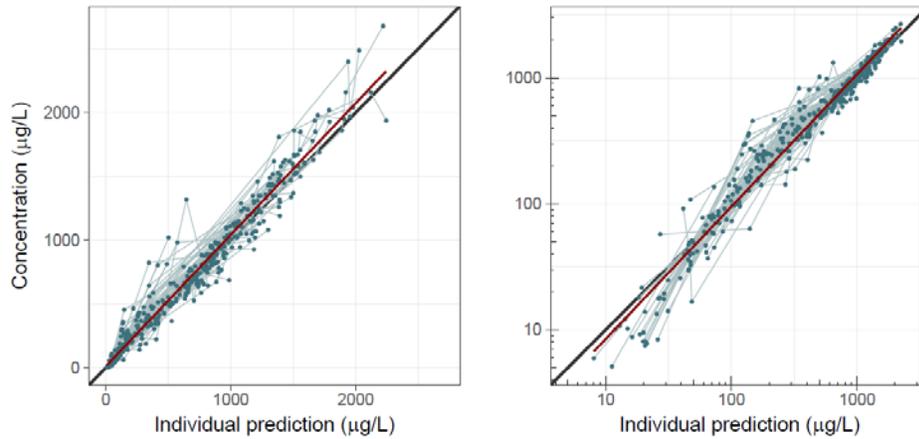
The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles, based on 100 simulated data sets.

Source: PMAR – Population PK (18 February 2019 cut-off) Page 101, Figure 47.

Updated data from study MS200095-0022 (January 1<sup>st</sup> 2020 cut-off) were evaluated by the final population PK model for tepotinib and its metabolite MSC2571109A. The predictive

performance for tepotinib and MSC2571109A for the new subjects was shown in Figure 37 and Figure 39; and the updated pcVPC was shown in Figure 38 and Figure 40.

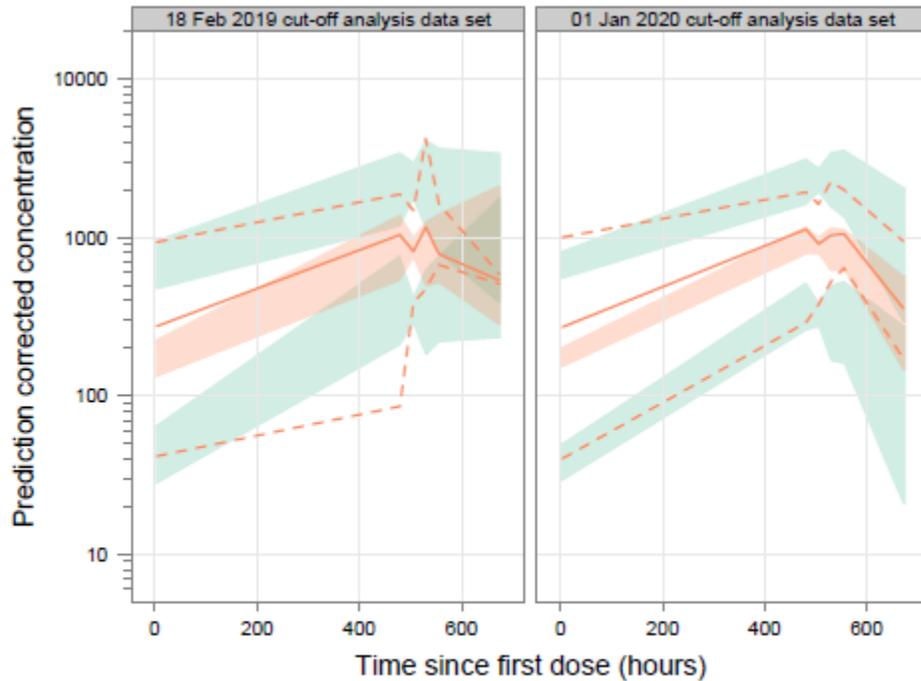
**Figure 37: Observations versus individual predictions of tepotinib plasma concentrations for the new subjects in the 01 January 2020 cut-off that were not in the 18 February 2019 cut-off.**



Individual data points are indicated by dots and the points for each individual are connected with a line. Left panel using linear scales and the right panel use logarithmic scales. The black line is the line of unity and the red line is a smooth non-parametric trendline.

Source: PMAR – Pharmacokinetic Addendum (01 January 2020 cut-off) Page 18, Figure 5.

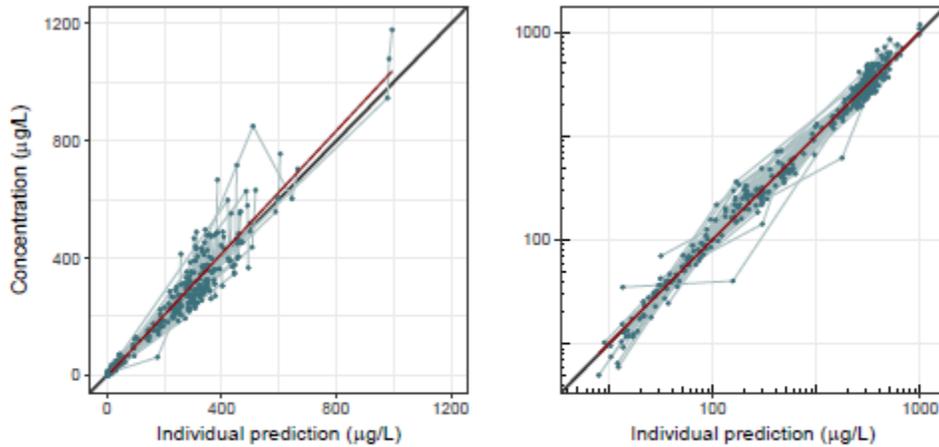
**Figure 38: pcVPC of tepotinib concentrations versus time since first dose in study MS200095-0022.**



The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles, based on 100 simulated data sets.

Source: PMAR – Pharmacokinetic Addendum (01 January 2020 cut-off) Page 19, Figure 6.

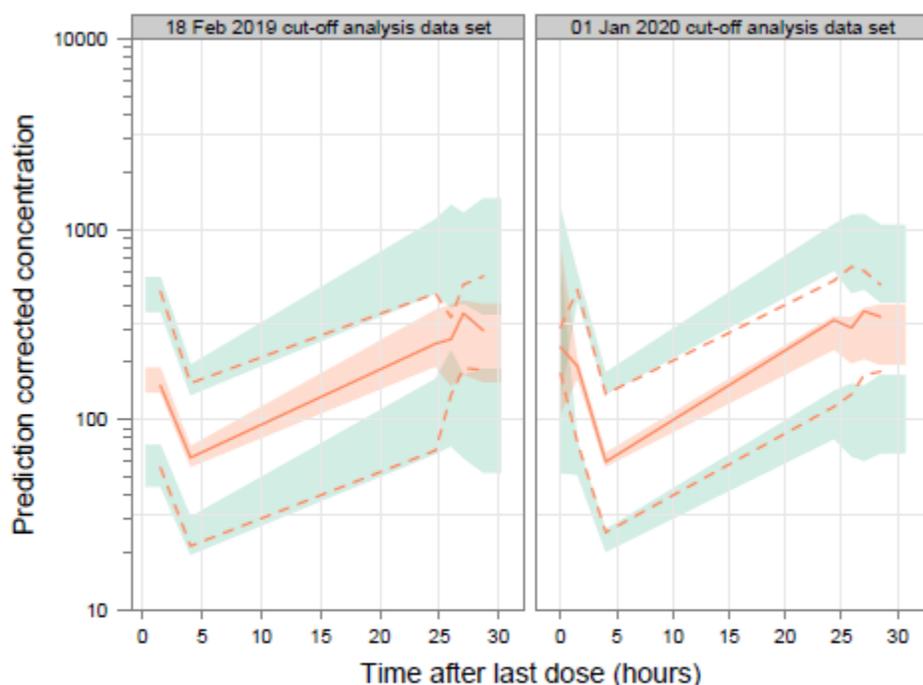
**Figure 39: Observations versus individual predictions of MSC2571109A plasma concentrations for the new subjects in the 01 January 2020 cut-off that were not in the 18 February 2019 cut-off**



Individual data points are indicated by dots and the points for each individual are connected with a line. Left panel using linear scales and the right panel use logarithmic scales. The black line is the line of unity and the red line is a smooth non-parametric trendline. One individual prediction associated with a CWRES=21.14 was excluded from the plot to improve readability.

Source: PMAR – Pharmacokinetic Addendum (01 January 2020 cut-off) Page 28, Figure 12.

**Figure 40: pcVPC of MSC2571109A concentrations versus time since first dose in study MS200095-0022.**



The data are presented on a log-linear scale. The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles, based on 100 simulated data sets. One observation associated with a CWRES=21.14 was excluded from the VPC of the 01 January 2020 cut-off analysis data set

Source: PMAR – Pharmacokinetic Addendum (01 January 2020 cut-off) Page 29, Figure 13.

The goodness-of-fit plots and model predictions showed the tepotinib and MSC2571109A concentrations from the 01 January 2020 cut-off and 18 February 2019 cut-off analysis data sets were generally in agreement with each other. The data in the 01 January 2020 cut-off analysis data set could be described by the final PK models, derived using the 18 February 2019 cut-off analysis data set.

**Reviewer's comments:**

*The population PK model developed by the applicant was verified by the reviewer. The model of tepotinib appears to be reasonable in general because there was a good agreement between observations and predictions. In the population PK model of MSC2571109A, the fraction of tepotinib metabolized to MSC2571109A (FM) was fixed to 1. The applicant assumed all the eliminated parent drug formed MSC2571109A, which is not consistent to the result of mass balance and bioavailability study EMR200095-007. The mass balance study suggested that metabolites accounting for substantial amount (48%) of recovered radioactivity (Figure 19).*

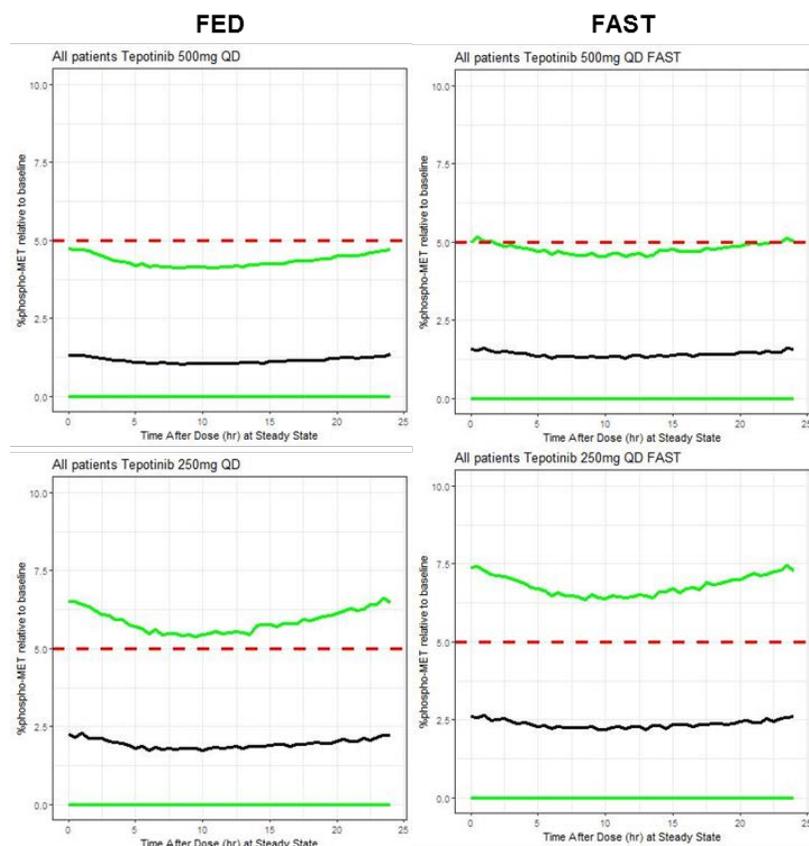
*Based on the final population PK model and previous developed population PKPD model for phosphor-c-Met inhibition, simulations were conducted to evaluate tepotinib exposures and phosphor-c-Met for patients at 250 mg q.d. or 500 mg q.d. dose regimens. The formulation of tepotinib is TF3 and tepotinib is taken with or without food. The simulation results showed that 500 mg q.d. of tepotinib in TF3 with food was expected to maintain the biologically meaningful target inhibition with  $\geq 95\%$  phosphor-MET inhibition at steady state in vast majority of patients. And 250mg and 500mg tepotinib in TF3 with food are predicted to be 6% and 4.8% higher than without food in population to maintain biologically meaningful target inhibition at steady state (Table 78 and Figure 41).*

**Table 78. Results of simulation of phospho-MET relative to baseline in human solid tumors**

Percentile of Patients not reach 95% Inhibition				
All Patients	Dose	Median	10 <sup>th</sup> – 90 <sup>th</sup> percentile	
FED	250	23.1	20.1	28.3
	500	9.6	8.81	10.6
FAST	250	29.1	24.5	34.8
	500	14.4	11.9	17.4

Source: Reviewer’s analysis

**Figure 41: Simulation of phospho-MET relative to baseline in human solid tumors**



The solid black curve represents the time profile of population median prediction of percentage phospho-MET inhibition relative to baseline, and the green lines represents a simulation-based 10% - 90% prediction interval for phospho-MET inhibition relative to baseline. The dashed lines indicate the PD threshold of 5% phospho-MET corresponding to 95% phospho-MET inhibition.

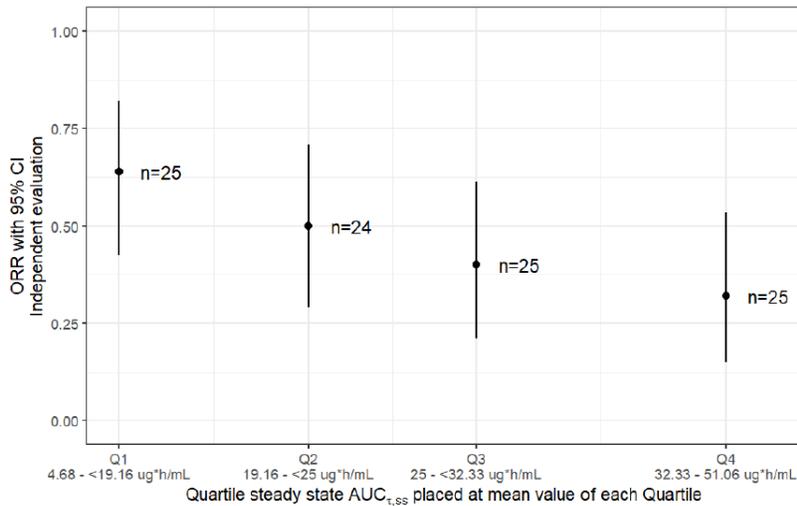
Source: Reviewer's analysis

### 19.4.3. Exposure-Response for Efficacy Analysis

The exposure-response relationships of overall response rate (ORR) and tepotinib exposure were evaluated with subjects in study MS200095-0022 cohort A. 99 subjects received first dose before April 02<sup>nd</sup> 2019 and overall 146 subjects had at least two post baseline assessments or discontinued treatment due to any reason. For subjects receiving first dose before April 2<sup>nd</sup>, 2019, Figure 42 showed that increasing exposures of tepotinib ( $AUC_{ss}$ ) were likely associated with decreased ORR. While the point estimates appear to decrease in a linear fashion, the 95% confidence interval (CI) of ORR overlap across all quartiles. For overall subjects, increasing tepotinib exposures,  $AUC_{ss}$ , were not associated with decreased ORR (Figure 43). Increasing

tepotinib exposures ( $AUC_{ss}$ ) were not associated with an increased DOR or PFS assessed by independent evaluation in subjects receiving first dose before April 02<sup>nd</sup>, 2019.

