CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214096Orig1s003

Trade Name:	**TEPMETKO**
Generic or Proper Name:	tepotinib
Sponsor:	EMD SERONO INC
Approval Date:	February 15, 2024
Indication:	**TEPMETKO** is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

CENTER FOR DRUG EVALUATION AND RESEARCH

214096Orig1s003

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 214096/S-003

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING
REQUIREMENT

EMD Serono Research and Development Institute
Attention: Srinivas Patchala
Director, Global Regulatory Affairs-Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Srinivas Patchala:

Please refer to your supplemental new drug application (sNDA) dated and received April 25, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TEPMETKO (tepotinib) tablets.

This Prior Approval supplemental new drug application provides for revisions to US Prescribing Information to support the fulfillment of the subpart H postmarketing requirement and traditional approval of TEPMETKO (tepotinib) for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

SUBPART H FULFILLED

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated April 25, 2023, containing the final report for the following postmarketing requirement listed in the February 3, 2021 approval letter.

4013-1 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

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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).

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing commitment listed in the February 3, 2021, approval letter that is still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Jacqueline Glen, Regulatory Health Project Manager, at Jacqueline.Glen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Harpreet Singh, M.D.
Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIN A LARKINS
02/15/2024 03:14:59 PM
Supervisory Associate Director, DO2, as designated signatory authority for Dr. Harpreet Singh

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEPMETKO safely and effectively. See full prescribing information for TEPMETKO.

TEPMETKO® (tepotinib) tablets, for oral use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------

Indication and Usage (1)	02/2024
Dosage and Administration (2.3, 2.4)	02/2024
Warnings and Precautions (5.3)	02/2024

----------INDICATIONS AND USAGE----------

TEPMETKO is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations. (1)

----------DOSAGE AND ADMINISTRATION----------

- Select patients for treatment with TEPMETKO on the presence of *MET*ex14 skipping. (2.1, 14)
- Recommended dosage: 450 mg orally once daily with food until disease progression or unacceptable toxicity. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 225 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Interstitial Lung Disease (ILD)/Pneumonitis: Immediately withhold TEPMETKO in patients with suspected ILD/pneumonitis. Permanently discontinue TEPMETKO in patients diagnosed with ILD/pneumonitis of any severity. (2.4, 5.1)
- Hepatotoxicity: Monitor liver function tests. Withhold, dose reduce, or permanently discontinue TEPMETKO based on severity. (5.2)
- Pancreatic Toxicity: Monitor amylase and lipase. Withhold, dose reduce, or permanently discontinue TEPMETKO based on severity. (5.3)
- Embryo-fetal toxicity: TEPMETKO can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 20%) were edema, nausea, fatigue, musculoskeletal pain, diarrhea, dyspnea, decreased appetite, and rash. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased sodium, increased gamma-glutamyltransferase, increased amylase, increased lipase, increased ALT, increased AST, and decreased hemoglobin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Certain P-gp substrates: Avoid coadministration of TEPMETKO with P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicities. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for *MET*ex14 Skipping Alterations

Select patients for treatment with TEPMETKO based on the presence of *MET* exon 14 skipping alterations in plasma or tumor specimens. 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. An FDA-approved test for detection of *MET* exon 14 skipping alterations in NSCLC for selecting patients for treatment with TEPMETKO is not available.

2.2 Recommended Dosage

The recommended dosage of TEPMETKO is 450 mg orally once daily with food *[see Clinical Pharmacology (12.3)]* until disease progression or unacceptable toxicity.

Instruct patients to take their dose of TEPMETKO at approximately the same time every day and to swallow tablets whole. Do not chew, crush or split tablets. Patients who have difficulty swallowing solids can disperse tablets in water *[see Dosage and Administration (2.3)]*.

Advise patients not to make up a missed dose within 8 hours of the next scheduled dose.

If vomiting occurs after taking a dose of TEPMETKO, advise patients to take the next dose at the scheduled time.

2.3 Administration to Patients Who Have Difficulty Swallowing Solids

Place TEPMETKO tablet(s) in a glass containing 30 mL (1 ounce) of non-carbonated water. No other liquids should be used or added. Stir, without crushing, until the tablet(s) is dispersed into small pieces (tablets will not completely dissolve) and drink immediately or within 1 hour. Swallow the tablet dispersion. Do not chew pieces of the tablet. Rinse the glass with an additional 30 mL and drink immediately ensuring no residue remains in the glass and the full dose is administered.

If an administration via a naso-gastric tube (with at least 8 French gauge) is required, disperse the tablet(s) in 30 mL of non-carbonated water as described above. Administer the 30 mL of liquid immediately or within 1 hour as per naso-gastric tube manufacturer's instructions. Immediately rinse twice with 30 mL each time to ensure that no residue remains in the glass or syringe and the full dose is administered.

2.4 Dose Modifications for Adverse Reactions

The recommended dose reduction of TEPMETKO for the management of adverse reactions is 225 mg orally once daily.

Permanently discontinue TEPMETKO in patients who are unable to tolerate 225 mg orally once daily.

The recommended dosage modifications of TEPMETKO for adverse reactions are provided in Table 1.

Table 1: Recommended TEPMETKO Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.1)]*	Any Grade	Withhold TEPMETKO if ILD is suspected. Permanently discontinue TEPMETKO if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin *[see Warnings and Precautions (5.2)]*	Grade 3	Withhold TEPMETKO until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume TEPMETKO at the same dose; otherwise resume TEPMETKO at a reduced dose.
	Grade 4	Permanently discontinue TEPMETKO.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis *[see Warnings and Precautions (5.2)]*	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue TEPMETKO.
Increased total bilirubin without concurrent increased ALT and/or AST *[see Warnings and Precautions (5.2)]*	Grade 3	Withhold TEPMETKO until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume TEPMETKO at a reduced dose; otherwise permanently discontinue.
	Grade 4	Permanently discontinue TEPMETKO.
Increased lipase or amylase *[see Warnings and Precautions (5.3)]*	Grade 3	Withhold TEPMETKO until ≤ Grade 2 or baseline. If recovered to baseline or ≤ Grade 2 within 14 days, resume TEPMETKO at a reduced dose; otherwise permanently discontinue TEPMETKO.
	Grade 4	Permanently discontinue TEPMETKO.
Pancreatitis *[see Warnings and Precautions (5.3)]*	Grade 3 or 4	Permanently discontinue TEPMETKO.
Other adverse reactions *[see Adverse Reactions (6.1)]*	Grade 2	Maintain dose level. If intolerable, consider withholding TEPMETKO until resolved, then resume TEPMETKO at a reduced dose.
	Grade 3	Withhold TEPMETKO until resolved, then resume TEPMETKO at a reduced dose.
	Grade 4	Permanently discontinue TEPMETKO.

* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 225 mg, white-pink, oval, biconvex film-coated tablets with embossment “M” on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis, which can be fatal, occurred in patients treated with TEPMETKO *[see Adverse Reactions (6.1)]*. ILD/pneumonitis occurred in 2% patients treated with TEPMETKO, with one patient experiencing a Grade 3 or higher event; this event resulted in death. Five patients (1%) discontinued TEPMETKO due to ILD/pneumonitis.

Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold TEPMETKO in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified *[see Dosage and Administration (2.4)]*.

5.2 Hepatotoxicity

Hepatotoxicity occurred in patients treated with TEPMETKO *[see Adverse Reactions (6.1)]*. Increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST) occurred in 18% of patients treated with TEPMETKO. Grade 3 or 4 increased ALT/AST occurred in 4.7% of patients. A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). Four patients (0.8%) discontinued TEPMETKO due to increased ALT/AST. The median time-to-onset of Grade 3 or higher increased ALT/AST was 47 days (range 1 to 262).

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TEPMETKO, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue TEPMETKO *[see Dosage and Administration (2.4)]*.

5.3 Pancreatic Toxicity

Elevations in amylase and lipase levels occurred in patients treated with TEPMETKO *[see Adverse Reactions (6.1)]*. Increased amylase and/or lipase occurred in 13% of patients treated with TEPMETKO. Grade 3 and 4 increased amylase and/or lipase occurred in 5% and 1.2% of patients, respectively. Monitor amylase and lipase at baseline and regularly during treatment with TEPMETKO. Based on the severity of the adverse drug reaction, temporarily withhold, dose reduce, or permanently discontinue TEPMETKO *[see Dosage and Administration (2.4)]*.

5.4 Embryo-Fetal Toxicity

Based on findings in animal studies and its mechanism of action TEPMETKO can cause fetal harm when administered to a pregnant woman. Oral administration of tepotinib to pregnant rabbits during the period of organogenesis resulted in malformations (teratogenicity) and anomalies at exposures less than the human exposure based on area under the curve (AUC) at the 450 mg daily clinical dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential or males with female partners of reproductive potential to use effective contraception during treatment with TEPMETKO and for one week after the last dose. *[See Use in Specific Populations (8.1, 8.3)]*

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Pancreatic Toxicity *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to TEPMETKO in 506 patients with solid tumors enrolled in five open-label, single-arm studies receiving TEPMETKO as single agent at a dose of 450 mg once daily. This included 313 patients with NSCLC positive for *MET*ex14 skipping alterations, who received TEPMETKO in VISION. Among 506 patients who received TEPMETKO, 44% were exposed for 6 months or longer, and 22% were exposed for more than one year.

The data described below reflect exposure to TEPMETKO 450 mg once daily in 313 patients with metastatic non-small cell lung cancer (NSCLC) with *MET*ex14 skipping alterations in VISION *[see Clinical Studies (14)]*.

Serious adverse reactions occurred in 51% of patients who received TEPMETKO. Serious adverse reactions in > 2% of patients included pleural effusion (6%), pneumonia (6%), edema (5%), general health deterioration (3.8%), dyspnea (3.5%), musculoskeletal pain (2.9%), and pulmonary embolism (2.2%). Fatal adverse reactions occurred in 1.9% of patients who received TEPMETKO, including pneumonitis (0.3%), hepatic failure (0.3%), dyspnea from fluid overload (0.3%), pneumonia (0.3%), sepsis (0.3%), and death of unknown cause (0.3%).

Permanent discontinuation due to an adverse reaction occurred in 25% of patients who received TEPMETKO. The most frequent adverse reactions (> 1%) leading to permanent discontinuations of TEPMETKO were edema (8%), pleural effusion (1.6%), and general health deterioration (1.6%).

Dosage interruptions due to an adverse reaction occurred in 53% of patients who received TEPMETKO. Adverse reactions which required dosage interruption in > 2% of patients who received TEPMETKO included edema (28%), increased blood creatinine (6%), pleural effusion (3.5%), nausea (3.2%), increased ALT (2.9%), pneumonia (2.6%), decreased appetite (2.2%), and dyspnea (2.2%).

Dose reductions due to an adverse reaction occurred in 36% of patients who received TEPMETKO. Adverse reactions which required dose reductions in > 2% of patients who received TEPMETKO included edema (22%), increased blood creatinine (2.9%), fatigue (2.2%), and pleural effusion (2.2%).

The most common adverse reactions (≥ 20%) in patients who received TEPMETKO were edema, nausea, fatigue, musculoskeletal pain, diarrhea, dyspnea, decreased appetite, and rash. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased sodium, increased gamma-glutamyltransferase, increased amylase, increased lipase, increased ALT, increased AST, and decreased hemoglobin.

Table 2 summarizes the adverse reactions in VISION.

Table 2: Adverse Reactions in ≥ 10% of Patients with NSCLC with *MET*ex14 Skipping Alterations Who Received TEPMETKO in VISION

Adverse Reactions	TEPMETKO (N=313)	
	All Grades* (%)	Grades 3 to 4* (%)
General disorders and administration-site conditions		
Edema[a]	81	16
Fatigue[b]	30	1.9
Gastrointestinal disorders		
Nausea	31	1.3
Diarrhea	29	0.6
Abdominal pain[c]	19	0.6
Constipation	19	0.3
Vomiting[d]	15	1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[e]	30	3.2
Respiratory, thoracic, and mediastinal disorders		
Dyspnea[f]	24	2.6
Cough[g]	18	0.3
Pleural effusion	14	4.2
Metabolism and nutrition disorders		
Decreased appetite	21	1.9
Skin and Subcutaneous Tissue Disorders		
Rash[h]	21	1.3
Infections and Infestations		
Pneumonia[i]	12	3.8

* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[a] Edema includes eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, peripheral swelling, periorbital edema, and scrotal edema.

[b] Fatigue includes asthenia and fatigue.

[c] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, and hepatic pain.

[d] Vomiting includes retching and vomiting.

[e] 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.

[f] Dyspnea includes dyspnea, dyspnea at rest, and dyspnea exertional.

[g] Cough includes cough, and productive cough.

[h] Rash includes rash, palmar-plantar erythrodysaesthesia syndrome, rash maculo-papular, eczema, exfoliative rash, rash erythematous, rash pustular, skin exfoliation, dermatitis acneiform, drug eruption, dermatitis, rash pruritic, dermatitis bullous, toxic skin eruption.

[i] Pneumonia includes pneumonia, pneumonia aspiration, and pneumonia bacterial.

Clinically relevant adverse reactions in < 10% of patients who received TEPMETKO included ILD/pneumonitis, fever, dizziness, pruritus, and headache.

Table 3 summarizes the laboratory abnormalities observed in VISION.

Table 3: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients Who Received TEPMETKO in VISION

Laboratory Abnormalities	TEPMETKO*	
	Grades 1 to 4** (%)	Grades 3 to 4** (%)
Chemistry		
Decreased albumin	81	9
Increased creatinine	60	1
Increased alkaline phosphatase	52	1.6
Increased alanine aminotransferase	50	4.9
Increased aspartate aminotransferase	40	3.6
Decreased sodium	36	9
Increased gamma-glutamyltransferase	29	6
Increased potassium	26	1.9
Increased amylase	25	5
Increased lipase	21	5
Hematology		
Decreased lymphocytes	57	15
Decreased hemoglobin	31	3.6
Decreased leukocytes	25	1.9
Decreased platelets	24	0.6

* The denominator used to calculate the rate varied from 268 to 309 based on the number of patients with a baseline value and at least one post-treatment value.
** Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Increased Creatinine
A median increase in serum creatinine of 30% was observed 21 days after initiation of treatment with TEPMETKO. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion.

7 DRUG INTERACTIONS

7.1 Effects of TEPMETKO on Other Drugs

Certain P-gp Substrates
Tepotinib is a P-gp inhibitor. Concomitant use of TEPMETKO increases the concentration of P-gp substrates *[see Clinical Pharmacology (12.3)]*, which may increase the incidence and severity of adverse reactions of these substrates. Avoid concomitant use of TEPMETKO with certain P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, reduce the P-gp substrate dosage if recommended in its approved product labeling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and the mechanism of action *[see Clinical Pharmacology (12.1)]*, TEPMETKO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TEPMETKO in pregnant women. Oral administration of tepotinib to pregnant rabbits during the period of organogenesis resulted in malformations (teratogenicity) and anomalies at maternal exposures less than the human exposure based on area under the curve (AUC) at the 450 mg daily clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies, pregnant rabbits received oral doses of 0.5, 5, 25, 50, 150, or 450 mg/kg tepotinib hydrochloride hydrate daily during organogenesis. Severe maternal toxicity occurred at the 450 mg/kg dose (approximately 0.75 times the human exposure at the 450 mg clinical dose). At 150 mg/kg (approximately 0.5 times the human exposure by AUC at the 450 mg clinical dose), two animals aborted and one animal died prematurely; mean fetal body weight was also decreased. A dose-dependent increase of skeletal malformations, including malrotations of fore and/or hind paws with concomitant misshapen scapula and/or malpositioned clavicle and/or calcaneous and/or talus, occurred at doses ≥ 5 mg/kg (approximately 0.003 times the human exposure by AUC at the 450 mg clinical dose); there was also an incidence of spina bifida at the 5 mg/kg dose level.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects on the breastfed infant or milk production. Advise women not to breastfeed during treatment with TEPMETKO and for one week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, TEPMETKO can cause malformations at doses less than the human exposure based on AUC at the 450 mg clinical dose *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TEPMETKO *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during TEPMETKO treatment and for one week after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during TEPMETKO treatment and for one week after the last dose.

8.4 Pediatric Use

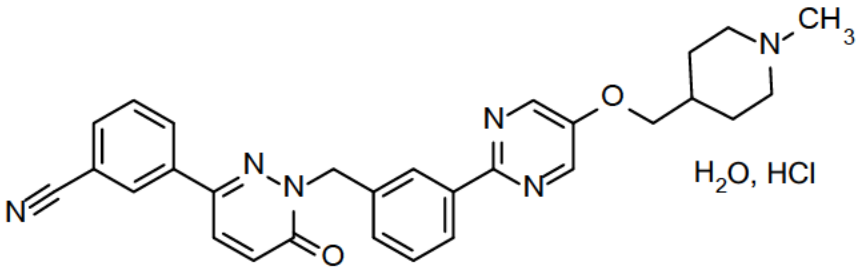
The safety and efficacy of TEPMETKO in pediatric patients have not been established.