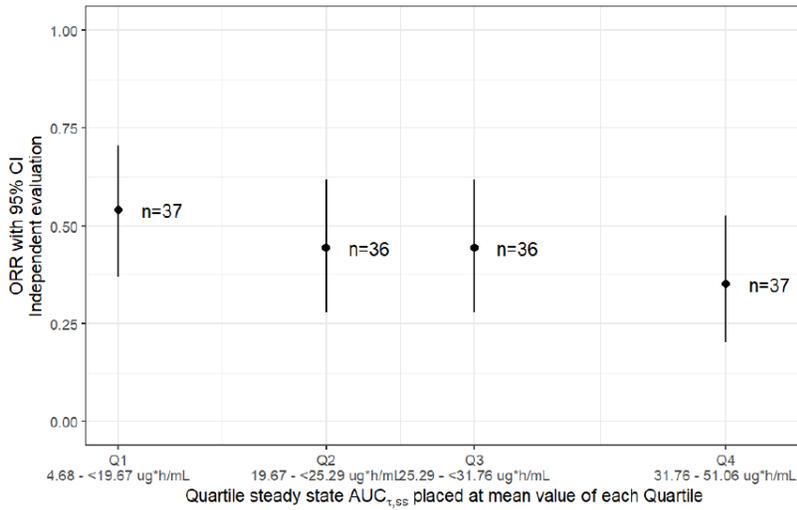
**Figure 42: ORR based on independent evaluation by tepotinib exposure ( $AUC_{ss}$ ) quartile in subjects receiving first dose before April 2<sup>nd</sup>, 2019**



Based on pooled data from patients positive for TBx+ (tumour biopsy) and/or LBx+ (liquid biopsy). The lines represent the Clopper-Pearson 95% CI (confidence interval) and the points are the observed ORR (objective response rate) per quartile. n is the number of subjects in each quartile. The values are placed at the mean value for each quartile on the x-axis.

Source: PMAR exposure - efficacy, 01 January 2020 cut-off, Page 41, Figure 6.

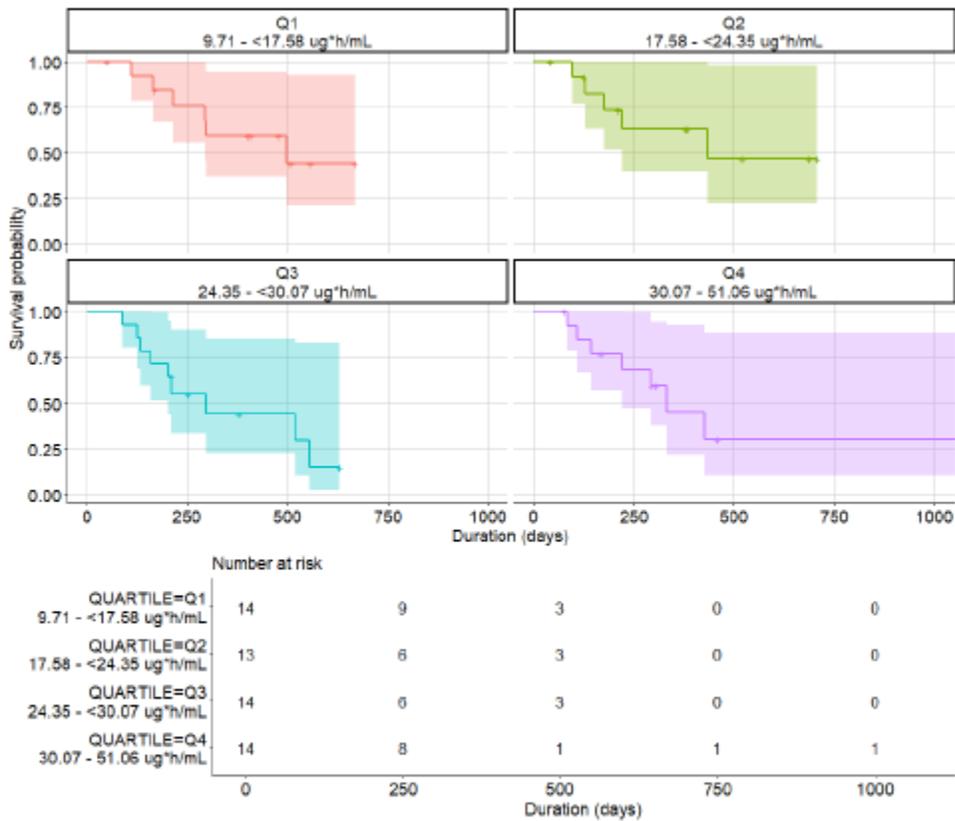
**Figure 43: ORR based on independent evaluation by tepotinib exposure (AUCs) quartile in overall subjects**



Based on pooled data from patients positive for TBx+ (tumour biopsy) and/or LBx+ (liquid biopsy). The lines represent the Clopper-Pearson 95% CI (confidence interval) and the points are the observed ORR (objective response rate) per quartile. n is the number of subjects in each quartile. The values are placed at the mean value for each quartile on the x-axis.

Source: PMAR exposure - efficacy, 01 January 2020 cut-off, Page 50, Figure 10.

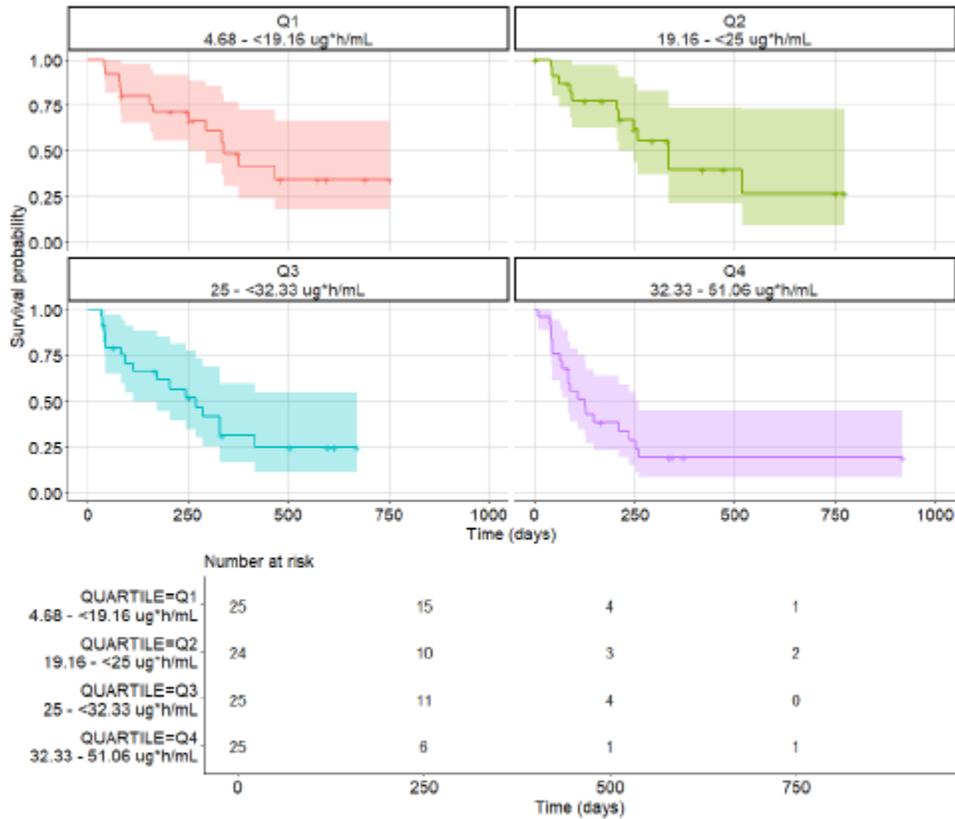
**Figure 44: KM plot of DOR based on investigator assessment, stratified by tepotinib steady state AUC (AUC<sub>ss</sub>) quartile - in subjects receiving first dose before.**



Based on pooled analysis data set from patients positive for TBx+ (tumour biopsy) and/or LBx+ (liquid biopsy). The lines represent the Kaplan-Meier (KM) estimate and the corresponding shaded area the 95% confidence interval.

Source: PMAR exposure - efficacy, 01 January 2020 cut-off, Page 66, Figure 16.

**Figure 45: KM plot of PFS based on investigator assessment, stratified by tepotinib steady state AUC (AUC<sub>ss</sub>) quartile - in subjects receiving first dose before.**



Based on pooled analysis data set from patients positive for TBx+ (tumour biopsy) and/or LBx+ (liquid biopsy). The lines represent the Kaplan-Meier (KM) estimate and the corresponding shaded area the 95% confidence interval.

Source: PMAR exposure - efficacy, 01 January 2020 cut-off, Page 67, Figure 17.

**Reviewer's comments:**

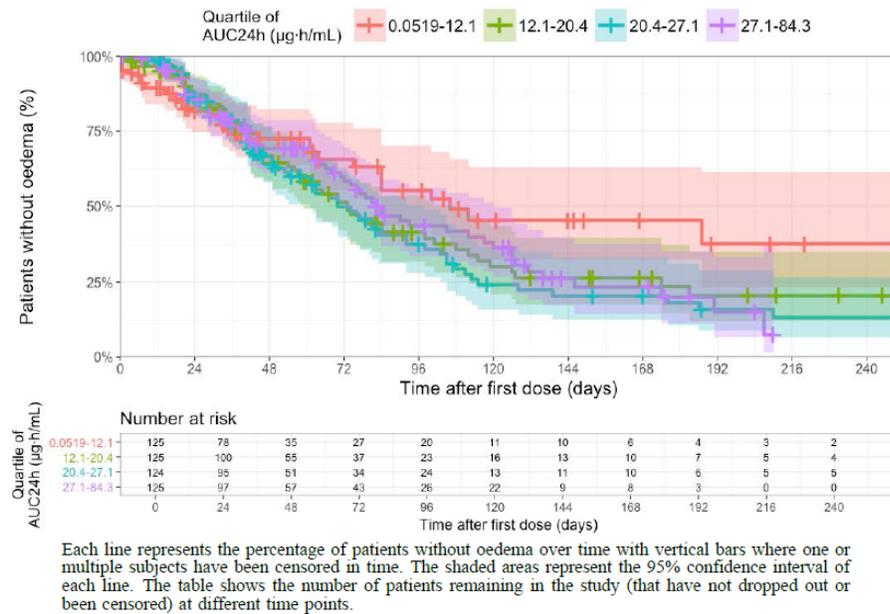
The results of the exposure-efficacy analysis for tepotinib were verified by the reviewer. Although the ORR appeared to decrease with increasing AUC<sub>ss</sub> quartiles in subjects receiving first dose before April 2<sup>nd</sup>, 2019, the confidence intervals for ORR overlapped from the first to fourth quartile. Overall, the ER relationships between ORR and exposures of tepotinib (AUC<sub>ss</sub>) is inconclusive because of the limited data from the trials at single dose level in small number of patients and potential confounding factors.

### 19.4.4. Exposure-Response for Safety Analysis

The relationship of safety endpoints and laboratory values including oedema (time to the first event and maximum severity grade of oedema), serum albumin, serum lipase, serum amylase, serum creatinine, AST and ALT concentrations with tepotinib exposures were evaluated in subjects from 5 completed studies: EMR200095-001, EMR200095-003, EMR200095-004, EMR200095-005 and EMR200095-007, and one ongoing study MS200095-0022 (Jan 1<sup>st</sup>, 2020 cut-off).

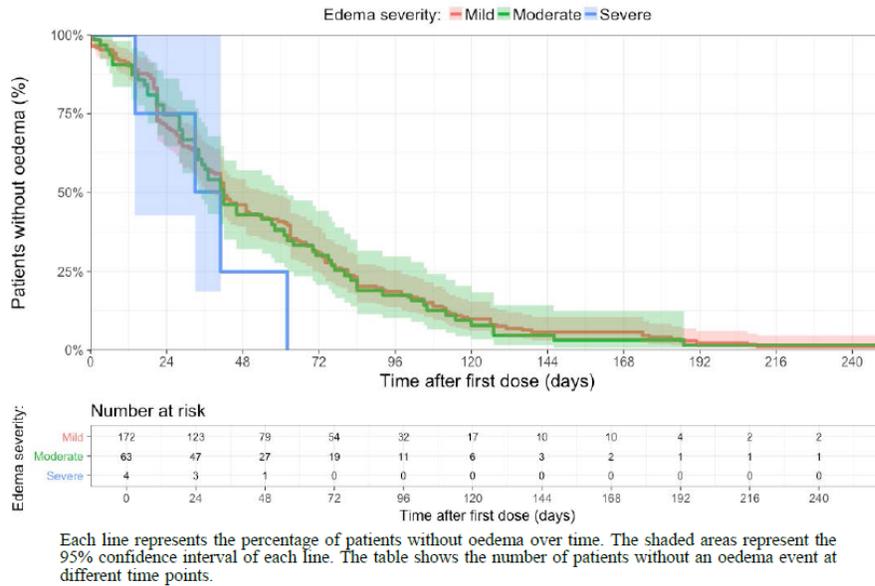
The ER analysis for oedema and tepotinib exposure ( $AUC_{24h}$ ) was shown in Figure 46. The KM plot indicates an increase in the risk of a first oedema event at  $AUC_{24h}$  above 12.1  $\mu\text{g}\cdot\text{h}/\text{mL}$  (first quartile). There is no clear association between severity grade of oedema and the time to the first oedema event (Figure 47), and the distribution of exposure appears to be similar across severity grades (Figure 48). The lack of association between exposure and severity grade is consistent across exposure metrics: the mean  $AUC_{24h}$  up until the event, the mean  $AUC_{24h}$  during the week prior to the event and the mean  $AUC_{24h}$  during the two weeks prior to the event.

**Figure 46: KM plot of time to the first oedema event stratified by quartiles of  $AUC_{24h}$  on the day of the oedema event or day of censoring.**



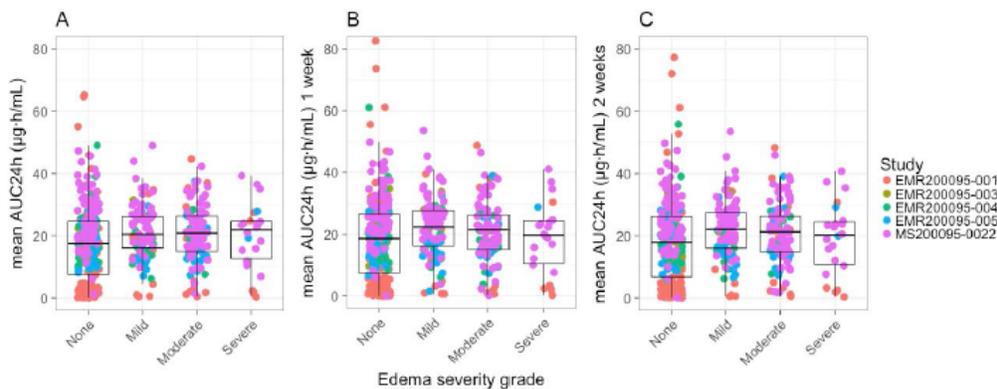
Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 46, Figure 8

**Figure 47: Time to first oedema event stratified by severity grade of the event.**



Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 47, Figure 9

**Figure 48: Distribution of mean AUC<sub>24h</sub> up until the time of the oedema event (A), mean AUC<sub>24h</sub> during one week prior to the oedema event (B) and mean AUC<sub>24h</sub> during two weeks prior to the oedema event (C) by oedema severity grade**



In the box plots, the middle line corresponds to the median, the upper and lower hinges correspond to the first and third quartiles (the 25<sup>th</sup> and 75<sup>th</sup>), the upper whisker extends from the hinge to the highest value that is within 1.5 IQR of the hinge, or distance between the first and third quartiles, the lower whisker extends from the hinge to the lowest value within 1.5 IQR of the hinge. IQR: inter quartile range.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 48, Figure 10.