8.5 Geriatric Use
Of 313 patients with NSCLC positive for *MET*ex14 skipping alterations in VISION who received 450 mg TEMETKO once daily, 79% were 65 years or older, and 41% were 75 years or older. No clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients.

8.6 Renal Impairment
No dosage modification is recommended in patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr < 30 mL/min) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
No dosage modification is recommended in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment. The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child Pugh Class C) have not been studied *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION
Tepotinib is a kinase inhibitor. TEPMETKO (tepotinib) tablets for oral use are formulated with tepotinib hydrochloride hydrate. The chemical name for tepotinib hydrochloride hydrate is 3-{1-[(3-{5-[(1-methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile hydrochloride hydrate. The molecular formula is $C_{29}H_{28}N_6O_2 \cdot HCl \cdot H_2O$ and the molecular weight is 547.05 g/mol for tepotinib hydrochloride hydrate and 492.58 g/mol for tepotinib (free base). The chemical structure is shown below:



Tepotinib hydrochloride hydrate is a white to off-white powder with a pKa of 9.5.

TEPMETKO is supplied as film-coated tablets containing 225 mg of tepotinib (equivalent to 250 mg tepotinib hydrochloride hydrate). Inactive ingredients in the tablet core are mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide. The tablet coating consists of hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, triacetin, and red iron oxides.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Tepotinib is a kinase inhibitor that targets MET, including variants with exon 14 skipping alterations. Tepotinib inhibits hepatocyte growth factor (HGF)-dependent and -independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations.

In vitro, tepotinib inhibited tumor cell proliferation, anchorage-independent growth, and migration of MET-dependent tumor cells. In mice implanted with tumor cell lines with oncogenic activation of MET,

including *MET*ex14 skipping alterations, tepotinib inhibited tumor growth, led to sustained inhibition of MET phosphorylation, and, in one model, decreased the formation of metastases.

12.2 Pharmacodynamics

Exposure-Response

Tepotinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

At the recommended dosage, no large mean increases in QTc (i.e. > 20 ms) were detected in patients with various solid tumors. A concentration-dependent increase in QTc interval was observed. The QTc effect of tepotinib at high clinical exposures has not been evaluated.

12.3 Pharmacokinetics

The pharmacokinetics of tepotinib were evaluated in patients with cancer administered 450 mg once daily unless otherwise specified. Tepotinib exposure ($AUC_{0\text{-}12h}$ and C_{max}) increases dose-proportionally over the dose range of 27 mg (0.06 times the recommended daily dosage) to 450 mg. At the recommended dosage, the geometric mean (coefficient of variation [CV] %) steady state C_{max} was 1,291 ng/mL (48.1%) and the $AUC_{0\text{-}24h}$ was 27,438 ng·h/mL (51.7%). The oral clearance of tepotinib did not change with respect to time. The median accumulation was 2.5-fold for C_{max} and 3.3-fold for $AUC_{0\text{-}24h}$ after multiple daily doses of tepotinib.

Absorption

The median T_{max} of tepotinib is 8 hours (range from 6 to 12 hours). The geometric mean (CV%) absolute bioavailability of TEPMETKO in the fed state was 71.6% (10.8%) in healthy subjects.

Effect of Food

The mean $AUC_{0\text{-}INF}$ of tepotinib increased by 1.6-fold and C_{max} increased by 2-fold, 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_{max} shifted from 12 hours to 8 hours.

Distribution

The geometric mean (CV%) apparent volume of distribution (V_Z/F) of tepotinib is 1,038 L (24.3%). Protein binding of tepotinib is 98% and is independent of drug concentration at clinically relevant exposures.

Elimination

The apparent clearance (CL/F) of tepotinib is 23.8 L/h (87.5%) and the half-life is 32 hours following oral administration of TEPMETKO in patients with cancer.

Metabolism

Tepotinib is primarily metabolized by CYP3A4 and CYP2C8. One major circulating plasma metabolite (M506) has been identified.

Excretion

Following a single oral administration of a radiolabeled dose of 450 mg tepotinib, approximately 85% of the dose was recovered in feces (45% unchanged) and 13.6% in urine (7% unchanged). The major circulating metabolite M506 accounted for about 40.4% of the total radioactivity in plasma.

Specific Populations
No clinically significant effects on tepotinib pharmacokinetics were observed based on 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 (CLcr 30 to 89 mL/min), or mild to moderate hepatic impairment (Child-Pugh A and B). The effect of severe renal impairment (CLcr < 30 mL/min) and severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of tepotinib has not been studied.

Drug Interaction Studies
Clinical Studies and Model-Informed Approaches
No clinically significant differences in the pharmacokinetics of tepotinib were observed when coadministered with the following drugs: itraconazole (strong CYP3A and P-gp inhibitor), carbamazepine (strong CYP3A inducer) or omeprazole (proton pump inhibitor/acid reducing agent) under fed conditions.

No clinically significant differences in the pharmacokinetics of the following drugs were observed or predicted when coadministered with tepotinib: midazolam (sensitive CYP3A substrate) or CYP2C9 substrates.

P-gp Substrates: Coadministration of TEPMETKO with dabigatran etexilate (P-gp substrate) increased dabigatran C_{max} by 40% and $AUC_{0\text{-}INF}$ by 50%.

MATE2 and OCT2 Substrates: No clinically relevant differences in glucose levels were observed when metformin (MATE2 and OCT2 substrate) was coadministered with tepotinib.

In Vitro Studies
Cytochrome P450 Enzymes: Tepotinib is a substrate of CYP3A4 and CYP2C8. Tepotinib and M506 do not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 or CYP2E1, and do not induce CYP1A2 or 2B6 at clinically relevant concentrations.

UDP-Glucuronosyltransferase (UGT): Tepotinib and M506 do not inhibit UGT 1A1, 1A9, 2B17, 1A3/4/6 and 2B7/15 at clinically relevant concentrations.

Transporter Systems: Tepotinib is a P-gp substrate. Tepotinib may inhibit intestinal BCRP at clinically relevant concentrations. Tepotinib does not inhibit bile salt export pump (BSEP), organic anion transporter polypeptide (OATP) 1B1, B3, or organic anion transporter (OAT) 1 and 3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with tepotinib. Tepotinib and its major circulating metabolite were not mutagenic in vitro in the bacterial reverse mutation (Ames) assay, or a mouse lymphoma assay. In vivo, tepotinib was not genotoxic in a rat micronucleus test.

Fertility studies of tepotinib have not been performed. There were no morphological changes in male or female reproductive organs in repeat-dose toxicity studies in dogs.

14 CLINICAL STUDIES

The efficacy of TEPMETKO was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring *MET*ex14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study.

Identification of *MET*ex14 skipping alterations was prospectively determined using central laboratories employing either a PCR-based or next-generation sequencing-based clinical trial assay using tissue (66%) and/or plasma (57%) samples.

Patients received TEPMETKO 450 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by a Blinded Independent Review Committee (BIRC). An additional efficacy outcome measure was duration of response (DOR) by BIRC.

The efficacy population included 164 treatment naïve patients and 149 previously treated patients. The median age was 72 years (range 41 to 94 years); 51% female; 62% White, 34% Asian; 26% had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 74% had ECOG PS 1; 49% never smoked; 81% had adenocarcinoma; 94% had metastatic disease; and 13% had CNS metastases. Amongst previously treated patients, 84% received prior platinum-based chemotherapy.

Efficacy results are presented in Table 4.

Table 4: Efficacy Results in the VISION study

Efficacy parameter	**Treatment-Naïve (N=164)**	**Previously Treated (N=149)**
Overall response rate (95% CI)[a,b]	57% (49, 65)	45% (37, 53)
Duration of Response		
Range in months[c]	1.3+, 56.6+	1.4+, 67.6+
Patients with DOR ≥ 6 months[c]	66%	66%
Patients with DOR ≥ 12 months[c]	40%	36%

CI: Confidence interval, + denotes ongoing response.
[a] Blinded Independent Review Committee (BIRC) review.
[b] Confirmed responses.
[c] Based on observed duration of response.

16 HOW SUPPLIED/STORAGE AND HANDLING

TEPMETKO (tepotinib) tablets: 225 mg tepotinib, white-pink, oval, biconvex film-coated tablet with embossment “M” on one side and plain on the other side.

NDC number	**Size**
44087-5000-3	Box of 30 tablets: 3 blister cards each containing 10 tablets
44087-5000-6	Box of 60 tablets: 6 blister cards each containing 10 tablets

The blister cards consist of a child-resistant blister foil.

Store TEPMETKO at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP-NF Controlled Room Temperature]. Store in original package.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risk of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

Hepatotoxicity

Inform patients that they will need to undergo lab tests to monitor liver function. Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction *[see Warnings and Precautions (5.2)]*.

Pancreatic Toxicity

Inform patients that they will need to undergo lab tests to monitor pancreatic function. Advise patients to immediately contact their healthcare provider for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

Advise males and females of reproductive potential that TEPMETKO can cause fetal harm.

Advise females of reproductive potential to use effective contraception during and for one week after the last dose of TEPMETKO *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TEPMETKO and for one week after the last dose of TEPMETKO *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with TEPMETKO and for one week after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs and herbal products *[see Drug Interactions (7)]*.

Dosing and Administration

Instruct patients to take 450 mg TEPMETKO once daily with food *[see Dosage and Administration (2.2)]*.

Missed Dose

Advise patients that a missed dose of TEPMETKO can be taken as soon as remembered on the same day, unless the next dose is due within 8 hours. If vomiting occurs after taking a dose of TEPMETKO, advise patients to take the next dose at the scheduled time *[see Dosage and Administration (2.2)]*.

Manufactured for:
EMD Serono, Inc.
Rockland, MA 02370
U.S.A.

TEPMETKO is a trademark of Merck KGaA,
Darmstadt, Germany

PATIENT INFORMATION

TEPMETKO® (tep-MET-co)

(tepotinib)

tablets, for oral use

What is the most important information I should know about TEPMETKO?

TEPMETKO may cause serious side effects, including:

- **Lung problems.** TEPMETKO may cause severe or life-threatening swelling (inflammation) of the lungs during treatment that can lead to death. Tell your healthcare provider right away if you develop any new or worsening symptoms of lung problems, including:
  - trouble breathing
  - shortness of breath
  - cough
  - fever

See "What are possible side effects of TEPMETKO?" for more information about side effects.

What is TEPMETKO?

TEPMETKO is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that:

- has spread to other parts of the body (metastatic), and
- whose tumors have an abnormal mesenchymal epithelial transition (MET) gene. Your healthcare provider will perform a test to make sure that TEPMETKO is right for you.

It is not known if TEPMETKO is safe and effective in children.

Before you take TEPMETKO, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had lung or breathing problems other than your lung cancer
- have or have had liver problems
- have or have had pancreatic problems
- are pregnant or plan to become pregnant. TEPMETKO can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider may do a pregnancy test before you start treatment with TEPMETKO.
  - You should use effective birth control (contraception) during treatment and for 1 week after the last dose of TEPMETKO. Talk to your healthcare provider about birth control methods that may be right for you.

  Males with female partners who are able to become pregnant should use effective birth control (contraception) during treatment with TEPMETKO and for 1 week after the last dose of TEPMETKO.
- are breastfeeding or plan to breastfeed. It is not known if TEPMETKO passes into your breast milk. Do not breastfeed during treatment and for 1 week after the last dose of TEPMETKO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take TEPMETKO?

- Take TEPMETKO exactly as your healthcare provider tells you to. Do not change your dose or stop taking TEPMETKO unless your healthcare provider tells you to.
- Take TEPMETKO 1 time a day with food.
- Take your dose of TEPMETKO at about the same time each day.
- Swallow TEPMETKO tablets whole. **Do not chew, crush or split the tablets**.

  If you cannot swallow TEPMETKO tablets whole:
  - Place your prescribed dose of TEPMETKO tablets in a glass that contains 30 mL (1 ounce) of non-carbonated water. **Do not** use or add any other liquids.
  - Stir the TEPMETKO tablets and water until the TEPMETKO tablets are in small pieces (the tablets will not completely dissolve). **Do not** crush TEPMETKO tablets.
  - Drink the TEPMETKO and water mixture right away or within 1 hour. Make sure to swallow the mixture. **Do not** chew pieces of the tablet.
  - Add another 30 mL of non-carbonated water to the glass and drink it right away to get your full dose of TEPMETKO.

If you have a nasogastric (NG) tube that is 8 French gauge or larger:

- Follow the same instructions for mixing TEPMETKO tablets in a glass that contains 30 mL of non-carbonated water.
- **Do not** use or add any other liquids.
- Stir the TEPMETKO tablets and water until the TEPMETKO tablets are in small pieces (the tablets will not completely dissolve). **Do not** crush TEPMETKO tablets.
- Give the TEPMETKO tablet and water mixture using the NG tube manufacturer instructions right away or within 1 hour.
- Pieces of the tablet may remain in the glass. Right away, add 30 mL of non-carbonated water into the glass. Give the water and any remaining TEPMETKO through the NG tube right away to make sure that all of the medicine is given. Repeat this step. This will help to ensure that no medicine is left in the glass or syringe and the full prescribed dose of TEPMETKO is given.

- If you miss a dose of TEPMETKO, take it as soon as you remember. If your next dose is due within 8 hours, skip the missed dose and take your next dose at your regular scheduled time.
- If you vomit after taking a dose of TEPMEKTO, take your next dose at your regular scheduled time.

What are the possible side effects of TEPMETKO?

TEPMETKO may cause serious side effects, including:

- See "**What is the most important information I should know about TEPMETKO?"**
- **Liver problems**. TEPMETKO may cause abnormal liver blood test results. Your healthcare provider will do blood tests to check your liver function before you start treatment and during treatment with TEPMETKO. Tell your healthcare provider right away if you develop any signs and symptoms of liver problems, including:
  - your skin or the white part of your eyes turns yellow
  - dark or "tea colored" urine
  - light-colored stools (bowel movements)
  - confusion
  - tiredness
  - loss of appetite for several days or longer
  - nausea and vomiting
  - pain, aching, or tenderness on the right side of your stomach-area (abdomen)
  - weakness
  - swelling in your stomach-area
- **Pancreas problems.** TEPMETKO may cause increases in your blood amylase and lipase levels that may indicate a problem with your pancreas. Your healthcare provider will do blood tests to check your pancreatic function before you start treatment and during treatment with TEPMETKO. Tell your healthcare provider right away if you develop any signs and symptoms of pancreas problems, including:
  - upper stomach (abdominal) pain that may spread to your back and get worse with eating
  - weight loss
  - nausea
  - vomiting

The most common side effects of TEPMETKO include:

- swelling in your face or other parts of your body
- nausea
- tiredness
- muscle and joint pain
- diarrhea
- shortness of breath
- loss of appetite
- rash
- changes in certain blood tests

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with TEPMETKO if you develop serious side effects during treatment.

These are not all of the possible side effects of TEPMETKO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TEPMETKO?

- Store TEPMETKO at room temperature between 68°F to 77°F (20°C to 25°C).
- TEPMETKO tablets come in blister cards with a child-resistant blister foil.
- Store TEPMETKO in original package.

Keep TEPMETKO and all medicines out of the reach of children.

General information about the safe and effective use of TEPMETKO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TEPMETKO for a condition for which it was not prescribed. Do not give TEPMETKO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TEPMETKO that is written for health professionals.

What are the ingredients in TEPMETKO?

Active ingredient: tepotinib

Inactive ingredients: mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide.

Tablet coating: hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, triacetin, and red iron oxides.

Manufactured for: EMD Serono, Inc., Rockland, MA 02370, U.S.A.

Product of Germany.

For more information, call toll-free 1-844-662-3631 or go to www.TEPMETKO.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised 02/2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214096Orig1s003

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

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.

Application Type	NME
Application Number(s)	NDA 214096
Priority or Standard	Standard
Submit Date(s)	May 16, 2023
Received Date(s)	May 16, 2023
PDUFA Goal Date	February 25, 2024
Division/Office	Division of Oncology 2/OND
Review Completion Date	February 15, 2024
Established Name	Tepotinib
(Proposed) Trade Name	Tepmetko
Pharmacologic Class	Kinase inhibitor
Code Name	MSC2156119J
Applicant	EMD Serono, Inc.
Formulation(s)	Tablet
Dosing Regimen	450 mg orally once daily with food
Applicant Proposed Indication(s)/Population(s)	for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping alterations
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	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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Reviewers of Multi-Disciplinary Review and Evaluation

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Pharmacology/Toxicology Team Leader(s)	Claudia Miller
Office of Clinical Pharmacology Reviewer(s)	N/A
Office of Clinical Pharmacology Team Leader(s)	N/A
Clinical Reviewer	Luckson Mathieu
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Safety Analyst (if applicable)	Not applicable
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Additional Reviewers of Application

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Microbiology	
OPDP	
OSI	
OSE/DEPI	
OSE/DMEPA	
OSE/DRISK	
Other	

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

DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
BCRP	breast cancer resistance protein
BLA	biologics license application
CF	capsule formulation
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
IDMC	independent data monitoring committee
IRC	independent review committee
DOR	duration of response
DCO	data cutoff
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
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
ILD	interstitial lung disease
IRC	Independent Review Committee
LBx	liquid biopsy
MATE	multidrug and toxin extrusion protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
MET	MET gene
*MET*ex14	*MET* exon 14
METamp	*MET* amplification
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
(s)NDA	supplemental new drug application
NME	new molecular entity

NSCLC	non-small cell lung cancer
OCT	organic cation transporter
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	progressive disease
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetics
PRO	patient reported outcome
PT	preferred term
SAE	serious adverse event
SAF	safety analysis set
SMQ	Standardized MedDRA Query
SOC	system organ class
TBx	tissue biopsy
TF	tablet formulation
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1. Product Introduction

Tepotinib is an orally bioavailable kinase inhibitor that inhibits hepatocyte growth factor (HGF) dependent and independent mesenchymal-epithelial transition factor (MET) phosphorylation and subsequently MET-dependent downstream signaling pathways. Tepotinib targets MET receptor tyrosine kinase, including variants with exon 14 skipping alterations. FDA granted accelerated approval to tepotinib for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (or MET) exon 14 skipping alterations on February 3, 2021.