A time-to-event model of the first oedema event was further developed by the applicant with a constant hazard. Tepotinib exposure did not have a significant impact on the hazard and only age was identified as a significant covariate in the final model (Table 79 and Figure 49)

**Table 79: Parameter estimates of the base and final TTE models**

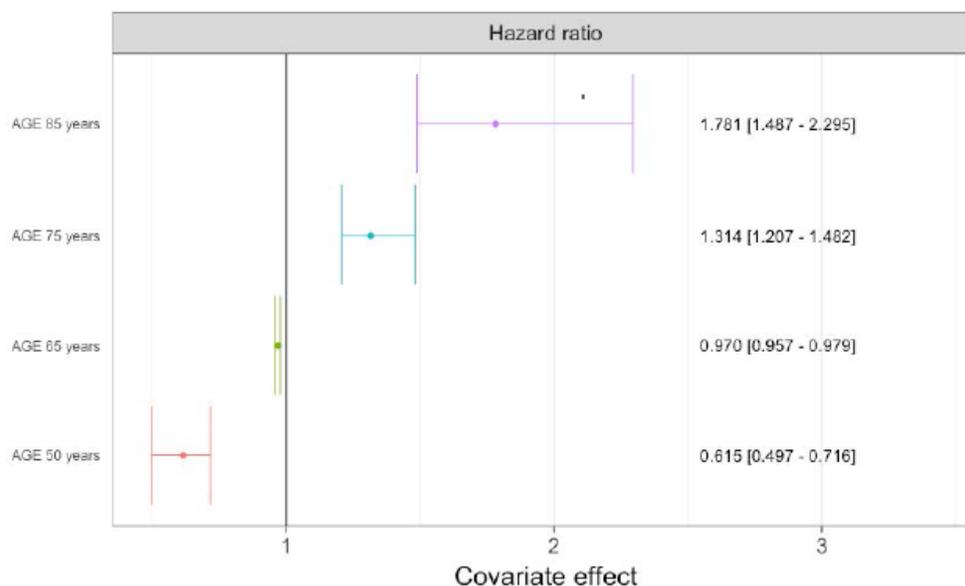
	Base TTE model		Final TTE model	
Run	1		7	
OFV	2808		2778.86	
Condition number	1		1.47	

	Unit	Base TTE model		Final TTE model	
		Value	RSE (%)	Value	RSE (%)
Base hazard		0.00764	6.47	0.00761	6.59
Age covariate on base hazard				0.0309	19.2

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 55, Table 17.

**Figure 49: Forest plot showing the impact of age on the predicted hazard ratio.**



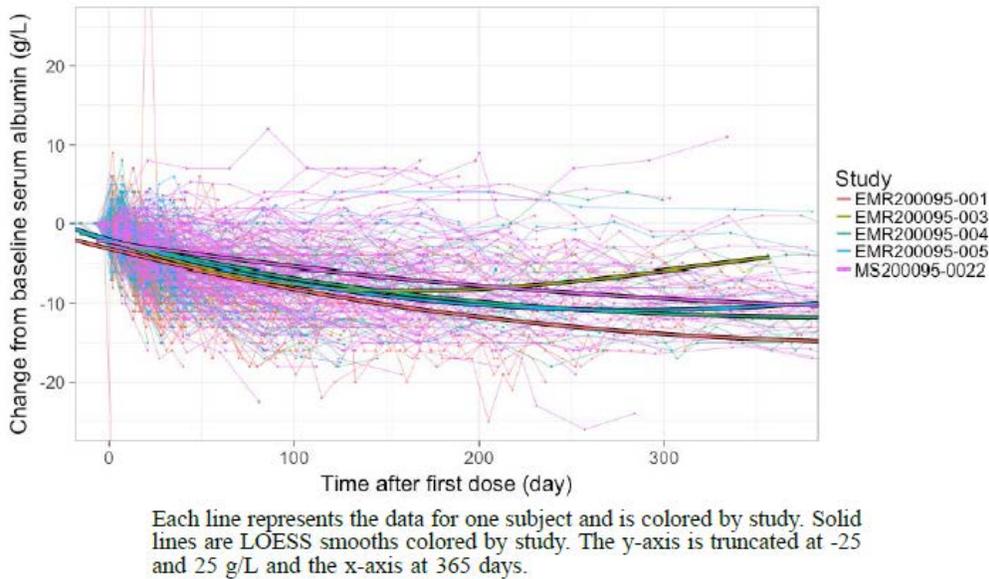
The closed symbols represent the median hazard ratio for the applicable age category. The whiskers represent the 90% CI of the median values, based on 100 bootstrap datasets. The vertical black line represents the hazard ratio for a typical patient in the analysis data set, aged 66 years.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 57, Figure 19.

Figure 50 showed the change from baseline serum albumin concentrations over time. There is a consistent trend towards a decrease in the observed serum albumin concentration over time. Figure 51 showed the maximal change from baseline in serum albumin concentration vs AUC<sub>24h</sub>

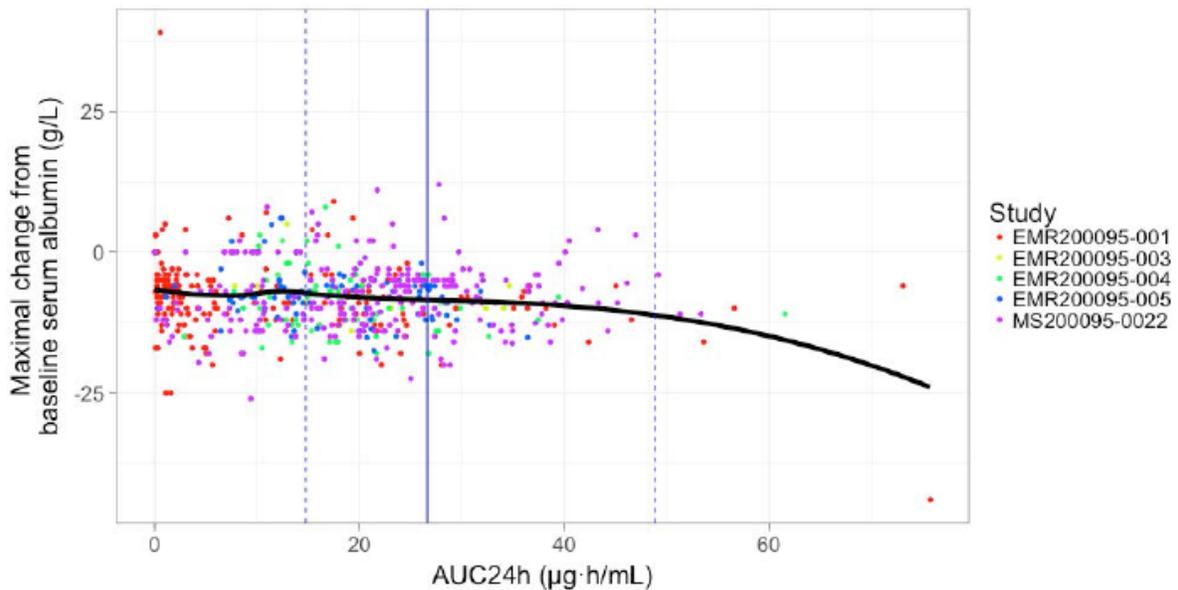
of tepotinib, and there is no clear association between the extent of tepotinib exposure and the maximum change from baseline serum albumin concentration.

**Figure 50: Observed change from baseline serum albumin concentration vs time after first dose stratified by study.**



Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 59, Figure 21.

**Figure 51: Observed individual maximal change from baseline serum albumin concentration vs AUC<sub>24h</sub> stratified by study.**



Dots represent observations and are colored by study. The solid black line is a LOESS smooth. The vertical blue lines indicate the PK model simulated median (solid line), 5<sup>th</sup> and 95<sup>th</sup> percentiles (dashed lines) of 24-hour area under the curve at steady state (AUC<sub>t,ss</sub>).

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 61, Figure 26.

An indirect pharmacodynamic response model was developed by the applicant to describe the time course of the changes in serum albumin over time. Parameter estimates and VPC plot were shown in Table 80 and Figure 52. The model estimated typical effect of tepotinib exposure

is to cause a maximum 26.1% decrease in serum albumin concentrations. The AUC<sub>50</sub> was estimated to be 0.215 µg·h/mL, which is small in relation to the expected AUC<sub>24</sub>.

**Table 80: Parameter estimates of the IDR model.**

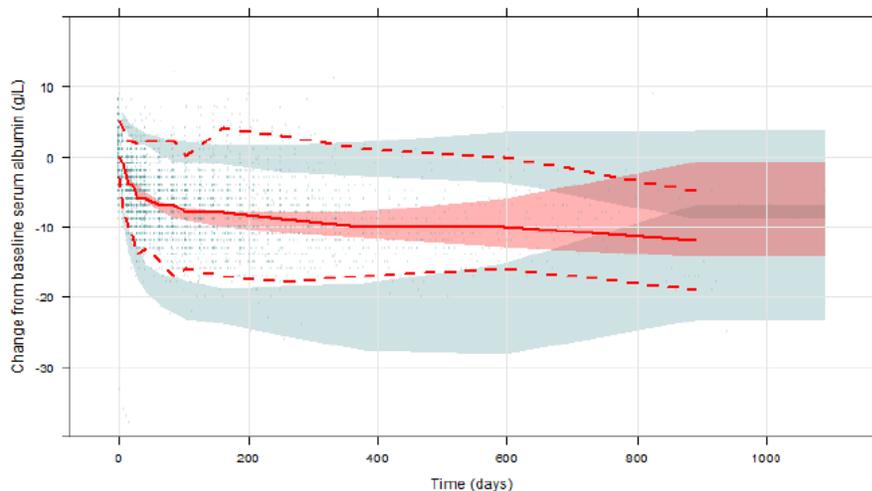
		Final IDR model	
Run		17	
OFV		16814.7	
Condition number		5.2	

		Final IDR model	
	Unit	Value	RSE (%)
Albumin baseline	(g/L)	37.9	0.627
K <sub>out</sub>	(days <sup>-1</sup> )	0.0240	3.74
AUC <sub>50</sub>	(µg · h/mL)	0.215	24.5
I <sub>max</sub>		0.261	2.21
IIV Albumin baseline		0.132	5.07
IIV K <sub>out</sub>		0.712	10.8
IIV I <sub>max</sub>		0.615	7.97

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 64, Table 20.

**Figure 52: VPC of the IDR of serum albumin, with and effect of tepotinib exposure (I<sub>max</sub> model)**



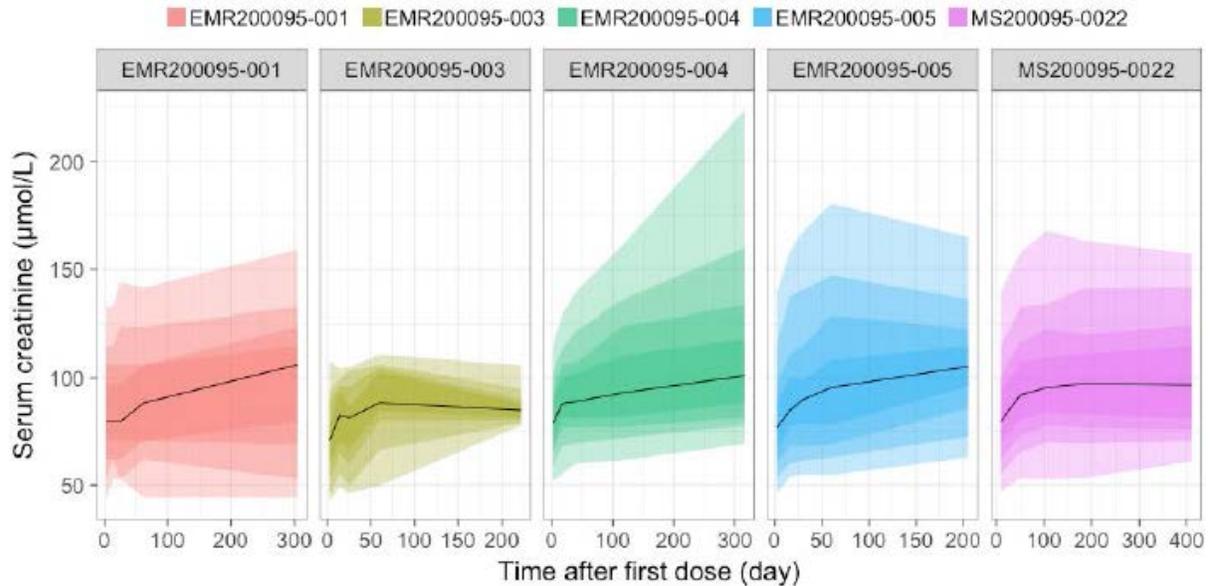
The solid and dashed red lines represent the observed median, 5<sup>th</sup> and 95<sup>th</sup> percentiles; the shaded red area represents the 95% confidence interval of the model predicted median and the shaded blue areas represent the 95% confidence interval of the model predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 62, Figure 27.

Figure 53 showed that there is an increase in the median observed serum creatinine concentration over time in all studies, while the observed change over time and individual

maximum change from baseline in serum creatinine does not indicate an association to tepotinib exposure (Figure 54 and Figure 55). Similar patterns were observed with the exposure of MSC2571109A (Figure 56 and Figure 57).

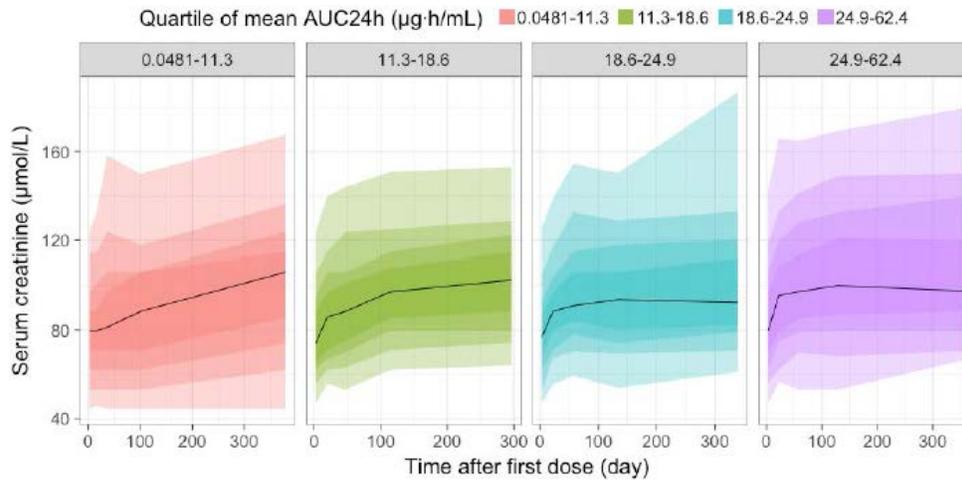
**Figure 53: Observed median serum creatinine concentration vs time after first dose stratified by study.**



The solid line is the median and the shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 5 intervals with an equal number of observations in each bin.

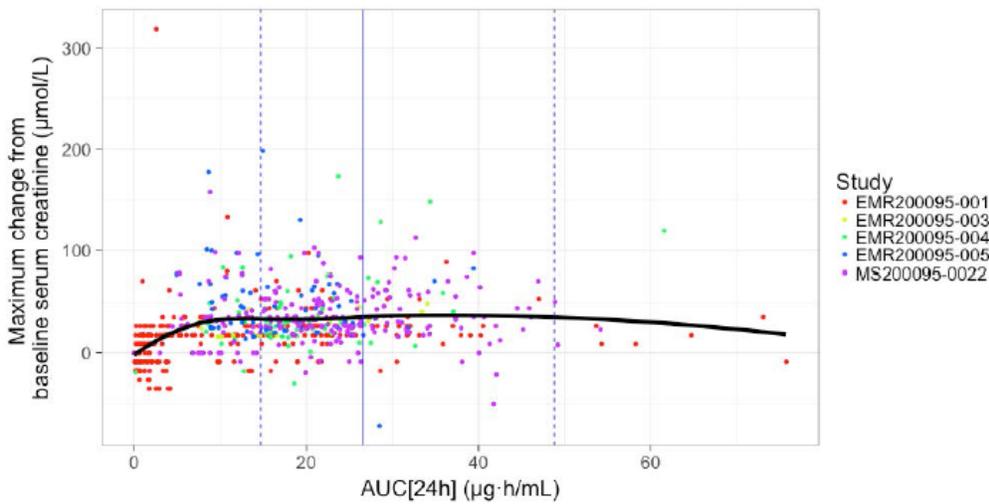
Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 75, Figure 45.

**Figure 54: Observed median serum creatinine concentration vs time after first dose stratified by mean tepotinib AUC24 quartile.**



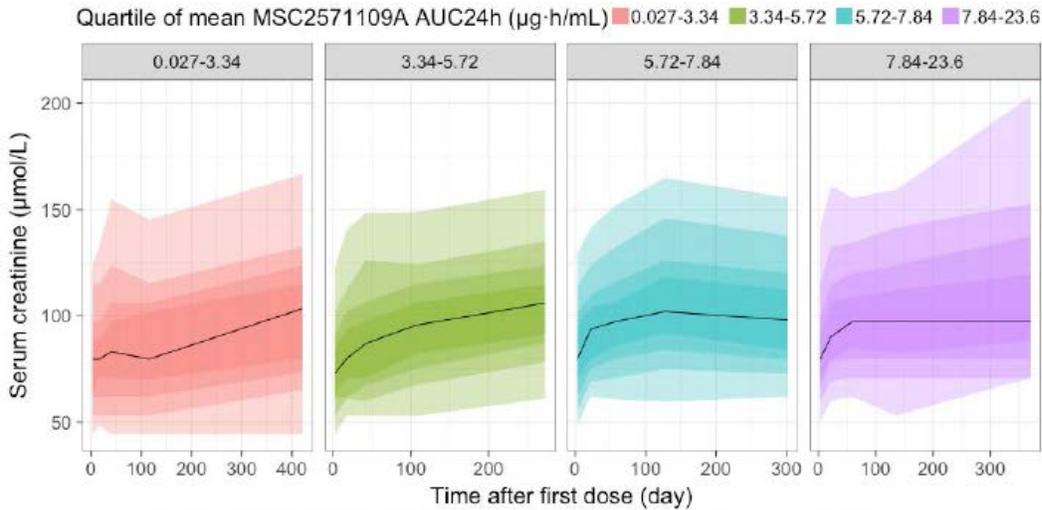
Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 76, Figure 47.

**Figure 55: Observed individual maximal change from baseline serum creatinine concentration vs tepotinib AUC24h stratified by study.**



Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 77, Figure 49.

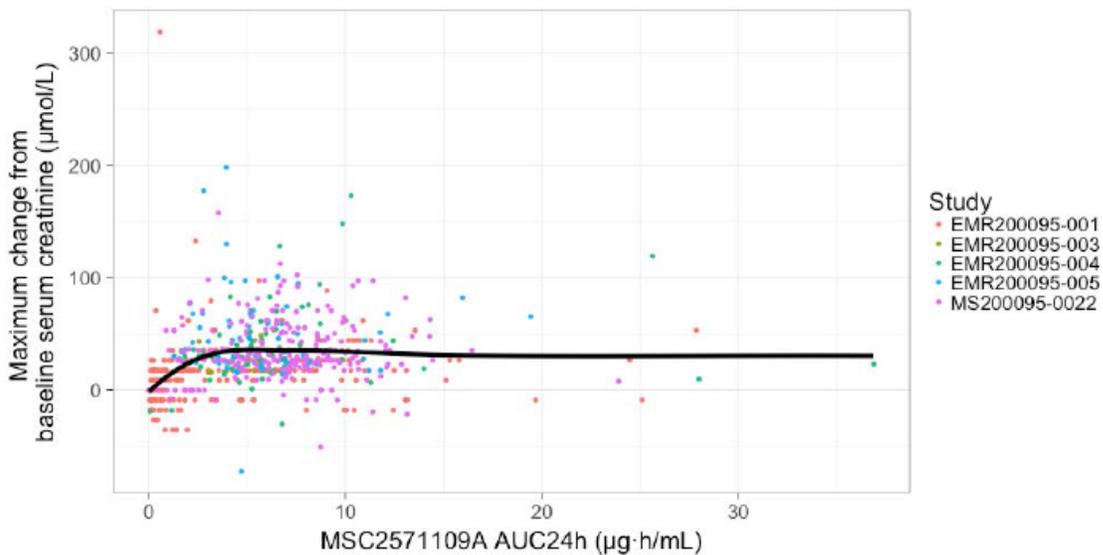
**Figure 56: Observed median serum creatinine concentration vs time after first dose stratified by mean MSC2571109A AUC<sub>24</sub> quartile.**



The solid line is the median and the shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 4 intervals with an equal number of observations in each bin.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 77, Figure 50.

**Figure 57: Observed individual maximal change from baseline serum creatinine concentration vs MSC2571109A AUC<sub>24</sub>h stratified by study.**

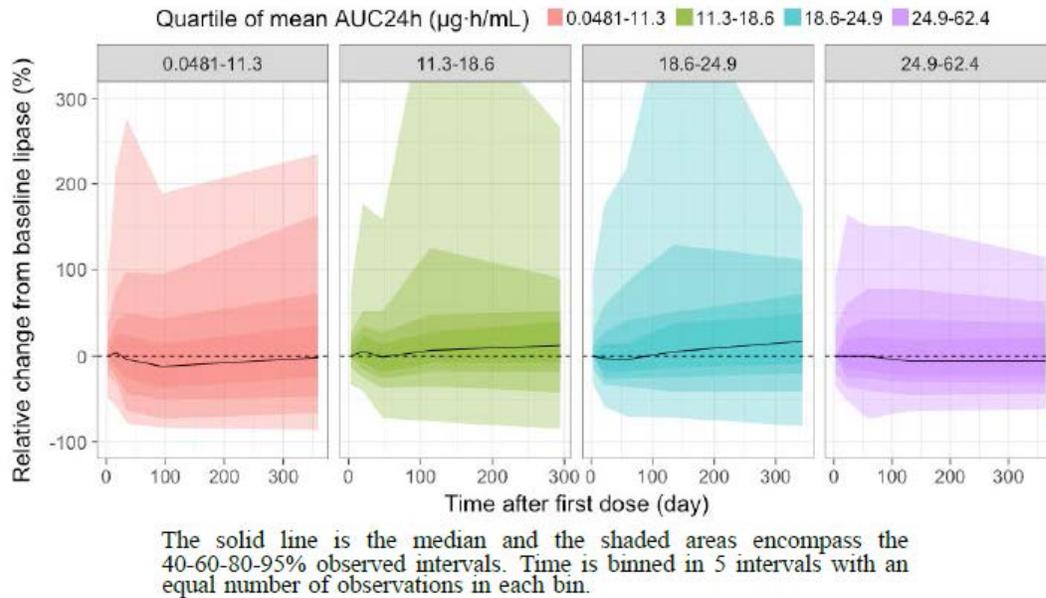


Dots represent observations and are colored by study. The solid black line is a LOESS smooth.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 78, Figure 52.

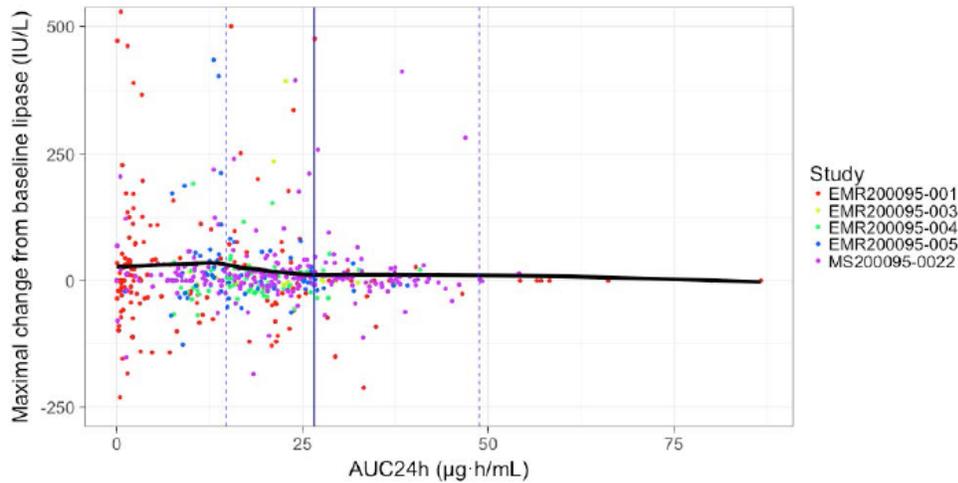
The relationship of other laboratory values: serum lipase, serum amylase, AST and ALT concentrations with tepotinib exposures were shown in Figure 58 - Figure 65. The graphical analysis do not suggest a correlation between the extent of tepotinib exposure and the change of the above laboratory values.

**Figure 58: Relative median change from baseline lipase concentration vs time after first dose stratified by mean AUC<sub>24</sub> quartile.**



Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 68, Figure 34.

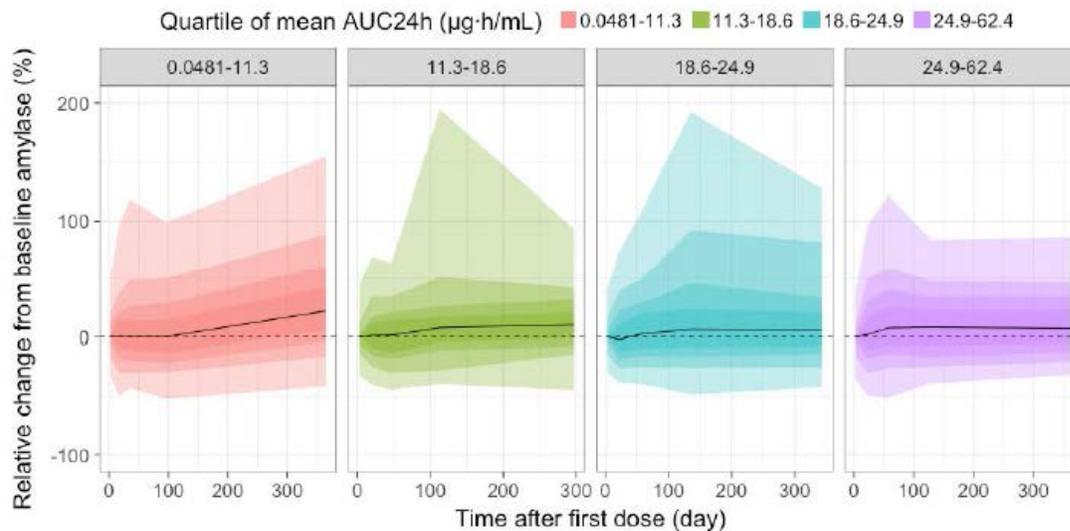
**Figure 59: Observed individual maximal change from baseline serum lipase concentration vs AUC24h stratified by study.**



Dots represent observations and are colored by study. The solid black line is a LOESS smooth. The vertical blue lines indicate the PK model simulated median (solid line), 5<sup>th</sup> and 95<sup>th</sup> percentiles (dashed lines) of AUC<sub>τ,ss</sub> at a dose of 500 mg. The y-axis is truncated at -250 and 500 IU/L.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 68, Figure 35.

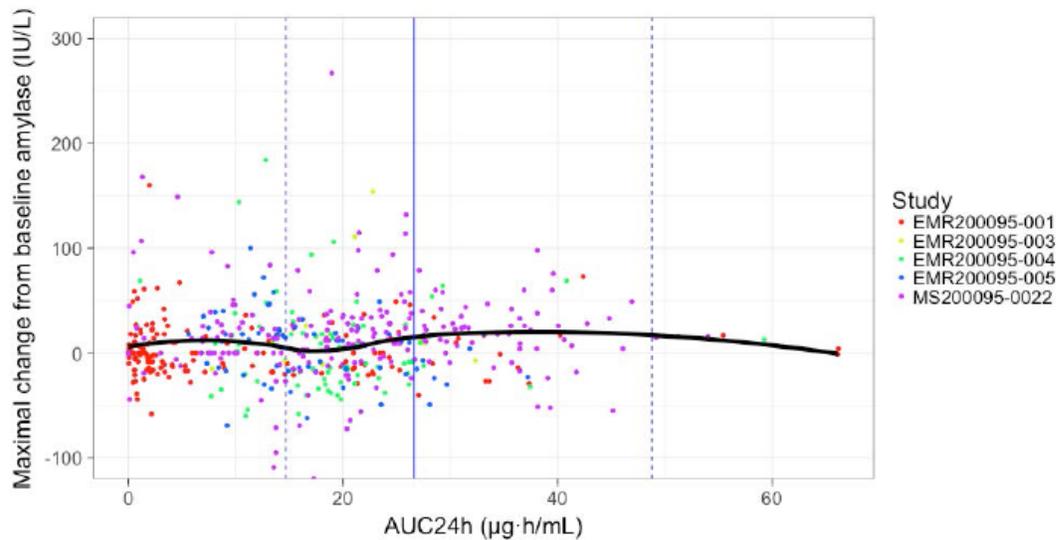
**Figure 60: Relative median change from baseline amylase concentration vs time after first dose stratified by mean AUC24 quartile.**



The solid line is the median and the shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 5 intervals with an equal number of observations in each bin.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 72, Figure 41.

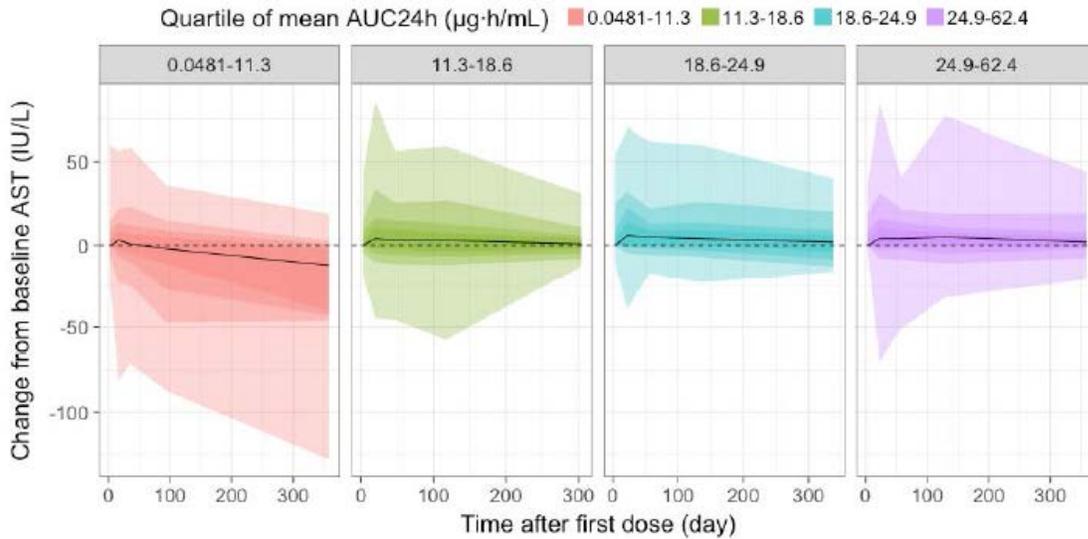
**Figure 61: Observed individual maximal change from baseline serum amylase concentration vs AUC24h stratified by study.**



Dots represent observations and are colored by study. The solid black line is a LOESS smooth. The vertical blue lines indicate the PK model simulated median (solid line), 5<sup>th</sup> and 95<sup>th</sup> percentiles (dashed lines) of  $AUC_{\tau,ss}$  at a dose of 500 mg. The y-axis is truncated at -100 and 300 IU/L.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 72, Figure 42.