The approved dosing regimen for tepotinib is 450 mg orally once daily (QD) with food on a continuous schedule.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In the opinion of the review team, EMD Serono has provided substantial evidence of effectiveness to support the traditional approval of tepotinib for the treatment of adult patients with metastatic NSCLC harboring MET exon 14 skipping alterations. The recommendation for traditional approval is based on additional data with longer follow up demonstrating substantial durability of responses, supported by a consistent clinically meaningful magnitude of the overall response rate (ORR), in both treatment-naïve and previously treated patients enrolled in the multicenter, nonrandomized, multi-cohort trial (VISION, NCT02864992) that supported the accelerated approval of tepotinib.

Based on Blinded Independent Review Committee (BIRC) assessment, in the treatment-naïve cohort, 66% of responders had a duration of response (DOR) ≥6 months and 40% had a DOR ≥12 months, and in the previously treated cohort, 66% of responders had a duration of response (DOR) ≥6 months and 36% had a DOR ≥12 months. The observed median duration of response (DOR) was 9.1 months (range 1.3+, 56.6+ months) for treatment-naïve patients and 8.4 months (range 1.4+, 67.6+ months) for previously treated patients. The durability of the responses seen with tepotinib in both treatment-naïve and previously treated patients provides substantial evidence of the sustained antitumor activity of tepotinib over time. Of note, the review team identified that due to censoring, median durations of response by Kaplan-Meier analyses, particularly for treatment-naïve patients, were misleading and inconsistent with observed duration of response among responders. (b) (4) (b) (4) The effectiveness of tepotinib is also supported by the consistent demonstration of clinically meaningful ORR results among additional patients relative to the efficacy population

which supported the accelerated approval. With the inclusion of results from these additional patients, the ORR per BIRC is 57% (95% CI 49, 65) among 164 treatment-naïve patients and 45% (95% CI 37, 53) among 149 previously treated patients.

The submitted evidence meets the statutory evidentiary standard for traditional approval. Given the rarity of NSCLC with MET exon 14 skipping mutations, the conduct of a randomized clinical trial enrolling a population reflective of the US patient population is considered infeasible. In this context, the observed DOR supporting this application demonstrates a beneficial effect on a clinically meaningful endpoint. The review team considers these DOR results, supported by ORR in additional patients consistent with the ORR results upon which accelerated approval was based, sufficient to verify the clinical benefit of tepotinib in the genetically defined, rare subgroup of patients with metastatic NSCLC harboring MET exon 14 skipping alterations.

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%. Mutations that lead to mesenchymal-epithelial transition (MET) exon 14 skipping have been identified as an oncogenic driver mutation in NSCLC and have been reported to be present in 2-4% of all NSCLC tumors[1-3]. Patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping tend to be older (median age of approximately 70 years) than those with other oncogenic driver mutations, similar to the general population of patients with NSCLC. Based on the limited data available in this patient population, 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. Capmatinib and tepotinib were granted accelerated approval for the proposed indication in 2020 and 2021, respectively[4-5]. Capmatinib was granted traditional approval in August 2022 and is the only targeted therapy with traditional approval specifically for the treatment of patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping.

Tepotinib is a kinase inhibitor that targets MET, including the variant(s) with MET exon 14 skipping alterations[6-7]. The approved dosing regimen is 450 mg orally once daily (QD) with food. The accelerated approval for tepotinib was based on data from 152 patients with metastatic NSCLC harboring MET exon 14 skipping alterations treated with tepotinib 450 mg QD in the multi-cohort clinical trial, the VISION study. This population included 69 treatment-naïve patients and 83 patients with disease progression following one or two prior therapies ("previously treated"). The confirmed overall response rate (ORR) assessed by blinded independent central review (BICR) in treatment-naïve patients was 43% (95% CI: 32, 56), with 67% of responders having observed DOR of ≥ 6 months. In the previously treated population, the confirmed ORR per BICR was 43% (95% CI: 33, 55), with 75% of responders having observed DOR of ≥ 6 months.

At the time of accelerated approval, post marketing requirement (PMR) 4013-1 was issued for the submission of "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." The PMR specified that data should be provided from at least 130 treatment-naïve patients with at least 12 months of response follow up and from at least 143 patients previously treated with systemic therapy with at least 6 months of response follow up. The data submitted in this supplemental new drug application (sNDA) are intended to fulfill PMR 4013-1 and verify the clinical benefit of tepotinib for the treatment of patients with metastatic NSCLC harboring MET exon 14 skipping alterations.

Relative to the data supporting accelerated approval, the primary efficacy population for this review includes an additional 95 treatment-naïve patients and 66 previously treated patients, resulting in a total of 164 treatment-naïve patients and 149 previously treated patients who were treated with tepotinib 450 mg QD in VISION. The updated assessment of DOR in this sNDA provides an additional follow-up time of approximately 28 months for the responders from

the primary efficacy population which supported the accelerated approval of the original NDA.

Among the 164 treatment-naïve patients, the confirmed ORR assessed by BIRC was 57% (95% CI: 49, 65), with an observed median duration of response (DOR) of 9.1 months (range 1.3+, 56.6+ months) and an observed DOR of ≥12 months in 40% of the 94 responders. In the previously treated population, the confirmed ORR per BIRC was 45% (95% CI: 37, 53), with an observed median DOR of 8.4 months (range 1.4+, 67.6+ months) and an observed DOR of ≥12 months in 36% of the 67 responders. Kaplan-Meier analyses of duration of response were affected by censoring rules and found to be misleading. The consistency of the ORR results in this larger efficacy population relative to the results supporting the accelerated approval provide additional confidence in the magnitude of ORR and its clinical meaningfulness. The DOR results are consistent with substantial durability of responses when considering the indicated population.

Tepotinib appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. The most common (≥ 20%) adverse reactions were edema, nausea, fatigue, musculoskeletal pain, diarrhea, dyspnea, decreased appetite, and rash. Permanent discontinuation of tepotinib due to adverse reactions occurred in 25% of patients; the most frequent adverse reactions leading to permanent discontinuation were edema (8%), pleural effusion (1.6%), and general health deterioration (1.6%). Safety issues identified as significant and serious during the initial NDA review were interstitial lung disease/pneumonitis and hepatotoxicity. During review of this sNDA, increased amylase and lipase were identified as an additional safety issues suggestive of pancreatic toxicity and warranting inclusion in the Warnings and Precautions section of the US prescribing information (USPI). 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 sNDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

The submitted data from the VISION study meets the evidentiary standard for traditional approval. Tepotinib has a favorable benefit-risk profile based on the durability of responses observed with longer follow up, supported by consistency of clinically meaningful ORR and DOR results among a larger number of patients, in a patient population with a life-threatening disease. Given the rarity of NSCLC with MET exon 14 skipping mutations and the availability of currently approved therapies, the conduct of a randomized clinical trial enrolling a population reflective of the US patient population is considered infeasible. In this context, the demonstrated DOR, supported by ORR in additional patients consistent with the ORR results upon which accelerated approval was based, are considered adequate to verify the clinical benefit of tepotinib in the indicated population.

The review team recommends traditional 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."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	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). Mutations that lead to mesenchymal-epithelial transition (MET) exon 14 skipping have been identified as an oncogenic molecular driver mutation in NSCLC and have been reported in approximately 2-4% of NSCLC tumors. The 5-year survival rate for patients with metastatic NSCLC is <10%. There is no randomized trial data available regarding survival specifically for patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. Based on the available data, 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.	Metastatic NSCLC with mutation leading to MET exon 14 skipping is a life-threatening disease with poor survival. NSCLC with mutations that lead to MET exon 14 skipping is a rare subset of NSCLC: approximately 2- 4% of NSCLC tumors have a mutation that leads to MET exon 14 skipping.
Current Treatment Options	FDA granted capmatinib and tepotinib accelerated approval for the treatment of patients with metastatic NSCLC with MET exon 14 skipping mutations on May 6, 2020, and February 3, 2021, respectively. Capmatinib was granted traditional approval in 2022 for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping mutation. Prior to the approvals of capmatinib and tepotinib, the only standard treatment options for patients with NSCLC with MET exon 14 skipping mutations were the same as those used for NSCLC without a specific oncogenic driver mutation. For treatment-naïve patients, this includes platinum-based chemotherapy and/or anti-PD(L)1 antibody. The highest ORRs, ranging from 46% to 58%, have been reported for platinum-based chemotherapy plus pembrolizumab (regardless of	There is a need for treatment options for patients with metastatic NSCLC harboring MET exon 14 skipping alterations. This conclusion is based on the observed ORRs, DORs, and overall survival reported for the available nontargeted therapies previously used for treatment of this patient population. The only other approved targeted therapy for this patient population is capmatinib, which was granted traditional approval based on demonstration of clinically meaningful ORR and DOR.

	histology) and platinum-based chemotherapy plus atezolizumab with or without bevacizumab (for nonsquamous NSCLC) with median durations of response of approximately 11 months. 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.	
Benefit	The primary efficacy data supporting this application are from patients with advanced or metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping enrolled in the multicenter, nonrandomized, open-label, multi-cohort VISION study. This included patients who were treatment-naïve and patients who were previously treated with systemic therapy, including platinum-based chemotherapy. The treatment-naïve population includes an additional 95 patients relative to the population supporting the accelerated approval of tepotinib (n=69). Among 164 treatment-naïve patients, the confirmed ORR per BIRC was 57% (95% CI: 49, 65) with an observed median DOR of 9.1 months (range 1.3+, 56.6+ months). Among responders, 40% of patients had a DOR ≥12 months. The previously treated population includes an additional 66 patients relative to the population supporting the accelerated approval of tepotinib (n=83). Among 149 patients who had disease progression following prior systemic therapy, the confirmed ORR per BIRC was 45% (95%CI: 37%, 53%) with a median DOR of 8.4 months (range 1.4+, 67.6+ months). Among responders, 36% of patients had a DOR ≥12 months. A limitation of single arm trials is the potential for known and unknown patient selection bias.	The additional data from the VISION study verifies the clinical benefit of tepotinib for the treatment of patients with metastatic NSCLC with MET exon 14 skipping mutations. With the additional duration of follow-up for patients from the primary efficacy population for the original accelerated approval and the increased number of patients in the primary efficacy analysis population for this sNDA, the observed DOR, supported by consistency of ORR results in this larger efficacy population, are adequate to support traditional approval. This takes into consideration that, given the relative rarity of the patient population, it is considered infeasible to conduct a randomized clinical trial enrolling a population reflective of the US patient population to verify clinical benefit. 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

		postmarket setting.
Risk and Risk Management	The safety database for this supplemental NDA includes 506 patients with solid tumors who were treated with tepotinib at the recommended dose of 450 mg once daily, including 313 patients with NSCLC harboring METex14 skipping alterations from the VISION study. The safety data in this application is adequate to assess safety with reference to the overall U.S. target population. Permanent discontinuation of tepotinib due to adverse reactions occurred in 25% of patients. The most frequent adverse reactions leading to permanent discontinuation were edema (8%), pleural effusion (1.6%), and general health deterioration (1.6%). 53% of patients had an interruption of tepotinib dosing for an adverse reaction, and dose reductions due to adverse reactions occurred in 36% of patients. The most common adverse reactions (AEs) were edema, nausea, fatigue, musculoskeletal pain, abdominal pain, diarrhea, dyspnea, decreased appetite, and rash. 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, hepatotoxicity, and pancreatic toxicity. Pancreatic toxicity was identified as an additional safety issue during the current review based on indications of a class effect and elevated amylase and lipase reported among study participants. 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 (capmatinib or chemotherapy with anti-PD(L)1 antibodies) is not possible.	The observed safety profile of tepotinib is acceptable when assessed in the context of the treatment of this life-threatening disease. Although tepotinib can cause serious/severe 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 safety concerns identified during sNDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

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			[e.g., Section 6.1 Study endpoints]
			x	Patient reported outcome (PRO)	Section 8.1.2
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

As requested by the agency, the Sponsor is submitting the assessment aid for tepotinib sNDA 214096/S-003 to fulfill PMR 4013-1. The scope of the assessment aid (as per response to IR NDA 214096/Seq No. 0298) will align with the sNDA, which is based on the VISION Clinical Study Report and will focus on sections which have been affected since the last assessment aid submitted for the initial NDA.

Hence, all sections of the assessment aid, which are not in the scope of this supplement (S-003) have therefore been considered as 'not applicable'.

This sNDA seeks the conversion to full approval of the tepotinib indication for the treatment of adult patients with metastatic NSCLC harboring METexon 14 skipping alterations, which was previously obtained under accelerated approval.

This supplement (S-003) provides updated results from the VISION study with a data cutoff (DCO) of 20 November 2022, thereby providing at least 18 months follow-up from start of tepotinib treatment for each participant, including 164 treatment-naïve (1 L) and 149 pretreated (2 L+) participants.

The VISION study data, consisting of 313 participants with a longer follow-up of at least 18 months after start of tepotinib, substantiate previous efficacy and safety results and confirm the clinical benefit of tepotinib in advanced NSCLC patients with METex14 skipping alterations. The VISION study evaluates the efficacy and safety/tolerability of the recommended dose of tepotinib, which is 450 mg (2 tablets) once daily (equivalent to 500 mg tepotinib hydrochloride hydrate), in patients with advanced NSCLC of all histology types who tested positive for METex14 skipping alterations by next-generation sequencing in tissue (RNA-based) or plasma (circulating tumor DNA based).

The FDA's Assessment:

The Applicant's position above does not address the analysis of the condition. Lung cancer remains the leading cause of cancer death in men and the second leading cause of cancer death in women worldwide, with 80% to 85% of all lung cancer cases identified as non-small cell lung cancer (NSCLC). 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.[1-3]

The 5-year survival rate for patients with metastatic NSCLC is <10%. There is no randomized trial data available regarding survival specifically for patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. Based on the available data, 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.

2.2. Analysis of Current Treatment Options

The FDA's Assessment:

The Applicant did not provide a position for Analysis of Current Treatment Options. Capmatinib, another kinase inhibitor that targets MET, was granted traditional approval by the FDA on August 10, 2022, for the treatment of patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping.

Additional 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. In the first-line setting, additional therapies for NSCLC include chemotherapy and immunotherapy combinations (i.e., chemotherapy/pembrolizumab[8], chemotherapy/bevacizumab/atezolizumab[9], nivolumab/ipilimumab/chemotherapy[10], and single agent immunotherapy). The highest ORRs, ranging from 46% 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 nonsquamous NSCLC) with median durations of response of approximately 11 months. 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 or immunotherapy compared to the general population of patients with NSCLC. Second-line NSCLC available therapies include single agent immunotherapy with anti-PD(L)-1 antibodies (atezolizumab, pembrolizumab, and nivolumab) if not previously received, associated with ORR 14-20% with median durations of response in the range of 16 to 17 months, or 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.

3 Regulatory Background

TEPMETKO (tepotinib) is a kinase inhibitor indicated for the treatment of adult patients with metastatic NSCLC harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. This indication was granted an accelerated approval on 03 February 2021 (NDA 214096) based on overall response rate and duration of response from the Phase 2 single-arm VISION study investigating tepotinib in patients with advanced (locally advanced or metastatic) NSCLC harboring METex14 skipping alterations.

In the NDA 214096 approval letter dated February 3, 2021, the Agency included the following Accelerated Approval Requirement:

- PMR 4013-1: 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).

Upon successful execution of the confirmatory VISION study (Cohort A + C) and in line with the above PMR 4013-1, the Applicant filed sNDA (NDA 214096/S-003) to fulfill PMR 4013-1 and to subsequently convert the accelerated approval to full approval.

The supplement S-003 (NDA 214096, SeqNo: 290) provides updated results from the VISION study with a data cutoff (DCO) of 20 Nov 2022, thereby providing at least 18 months follow-up from start of tepotinib treatment for each participant, including 164 treatment-naïve (1 L) and 149 pretreated (2 L+) participants.

Tepotinib is approved globally in more than 40 countries, including EU, Japan, and US, for the treatment of patients with advanced or metastatic NSCLC harboring METex14 skipping alterations. Confirmatory data including efficacy results from Cohorts A and C, using the 20 Nov 2022 DCO, are submitted to respective health authorities as per agreed timelines to fulfill postmarketing requirements and to seek full approval where applicable. With 313 advanced NSCLC participants with METex14 skipping alterations enrolled in Cohorts A + C, the VISION study provides the largest dataset of its kind evaluating a MET inhibitor in this rare population as of today.