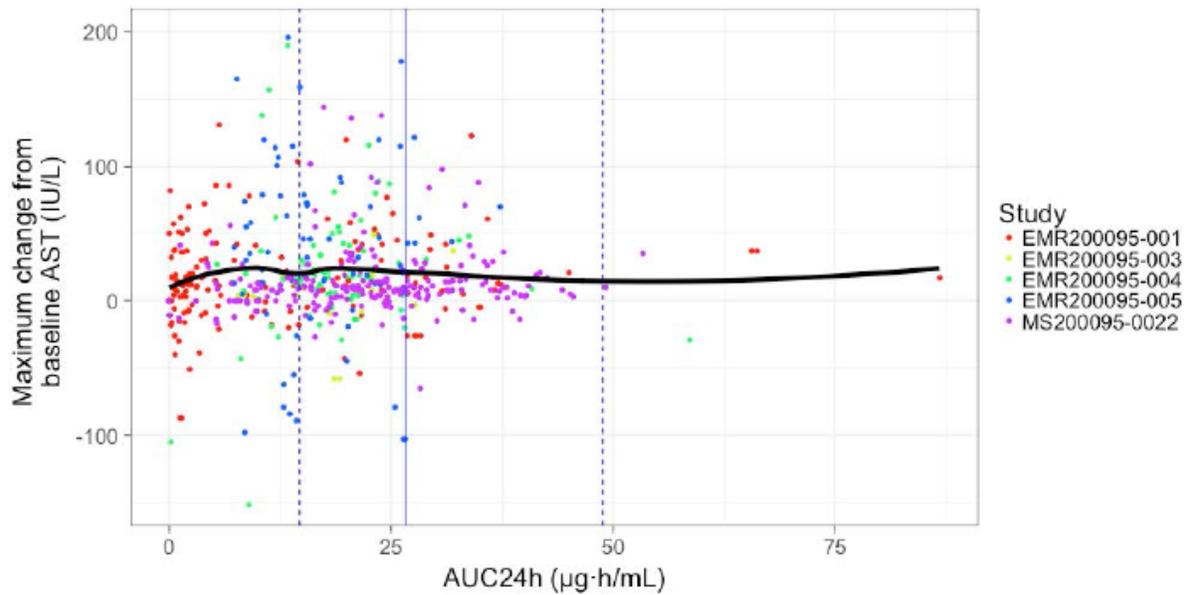
**Figure 62: Relative median change from baseline AST concentration vs time after first dose stratified by mean AUC24 quartile.**



The solid line is the median and the shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 4 intervals with an equal number of observations in each bin.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 83, Figure 59.

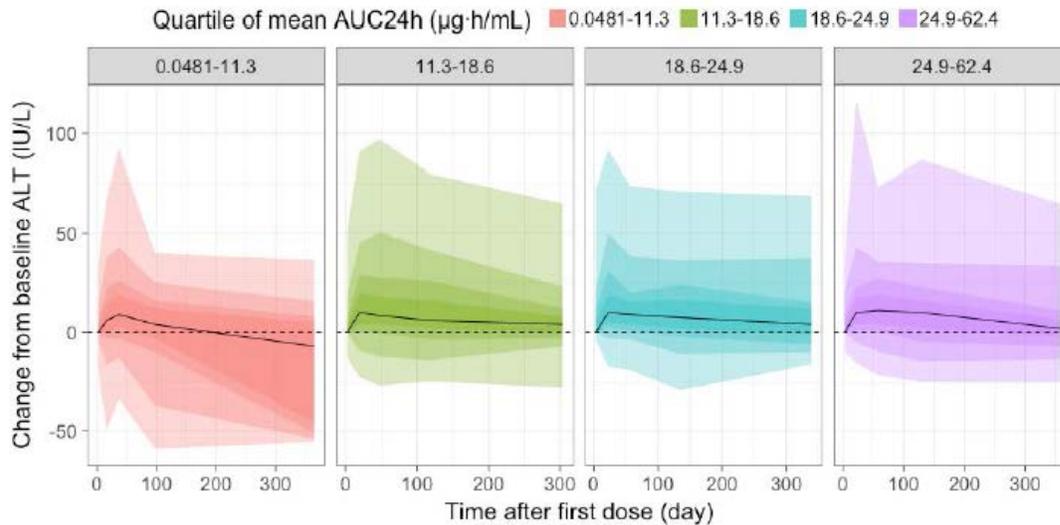
**Figure 63: Observed individual maximal change from baseline serum AST concentration vs AUC<sub>24h</sub> stratified by study.**



Dots represent observations and are colored by study. The solid black line is a LOESS smooth. The vertical blue lines indicate the PK model simulated median (solid line), 5<sup>th</sup> and 95<sup>th</sup> percentiles (dashed lines) of AUC<sub>τ,ss</sub> at a dose of 500 mg. The y-axis is truncated at -150 and 200

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 83, Figure 60.

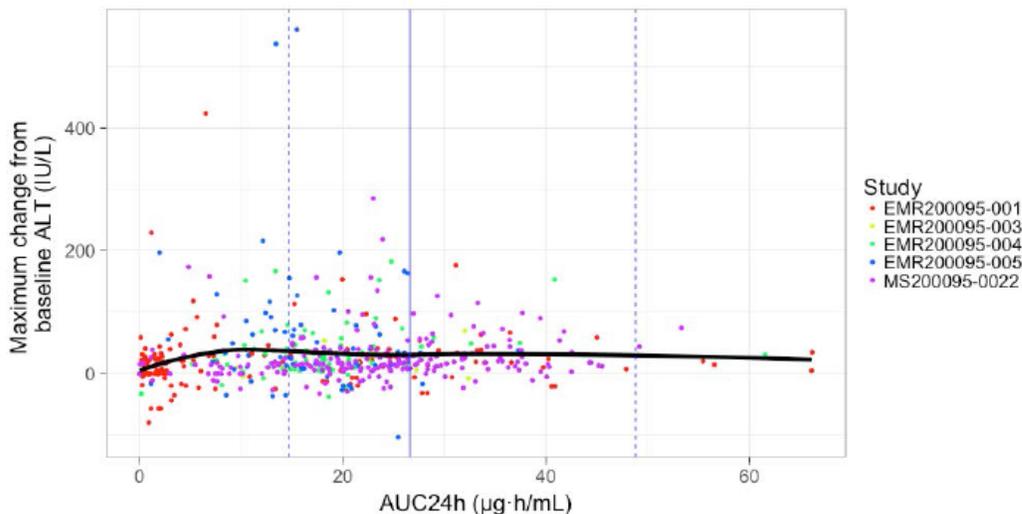
**Figure 64: Relative median change from baseline ALT concentration vs time after first dose stratified by mean AUC24 quartile.**



The solid line is the median and the shaded areas encompass the 40-60-80-95% observed intervals. Time is binned in 4 intervals with an equal number of observations in each bin.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 87, Figure 66.

**Figure 65: Observed individual maximal change from baseline serum ALT concentration vs AUC24h stratified by study.**



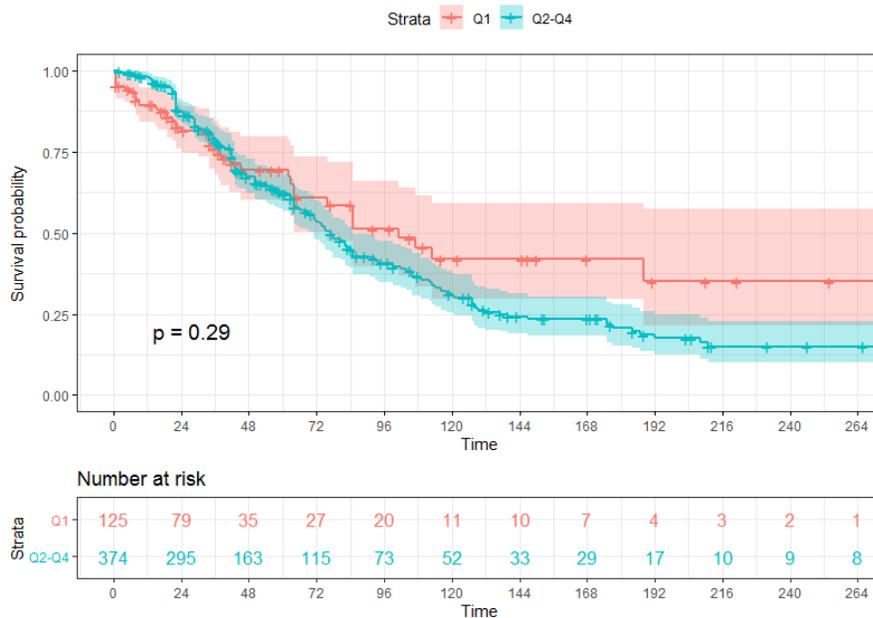
Dots represent observations and are colored by study. The solid black line is a LOESS smooth. The vertical blue lines indicate the PK model simulated median (solid line), 5<sup>th</sup> and 95<sup>th</sup> percentiles (dashed lines) of  $AUC_{\tau,ss}$  at a dose of 500 mg.

Source: PMAR exposure - safety, 01 January 2020 cut-off, Page 87, Figure 67.

**Reviewer’s comments:**

The results of the exposure-safety analysis for tepotinib were checked by the reviewer. Although The KM plots(Figure 46) indicates an increase in the risk of a first oedema event of oedema at AUC<sub>24h</sub> above 12.1 µg\*h/mL (above first quartile), the result is not statically significant (Figure 66).

**Figure 66: KM plot of time to the first oedema event stratified by AUC24h (Quartile1 vs Quartile2-4) on the day of the oedema event or day of censoring.**



Source: Reviewer’s Analysis

**19.4.5. Physiologically-based Pharmacokinetic Modeling**

**Executive Summary**

The aim of this review is to evaluate the adequacy of physiologically-based pharmacokinetic (PBPK) modeling to predict the drug-drug interaction (DDI) potential of tepotinib and metabolite MSC2571109A as CYP perpetrators. Specifically, the Applicant applied the PBPK modeling approach to assess the effects of tepotinib treatment on the exposures of warfarin (CYP2C9) and bupropion (CYP2B6).

The Division of Pharmacometrics has reviewed the PBPK reports [17-QPD200-P0, 17-QPD211-P0 and 17-QPD211-P0-addendum], response to request for information (submitted on 31 August 2020) and supporting modeling files to conclude the following:

- There is low potential for a clinically relevant interaction, via CYP2C9 inhibition, between tepotinib and a sensitive CYP2C9 substrate.
- PBPK analysis could not be used to estimate the effects of tepotinib treatment on a CYP2B6 substrate, such as bupropion, due to the uncertainty of the percentage contribution of CYP2B6 to bupropion clearance in the PBPK model. However, an assessment using the static model suggested the DDI risk for tepotinib treatment with a CYP2B6 substrate, via induction by MSC2571109A, is considered low.

## Background

Tepotinib and its main circulating metabolite MSC2571109A were evaluated as inhibitors of CYP enzymes. In vitro (HLM), tepotinib inhibited CYP2C8, CYP2C9, CYP2C19 and CYP3A; while MSC2571109A was a reversible inhibitor of CYP2C9 [XT085043- DMPK68-08] and showed a signal for CYP3A inactivation. The clinical liability of inhibition of CYP3A by parent and metabolite were excluded using the static model ( $R=1.01$ ) and the empirical shifted  $IC_{50}$  model (AUC ratio=1.00), respectively.

In vitro, metabolite MSC2571109A showed potential for induction of CYP3A4 and CYP2B6: a 23-fold increase in CYP3A4 mRNA and 7-fold increase in CYP2B6 mRNA were reported. Similarly, tepotinib induced up to 7-fold CYP3A4 mRNA in a concentration-dependent manner [XT163099]. Based on the static model, there was a potential for CYP3A induction by both parent and metabolite ( $R$  values of 0.25 and 0.07, respectively). Tepotinib treatment showed no clinically relevant effect on the exposure of the CYP3A substrate midazolam (AUC ratio=1.01 and  $C_{max}$  ratio =1.03) in the clinical DDI study MS200095-0030.

Although the potential for induction of CYP2C enzymes has not been evaluated in vitro, the negative DDI study with midazolam can be used to infer that the potential for induction of CYP2C enzymes via PXR activation is low.

At the plasma levels expected for the proposed therapeutic dose of 500 mg QD, the risk of clinical CYP-mediated DDIs were evaluated based on in vitro data for tepotinib and MSC2571109A, using the static model [18-DA0624-0] and PBPK modeling.

The aim of this review was verifying the adequacy of the PBPK analysis related to potential for clinical DDIs mediated by inhibition of CYP2C9 and induction of CYP2B6 with tepotinib treatment.

## Methods

### PBPK Model Structure

The PBPK analyses were performed using the population-based PBPK software Simcyp® (V17, Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). Predictions of plasma concentration-time profiles and drug-drug interactions were conducted using the software's

default healthy volunteer virtual population. The default compound files (software's library V17) for the CYP2C9 substrate Sim-S-Warfarin and the CYP2B6 substrate SV-bupropion were used in the DDI simulations.

The PBPK model of tepotinib was developed based on physicochemical properties, in vitro, and clinical PK data. The input parameters are described as follows. A first-order absorption model was used. The fraction absorbed ( $f_a=0.85$ ) was estimated according to the first-pass extraction ( $FPE=1-CL_{iv}/Q_h=0.15$ , where  $CL_{iv}$ = intravenous clearance =12.8 L/h [EMR200095-007] and  $Q_h$ =liver blood flow= 87 L/h) and the absolute bioavailability (=71.6%) from a tablet formulation (TF1) [Mass balance report 19-DA0128-0]. The unbound fraction in enterocytes (fugut) was assumed to be 1. An absorption constant rate ( $k_a=0.278$  1/h) was estimated from Population PK analysis [Pharmacometrics Pooled Population PK Report, April 2020]. The clearance value of 12.8 L/h following intravenous administration [EMR200095-007] was used to characterize tepotinib elimination. A minimal PBPK distribution model with single-adjustment compartment (SAC,  $Q=1.32$  L/h,  $V_{sac}=16.9$  L/kg,  $V_{ss}=31.4$  L/kg) was used to characterize tepotinib distribution based on estimates from Population PK analysis ( $Q/F=1.32$  L/h,  $V_c/F = 1020$  L and  $V_p /F= 1180$  L, using  $V_{ss}= V_c + V_p$  and  $V_{sac} = V_p$ , typical body weight of 70 kg). In vitro, the unbound fraction of tepotinib in plasma (fup) was 0.023 [DMPK 144-08], blood-to plasma ration (B/P) was 1 [DMPK 133-08] and albumin was the main plasma binding protein [DMPK 94-11 and DMPK 55-12].

The PBPK model of tepotinib metabolite MSC2571109A was developed based on physicochemical properties, in vitro, and clinical PK data. The model was built independently of the parent tepotinib model. Given the metabolite showed low peak-trough fluctuation, the Applicant used a continuous infusion model to describe a constant steady-state concentration. The clearance ( $CL_{iv}=3.5$  L/h) and dose were refined to recover the exposure of MSC2571109A observed in the clinical studies EMR200095-001, EMR200095-004, and EMR200095-005 (500 mg tepotinib QD in the fed state). The input parameters are described as follows. In vitro, the fup of MSC2571109A was 0.012, albumin was the main plasma binding protein [15-GR031-P0], and the B/P ratio was 0.77 [WBD 15-001]. A minimal PBPK distribution model with SAC ( $Q=106$  L/h,  $V_{sac}=2.17$  L/kg,  $V_{ss}=4.04$  L/kg) was used to characterize MSC2571109A distribution based on estimates from Population PK analysis ( $V_c = 131$  L and  $V_p = 152$  L, using  $V_{ss} = V_c + V_p$  and  $V_{sac} = V_p$ , typical body weight of 70 kg).

Of note, different formulations have been used in the development program of tepotinib, including capsule formulations CF1 and CF2, and tablet formulations TF1, TF2 and TF3. The tablet formulation TF1 showed higher bioavailability compared with the capsule formulation CF2 [EMR200095-001], providing the basis for the program to continue with TF1. Bioequivalence were demonstrated between TF1 and the subsequent TF2 [MS200095-0012] and between TF2 and TF3 [MS200095-0044]. TF3 is the commercial formulation, provided as

film-coated tablet containing (b) (4) drug substance (hydrochloride hydrate 250 mg). PBPK analysis mostly relied on data from TF1 for model development and validation.

**Reviewer’s comment:**

*The Applicant used a simplified PBPK model structure for the metabolite MSC2571109A. The metabolite was not formed via parent but considered as an independent compound, administered via continuous infusion, to recover the mean observed steady-state concentrations (low fluctuation) in the pivotal trials in patients. The Applicant claimed that it was not necessary to describe the disposition processes of MSC2571109A mechanistically, if the mean exposure was reasonably predicted, because the exposure drives the interaction effect. The Reviewer considered the Applicant’s simplified model structure acceptable for the intended purpose.*

The in vitro reversible inhibition  $K_i$  values for tepotinib and MSC2571109A towards CYP2C9, were 13.5 and 4.4  $\mu\text{M}$ , respectively [DMPK 68-08]. The unbound fraction in in vitro incubations (f<sub>u</sub>), was calculated to be 0.9 based on experimental conditions and Halifax-Houston method.

**Model performance**

The performance of the PBPK models for tepotinib and MSC2571109A was evaluated against steady-state PK from clinical studies EMR200095-001, -004, -005 and -006.

**Table 1. Simulations settings for model performance evaluation**

Parameter	Virtual population	Age	Gender	Trial x n subjects	Dose (mg/day)	Schedule	Simulation duration
Value/Input	North European Caucasian	18-95 years old	0.5 female	10 x 10	Tepotinib= 450 <sup>a</sup>	QD, orally, Fed state	Day 1 to Day 16
					MSC2571109=17.8 <sup>b</sup>	Continuous 24h infusion	

<sup>a</sup>450 mg tepotinib free base (MW 492.58 g/mol) corresponds to 500 mg tepotinib hydrochloride hydrate (MW 547.05 g/mol).

<sup>b</sup>This posology was selected to reproduce the steady-state exposure of MSC2571109 after administration of 500 mg tepotinib QD. (Source: Tables 9 and 10 of PBPK report 17-qpd211-p0-addendum).

**Sensitivity analyses**

Sensitivity Analysis of interaction parameters, i.e., the inhibition constant and the unbound fraction, were performed as part of risk analysis. The  $K_i$  and f<sub>u</sub> parameters were tested as 10-fold and 0.5-fold lower values than baseline, respectively, for both tepotinib and MSC2571109A. The AUC and C<sub>max</sub> ratios of S-Warfarin (in the presence/absence of inhibitors) was used as the end point of interest.

Sensitivity Analysis was also performed for the fraction unbound in plasma for both tepotinib and MSC2571109A, as part of the risk analysis to cover the uncertainty in parameters considered critical for the interaction potential. The sensitivity analyses regarding f<sub>u</sub> was

conducted within a 2-fold range of measured values, with the AUC and Cmax ratios of S-Warfarin as the end point of interest.

## Results

### Q1. Can PBPK analysis provide a reasonable description of the PK of tepotinib and its metabolite MSC2571109A in oncology population?

The concentration-time profile of tepotinib and its metabolite MSC2571109A were simulated following administration of 450 mg QD dosing of tepotinib (as free base and 17.85 mg metabolite). The comparison between observed PK parameters (Cmax and AUC) from studies EMR200095-001, -004, -005, and -006 the PBPK predictions are presented in Table 2. The steady-state exposure observed in individual studies is reasonably predicted by the PBPK model.

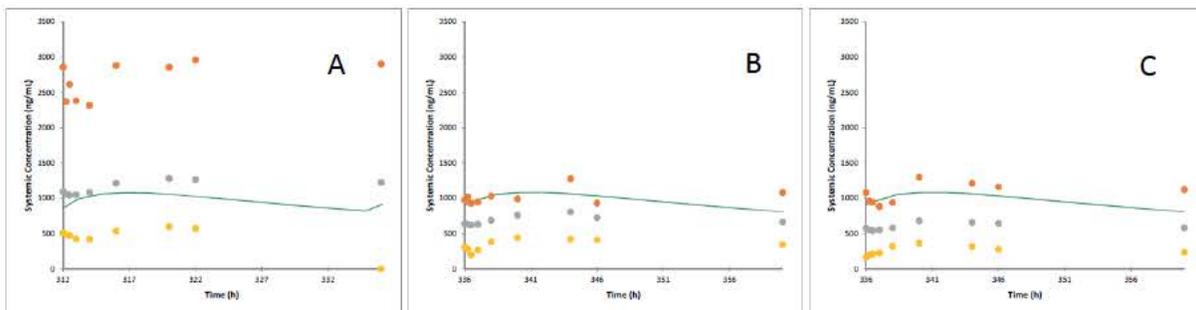
**Table 2. Predicted and observed tepotinib and MSC2571109A steady-state PK parameters**

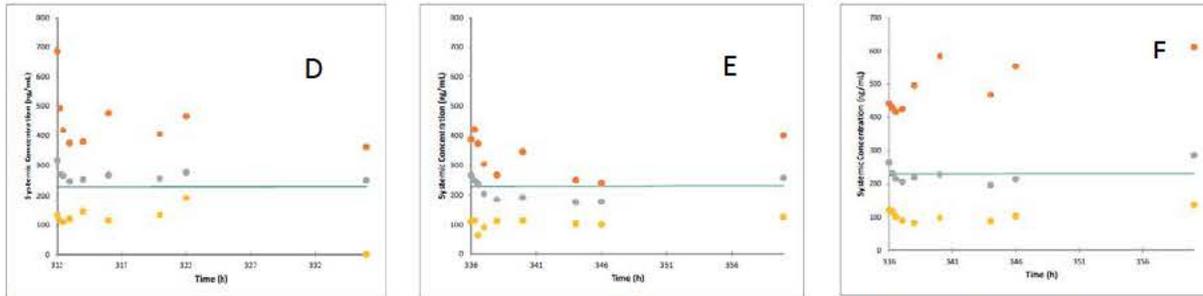
Clinical Study	Tepotinib				MSC2571109A			
	Observed		Predicted		Observed		Predicted	
	Cmax	AUC <sub>τ</sub>	Cmax	AUC <sub>τ</sub>	Cmax	AUC <sub>τ</sub>	Cmax	AUC <sub>τ</sub>
EMR200095-001 <sup>a</sup>	1291	27437	1026 (949- 1111)	21500 (20045- 23060)	335	6351	220 (209- 231)	5280 (5023- 5551)
EMR200095-004 <sup>b</sup>	815	16700			281	4690		
EMR200095-005 <sup>b</sup>	677	12900			303	4980		
EMR200095-006 <sup>c</sup>	1050	22200			444	7530		

Data presented as geometric means (and 90% confidence interval for the PBPK predictions). Units: Cmax (ng/mL) and AUC (ng/mL.h). Source: Respective CSR and PBPK report 17-qp211-p0-addendum). <sup>a</sup>Observed PK on Day 14 in subjects with solid tumors administered the tablet formulation TF1. <sup>b</sup>Observed PK on Day 15 in subjects with hepatocellular carcinoma administered the tablet formulation TF1. <sup>c</sup>Observed PK on Day 15 in subjects with Non-small Cell Lung Cancer administered the tablet formulation TF1.

Overall, there was also a reasonable agreement between PBPK predicted and observed PK profiles of tepotinib (Figures 1A, 1B and 1C) and MSC2571109A (Figures 1D, 1E, 1F).

**Figure 1. Predicted and observed steady-state plasma concentration-time profiles of tepotinib and MSC2571109A in phase 3 trials**





Plasma concentration time-profiles of tepotinib (A, B, and C) and MSC2571109A (D, E, and F) at steady-state. Mean PBPK predicted (green lines, n= 10 x 10), and observed data (mean [grey circles], minimum [yellow circles] and maximum concentrations [orange circles] at each sampling time point) from clinical studies (A,D) EMR200095-001, (B,E) EMR200095-004, and (C,F) EMR200095-005. (Source: Figures 5 and 6 of PBPK report 17-qpd211-p0-addendum)

Of note, the exposure to tepotinib and metabolite were in some degree lower in patients with hepatocellular carcinoma treated in clinical studies EMR200095-004 and -005. Population PK analysis concluded that hepatocellular carcinoma (disease covariate) significantly influenced the apparent clearance (CL/F) of tepotinib.

**Q2. Can PBPK analysis be used to estimate the effects of tepotinib treatment on a CYP2C9 substrate?**

Yes. PBPK DDI simulations were conducted between repeated doses of tepotinib (450 mg QD for 19 days, fed state) and MSC2571109A (17.8 mg over 24 h, for 19 days) and a single dose of S-warfarin (10 mg on Day 14), a CYP2C9 index substrate, using the default North European Caucasian population model (18-95 years-old, 50% female, 10 trials of 10 subjects per trial). The interaction effect of tepotinib treatment on S-warfarin in terms of predicted geometric mean [5<sup>th</sup>-95<sup>th</sup> percentiles] ratios for Cmax and AUC were 1.00 [1.00-1.00] and 1.01 [1.00-1.01], respectively (Table 3, baseline values).

In the sensitivity analyses of the in vitro CYP2C9 interaction parameter, namely Ki and fupic, and fup values, for both tepotinib and MSC2571109A, the geometric mean ratios for Cmax and AUC of S-warfarin were below the threshold of 1.25 for weak inhibition, in all cases individually and simultaneously. Results suggested minor risk of underprediction of inhibition potential of tepotinib treatment towards S-warfarin (Table 3).

Overall, PBPK analysis suggested the DDI risk, via CYP2C9 inhibition, between tepotinib treatment and a sensitive CYP2C9 substrate is low.

**Table 3. Warfarin AUC and Cmax ratio in the presence of tepotinib treatment (baseline and sensitivity analysis)**

Parameters	Fold-change	Value for tepotinib	Value for MSC2571109A	S-Warfarin AUC ratio <sup>a</sup>	S-Warfarin Cmax ratio <sup>b</sup>
CYP2C9 Ki (µM)	baseline	13.5	4.4	1.01 [1.00-1.01]	1.00 [1.00-1.00]

	0.1	1.35	0.44	1.05 [1.02-1.08]	1.01 [1.00-1.01]
fumic	baseline	0.9	0.9	1.01	1.00
	0.5	0.45	0.45	<1.01 [1.00-1.02]	1.00 [1.00-1.01]
fup	baseline	0.023	0.012	1.01	1.00
	2.0	0.046	0.024	<1.01 [1.00-1.02]	1.00 [1.00-1.00]
<i>All parameters simultaneously</i>	<i>0.1-2.0</i>			1.16 [1.05-1.28]	1.02 [1.02-1.3]

<sup>a</sup>Geometric mean [5<sup>th</sup>-95<sup>th</sup> percentiles] ratios of S-warfarin AUC and Cmax in the presence/absence of tepotinib treatment. Abbreviations: fup, fraction unbound in plasma; fumic, fraction unbound in microsomal incubation; Ki, inhibition constant. (Source: Tables 6 and 7 of PBPK report 17-qpd211-p0-addendum, and reviewer's analysis) .

### Q3. Can PBPK analysis be used to estimate the effects of tepotinib on a CYP2B6 substrate?

No. Limitations were found in the default bupropion library model that precluded its use as a CYP2B6 substrate for estimation of the effect of tepotinib using in vitro data. Bupropion is metabolized by several clearance pathways (CYP2B6, CYP2C19, CYP3A and dehydrogenases) and has a stereoselective metabolism<sup>1</sup>. The software developer has noted there is a divergence between emerging in vitro metabolic data and bupropion clinical DDI data. These factors led to difficulties in the characterization of contribution of CYP2B6 to bupropion clearance. Given the uncertainty in the fmCYP2B6 value in the bupropion PBPK model, any PBPK simulation predictions are inconclusive.

Given these uncertainties, the Applicant provided an assessment of DDI risk via CYP2B6 induction using the static model (Equation 1), assuming a maximum contribution of CYP2B6 (fm,CYP2B6 = 1) for a hypothetical sensitive substrate of CYP2B6.

$$\frac{AUC_i}{AUC} = \frac{1}{f_m \times f_{m,CYP2B6} \times \left(1 + \frac{Ind_{max} \times I_u}{IndC_{50} + I_u}\right) + \left(1 - (f_m \times f_{m,CYP2B6})\right)} \quad (1)$$

Where, fm (fraction metabolized)=1; fmCYP2B6 (contribution of CYP2B6 to clearance) =1; Indmax= 7.95 fold (Measured XT163099); IndC50=1.87 μM (Measured XT163099); Iu (perpetrator unbound steady-state concentration)= 0.00744 μM [0.62 μM (Steady-state average from Pop PK analysis) \* 0.012 (fraction unbound in plasma measured in 15-GR031-P0)].

The calculated AUC ratio of the hypothetical sensitive substrate of CYP2B6 in the presence and absence of the metabolite MSC2571109A was 0.97, in this worst-case scenario. Using a 10-fold lower IndC50 resulted in an AUC ratio of 0.77.

<sup>1</sup> Sager JE, Price LS, Isoherranen N. (2016) Stereoselective metabolism of bupropion to OH-bupropion, threohydrobupropion, erythrohydrobupropion, and 4'-OH-bupropion in vitro. Drug Metab Dispos.;44:1709-1719.

The results using the static model suggested the DDI risk for tepotinib treatment with a CYP2B6 substrate, via CYP2B6 induction by MSC2571109A, is considered low.

### Conclusions

PBPK analysis predicted that tepotinib treatment at the proposed therapeutic dose has low potential for a clinically relevant interaction via CYP2C9 inhibition with a sensitive CYP2C9 substrate such as S-warfarin.

PBPK analysis could not be used to estimate the effects of tepotinib treatment on a CYP2B6 substrate, such as bupropion, due to the uncertainty of the percentage contribution of CYP2B6 to bupropion clearance in the PBPK model. However, an assessment using the static model suggested the DDI risk for tepotinib treatment with a CYP2B6 substrate, via CYP2B6 induction by MSC2571109A, is considered low.

## 19.5. Additional Analyses Conducted by FDA

### The FDA's Assessment:

Please refer to section 8.1.2 Data Quality and Integrity further above for additional details regarding the 90-day efficacy update information in which FDA identified that some of the patients with responses reported in the 90-day efficacy update (July 2020 data cut-off) differed from some of the patients identified as responders in the original efficacy data (January 2020 data cut-off).