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

TEPMETKO (tepotinib) was granted accelerated approval on 03 February 2021 (NDA 214096) for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations and being marketed in US since the NDA approval.

On 23 March 2023, supplemental new drug application S-001 for an alternative method of administration of TEPMETKO tablets (to allow administration of TEPMETKO tablets dispersed in water as oral drinking suspension or via feeding tubes) and supplemental new drug application S-002 for the Proposed US PI update based on Drug Drug Interaction clinical study results for TEPMETKO tablets were approved by the agency.

The FDA's Assessment:

FDA agrees with the Applicant's summary of U.S. regulatory actions and marketing history.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 1: Key Interactions with FDA for METex14 Skipping Alterations

Interaction	Description
Type C meeting (CMC)	To align with the agency on the available PK and CMC data to support the labeling changes for the alternative administration of TEPMETKO as suspension of the commercial formulation after disintegration in water, either via direct oral administration or administration via feeding tubes.

CMC = Chemistry, Manufacturing, and Controls, *MET*ex14 = *MET* exon 14,
PK = pharmacokinetics.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the pre-submission regulatory activity.

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

4.1. Office of Scientific Investigations (OSI)

Not applicable for this application.

4.2. Product Quality

Not applicable for this application.

4.3. Clinical Microbiology

Not applicable for this application.

4.4. Devices and Companion Diagnostic Issues

Patient selection for treatment with tepotinib is based on the presence of *MET* exon 14 skipping alterations in plasma or tumor specimens. 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, the feasibility of biopsy for tumor tissue testing should be re-evaluated. An FDA-approved test for detection of MET exon 14 skipping alterations in NSCLC for selecting patients for treatment with tepotinib is not currently available.

During review of the original NDA for tepotinib, EMD Serono agreed to a post-marketing commitment (PMC 4013-4) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic (CDx) device to detect MET exon 14 skipping for identifying patients who may benefit from tepotinib. (b) (4)

(b) (4)

(b) (4)

(b) (4) In November 2023, FMI submitted a 180-Day PMA Supplement (P190032/S015), for their NGS based LBx, FoundationOne®Liquid CDx (F1LCDx), for the proposed expanded intended use to identify patients with NSCLC harboring METex14 skipping alterations who are eligible for treatment with tepotinib. (b) (4)

(b) (4)

(b) (4)

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.

5 Nonclinical Pharmacology/Toxicology

The FDA's Assessment:

No new information is provided in the current submission. This section is not applicable for this application.

X X

Primary Reviewer Supervisor

6 Clinical Pharmacology

The FDA's Assessment:

No new information is provided in the current submission. This section is not applicable for this application.

X X

Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 2: Overview of Clinical Trial Relevant to this sNDA

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)[a]/Dosage Regimen/ Route of Administration[b]	Number of Participants	Study Population	Duration of Treatment	Study Status; Type of Report
Efficacy/ Safety	MS200095-0022 (VISION)	Efficacy, Safety, Tolerability, PK, and Pd	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	Cohort A (*MET*ex14): 152 Cohort B (*MET*amp): 24 Cohort C (*MET*ex14): 161	Patients with advanced or metastatic NSCLC with *MET*ex14 skipping alterations or *MET*amp	Until disease progression, intolerable toxicity, death, or withdrawal from treatment	Completed[c]; Full

MET = mesenchymal-epithelial transition factor, *MET*amp = MET amplification, *MET*ex14 = *MET* exon 14, NSCLC = non-small cell lung cancer, Pd = pharmacodynamic, PK = pharmacokinetic, QD = once daily.

a Includes the following tepotinib formulations: TF2 = Tepotinib Tablet Formulation 2, TF3 = Tepotinib Tablet Formulation 3.

b All formulations of tepotinib were taken orally.

c Study MS200095-0022 (VISION) is considered as completed since the CSR is available with at least 35 months follow-up in Cohort A and 18 months in Cohort C, relative to the last participant's first dose in the cohort. At the time of the 20 Nov 2022 cutoff for the CSR, 38 participants were still on study treatment (37 participants in Cohort A + C and 1 participant in Cohort B).

The Applicant's Position:

Table 2 provides information on the clinical study relevant to this supplemental application.

The FDA's Assessment:

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

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:

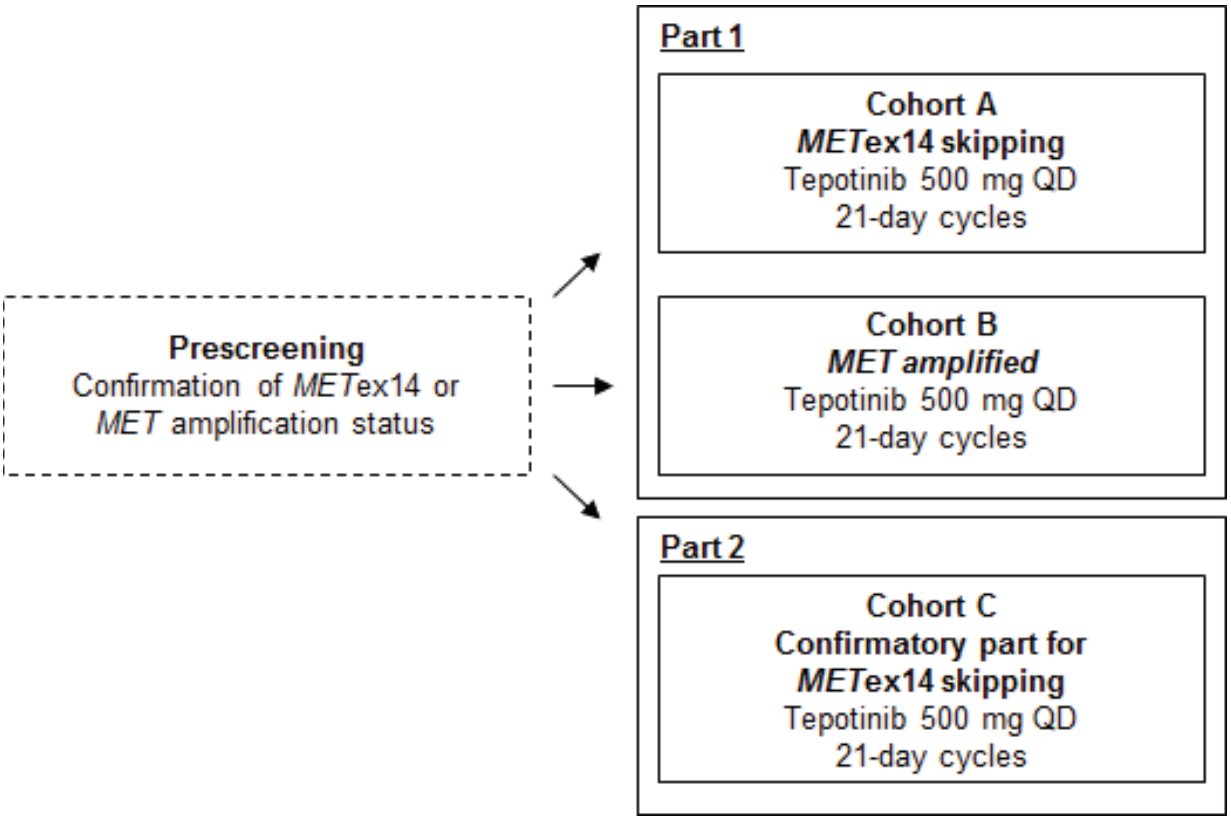
The pivotal VISION study is a Phase 2 single-arm study investigating tepotinib in participants with advanced (locally advanced or metastatic) NSCLC harboring *MET*ex14 skipping alterations (Cohorts A and C) or *MET* amplification (Cohort B, not applicable for this submission) for first to third line of systemic therapy selected based on prospective liquid (LBx) testing (*MET*ex14 and *MET*amp) and/or tissue (TBx)-based biopsy testing (*MET*ex14).

The VISION Study evaluates the efficacy and safety/tolerability of the recommended dose of tepotinib (TEPMETKO®), which is 450 mg (2 tablets) once daily (equivalent to 500 mg tepotinib hydrochloride hydrate), in participants with advanced NSCLC of all histology types who tested positive for *MET*ex14 skipping alterations by next-generation sequencing in tissue (RNA-based) or plasma (circulating tumor DNA based).

At the time of the 20 Nov 2022 DCO, VISION Clinical Study Protocol Global Version 8.0 (dated 17 January 2020) was in place.

3 Cohorts were planned in the study (see Figure 1). Cohorts A and C include patients with NSCLC who tested positive for *MET*ex14 skipping alterations; patients in these 2 cohorts are enrolled under the same inclusion criteria and undergo the same study procedures. Cohort B includes patients with NSCLC who tested negative for *MET*ex14 but positive for *MET* amplification.

Figure 1: VISION Study Design



MET = mesenchymal-epithelial transition factor, *METex*14 = MET exon 14, QD = once daily

Enrollment was completed with last participant first dose on 20 May 2021. At the time of the 20 Nov 2022 DCO, the VISION Cohorts A + C efficacy dataset included clinical information from 313 METex14 NSCLC participants, including 164 treatment-naïve (1 L) and 149 pretreated (2 L+) participants with at least 18 months follow-up from start of treatment.

Trial Location

This study was conducted at 156 centers in Austria, Belgium, mainland China, France, Germany, Israel, Italy, Japan, Poland, South Korea, Spain, Switzerland, Taiwan, the Netherlands, and the USA.

Diagnostic Criteria

Determination of patients' *MET*ex14 skipping alteration or *MET* amplification status was conducted during the prescreening period.

Prospective testing of *MET*ex14 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 ≥ 18 years of age with measurable disease according to response evaluation criteria in solid tumors (RECIST 1.1) and an 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.

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 ≤ 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 Applicant. Following the implementation of Clinical Study Protocol Version 8.0 (17 January 2020), the standard dose reduction was changed to 250 mg once daily.

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 (± 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 ± 3 days after the last dose of study treatment. Any 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 ± 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 EMD Serono's description of Study MS200095-0022 (VISION).

Study Endpoints

The Applicant's Description:

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

The secondary endpoints included OR as per Investigator determined 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:

FDA agrees with EMD Serono's description of the primary and secondary study endpoints, and notes that these endpoints are the same as those used in the prior submission of these data from this study for accelerated approval. Secondary endpoints that are time-to-event endpoints, such as PFS and OS, are difficult to interpret when used to evaluate treatment effect in single arm trials.

According to the protocol, patients were to continue tumor assessments until disease progression, withdrawal of consent, or death. The decision to stop treatment was based on the investigator's assessment, while the primary endpoint was based on IRC. For this reason, patients who were determined to have progressed per investigator assessment did not have further tumor scans available for the IRC to assess progression and evaluate DOR. This led to additional censoring for the DOR endpoint because many of the patients who progressed per investigator were censored in the analysis of DOR per IRC at the time of investigator-called progression.

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 mainly in order to reflect protocol amendments with regards to study design and populations, to omit the per protocol analysis, to describe the analyses of PROs in more detail, to include specific analyses on the impact of the COVID-19 pandemic on the study results, and to reflect country-specific submission-related additional analysis outputs.

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

The analysis populations for which efficacy results are based on are shown in *Figure 2*.

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 23.0. 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: ≥ 3, ≥ 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 EMD Serono's description of the primary and secondary endpoints and statistical analysis plan. However, while FDA considers the target ORR in the range of 40-50% selected by the EMD Serono as useful for sample size calculation, simply meeting this threshold is not considered to be the criteria for efficacy evaluation for regulatory purposes. Additionally, as mentioned in the previous section, time-to-event endpoints such as PFS and OS are not interpretable in non-randomized trials without a control arm.

The final versions of the protocol and SAP were submitted to this IND for FDA review and were found to be acceptable. There have been no SAP amendments since the finalization of SAP v9.0 dated December 20, 2022. The SAP was finalized prior to the database lock for this submission, which took place on December 21, 2022. The data cutoff (DCO) for this submission was November 20, 2022.

Data were submitted in the current application to fulfill the postmarketing requirement (PMR) issued at the time of the accelerated approval to provide a more precise estimation of ORR and DOR per IRC assessment among at least 130 treatment-naïve patients with responders followed for at least 12 months after onset of response and among at least 143 patients who had received prior platinum-based therapy with responders followed for at least 6 months.

Protocol Amendments

The Applicant's Description:

The original clinical study protocol, dated 14 January 2016, underwent 7 global amendments. At the time of the 20 Nov 2022 data cutoff, VISION Study Protocol Version 8.0 (dated 17 January 2020) 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 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 EMD Serono'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 EMD Serono'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 EMD Serono's position. EMD Serono has adequately disclosed financial interests/ arrangements with clinical investigators in accordance with the guidance for industry. Details of financial disclosures are presented in Section 19.2.

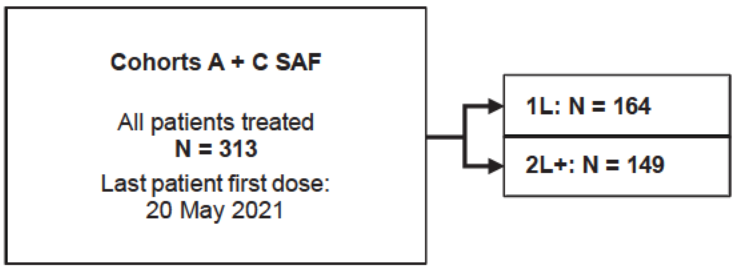
Patient Disposition

Data:

Efficacy results reported in this document are based on participants with METex14 positive NSCLC enrolled in Cohorts A and C. Data from both cohorts have been pooled to provide robust estimates of the efficacy endpoints.

Enrollment was completed with last participant first dose on 20 May 2021. At the time of the 20 Nov 2022 DCO, the VISION Cohorts A + C efficacy dataset included clinical information from 313 METex14 NSCLC participants, including 164 treatment-naïve (1 L) and 149 pretreated (2 L+) participants with at least 18 months follow-up from start of treatment (*Figure 2*).

Figure 2: Key VISION Cohorts A + C Study Populations Analyzed for Efficacy (20 Nov 2022 DCO)



Source: VISION CSR 20 Nov 2022 DCO, Table 15.1.1.2.

1 L = first line of therapy, 2 L+ = second or later line of therapy, CSR = Clinical Study Report, DCO = data cutoff, SAF = safety analysis set.

The Applicant's Position:

The analysis population is considered adequate to assess the clinical benefit of tepotinib in the current indication.

The FDA's Assessment:

The FDA agrees with EMD Serono's description of patient disposition. The accelerated approval of tepotinib for the same indication was based on data from 152 patients, including 83 previously treated patients and 69 treatment-naïve patients with a DCO date of July 1, 2020, for ORR and DOR. The sample size for verification of clinical benefit has increased to 313 patients, including 149 previously treated patients and 164 treatment-naïve patients with a DCO date of November 20, 2022.

Among the 313 patients with MET-mutated NSCLC included under the current DCO, 10 previously treated patients (6.7%) and 27 treatment-naïve patients (16.5%) were still on treatment as of the DCO. The primary reasons for treatment discontinuation were progressive disease, adverse event, death, and withdrawal of consent.

EMD Serono's analysis population is based on all patients pooled across Cohorts A and C, summarized separately for the two subpopulations of previously treated and treatment-naïve patients. The included population was defined as the population of patients who were administered at least one dose of tepotinib.

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, receival of prohibited medication, and GCP deviations. Each deviation was assessed for clinical importance, which was defined as a deviation potentially impacting efficacy.

For details on the important protocol deviations, refer to VISION CSR 20 Nov 2022 cutoff, Table 15.1.2.3 and for all clinically important protocol deviations, refer to Table 15.1.2.4, and refer to Table 15.1.2.5 for COVID-19 related important protocol deviations.

The Applicant's Position:

Observed protocol deviations are considered to have no impact on the integrity of study results and conclusions.

The FDA's Assessment:

EMD Serono excluded one patient from the analyses based on the DCO of January 1, 2020 for accelerated approval due the protocol deviation of "insufficient" METex14 skipping alteration data. FDA did not agree with excluding this patient from the analyses, and this patient was included in the safety and efficacy populations, as part of the November 20, 2022 DCO.

Of note, there were 12 patients, of which 9 had objective response, who did not have all scheduled tumor assessments performed or had incomplete tumor assessment(s), and 51 patients, of which 32 had objective response, for whom the tumor evaluation scan was performed outside the protocol defined window. For the 9 patients with missing or incomplete tumor assessments, 5 were censored in the DOR analysis for "no progression or death." For the 32 patients with tumor scans performed out of window, 5 were censored in the DOR analysis for progression or death after 2 or more missed visits. These protocol deviations are detailed here for completeness but were not considered to have a significant impact on the study results.

Table of Demographic Characteristics

Data:

Key demographic and baseline characteristics are summarized in *Table 3*.