### Information request sent from FDA to EMD Serono on December 3, 2020:

- 1) Provide the following:
  - a. The proportion of responders in the overall population who have at least 6 months of follow-up for DOR post-response. Also provide the reason for any patients who have not been followed for at least 6 months post-response (excluding progression of disease)
  - b. The proportion of responders who are receiving tepotinib as first line therapy who have at least 12 months of follow-up for DOR post response.
- 2) Provide justification for the 6 months decrease in DOR for patient (b) (6) per the updated efficacy datasets
- 3) Given that the updated efficacy dataset was to provide at least 6 months of additional DOR follow-up for patients with a response at per the initially submitted dataset, provide the reason that the following 21 patients have 5 or less months of additional follow-up for DOR in the updated efficacy dataset: (b) (6)

- (b) (6)
- (b) (6)
- 4) Provide justification for patients (b) (6) having IRC assessed partial responses in the initially submitted efficacy dataset, but not in the updated efficacy dataset
  - 5) Provide justification for patient (b) (6) having a DOR start date of (b) (6) in the updated efficacy dataset, despite not being considered as having a response in the initial dataset. Similar issues were observed for patients (b) (6) provide clarifications regarding these patients as well.

**Information request response from EMD Serono on December 9, 2020:**

Changes in Tumor Assessments up to 01 January 2020 resulting in changes in OR or DOR between the 01 January 2020 and 01 July 2020 cutoffs A programmatic comparison between the 01 January and 01 July 2020 cutoff datasets identified patients for whom changes in tumor assessments were reported up to 01 January 2020 and resulted in changes in OR or DOR between the two cutoffs. This document describes eight patients with impact on OR or DOR (five and three patients, respectively), including two patients that were not discussed within the FDA Information Request received December 03, 2020. The identified changes were within the scope of the pre-defined independent imaging review process as described above and in the independent review charter.

For each of these patients, the reasons for changes are summarized below based on information provided (b) (4) All details on the assessments by reviewers 1 and 2 and by the adjudicator for these cases are provided in the attached (b) (4) files (refer to (b) (4) subject summary).

(b) (6) – change by both reviewers due to new cytology results. The best overall response (BOR) for this patient was reported as progressive disease (PD) at the 01 January 2020 cutoff and changed to partial response (PR) for the 01 July 2020 data cutoff. New imaging timepoints and newly received clinical data resulted in new global reviews. Based on two newly received negative cytologies (both received on 20 July 2020) reviewer 2 updated the timepoint assessments to PR from PD with comment “two negative cytology”. Similarly, reviewer 1 updated the PD assessments for timepoint (TP)7-TP10 to PR and reviewer 1 already had the previous timepoints assessed as PR. No adjudication was needed for the later review as both reviewers then assessed all TPs as PR.

(b) (6) – change by reviewer 1, due to new histology result The BOR for this patient was PD at the 01 January 2020 cutoff and PR at the 01 July 2020 data cutoff. New imaging timepoints and new clinical data resulted in new global reviews and adjudication. Due to additional imaging data received on (b) (6) and clinical data provided on 20 July 2020, global reviews were conducted in July 2020. Histology data was introduced based on independent review charter version 5.0. Based on the histology data of a lung biopsy, reviewer 1 updated their assessments to PR from PD with comment “biopsy negative for malignancy”. Adjudication was triggered for the first time (not required before) and the adjudicator agreed with reviewer 1.

(b) (6) – change by reviewer 1, due to new cytology result The independent review assessment for the (b) (6) (TP3) tumor evaluation visit was PR at the 01 January 2020 cutoff and PD at the 01 July 2020 cutoff. This change led to the new BOR of PD for this patient. The reason is that newly received clinical data resulted in new global reads and new adjudication. In detail, the positive cytology (collected on (b) (6) and received on 15 July 2020) resulted in a change of the assessment for the (b) (6) timepoint (TP3) by reviewer 1 from PR to PD (“Pleural fluid cytology positive”). Differences between reviewer 1 and reviewer 2 for TP3 and TP4 (PD vs PR) necessitated a new adjudication and the adjudicator selected again the opinion of reviewer 1.

(b) (6) – adjudicator reversal of reviewer selection due to additional time points. The independent review assessment for the (b) (6) (TP10) and subsequent tumor evaluation visit was PR at the 01 January 2020 cutoff and stable disease (SD) at the 01 July 2020 cutoff. This change led to the new BOR of SD for this patient. New imaging timepoints resulted in new global reviews and new adjudication. Adjudicator selected different reviewer (reviewer 1) during the July 2020 read due to the following rationale: “I agree with reviewer 1 for better assessment of target lesions as well as equivocal lesion.”

(b) (6) – adjudicator reversal of reviewer selection due to retraction of cytology. Change in DOR censoring status (from censored to event) provided in the data set of 01 July 2020 cutoff is driven by the fact that the independent review assessment for the (b) (6) (b) (6) (TP6) tumor evaluation visit was PR at the 01 January 2020 cutoff and PD at the 01 July 2020 cutoff. Clinical data were removed as instructed by managing CRO (b) (4) which resulted in new global reviews and new adjudication. In detail cytology (collected (b) (6) and sent on 10 January 2020) was done after start of a new anticancer therapy after permanent discontinuation of study drug so that it was asked to be removed from the (b) (4) database. Clinical data retraction resulted in a new global review and new adjudication. Adjudicator then agreed with reviewer 2 who assessed PD for TP6. PD was assessed due to increase in sum of the diameters of target lesions with 23.9% increase which is PD in RECIST 1.1. Adjudicator agreed with reviewer 2 with the following rationale: “better assessment of target lesion”.

(b) (6) – adjudicator reversal of reviewer selection due to new cytology results. The longer DOR for this patient provided in the data set of 01 July 2020 cutoff is driven by the independent review assessment for the (b) (6) (TP2) - (b) (6) (TP5) tumor evaluation visit which was SD at the 01 January 2020 cutoff and PR at the 01 July 2020 cutoff. This led to an earlier start of response and longer DOR. New imaging timepoints and newly received clinical data resulted in new global reads and new adjudication. The adjudicator now selected the other reviewer (reviewer 2) based on the following: “Cytology is negative so cannot consider PD on basis of pleural effusion at TP8.”

(b) (6) – adjudicator reversal of reviewer selection based on non-target lesion. The shorter DOR for this patient provided in the data set of 01 July 2020 cutoff is driven by the independent review assessment for the (b) (6) (TP11) tumor evaluation visit which was PR at the 01 January 2020 cutoff and PD at the 01 July 2020 cutoff. PD at the 01 July 2020 cutoff was reported due to a progression of a nontarget lesion. Due to new pleural histology data received on 20 July 2020, global reviews were conducted in July 2020 which triggered a new adjudication review. Adjudicator had previously selected reviewer 2. Based on the new global review, the adjudicator now selected reviewer 1, who assessed PD at TP11-TP13 with comment “better assessment of non-target lesion.” Of note, changes in OR or DOR based on tumor assessment visits after 01 January 2020, i.e., are linked to the longer follow-up time, are not covered in this document with the exception of patient (b) (6) (as per Request 5 within the FDA Information Request received December 03, 2020):

(b) (6) – based on additional time points. The BOR of independent review assessment was SD at the 01 January 2020 cutoff and PR at the 01 July 2020 cutoff. New imaging timepoints resulted in new global reviews and new adjudication. There were no changes to previously read timepoints by either reviewer. Reviewer 1 assessed PR at TP3 with a 32% decrease in sum of the diameter of target lesions while reviewer 2 assessed SD. For TP6 and TP7 both reviewers provided PR. The adjudicator maintained his/her selection of the opinion of reviewer 1, resulting in a BOR of PR at the 01 July 2020 cutoff.

### Summary and Conclusion

The independent imaging review process, as per the independent review charter used in the VISION study, is consistent with FDA Guidance and is a commonly used process (b) (4) (b) (4) across oncology studies. Data were analyzed based on the Sponsor-predefined cutoffs of 01 January and 01 July 2020. The OR and DOR differences observed due to incremental data between the two cutoffs are based on the independent review process as defined in the independent review charter. This ensured that the latest data were provided in this cutoff. The 01 July 2020 cutoff dataset constitutes the most complete dataset leading to an accurate evaluation of OR and DOR.

In conclusion, changes made in accordance to the independent review process had no impact on the data integrity and scientific and clinical validity of the VISION study. The benefit/risk assessment for tepotinib is positive for the treatment of patients with metastatic NSCLC harboring *MET*ex14 skipping alterations and offers an effective therapeutic solution in the proposed indication.

**Information request from FDA on December 23, 2020 and response from EMD Serono on December 31, 2020:**

**FDA Comment 1:** Submit the full radiological reports (including documentation of measurements) for the January 2020 and July 2020 cut-off dates from the global assessments in ALL eight patients for both Reviewer 1 and Reviewer 2 along with all adjudicator assessments. Include the specific dates of each time point (TP).

**EMD Serono Response:** Please refer to the copy of all timepoint by timepoint electronic imaging case report forms (eiCRFs) (refer to Module 5), as assessed by independent reviewers. Please note the following:

- 01 January 2020 cutoff data contains timepoint by timepoint and global reviews plus applicable adjudication eiCRFs.
- 01 July 2020 cutoff data contains additional timepoint by timepoint reviews and new global reviews plus applicable adjudication reviews.
- The captured date, completed at the end of each eiCRF, captures the date the independent reviewer had completed their assessment for that form.
- Global forms capture the exam date (i.e., imaging date) for each timepoint under the overall responses by timepoint section.

**FDA Comment 2:** For patient (b) (6) also submit the reports of the “new clinical data” (ie: two negative cytologies) cited as the reason for change in assessment by reviewer 2. Include the site of cytology (e.g., pleural fluid, lesion) and the date cytology samples were obtained as well as the results.

**EMD Serono Response:** Please refer to the copy of clinical data presented to the independent reviewers for patient (b) (6). This clinical information triggered updates by both independent reviewers, as captured below.

- Clinical Data Collected by Investigator site: negative for cancer cells, on (b) (6)
- Clinical Data received by (b) (4): 20 July 2020
- Global Review with Clinical Data: 21 July 2020
- During timepoint by timepoint review for Timepoint (TP) 2-TP6, Reviewer 2 noted new equivocal lesion as right pleural fluid from TP2 onwards, which later unequivocally enlarged at TP7. Based on this information, Reviewer 2 updated the assessments from

TP2 to TP6 from Partial Response (PR) to Progressive Disease (PD) during global read conducted on 17 June 2019. This was captured for the 01 January 2020 cutoff, as shown below. Based on the information provided within the clinical data regarding the cytology on 20 July 2020, all previous reviewed timepoints were updated to PR on the global form, as the pleural effusion was negative for cancer cells.

**FDA Comment 3:** For patient (b) (6) also submit a copy of the “new histology” report along with the accompanying procedure report. Please indicate if the lesion biopsied was the only lesion leading to the prior assessment of PD by reviewer 1. Additionally, based on the submitted Table in the response to the FDA comments from December 4, 2020, it appears that patient (b) (6) was read as progressive disease by both reviewers since TP2. Provide an explanation as to why this patient continued to receive treatment if the disease had progressed.

**EMD Serono Response:** Please refer to the copy of clinical data presented to the independent reviewers for patient (b) (6). This clinical information triggered updates by Reviewer 1, as captured below.

- Clinical Data Collected by Investigator site: negative for cancer cells, on (b) (6)
- Clinical Data with histology received (b) (4): 20 July 2020
- Global Review with Clinical Data: 27 July 2020 (Reviewer 2) and 28 July 2020 (Reviewer 1)
- During timepoint by timepoint review, Reviewer 1 noted new unequivocal lesion at right lung at TP2. This lesion persisted and was the only assessment for PD throughout timepoints. This was captured for the 01 January 2020 cutoff, as shown below. Based on the information provided within the clinical data regarding the cytology and histology, all previously reviewed timepoints were updated to PR on the global form, as the right lung lesion was negative for cancer cells. The Adjudicator selected the opinion of Reviewer 1, who made the update after looking at the clinical info with negative biopsy results.

As per study protocol, the decision on whether a patient continues treatment or not is based on the Investigator assessment. For patient (b) (6) the Investigator reported PD for the first time on (b) (4) (corresponding to TP8 in Figure 2), and therefore treatment was discontinued (i.e., last tepotinib dose was on (b) (6)).

**FDA Comment 4:** For patient (b) (6) also submit a copy of the report for the “positive pleural fluid cytology” that resulted in Reviewer 1 changing TP 3 assessment from partial response to progressive disease.

**EMD Serono Response:** Please refer to the copy of clinical data presented to the independent reviewers for patient (b) (6). This clinical information triggered updates for TP3 by Reviewer 1, as captured below. This update was based on bilateral pleural fluid, which was selected as nontarget lesion.

- Clinical Data Collected by Investigator site: positive for cancer cells, on (b) (6) (b) (5)
- Clinical Data received (b) (4): 15 July 2020
- Global Review with Clinical Data: 17 July 2020 (Reviewer 2) and 20 July 2020 (Reviewer 1)

**FDA Comment 5:** For patient (b) (6) also submit the precise report/information that led the adjudicator to agree with Reviewer 1 stable disease assessment on TP10 based on a “better assessment of target lesions as well as equivocal lesion” (i.e., specify the specific target lesions and equivocal lesion referenced).

**EMD Serono Response:** Please refer to a copy of eiCRFs completed by independent reviewers for patient (b) (6) and associated clinical data presented to the independent reviewers. In summary regarding reviewers’ assessments, differences between Reviewer 1 and Reviewer 2 for TP10-TP12 (stable disease [SD] vs PR) resulted in adjudication review. The difference between the 2 reviewers relies on target lesion and new lesion assessments. For target lesion, both reviewers focused on the same liver lesion with minor differences in measurements leading to SD vs PR (see details below). Reviewer 1 focused on the right pleural fluid as new lesion where Reviewer 2 focused on ascites as new lesion, both starting at TP8. Adjudicator preferred the overall opinion of Reviewer 1 due to overall assessments of target lesion as well as new lesions.

The following assessments specific to target lesions and new lesions were made by **Reviewer 1**:

- Target Lesion:
  - o Baseline Liver Lesion: 14.3 mm
  - o TP10 Liver Lesion: 10.4 mm – SD for target lesion assessment.
  - o TP11 Liver Lesion: 13.1 mm – SD for target lesion assessment.
  - o TP12 Liver Lesion: 11.7 mm – SD for target lesion assessment.
  - o TP13 Liver Lesion: 11.9 mm – SD for target lesion assessment.
  - o TP14 Liver Lesion: 10.2 mm – SD for target lesion assessment.
- Non-Target Lesion:
  - o TP2 – 14 Non-Target lesions: mediastinal lymph nodes + bone axial skeleton: all remain Non-complete response (CR)/Non-PD throughout.
- New Lesion:
  - o Unequivocal new lesion as right pleural fluid leading to overall tumor assessment of PD starting with TP8 impacting TP10-14 leading to overall tumor assessment of PD.
- Overall assessment of PD for timepoint by timepoint review. Then, during global review,

clinical data (i.e., negative cytology) is provided. The overall assessment of PD is changed to SD for TP8-12.

The following assessments specific to target lesions and new lesions were made by Reviewer 2:

- Target Lesion:
  - o Baseline Liver Lesion: 14 mm
  - o TP10 Liver Lesion: 9.2 mm – PR for target lesion assessment.
  - o TP11 Liver Lesion: 9.3 mm – PR for target lesion assessment.
  - o TP12 Liver Lesion: 9.3 mm – PR for target lesion assessment.
  - o TP13 Liver Lesion: 11.9 mm – SD for target lesion assessment.
  - o TP14 Liver Lesion: 10.9 mm – SD for target lesion assessment.
- Non-Target Lesion:
  - o TP2 – 14 Non-Target lesions: liver right lobe + bone vertebrae: all remain Non-CR/Non-PD throughout.
- New Lesion:
  - o Equivocal new lesion as ascites starting with TP8 remained equivocal throughout all timepoints.
- The overall assessment was not changed.

**FDA Comment 6:** For patient (b) (6) also submit the results of the cytology report that was retracted and clarify the specific timeline for the cytology collection, start of tepotinib, end of tepotinib treatment and start of a new anti-cancer therapy.

**EMD Serono Response:** Please refer to a copy of the retracted clinical data presented to the independent reviewers for patient (b) (6) during the 01 January 2020 cutoff.

The retracted cytology was taken around 2.5 months after stop of tepotinib treatment and initiation of pembrolizumab as subsequent therapy.

**Start of Tepotinib:** (b) (6)

**End of Tepotinib treatment:** (b) (6) due to PD reported by the Investigator

**Start of new anti-cancer treatment:** Pembrolizumab (b) (6)

Paclitaxel/Carboplatin since (b) (6) ongoing.

**Timepoint of cytology collection:** Cytology was done on (b) (6), negative for cancer cells.

**FDA Comment 7:** For patient (b) (6) also submit the cytology reports (and all procedural reports) referenced that led to the adjudicator's assessment that progression of disease had not occurred. While this may explain why findings were considered not consistent with PD at TP8, this does not explain the change in assessment of onset of response since the adjudicator had previously agreed with reviewer 1 who assessed SD at the 01 Jan 2020 cutoff. Please clarify

if the adjudicator changed the assessment of response at the 01 Jan 2020 cut-off and now agreed that PR was the appropriate assessment at that cut-off date rather than SD. If this is not the case, then appropriate date for onset of response would be TP6.

**EMD Serono Response:** Please refer to a copy of clinical data presented to the independent reviewers for patient (b) (6). This clinical information triggered updates by Reviewer 2, as captured below.

- Clinical Data Collected by Investigator site: all 3 were negative for cancer cells, on (b) (6) (b) (6)
- Clinical Data received (b) (4): 29 June 2020
- Global Review with Clinical Data: 30 June 20 (Reviewer 1) and 01 July 2020 (Reviewer 2)
- Per independent review charter, during radiology adjudication review, an independent radiologist who did not participate in the timepoint by timepoint and global radiology review for the subject will choose the opinion of the independent radiologist whose global radiology review assessments he/she agrees with most as the final assessment and provide justifying comments. Please note per independent review design, the Adjudicator can only select the opinion of one reviewer for the entire case comprising all the timepoints. Hence, the Adjudicator's decision was based on the review of the entire case by Reviewer 2. Reviewer 2 has evaluated PR beginning with TP2 leading to an onset of response at TP2.

**FDA Comment 8:** For patient (b) (6) also submit a copy of the "new pleural histology data" (including the exact date, the histology sample was obtained) that you reference in your description. Provide the specific location / nature of the non-target lesion cited in "better assessment of nontarget lesion" in the adjudicator comment which led to adjudicator agreement with reviewer 1 (PD).

**EMD Serono Response:** Please refer to the copy of clinical data presented to the independent reviewers for patient (b) (6).

- Clinical Data for histology Collected by Investigator site: negative for cancer cells on (b) (6) (b) (6)
- Clinical Data for histology received (b) (4): 20 July 2020
- The histology data received indicated negative for cancer cells in pleura. Both reviewers selected right pleural fluid and multiple lobes in the lung as non-target lesions. Reviewer 1 assessed multiple lesions in the lungs as PD starting from TP10 due to significant increase, where Reviewer 2 assessed those as Non-CR/Non-PD (NN).
- The lung and subcarinal node as target lesions responded and shrank, however both reviewers selected pleural effusion and multiple lung lesions as non-target lesions. This case is PD due to Reviewer 1 opinion of unequivocal progression of non-target lesions. Reviewer 2 did not consider this to be unequivocal progression of non-target lesions and therefore did not diagnose PD. The Adjudicator preferred the opinion of Reviewer 1 and

agreed that the progression of non-target lesions was unequivocal at the 01 July 2020 cutoff.

**FDA Comment 9:** For patient (b) (6) explain the change in assessment by reviewer 2 from TP3 to TP4 since once PR has been assessed the next timepoint assessment should still be PR unless findings are consistent with PD. Please indicate if DOR for this patient was calculated based on PR date of TP3 or PR date of TP6.

**EMD Serono Response:** Change in assessment from TP3 to TP4 is associated with Reviewer 1; please see below an explanation for the change in the assessment.

Based on RECIST 1.1 guidelines and the independent review charter, all overall timepoint assessments are possible following a PR, depending on the changes in percentages with respect to Nadir and Baseline. Stable disease at a timepoint is assessed when there is neither sufficient regression with regard to Baseline nor progression when compared with the Nadir. Reviewer 1 assessed PR at TP3 with 32.1% decrease in sum of diameters of target lesions with respect to Baseline. However, Reviewer 1 assessed SD at TP4 with now only a 25.5% decrease in sum of diameters of target lesions with respect to Baseline and 9.7% increase with respect to Nadir (TP3). The 9.7% increase does not trigger PD, yet at the same time this case is no longer a valid PR assessment at that timepoint. Similarly, Reviewer 1 assessed SD at TP5 with now only 19.7% decrease in sum of diameters of target lesions with respect to Baseline and 18.2% increase with respect to Nadir (TP3). As such the SD assessment following the prior PR is correct based on the percentage changes in relation to Baseline and Nadir values as per RECIST 1.1 and the independent review charter-defined rules.

Duration of response (DOR) was calculated from the time of initial response (in the case of patient (b) (6) based on the IRC assessment at (b) (6) [TP3]) in accordance with the VISION Study Integrated Analysis Plan (IAP), RECIST 1.1 as well as the FDA guidance document 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics'.

**FDA Comment 10:** IR relating to all responders included in the primary analysis population(s): Provide details regarding any responders who started new anti-cancer treatment after response and specify how DOR has been calculated for these patients.

**EMD Serono Response:** Based on the VISION Study Integrated Analysis Plan (IAP), Section 14.2.2, DOR was determined as follows:

"The DOR will only be evaluated in subjects that have an objective response. DOR is the time from when the CR/PR (whichever is first) criteria are first met until PD or death due to any cause within 84 days of the last evaluable tumor assessment, whichever occurs first (see Eisenhauer et al., 2009). DOR data will be censored on the date of the last evaluable tumor assessment for subjects who do not have an event (PD or death) or for subjects with an event

more than 84 days after the last evaluable tumor assessment.” As per definition, DOR was determined irrespective of whether a subject received new anti-cancer therapy or not.

Twenty-one responders (based on IRC assessment) received new anti-cancer therapy (drug therapy or radiotherapy; no surgeries were reported) after response:

- For 11 out of 21 responders, progressive disease based on IRC assessment was reported before the patients started new anti-cancer therapy.
- For 10 out of 21 responders (see Table 1), the start of new anti-cancer therapy occurred before a DOR event (either PD based on IRC or death). Of those 10 responders:
  - o For 9 responders (see first 9 patients in Table 1), DOR was censored at the last evaluable IRC assessment, which occurred on a date before the start of new anticancer therapy. 7 of those patients were discontinued from study treatment due to PD as assessed by the Investigator and 2 were discontinued due to adverse events.
  - o 1 responder (b) (6) died within 1 month after start of subsequent radiotherapy.  
IRC did not assess a PD as reported by the Investigator at the last available tumor assessment, no further tumor assessments were performed. In accordance with the IAP, the death date was taken as the end of duration of response date (see details in Table 1).

For details on response-related data as well as on the first new anti-cancer therapy for all 21 responders based on IRC assessment in VISION cohort A who received new anti-cancer therapy, refer to NDA214096\_FDA IR\_23Dec20\_VISION\_JUL20\_FUP\_Additional7\_20201228, Listing 16.2.5.2a (type, start date of subsequent therapy and IRC based tumor assessments) and Listing 16.2.5.6 (details on DOR-related data side-by-side with subsequent therapy dates).

**Listing of All Responders According to IRC in VISION Cohort A who Started New Anti-Cancer Treatment Before a Duration of Response Event (PD as assessed by IRC or Death) was reported (n=10) – Safety Analysis Set (N=152) - Data Cutoff 01 July 2020**

Patient ID	Start Date of Response (IRC)	End Date of Response (IRC)	Date of PD by Investigator	Start Date of First New Anti-cancer Therapy	DOR (months) / Event or Censored
(b) (6)			(b) (4)	(b) (4)	6.93 / censored
					8.54 / censored
					11.17 / censored
					8.11 / censored
					4.17 / censored
					5.65 / censored
					6.93 / censored
					6.93 / censored
					11.83 / censored
					9.49 / event (death)

Source: NDA214096\_FDA IR\_23Dec20\_VISION\_JUL20\_FUP\_Additional7\_20201228, Listing 16.2.5.6.

<sup>a</sup> After start of new anti-cancer therapy.

**Information request from FDA on January 8, 2021 and response from EMD Serono on January 11, 2021:**

**FDA Request:** In a single document, provide a listing of timepoints with dates (date of the scan for each timepoint) for each subject under review.

**EMD Serono Response:** A listing of timepoints with dates for each patient under review is provided (refer to “All Patients Visit Dates”). This document includes the VISIT during the study, the DATE OF EXAM, the TIMEPOINT as used by (b) (4) and the corresponding EVALUATION VISIT as used in the statistical outputs.

**FDA Request:** Indicate the location in your response to IR dated 12/31/2020 of the copies of

pathology reports (cytology/histology) which led to changes in IRC reads. If not included in that response, provide copies of these reports.

**EMD Serono Response:** Clinical data, as extracted from the clinical database, were provided to (b) (4) and shared with the independent reviewers as per independent review charter. These data were previously provided in response to the FDA request received December 23, 2020 (refer to clinical data for patients (b) (6) as provided in NDA 214096 sequence number 0054, submitted December 31, 2020).

In addition, copies of redacted source documents from the clinical sites are provided for these patients. Respective translations are provided for relevant patients (refer to Table 1 for an overview of the source documents and respective translations for patients (b) (6)

Of note, per the process defined in the independent review charter, these source documents are not provided to the independent reviewer.

## Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewers	Stephanie Aungst, PhD	CDER/DHOT	Sections: 5	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Amy Skinner, PhD	CDER/DHOT	Sections: 5	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Stephanie L. Aungst -S <small>Digitally signed by Stephanie L. Aungst -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001570045, cn=Stephanie L. Aungst -S Date: 2021.02.02 12:28:18 -05'00'</small>		Signature: Amy M. Skinner -S <small>Digitally signed by Amy M. Skinner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy M. Skinner -S, 0.9.2342.19200300.100.1.1=2002675349 Date: 2021.02.02 14:23:46 -05'00'</small>	
Nonclinical Supervisor	Whitney Helms, PhD	CDER/DHOT	Sections: 5	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Whitney S. Helms -S <small>Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2021.02.02 11:30:44 -05'00'</small>			
Nonclinical Team Division Director N/A (NME only)	John K. Leighton, PhD	CDER/DHOT	Sections: 5	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: John K. Leighton -S <small>Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2021.02.02 13:35:01 -05'00'</small>			
Clinical Pharmacology Reviewer	Huiming Xia, PhD	CDER/OTS/OCP	Sections: 6, 19.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: Huiming Xia -S <small>Digitally signed by Huiming Xia -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Huiming Xia -S, 0.9.2342.19200300.100.1.1=2001860291 Date: 2021.02.02 11:17:00 -05'00'</small>			
Clinical Pharmacology Team Leader	Jeanne Fourie-Zirkelbach, PhD	CDER/OTS/OCP	Sections: 6, 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: Jeanne Fourie Zirkelbach -S <small>Digitally signed by Jeanne Fourie Zirkelbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300434575, cn=Jeanne Fourie Zirkelbach -S Date: 2021.02.02 14:26:49 -05'00'</small>			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Pharmacometrics	Yangbing Li, PhD	CDER/OTS/OCP	Sections: 6, 19.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
				Signature: Yangbing Li -S (Affiliate) <small>Digitally signed by Yangbing Li -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002587726, cn=Yangbing Li -S (Affiliate) Date: 2021.02.02 11:36:21 -05'00'</small>
Clinical Pharmacology Pharmacometrics TL	Jiang Liu, PhD	CDER/OTS/OCP	Sections: 6, 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Jiang Liu -S <small>Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2021.02.02 11:27:32 -05'00'</small>
Clinical Pharmacology Physiologically-based Pharmacokinetics	Manuela Grimstein, PhD	CDER/OTS/OCP	Sections: 6, 19.4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
				Signature: Manuela D. Grimstein -S <small>Digitally signed by Manuela D. Grimstein -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000561102, cn=Manuela D. Grimstein -S Date: 2021.02.02 15:53:13 -05'00'</small>
Clinical Pharmacology Physiologically-based Pharmacokinetics TL	Xinyuan Zhang, PhD	CDER/OTS/OCP	Sections: 6, 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Xinyuan Zhang -S <small>Digitally signed by Xinyuan Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xinyuan Zhang -S, 0.9.2342.19200300.100.1.1=2000431943 Date: 2021.02.02 12:56:03 -05'00'</small>
Clinical Pharmacology Acting Deputy Division Director	Stacy Shord, PharmD	CDER/OTS/OCP	Sections: 6, 19.4	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Stacy Shord -S <small>Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2021.02.02 13:30:38 -05'00'</small>
Clinical Reviewer	Luckson Mathieu, MD	CDER/OOD/DO2	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 19.2, and 19.4.	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
				Signature: Luckson Mathieu -S <small>Digitally signed by Luckson Mathieu -S Date: 2021.02.02 12:18:52 -05'00'</small>

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Erin Larkins, MD	CDER/OOD/DO2	Sections: see CDTL	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Approved
				Signature: Erin A. Larkins -S5 <small>Digitally signed by Erin A. Larkins -S5  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  0.9.2342.19200300.100.1.1=0011520339, cn=Erin A. Larkins -S5  Date: 2021.02.02 11:24:52 -05'00'</small>
Statistical Reviewer	Pourab Roy, PhD	CDER/OTS/DBV	Sections: 8	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
				Signature: Pourab Roy -S <small>Digitally signed by Pourab Roy -S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pourab Roy -S  0.9.2342.19200300.100.1.1=2002680627  Date: 2021.02.02 15:01:44 -05'00'</small>
Statistical Team Leader	Pallavi Mishra-Kalyani, PhD	CDER/OTS/DBV	Sections: 8	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Pallavi S. Mishra-kalyani -S <small>Digitally signed by Pallavi S. Mishra-kalyani -S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  0.9.2342.19200300.100.1.1=2001675542, cn=Pallavi S. Mishra-kalyani -S  Date: 2021.02.02 11:15:54 -05'00'</small>
Division Director (OB)	Shenghui Tang, PhD	CDER/OTS/DBV	Sections: 8	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Shenghui Tang -S <small>Digitally signed by Shenghui Tang -S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175  Date: 2021.02.02 15:35:07 -05'00'</small>
Associate Director for Labeling (ADL)	William Pierce, PharmD, MPH	CDER/OOD	Sections: 11, USPI	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: William F. Pierce -S5 <small>Digitally signed by William F. Pierce -S5  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5  Date: 2021.02.02 11:51:38 -05'00'</small>
Cross-Disciplinary Team Leader (CDTL)	Erin Larkins, MD	CDER/OOD/DO2	Sections: All	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Erin A. Larkins -S5 <small>Digitally signed by Erin A. Larkins -S5  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  ou=People, 0.9.2342.19200300.100.1.1=0011520339,  cn=Erin A. Larkins -S5  Date: 2021.02.02 11:25:31 -05'00'</small>
Deputy Division Director (Clinical)	Harpreet Singh, MD	CDER/OOD/DO2	Sections: All	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Bonnie H. Moore -S <small>Digitally signed by Bonnie H. Moore -S  DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  ou=People, 0.9.2342.19200300.100.1.1=2001042285,  cn=Bonnie H. Moore -S  Date: 2021.02.02 17:39:25 -05'00'</small>

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/s/  
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STACIE A WOODS  
02/03/2021 09:55:44 AM

ERIN A LARKINS  
02/03/2021 10:07:43 AM

B HARPREET SINGH  
02/03/2021 10:11:12 AM

JULIA A BEAVER  
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