Table 3: Demographics and Baseline Characteristics by Line of Therapy and Overall, VISION Cohorts A + C, SAF

	Overall N = 313	1 L N = 164	2 L+ N = 149
Sex, n (%)			
Male	154 (49.2)	83 (50.6)	71 (47.7)
Female	159 (50.8)	81 (49.4)	78 (52.3)
Race, n (%)			
White	195 (62.3)	112 (68.3)	83 (55.7)
Black or African American	3 (1.0)	1 (0.6)	2 (1.3)
Asian	106 (33.9)	50 (30.5)	56 (37.6)
Not collected at this site	7 (2.2)	1 (0.6)	6 (4.0)
Other	1 (0.3)	0 (0.0)	1 (0.7)
Missing	1 (0.3)	0 (0.0)	1 (0.7)
Age (years)			

Mean (StD)	72.2 (9.13)	73.7 (8.56)	70.6 (9.49)
Median	72.0	74.0	70.8
Min; Max	41; 94	47; 94	41; 89
Age Categories, n (%)			
< 65 years	67 (21.4)	29 (17.7)	38 (25.5)
≥ 65 years	246 (78.6)	135 (82.3)	111 (74.5)
65 - < 75 years	117 (37.4)	58 (35.4)	59 (39.6)
75 - < 85 years	105 (33.5)	61 (37.2)	44 (29.5)
≥ 85 years	24 (7.7)	16 (9.8)	8 (5.4)
Country, n (%)			
Belgium	11 (3.5)	10 (6.1)	1 (0.7)
France	35 (11.2)	13 (7.9)	22 (14.8)
Germany	26 (8.3)	17 (10.4)	9 (6.0)
Italy	28 (8.9)	12 (7.3)	16 (10.7)

	Overall N = 313	1 L N = 164	2 L+ N = 149
Japan	38 (12.1)	18 (11.0)	20 (13.4)
Poland	6 (1.9)	4 (2.4)	2 (1.3)
Spain	26 (8.3)	14 (8.5)	12 (8.1)
United States of America	54 (17.3)	24 (14.6)	30 (20.1)
South Korea	20 (6.4)	3 (1.8)	17 (11.4)
Taiwan	12 (3.8)	0 (0.0)	12 (8.1)
Netherlands	19 (6.1)	17 (10.4)	2 (1.3)
Israel	7 (2.2)	4 (2.4)	3 (2.0)
Switzerland	1 (0.3)	1 (0.6)	0 (0.0)
Mainland China	30 (9.6)	27 (16.5)	3 (2.0)
Geographic Region, n (%)			
North America	54 (17.3)	24 (14.6)	30 (20.1)
Europe	152 (48.6)	88 (53.7)	64 (43.0)
Asia	107 (34.2)	52 (31.7)	55 (36.9)

Source: VISION CSR 20 Nov 2022 DCO, Tables 15.1.3.1a and 15.1.3.1b.

1 L = first line of therapy, 2 L+ = second line or later line of therapy, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, max = maximum, min = minimum, SAF = safety analysis set, StD = standard deviation.

The Applicant's Position:

In Cohorts A + C, 50.8% of participants were female, 62.3% were White, and 33.9% were Asian (see *Table 3*). Most participants (78.6%) were ≥ 65 years of age and 41.2% were ≥ 75 years of age. Demographic and baseline characteristics were generally consistent across treatment naïve (first line; 1 L) and pretreated participants (second or later line of therapy; 2 L+).

The FDA's Assessment:

FDA agrees with EMD Serono's description of the demographic characteristics.

Other Baseline Characteristics

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Data:

The majority of participants (94.2%) in Cohorts A+C had Stage IV disease (metastatic; including IVA and IVB) at study entry. The most frequent site of the primary tumor was the upper lung lobe (44.7%). Nontarget lesions were found most frequently in the bone, followed by brain (37.4% and 12.5%, respectively) (VISION CSR, 20 Nov 2022 DCO, Table 15.1.5.1a).

The prior anticancer drug therapy patterns in the VISION study reflect the current therapy standards in NSCLC. In Cohorts A + C, 149 (47.6%) participants received prior anticancer drug therapy for advanced or metastatic NSCLC, including 142 (45.4%) participants treated for metastatic disease (see *Table 4*). In addition, 44.4% had received prior anticancer radiotherapy; 29.7% had received prior anticancer surgery; and 11.2% had received prior anticancer drug therapy for nonadvanced disease (refer to VISION CSR, 20 Nov 2022 DCO, Table 38).

Table 4: Prior Anticancer Therapy, VISION Cohorts A + C, SAF

	Overall **N = 313 (100%)**
Prior anticancer drug therapy for advanced NSCLC, n (%)	
Yes	149 (47.6)
No	164 (52.4)
Number of prior anticancer drug therapy lines for advanced NSCLC, n (%)	
1	92 (29.4)
2	54 (17.3)
3[a]	3 (1.0)
Prior anticancer therapy for metastatic disease	
n (%)	142 (45.4)

Source: VISION CSR 20 Nov 2022 DCO, Table 15.1.4.2.

DCO = data cutoff, NSCLC = non-small cell lung cancer, SAF = safety analysis set.

a Participants (b) (6) were enrolled despite of 3 prior lines of therapy, as listed in the protocol deviations in the VISION CSR.

In Cohorts A + C, the most frequent prior drug therapy with palliative intent were either cytotoxic therapy (40.3% of participants) and/or immunotherapy (25.9% of participants) (VISION CSR Table 15.1.4.2).

In Cohorts A + C, the median treatment duration with tepotinib was 7.5 months (range: 0.03 to 71.85) (VISION CSR Table 15.1.7.1).

The Applicant's Position:

The study population was representative of the targeted METex14 NSCLC population, based on

the reported disease history and the prior anticancer drug therapy patterns in the VISION study reflect the current therapy standards in NSCLC.

The FDA's Assessment:

FDA agrees with EMD Serono's description of the baseline characteristics. Of note, among previously treated patients, 62% received one line, 36% received two lines, and 2% received three lines of prior systemic therapy. Amongst previously treated patients, 84% received prior platinum-based chemotherapy. Additional relevant baseline characteristics not addressed in the Applicant's position include the following: 24% of patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 and 74% had ECOG PS of 1; 49% never smoked; and 81% had adenocarcinoma.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

The median duration of exposure to tepotinib was 7.46 months in the combined analysis set (N = 313). The majority of participants were exposed to tepotinib at a relative dose intensity of 90% to 110% (combined analysis set: 63.6%,). Protocol deviations related to compliance with intervention were reported in 10.2% of participants in Cohorts A + C (refer to VISION CSR Section 4.6.3.3).

The Applicant's Position:

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

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Tepotinib exhibited high and meaningful clinical activity in advanced NSCLC harboring METex14 skipping alterations across the endpoints studied in the VISION study (*Table 5*).

Table 5: Efficacy Results, Independent Evaluation, VISION Cohorts A + C by Line of Therapy and Overall, SAF

	Overall N = 313	1 L N = 164	2 L+ N = 149
ORR[a] n (%) [95% CI][b]	161 (51.4) [45.8, 57.1]	94 (57.3) [49.4, 65.0]	67 (45.0) [36.8, 53.3]
mDOR, months[c] [95% CI][d]	18.0 [12.4, 46.4]	46.4 [13.8, NE]	12.6 [9.5, 18.5]

DOR ≥ 6 months, n (% of responders)	106 (65.8)	62 (66.0)	44 (65.7)
DOR ≥ 9 months, n (% of responders)	80 (49.7)	48 (51.1)	32 (47.8)
DOR ≥ 12 months, n (% of responders)	62 (38.5)	38 (40.4)	24 (35.8)
mPFS, months[c] [95% CI][d]	11.2 [9.5, 13.8]	12.6 [9.7, 17.7]	11.0 [8.2, 13.7]
Patients with event (PD/Death), n (%)	165 (52.7)	81 (49.4)	84 (56.4)
mOS time,[c] months [95% CI][d]	19.6 [16.2, 22.9]	21.3 [14.2, 25.9]	19.3 [15.6, 22.3]
Patients with event, n (%)	200 (63.9)	98 (59.8)	102 (68.5)

Source: VISION CSR DCO 20 Nov 2022 Tables 15.2.1.1nsf, 15.2.1.17nsbf, 15.2.2.1b, 15.2.2.3ab, 15.2.2.3sc, 15.2.3.1b, and 15.2.4.1b.

1L = first line of therapy, 2L+ = second or later line of therapy, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, CI = confidence interval, mDOR = median duration of response, mOS = median overall survival, mPFS = median progression-free survival, NE = not estimable, ORR = objective response rate, PD = progressive disease, SAF = safety analysis set.

a Confirmed complete response/partial response.

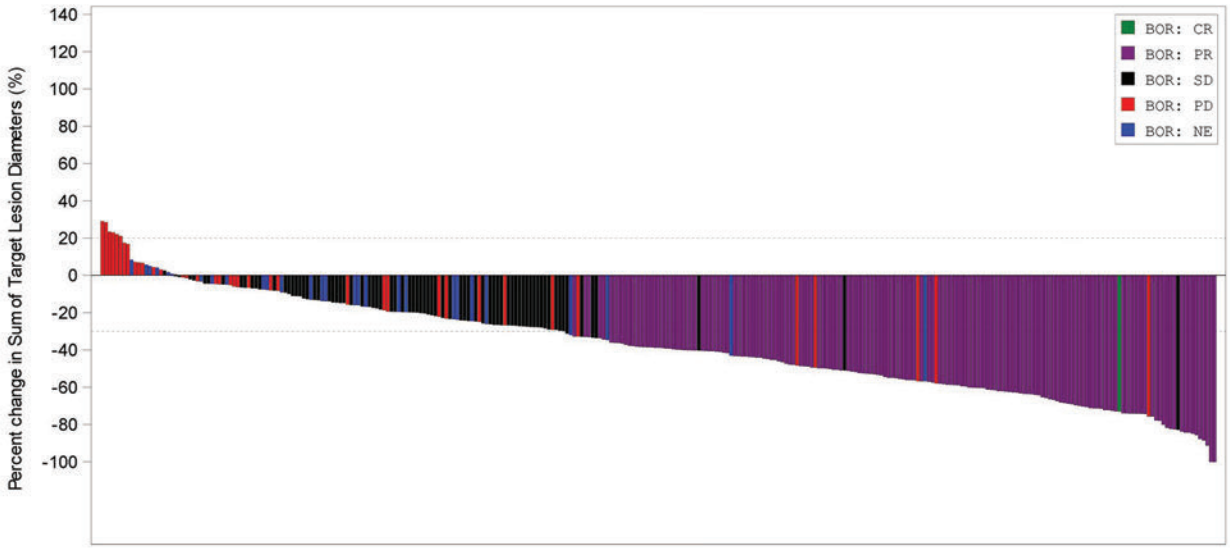
b 95% exact CI using the Clopper-Pearson method.

c Product-limit (Kaplan-Meier) estimates.

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

Objective response (OR) based on independent evaluation was the primary endpoint of the study and confirmed response according to RECIST 1.1 was observed in 161 participants in Cohorts A + C, yielding a clinically meaningful ORR of 51.4% (95% CI: 45.8, 57.1) (see *Table 5*). As shown in *Figure 3*, the vast majority of participants with METex14 NSCLC presented with tumor shrinkage after start of tepotinib. This is also reflected by 78 (24.9%) participants with stable disease as best overall response (VISION CSR, 20 Nov 2022 DCO, Table 15.2.1.1nsf).

Figure 3: Percent Change in Sum of Longest Diameters Between Baseline and Best Postbaseline Assessment, Independent Evaluation, VISION Cohorts A+C, SAF

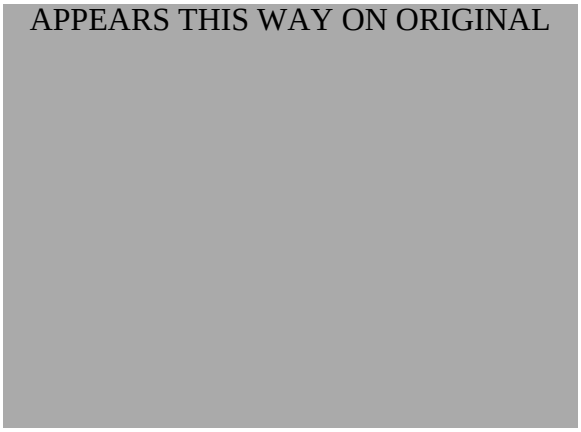


Tepotinib efficacy is consistently high and clinically meaningful also across different lines of therapy, i.e. independent of whether a participant has received prior anticancer therapy for advanced NSCLC or not (*Table 5*). The meaningful ORR in the overall population is supported by high ORR in treatment-naïve 57.3% (95% CI: 49.4, 65.0) and pretreated 45.0% (95% CI: 36.8, 53.3) participants.

Source: VISION CSR, DCO 20 Nov 2022, Figure 15.2.1.14sa.

BOR = best overall response, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, CR = complete response, NE = not estimable, PD = progressive disease, PR = partial response, SAF = safety analysis set, SD = stable disease.

8 participants were excluded due to missing baseline/on treatment measurements.



The combination of Cohorts A and C enables a robust estimation of potential effect modifiers in this large and comprehensive dataset evaluating a MET inhibitor in 313 patients with METex14 positive NSCLC.

A forest plot with all subgroup analyses is presented in *Figure 4* for Cohorts A + C by independent evaluation. It shows that the analyses for OR provided consistent results in all subgroups analyzed, underscoring the robustness of tepotinib efficacy in the METex14 positive NSCLC population.

Considering that METex14 NSCLC is more frequent in elderly patients, the consistent efficacy independent of age is remarkable as shown for the different age categories with thresholds at 65, 75, and even 80 years of age.

Moreover, the role of tepotinib in the commonly underserved NSCLC population of patients with brain metastasis is to be emphasized. Despite the generally poor prognosis of this NSCLC subpopulation, tepotinib showed an ORR of 64.1% (95% CI: 47.2, 78.8) in participants who presented with brain metastasis at baseline, as per independent evaluation.

In addition, the fact that ORR was consistent independent of prior treatment as evaluated via different categories (i.e. across line of therapy and post platinum-based chemotherapy, see *Figure 4*) again supports the scientific concept of METex14 being an oncogenic driver for NSCLC demanding a targeted therapy.

As expected for a targeted treatment administered to patients with NSCLC selected by a functional oncogenic driver, the subgroup analyses showed consistency in the efficacy of tepotinib regardless of race, geographic region, or ethnicity.

Figure 4: Forest Plot of OR, Independent Evaluation, VISION Cohorts A + C, SAF

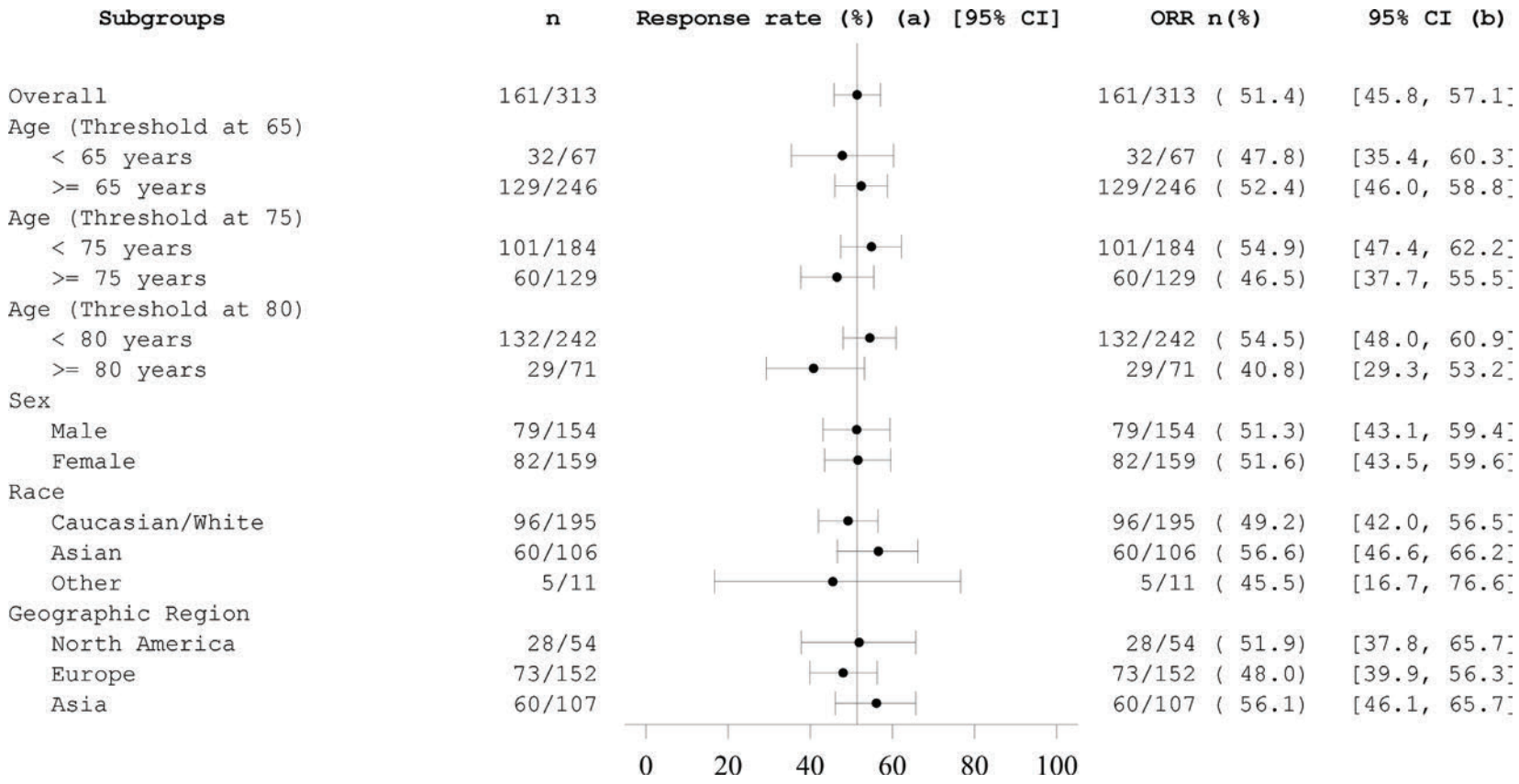
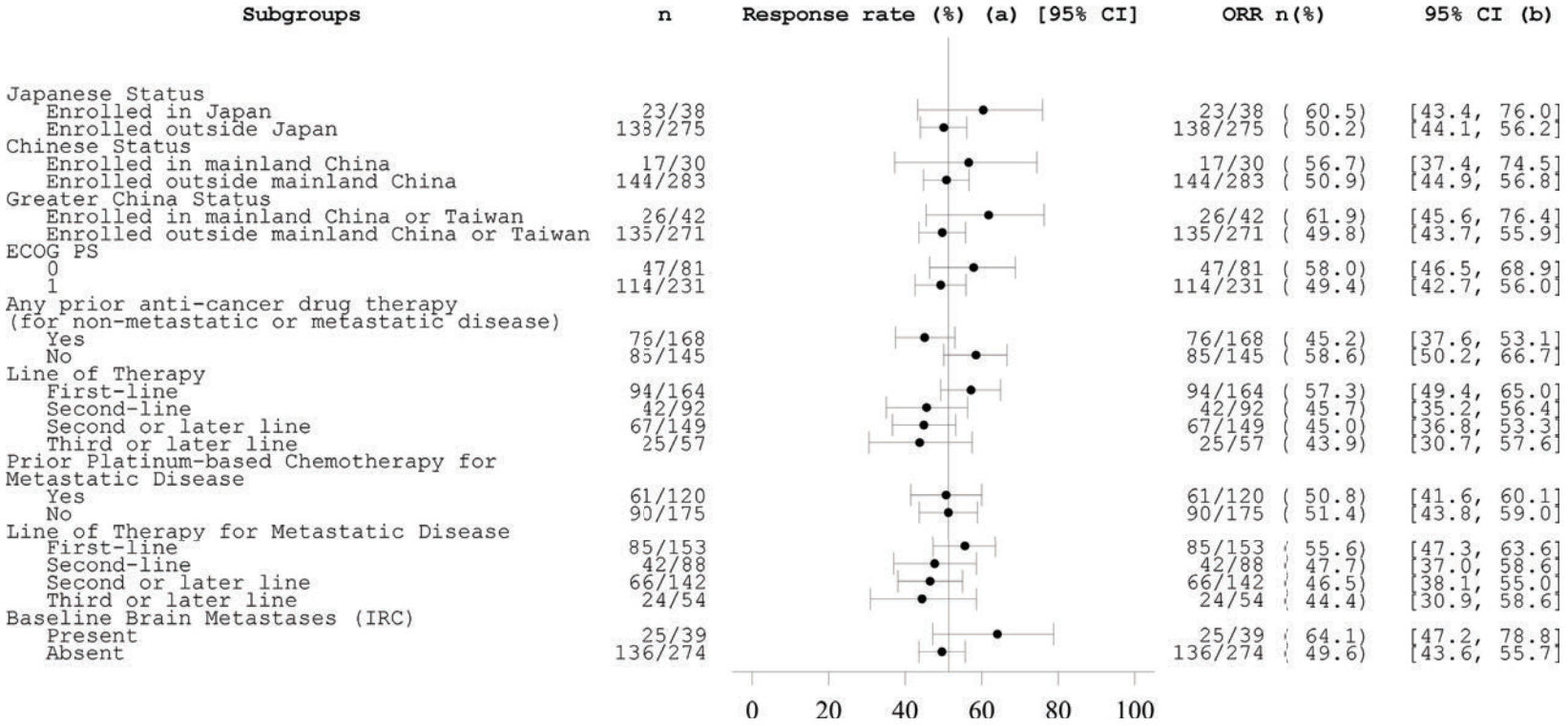


Figure 4 **Forest Plot of OR, Independent Evaluation, VISION Cohorts A + C, SAF (Cont.)**



Source: VISION CSR 20 Nov 2022 DCO, Figures 15.2.1.6nbsf.

CI = confidence interval, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, CSR = Clinical Study Report, ECOG PS = Eastern Cooperative Oncology Group performance status, IRC = Independent Review Committee, NE = not estimable, ORR = objective response rate, SAF = safety analysis set.

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

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

Only prior anticancer drug therapies administered for advanced (stage IIIb/IIIc) or metastatic (IV) diseases are taken into account for the categorization of line of therapy. Participants in second or later line: only participants with tepotinib as second or later line are considered for this subgroup.

The Applicant's Position:

Efficacy data from 313 participants with METex14 NSCLC, including 164 treatment-naïve (1 L) and 149 pretreated (2 L+) participants, show high and clinically meaningful ORRs and long lasting and durable responses.

Consistent benefit was observed across all displayed subpopulations, including age, sex, race, baseline brain metastases, and advanced and metastatic participants (see *Figure 4*). This substantiates the robustness of the efficacy with tepotinib.

The FDA's Assessment:

FDA agrees with EMD Serono's description of the results observed for ORR in the primary efficacy population and with EMD Serono's subgroup analyses of the primary endpoint. In this marketing application, additional response and DOR data (from after the DCO for the accelerated approval) were provided for responders from the efficacy population supporting the accelerated approval of tepotinib.

For the efficacy population supporting the current sNDA, the ORR among 164 previously treated patients was 57% (95% CI 49, 65), and the ORR among 149 previously treated patients was 45% (95% CI 37, 53).

In general, consistent results for ORR per BIRC were observed across the subgroups based on the combined data from Cohorts A and C (Figure 4). ORR results among patients previously treated with platinum-based chemotherapy were consistent with the results in the overall population of previously treated patients.

FDA agrees with EMD Serono's subgroup analyses. The small sample sizes of the subgroup categories for Race of "Other" and Chinese status of enrolled in Mainland China likely explain the wide confidence intervals. The ORR estimates for these subgroups may be imprecise and should be interpreted with caution.

Data Quality and Integrity

Data:

The study was monitored in accordance with ICH GCP (ICH E6 (R2), 2016) and any other applicable regulations.

Since previously reported in the context of the accelerated approval, Investigator site audits were conducted in France (Site 304) and China (850 and 862). No concerns regarding data integrity were reported following the completion of these audits.

The VISION study began in September 2016 and was ongoing at the 20 Nov 2022 DCO, which

included the period during which the COVID-19 pandemic was occurring globally. Appropriate safeguards had been adopted to minimize the disruption of the VISION study by the COVID-19 pandemic and to ensure the integrity of the study data in keeping with the applicable FDA guidance.

Tables and listings have been prepared addressing any potential effect of the COVID-19 pandemic on the available study results with respect to adverse events, missed visits, missed tumor assessments, and pertinent protocol deviations. A summary of all COVID-19 related analyses is provided in the CSR Appendix P.

For the applicable tables, figures, and listings, refer to the VISION CSR 20 Nov 2022 DCO, Tables 15.1.1.1, 15.1.1.8, 15.1.2.5, 15.1.2.6, and Listings 16.2.1.4, 16.2.2.3, and 16.2.6.5.

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. There has been no relevant impact of the COVID-19 pandemic on the evaluation of the efficacy outcomes reported.

The FDA's Assessment:
FDA agrees with EMD Serono's position.

Efficacy Results – Secondary and other relevant endpoints

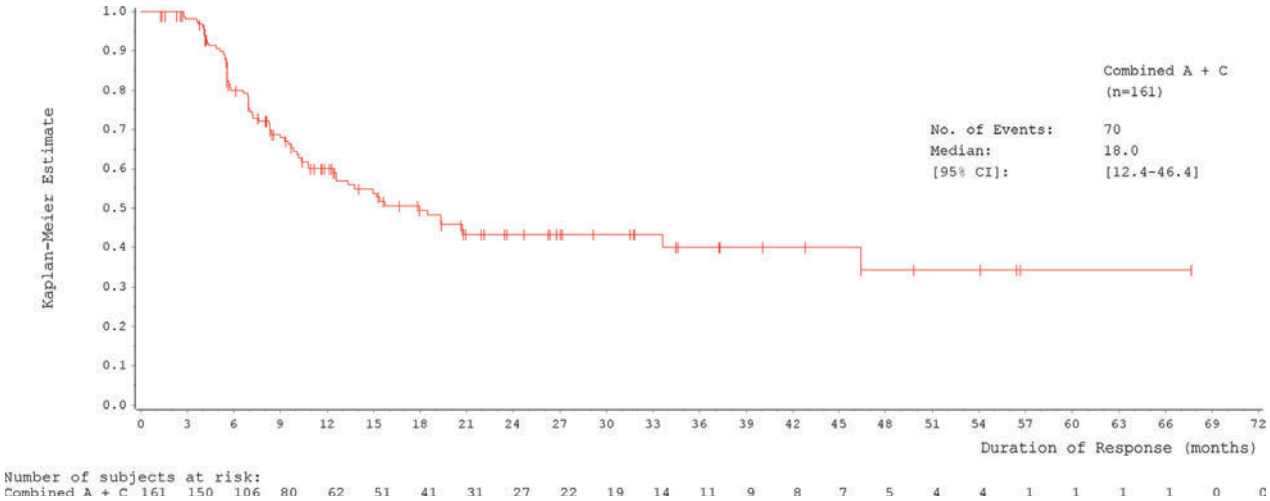
Data:

The Kaplan-Meier estimate of mDOR strongly supports the clinical benefit of treatment with tepotinib. The mDOR based on independent evaluation was 18.0 months (95% CI: 12.4, 46.4) in the overall population (see *Table 5* and *Figure 5*). As shown in *Figure 6*, the sustained response in the overall population is substantiated by the Kaplan-Meier estimates for mDOR in treatment-naïve (46.4 months [95% CI: 13.8, NE]) and pretreated (12.6 months [95% CI: 9.5, 18.5]) participants. A trend towards higher ORR in treatment-naïve than in pretreated participants was observed, but the associated 95% CIs largely overlap. Most of the responses to tepotinib occurred early (within 3 months of first dose) and were deep and durable, up to 67.6 months (VISION CSR Table 15.2.2.1b).

The durable efficacy of tepotinib was further reflected by the clinically meaningful median PFS (mPFS) of 11.2 months (95% CI: 9.5, 13.8) and a mOS of 19.6 months (95% CI: 16.2, 22.9) in the overall population (see *Figure 7* and *Figure 9*). Among 161 participants in the combined analysis set with confirmed CR or PR, 62 participants (38.5%) had a DOR ≥ 12 months (*Table 5*). One participant (0.6%) had an ongoing response with late onset of response (16.7 months after the first dose of study treatment), thus, the duration of follow-up from onset of response is less than 12 months for this single participant (i.e. 10.4 months) (refer to VISION CSR Section 5.1.4.3).

The mPFS and mOS estimates observed in treatment-naïve and pretreated Cohorts A + C population again point to the meaningful efficacy of tepotinib independent of prior nontargeted anticancer therapy in advanced METex14 NSCLC in line with the common observation in a population selected for an oncogenic NSCLC driver (*Figure 8* and *Figure 10*).

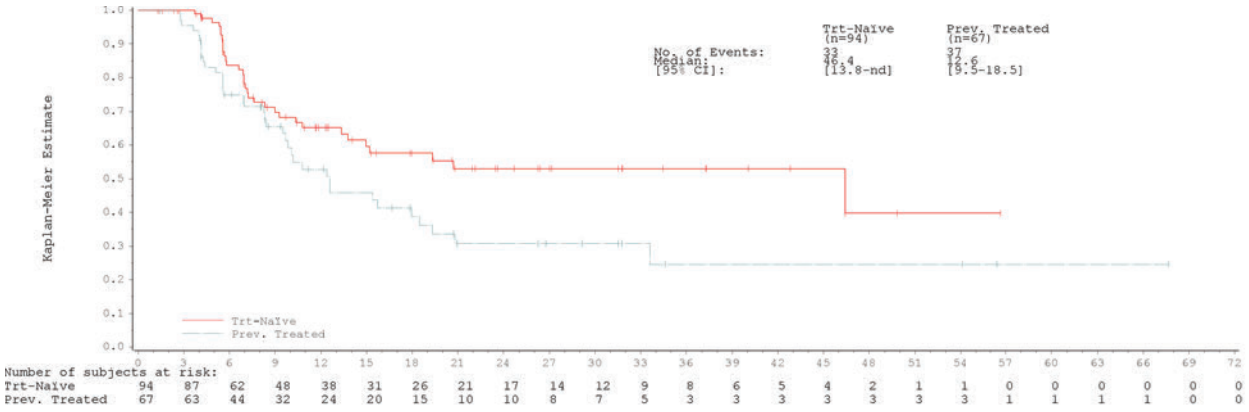
Figure 5: Kaplan-Meier Curve Showing Duration of Response, Independent Evaluation, VISION Cohorts A + C, SAF



Source: VISION CSR 20 Nov 2022 DCO, Figure 15.2.2.2s.

CI = confidence interval, CSR = Clinical Study Report, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, DCO = data cutoff, SAF = safety analysis set.

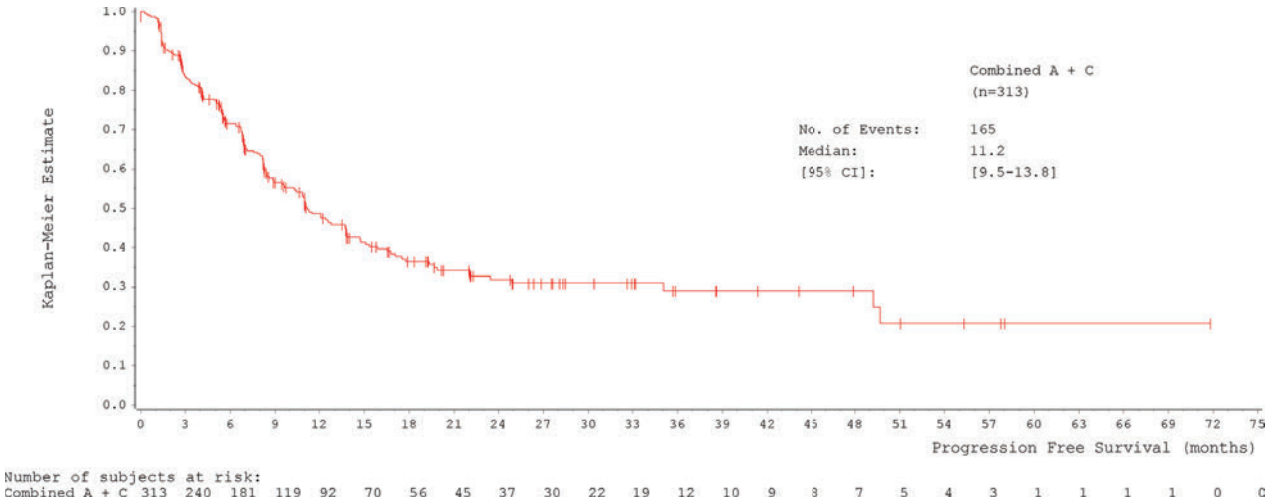
Figure 6: Kaplan-Meier Curve Showing Duration of Response by Prior Anticancer Drug Therapy, Independent Evaluation, VISION Cohorts A + C, SAF



Source: VISION CSR 20 Nov 2022 DCO, Figure 15.2.2.5s.

CI = confidence interval, CSR = Clinical Study Report, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, DCO = data cutoff, SAF = safety analysis set.

Figure 7: Kaplan-Meier Curve Showing PFS, Independent Evaluation, VISION Cohorts A + C, SAF

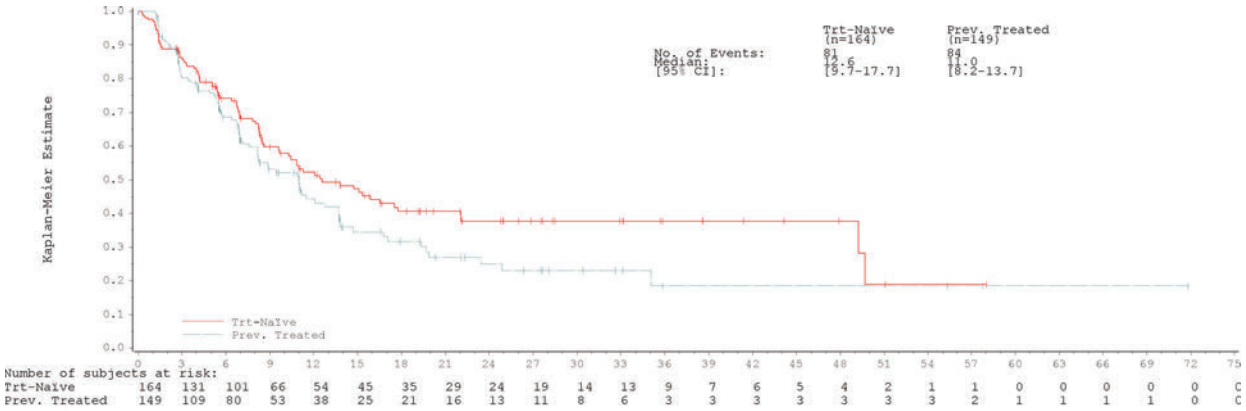


Source: VISION CSR 20 Nov 2022 DCO Figure 15.2.3.2s.

CI = confidence interval, CSR = Clinical Study Report, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, DCO = data cutoff, PFS = progression free survival, SAF = safety analysis set.

Only prior anticancer drug therapies administered for advanced (stage IIIb/IIIc) or metastatic (IV) diseases are considered for the categorization of line of therapy.

Figure 8: Kaplan-Meier Curve Showing PFS by Prior Anticancer Drug Therapy, Independent Evaluation, VISION Cohorts A + C, SAF

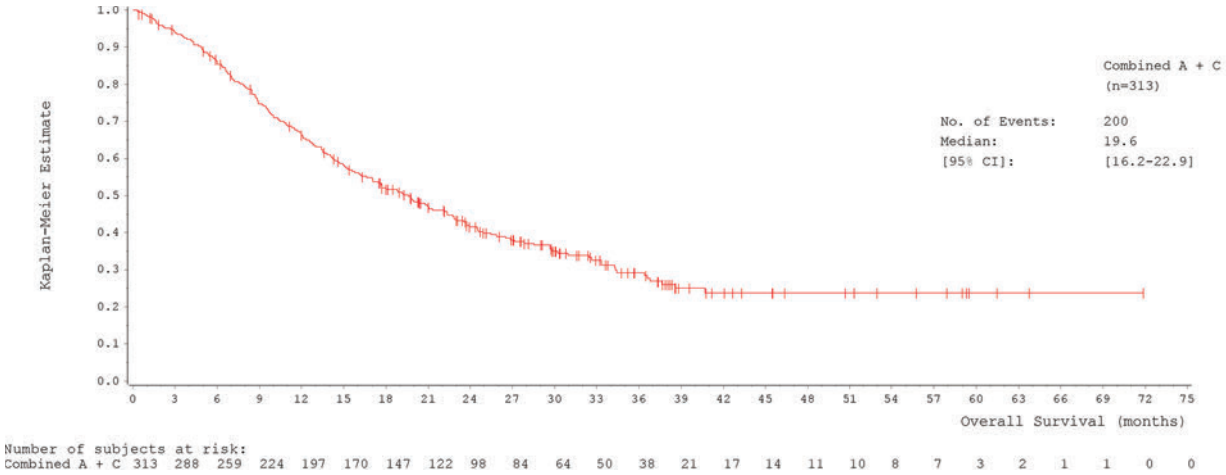


Source: VISION CSR 20 Nov 2022 DCO Figure 15.2.3.10s.

CI = confidence interval, CSR = Clinical Study Report, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, DCO = data cutoff, PFS = progression free survival, SAF = safety analysis set.

Only prior anticancer drug therapies administered for advanced (stage IIIb/IIIc) or metastatic (IV) diseases are considered for the categorization of line of therapy.

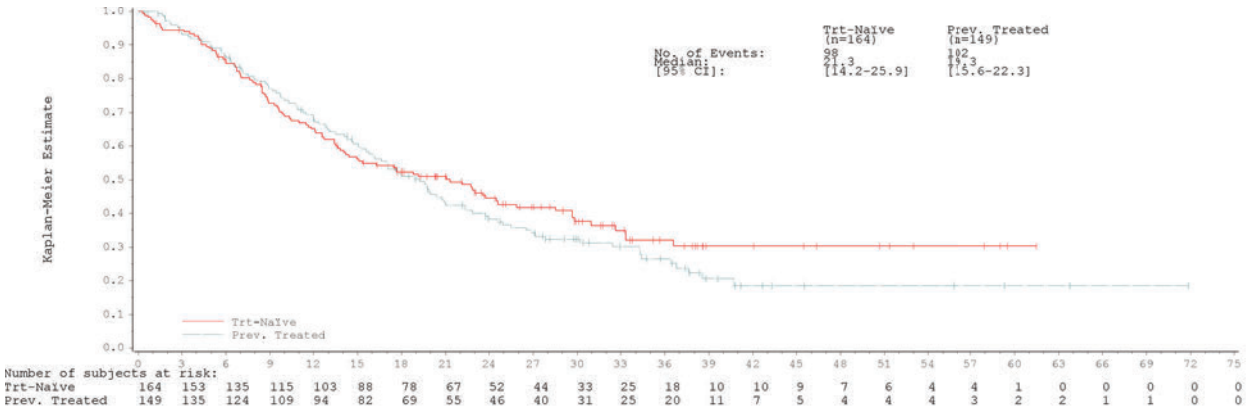
Figure 9: Kaplan-Meier Curve Showing OS, VISION Cohorts A + C, SAF



Source: VISION CSR 20 Nov 2022 DCO, Figure 15.2.4.2s.

CI = confidence interval, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, OS = overall survival, SAF = safety analysis set.

Figure 10: Kaplan-Meier Curve Showing OS by Prior Anticancer Drug Therapy, VISION Cohorts A + C, SAF



Source: VISION CSR 20 Nov 2022 DCO, Figure 15.2.4.5s.

CI = confidence interval, Combined analysis set = liquid biopsy positive and/or tumor tissue biopsy positive, CSR = Clinical Study Report, DCO = data cutoff, OS = overall survival, SAF = safety analysis set.

The Applicant's Position:

Tepotinib, administered at an oral dose of 500 mg once daily, exhibited substantial, and sustained clinical activity in advanced NSCLC harboring METex14 skipping alterations. The new efficacy analyses based on a large population of 313 participants with a longer follow-up of at least 18 months after start of tepotinib treatment further substantiate the available strong evidence of clinically meaningful response rate, deep and durable responses, and rapid onset of responses. PFS and OS analyses provided additional supportive evidence. Clinically meaningful improvements were observed in OR, DOR, PFS, and OS for this patient population with high unmet medical need.

The FDA's Assessment:

Based on Blinded Independent Review Committee (BIRC) assessment, in the treatment-naïve cohort, 66% of responders had a duration of response (DOR) ≥6 months and 40% had a DOR ≥12 months, and in the previously treated cohort, 66% of responders had a duration of response (DOR) ≥6 months and 36% had a DOR ≥12 months. The observed median duration of response (DOR) was 9.1 months (range 1.3+, 56.6+ months) for treatment-naïve patients and 8.4 months (range 1.4+, 67.6+ months) for previously treated patients.

FDA does not agree with EMD Serono's description of DOR results in this study. The estimated median DOR per IRC calculated using the Kaplan-Meier method is not reliable due to a high amount of informative censoring. This effect is more pronounced in the treatment-naïve subpopulation, in part due to a large proportion of patients censored before the median was reached, and therefore removed from the at-risk set for determining the Kaplan-Meier estimate of the median (*Figure 6*). The high amount of censoring was for two reasons 1) 21.1% of patients progressed or died after two missed assessments and 2) for 6.8% of patients, there was a lack of scans available for assessment by the IRC following investigator determination of PD. An important assumption of the Kaplan-Meier method is that censoring is independent of the risk of an event, and in both these cases patients who were at higher risk of progression were censored for the DOR by BICR analysis.

An IR was sent to EMD Serono to better understand the reasons for censoring and to perform sensitivity analyses for DOR that would better characterize the Kaplan-Meier curve based on data from the November 20, 2022 DCO. EMD Serono also provided DOR data with longer follow-up using a DCO of September 20, 2023. Based on the updated data cutoff, the Kaplan-Meier estimate of the median DOR in the treatment-naïve arm was 31.8 months (95% CI: 13.8, NR) and the median DOR in the previously treated arm was 12.6 months (95% CI: 9.5, 18.5). There were 95 responders in the treatment-naïve arm and a total of 36 events for DOR. In the previously treated arm, there were 67 responders and 37 events. There was one additional patient counted as a responder, who had their best response changed from SD to PR. This PR was recorded by the

IRC on February 20, 2023. The Kaplan-Meier estimate of the median in the updated data is similarly affected by the pattern of censoring before the median observed in the November 20, 2022 DCO. Additional sensitivity analyses conducted by FDA and information regarding reasons from censoring from the IR can be found in Section 8.3

Additionally, FDA conducted an analysis of DOR using investigator assessment. According to the investigator assessment, 87 treatment-naïve patients had objective response (53%) and 82 previously treated patients had objective response (55%). For treatment-naïve patients, there were 45 disease progressions or deaths, and the Kaplan-Meier estimate of median DOR was 16.4 months (95% CI: 10.94, NE). For previously treated patients, there were 53 disease progressions or deaths and the Kaplan-Meier estimate of median DOR was 11.5 months (95% CI: 8.02, 14.3).

Based on the FDA's review of data from both the November 20, 2022 and September 20, 2023 data cuts, the estimated median DORs per the ICR do not appear to be robust. The high amount of informative censoring of DOR has led to overestimation of the DOR by the Kaplan-Meier method, particularly for the treatment-naïve cohort. Other time-to-event endpoints such as PFS and OS are not interpretable to assess efficacy in non-randomized settings, and thus are considered descriptive only. While not investigated in this review, the PFS endpoint is also likely affected by the same censoring issues as DOR.

Dose/Dose Response

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

Not Applicable.

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:

While FDA agrees that the responses in this study were durable, the data to characterize median duration of response based on Kaplan-Meier estimates were not reliable due to several issues, as described in section 8.3.

Persistence of Effect

Data:

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

The Applicant's Position:

The durable efficacy of tepotinib was further reflected by the clinically meaningful median PFS (mPFS) of 11.2 months (95% CI: 9.5, 13.8) and a mOS of 19.6 months (95% CI: 16.2, 22.9) in the overall population.

The FDA's Assessment:

In the context of this single arm trial, FDA considers these analyses of PFS and OS to be uninterpretable and, therefore, descriptive only.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Overall, the completion rate for PRO questionnaires in this study was high (> 80%) in the majority of treatment cycles.

Results in Cohorts A + C SAF 20 Nov 2022 (N = 313) were consistent across the 3 PRO tools (EuroQol Five dimension Five-level Scale, EORTC QLQ-C30, and EORTC QLQ-LC13) and showed stability in health-related quality of life over time (refer to Section 2.7.3 Addendum, Figures 10 to 14).

For EORTC QLQ-LC13, favorable effects regarding stability of symptom intensities for dyspnea and pain in chest, and a clinically meaningful improvement in the coughing symptom scale were observed (refer to Section 2.7.3 Addendum, Figures 12 to 14).

The Applicant's Position:

High compliance rates were observed for all the patient reported outcome questionnaires, and results were consistent and showed stability in health-related quality of life over time.

The FDA's Assessment:

FDA acknowledges that PRO data were collected and demonstrated stable symptom intensity for dyspnea and chest pain and an improvement in coughing on the EORTC QLQ-LC13; however, these data are challenging to interpret in the setting of a single-arm trial. FDA reviewed the compliance rates for the 3 PRO questionnaires: EQ-5D-5L, EORTC-QLQ-C30, and EORTC QLQ-LC13, based on the number of patients expected to have a PRO assessments. Compliance rates at Day 84 (Cycle 5 Day 1) were 87.5% for EQ-5D-5L, 88.3% for EORTC-QLQ-C30, and 87.5% for EORTC-QLQ-LC13. Compliance rates at Day 168 (Cycle 9 Day 1) were 86.5% for EQ-5D-5L, 87.1% for EORTC-QLQ-C30 and 86.5% for EORTC-QLQ-LC13. Compliance rates at Day 252 (Cycle 13 Day 1) were 86.5% for EQ-5D-5L, 87.2% for EORTC-QLQ-C30, and 87.2% for EORTC-QLQ-LC13.

Additional Analyses Conducted on the Individual Trial

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

N/A

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
Please refer to Section 8.1.5. below.

8.1.4. Assessment of Efficacy Across Trials

Data:

N/A

The Applicant's Position:

N/A

Additional Efficacy Considerations

The FDA's Assessment:
No additional efficacy data were considered other than the data from the VISION study described in Section 8.1.2.

8.1.5. Integrated Assessment of Effectiveness

Data:

Tepotinib, administered at an oral dose of 500 mg once daily, exhibited substantial, and sustained clinical activity in advanced NSCLC harboring METex14 skipping alterations. The new efficacy analyses based on a large population of 313 participants with a longer follow-up of at least 18 months after start of tepotinib treatment further substantiate the available strong evidence of clinically meaningful response rate, deep and durable responses, and rapid onset of responses. PFS and OS analyses provided additional supportive evidence. Clinically meaningful improvements were observed in OR, DOR, PFS, and OS for this patient population with high unmet medical need. Benefit was consistent between elderly and younger participants, supporting the suitability of tepotinib for METex14 NSCLC, which typically manifests in the elderly:

- Efficacy data from 313 participants with METex14 NSCLC, including 164 treatment-naïve (1 L) and 149 pretreated (2 L+) participants, show high and clinically meaningful ORRs and long lasting and durable responses.
- Consistent benefit was observed across all displayed subpopulations, including age, sex, race, baseline brain metastases, and advanced and metastatic participants (see *Figure 4*. This substantiates the robustness of the efficacy with tepotinib.

- Consistent efficacy results for ORR and mDOR were also observed between participants identified by L+ and T+ methodology. The estimates for mPFS and mOS are clinically

meaningful and support the use of both test methodologies for the identification of METex14 NSCLC patients for tepotinib treatment.

- High compliance rates were observed for all the patient reported outcome questionnaires, and results were consistent and showed stability in health-related quality of life over time.

The Applicant's Position:

In conclusion, tepotinib, administered at 500 mg once daily, exhibited substantial and sustained clinical activity in the study population of patients with advanced or metastatic NSCLC whose disease is driven by METex14 skipping alterations. The efficacy analyses from the 20 Nov 2022 DCO provide evidence of clinically meaningful ORRs, deep and durable responses, and rapid onset of responses. The PFS and OS analyses are overall supportive irrespective of whether participants had been pretreated or not. The data from all VISION participants constitute the largest data set from a clinical study in METex14 NSCLC so far.

The increased sample size and longer follow-up from this study provide a robust estimate of the efficacy data confirming the continued clinical benefit of tepotinib for treatment in patients with advanced NSCLC harboring METex14 skipping alterations.

The FDA's Assessment:

The data provided in this submission supports the clinically meaningful benefit over available non-targeted therapy observed in the accelerated approval and demonstrates long-term efficacy with a clinically meaningful response rate and durable antitumor responses with tepotinib in both treatment-naïve and previously treated patients with NSCLC harboring MET exon 14 skipping mutations.

Observed median DOR was 8.4 months (range 1.4+, 67.6+ months) in previously treated patients, with 36% of responders having a DOR ≥12 months, and 9.1 months (range 1.3+, 56.6+ months) in treatment-naïve patients, with 40% of responders having a DOR ≥12 months. ORR was 45% in previously treated patients and 57% in treatment-naïve patients. The observed DOR per BIRC, supported by the consistency of ORR results in a larger number of patients relative to the accelerated approval, provide substantial evidence of effectiveness of tepotinib in both previously treated and treatment-naïve patients.

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:

The updated safety analyses in this addendum report focus on the data from participants in Cohorts A + C of the pivotal VISION study. These are patients with advanced NSCLC harboring METex14 skipping alterations, treated at the approved oral dose of 500 mg tepotinib once daily,

who are representative of the population targeted in this application. The study is currently ongoing; enrollment was completed on 20 May 2021.

The updated safety data presented in this document are derived from all 313 participants with METex14 NSCLC (VISION Cohorts A + C) participants, who had at least 18 months of follow-up after start of tepotinib treatment as of 20 Nov 2022 DCO.

The analysis of AE data was based on TEAEs only, defined as AEs which emerged or worsened during the on-treatment period. 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.

Applicant's Position

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 ≥ 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 6*.

Table 6: Search Criteria for Identified and Potential Risks and AEs of Clinical Interest

Category	MedDRA Terms
	Identified Risks
Interstitial lung disease (ILD)	SMQs: Interstitial lung disease – narrow
Edema	PTs: Face oedema, Oedema, Oedema peripheral, Localized oedema, Oedema genital, Periorbital oedema, Scrotal oedema, Peripheral swelling, Abdominal wall oedema, Generalized oedema
Creatinine increase	PTs: Hypercreatininaemia, Blood creatinine increased, Blood creatinine abnormal
Hypoalbuminemia	PTs: Blood albumin abnormal, Blood albumin decreased, Hypoalbuminaemia
Serum amylase increase and Serum lipase increase	PTs: Amylase abnormal, Amylase increased, Hyperamylasaemia Lipase abnormal, Lipase increased, Hyperlipasaemia Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, Pancreatic enzymes increased
ALT and/or AST increase	PTs: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Transaminases increased Transaminases abnormal, Hypertransaminasaemia, AST/ALT ratio abnormal
ALP increased	PT: Blood alkaline phosphatase increased
Diarrhea	PT: Diarrhea
Nausea	PT. Nausea
Vomiting	PT: Vomiting
	Potential Risks
Pleural effusion	PT: Pleural effusion
QT prolongation	SMQ: Torsade de pointes/QT prolongation – broad; PTs: Seizure, Tonic convulsion, Clonic convulsion, Generalized tonic−clonic seizure

Category	MedDRA Terms
Severe hepatotoxicity	SMQs: Hepatic failure, fibrosis and cirrhosis and other liver damage−related conditions - narrow and Hepatitis, noninfectious - narrow
Adverse Events of Clinical Interest	
Hepatobiliary toxicity	SMQ: Drug related hepatic disorders - comprehensive search

AE = adverse event; ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = Preferred term; SMQ = Standardized MedDRA Query.

Applicant's Position

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.

No additional safety (see Section 8.2.7 and 8.2.9) explorations have been performed.

The FDA's Assessment:

The safety review approach is appropriate to allow for an adequate assessment of safety to inform the risk-benefit assessment for this sNDA. The updated safety primary analysis population included all patients in Cohorts A and C of the VISION Study as of the November, 20 2022 data cutoff. The pooled safety population, used to inform Section 5 of labeling, included 506 patients with solid tumors; this included 58 additional patients compared to prior analyses performed at the time of the accelerated approval. Among the pooled safety population, there were 313 patients with NSCLC harboring MET exon 14 skipping alterations; data from this subpopulation was used to inform Section 6 of labeling.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

At the time of the 20 Nov 2022 DCO, 313 participants in VISION Cohorts A + C had been treated with tepotinib (SAF population). The median duration of tepotinib exposure in VISION Cohorts A + C was 7.5 months (range 0 to 72 months) (refer to VISION CSR Table 15.1.7.1). 63.6 participants received between 90% and 110% of the planned dose (refer to VISION CSR

Table 15.1.7.3).

276 (88.2%) participants permanently discontinued treatment. As per the study protocol, Investigators discontinued participants from treatment due to disease progression (57.2% of participants). In 16.9% of participants, a TEAE was the reason for permanent treatment discontinuation. At the DCO, 37 (11.8%) participants in VISION Cohorts A + C were still on treatment (refer to VISION CSR Table 15.1.1.1).

The Applicant's Position:

The overall exposure duration was sufficient to assess the safety of tepotinib monotherapy.

The FDA's Assessment:

Results are presented below for the safety populations assessed by FDA. Among 506 patients who received tepotinib, FDA verified that 44% were exposed for at least 6 months and 22% were exposed for at least one year as shown in the table below.

Table 7 (FDA): Overall Exposure of tepotinib in VISION

Treatment Duration	Number of Patients (N=506)	Percent
< 6 months	283	56
>= 6 months	223	44
< 12 months	393	78
>= 12 months	113	22

FDA generated analysis.

Relevant Characteristics of the Safety Population:

Data:

In Cohorts A + C, 50.8% of participants were female, 62.3% of participants were White and 33.9% participants were Asian (see *Table 3*). Most participants (78.6%) were ≥ 65 years of age and 41.2% of participants were ≥ 75 years of age.

The Applicant's Position:

The participant characteristics in VISION Cohorts A + C were as expected for the study population, i.e. predominantly elderly patients with advanced disease.

The FDA's Assessment:

FDA agrees with the EMD Serono's position on the demographics of the safety population. The characteristics of the safety population from the VISION study are consistent with the epidemiology of patients with MET exon 14 skipping metastatic non-squamous NSCLC.

Adequacy of the Safety Database:

Data:

At the DCO, the safety profile of tepotinib was re-evaluated based on the data from the 313 *MET*ex14 NSCLC patients who were treated with 500 mg tepotinib once daily 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 *MET*ex14 NSCLC and intended dosage. See Section 8.2.1 for further details.

The Applicant's Position:

As *MET*ex14 NSCLC is a rare and life-threatening disease with a high unmet medical need, the VISION study design, 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, provide guidance on the management of risks and assess the benefit- risk profile of tepotinib.

The FDA's Assessment:

FDA agrees that, overall, the safety database of 313 tepotinib-treated patients with NSCLC with MET mutations taken together with data from the 506 patients with solid tumors who received tepotinib included in the current supplemental application is adequate to evaluate the toxicities and confirm the safety profile 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. See subsection "Data Quality and Integrity" of Section 8.1.2 regarding the impact of the COVID-19 pandemic on the VISION study.

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. There has been no relevant impact of the COVID-19 pandemic on the safety outcomes reported in this document.

The FDA's Assessment:

The data submitted were adequate and sufficiently organized to allow for a complete review of the safety data. Overall, FDA agrees that there were no significant data quality or reporting issues identified during the review of this supplemental application. FDA requested additional information during the review cycle to obtain clarification regarding some aspects of the safety and efficacy data; these information requests were adequately addressed by the Applicant.

Categorization of Adverse Event

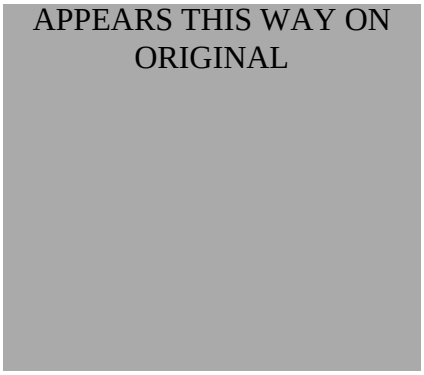
Data:

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. 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.

For this update, AEs were coded using Version 25.1 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 4.03).

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 were analyzed using the search strategies described in *Table 6*.

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's description of the categorization of adverse events.

Routine Clinical Tests

Data:

Clinical safety tests carried out in the VISION Study are summarized in *Table 8*.

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Table 8: Schedule of Safety Tests in the VISION Study

	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 ± 3d	Cycle 4, 6, 8, 10 and 12 ± 3d		
Day		**–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	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 [a]		X	X	X	X	X	X	X

	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 ± 3d	Cycle 4, 6, 8, 10 and 12 ± 3d		
Day		**–28 to –1**	**1**	**1**	**1**	**1**	**≤ 14d of the Last Dose**	
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			X

Source: VISION Study Protocol Version 8.0, 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, and the assessment of the safety profile of tepotinib.

The FDA's Assessment:

The routine clinical tests performed in the VISION study were consistent with standard clinical practice and appropriate for the population and underlying disease and were based on the known safety profile of tepotinib.

8.2.4. Safety Results

The FDA's Assessment:

Table 9 provides an overview of the adverse events (AEs) observed in VISION with a comparison of the safety population included in the current submission (N=313) to data included in the submission used to support accelerated approval (N=255). Overall, there were no major changes in of the frequency of adverse event severity and causes of observed between the two DCOs (July 1, 2020, and November 20, 2022) for the accelerated approval and regular approval data.

Table 9 (FDA): Overview of Adverse Events (VISION Safety Population)

	VISION – DCO11/20/2022 N = 313 (%)	**VISION – DCO 7/1/2020 N = 255 (%)**
All-Grade TEAEs	99	95
Grade 3-4 TEAEs	52	36
Grade 5 (TEAEs)	13	15
Serious TEAEs (SAEs)	51	45
Study treatment - dose reduced - due to AEs	36	30
Study treatment - drug interrupted - due to AEs	53	44
Study treatment - drug withdrawn - due to AEs	25	20

Source: ADSL (Subject-Level Analysis Dataset) - 2023-04-25, ADAE (Adverse Events AD) - 2023-04-25. Variables used: USUBJID, TRT01A, SAFFL, AARM, TRTEMFL, AETOXGR, AESER, AEACN

Deaths

Data:

In VISION Cohorts A + C, 200 (63.9%) participants died due to any reason as reported in the Death page of the study case report form (VISION CSR DCO 20 Nov 2022 Table 15.3.2.1). Disease progression was the most common primary cause of death, occurring in 157 (50.2%) participants. During the on-treatment period (within 30 days after the last dose of study drug), 45 (14.4%) participants died, and the primary cause of death was disease progression in 23 (7.3%) participants (*Table 10*).

Table 10: Primary Cause of Death

Primary Cause of Death	VISION Cohorts A + C (N = 313) n (%)
All deaths	200 (63.9)
Disease Progression and/or disease related condition	157 (50.2) 66 (25.9)
Related AE	2 (0.6)
Unrelated AE	22 (7.0)
Unknown	19 (6.1)
Deaths up to 30 days of last dose	45 (14.4)
Disease Progression and/or disease related condition	23 (7.3)
Related AE	2 (0.6)
Unrelated AE	18 (5.8)

Primary Cause of Death	VISION Cohorts A + C (N = 313) n (%)
Unknown	2 (0.6)
Deaths up to 60 days of first dose	13 (4.2)
Disease Progression and/or disease related condition	7 (2.2)
Related AE	1 (0.3)
Unrelated AE	5 (1.6)
Unknown	0 (0.0)

Source: VISION CSR DCO 20 Nov 2022 Table 15.3.2.1

AE = adverse event, CSR = Clinical Study Report, DCO = data cutoff

41 (13.1%) participants had TEAEs leading to death. The most frequent fatal TEAEs were disease progression (10 participants, 3.2%) and general physical health deterioration (5 participants, 1.6%) (refer to VISION CSR DCO 20 Nov 2022 Table 15.3.1.8).

For 3 participants, TEAEs leading to death were documented as treatment-related:

- Participant (b) (6) experienced a fatal acute respiratory failure secondary to ILD. There is a variety of possible causes, including drug-induced ILD, a massive allergic reaction or an atypical pneumonia (e.g. a viral infection). The Investigator and the Applicant assessed the event as possibly related to tepotinib.
- Participant (b) (6) experienced respiratory failure after severe worsening of dyspnea. The participant was hospitalized in another hospital and died 4 days later. Worsening of the participant's condition occurred 13 days after stopping tepotinib (t1/2 32 hours) and after disease progression had been confirmed. The Investigator could not exclude a potential causal relationship between respiratory failure and tepotinib. The Investigator also considered the disease under study as a possible cause of the event.
- Participant (b) (6) died at home without known symptoms preceding the death. According to the death certificate, the cause of the death was disease progression or disease-related condition (lung cancer) leading to multiple organ failure. The Investigator reported the possibility of multiple organ failure as high and considered disease under study as possible cause of the event. As the Investigator did not report the causality for the event of multiple organ failure, the event had to be considered as related to trial treatment as per the integrated analysis plan.

The Applicant's Position:

Most of the reported deaths were related to the underlying cancer disease or its progression. For the purposes of this application, the Applicant considers that 3 patients in VISION Cohorts A + C had a treatment-related TEAE with fatal outcome. Events with a fatal outcome considered related to tepotinib were infrequent, with no specific pattern.

The FDA's Assessment:

FDA reviewed all available narratives for patients enrolled in VISION who had a fatal adverse event. In the original accelerated approval submission, 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) (b) (6) due to dyspnea from fluid overload (within 30 days of the last treatment dose). These three cases are included in the current product labeling.

In VISION Cohorts A + C, 200 (64%) patients died due to any reason. Disease progression was the most common primary cause of death, occurring in 157 (50%) patients. Death within 30 days of last dose of study drug was reviewed for all cases. FDA confirmed that 41 (13%) patients had TEAEs leading to death if including progressive disease as a TEAE.

From the 41 cases of TEAEs leading to death, 27 cases of treatment-emergent death other than progressive disease within 30 days were identified and reviewed. FDA previously reviewed 14 of the 27 deaths occurring within 30 days of last dose of tepotinib reported due to TEAE during the accelerated approval review. The subject IDs for the 14 previously reviewed patients are (b) (6) (b) (6)

The review team concluded based on the death narratives of the additional 13 cases of treatment-emergent death within 30 days of treatment, 10 were due to either progression of disease or underlying disease or comorbidities, and these were not included in labeling as fatal adverse reactions. Three cases (pneumonia, sepsis, and fatal TEAE of unknown cause) listed below could not be definitively categorized as being unrelated to tepotinib and were therefore included in labeling.

A brief narrative of the additional 13 cases of fatal adverse events are presented below:

Patient (b) (6): Disease progression followed by CVA and cardiac arrest

On (b) (6) a 58-year-old White male was diagnosed with NSCLC and underwent chemotherapy. On (b) (6) a computed tomography (CT) scan with contrast showed primary recurrent target lesion. On (b) (6) the patient received tepotinib. On (b) (6) (b) (6) a computed tomography (CT) of chest abdomen and pelvis showed possible

infectious/inflammatory process and was treated with antibiotics. He also developed a lung infection and was treated with antibiotics. On (b) (6) following an episode of shortness of breath, a thoracic ultrasound was performed, and the patient was reported with pericardial effusion malignant (Grade 3) and serious pleural effusion (Grade 1). The patient was referred to interventional radiology for pericardial drain. The pericardial fluid analysis showed positive result for adenocarcinoma (malignant) cells. On the same day, tumor assessment with CT scan (with contrast) showed metastatic pericardial effusion. On (b) (6) the patient developed serious hyponatremia (Grade 3) and required hospitalization. On (b) (6) the patient underwent lumbar puncture and ventriculoperitoneal shunt and 20 cc fluid was removed and was suggestive of widespread leptomeningeal disease. On (b) (6) the patient experienced severe hypoxemia, bradycardia, and oxygen desaturation, and diagnosed with cardiac arrest.

Patient (b) (6): Disease progression followed by spinal fracture, pleural effusion, and pneumothorax

On (b) (6) a spiral CT scan with contrast showed new lesion in the pleural cavity in a 49-year-old White male diagnosed with NSCLC. He was initially diagnosed with NSCLC on (b) (6) (b) (6) and underwent treatment with tepotinib on (b) (6). On (b) (6) the patient presented to hospital with back pain (Grade 2) and on the same day, a CT scan showed bulging discs. He represented in (b) (6) with back pain. In the emergency room, scans were performed which showed significant progression of disease, increased lung masses compressing upper lobes with collapsed right bronchus, sizable right pleural effusion, and an increase in size and number of new metastatic bone lesions at T12 and L5 fractures. A CT scan of abdomen and pelvis showed extensive skeletal metastatic disease, multiple pulmonary masses, and pleural effusion at the lung bases. The administration of tepotinib was permanently discontinued with the last administration on (b) (6) due to spinal fracture, pleural effusion, and pneumothorax. The patient was transitioned to comfort care during hospitalization and on (b) (6) the patient died.

Patient (b) (6) Disease progression followed by pulmonary embolism

On (b) (6) a 74 year old White male was diagnosed with metastatic NSCLC and received chemotherapy. On (b) (6) a CT scan showed metastatic lesion in the brain. On (b) (6) the patient received tepotinib. On (b) (6) the patient experienced dyspnea and desaturation and was hospitalized. During the hospitalization, a CT scan showed evidence of disease progression with neoplastic lymphangitis, pleural effusion and pulmonary thromboembolism was confirmed. The patient remained hospitalized in a poor clinical condition and received treatment with oxygen and unspecified anticoagulant, antibiotic, and steroid therapy. The patient died on (b) (6) and the primary reason for death was reported as

progressive disease and an autopsy was not performed.

Patient (b) (6): Disease progression followed by physical health deterioration

A 77-year-old male was diagnosed with metastatic NSCLC in 2018 and received chemotherapy with pembrolizumab. On (b) (6) a contrast enhanced CT scan showed primary recurrence target lesion in lung, nodal target lesion in mediastinal lymph node, and metastatic nontarget lesions in pleura. On (b) (6) the patient received tepotinib. On (b) (6) (b) (6) the experienced fatigue and general health deterioration. On (b) (6) a computed tomography scan showed bilateral consolidation of lungs that was consistent with inflammation and pulmonary cause of dyspnea consistent with progressive disease in the lungs. The patient was also noted to have new lesion in bone and the overall response was progressive disease. On (b) (6) it was reported that the patient's clinical status progressively worsening (no further specific information was reported). On (b) (6) the event of general physical health deterioration became fatal, and the participant died. An autopsy was not performed.

Patient (b) (6): Disease progression followed by tumor hemorrhage

A 63-year-old female diagnosed with NSCLC on (b) (6) and underwent treatment with chemotherapy and pembrolizumab. On (b) (6) a tumor assessment by spiral computed tomography scan with contrast showed primary recurrent target lesion at right lower lobe of the lung. On (b) (6) the patient received tepotinib. On (b) (6) a tumor assessment by spiral computed tomography scan with contrast showed disease progression with primary recurrent target lesion at right lower lobe of the lung and metastatic lesions at soft tissue of the thoracic wall. Tumor assessment of the nontarget lesions showed nodal lesions at right hilar lymph nodes and retroperitoneal lymph nodes; and metastatic lesions at the left Segment 3, right Segment 8, and right Segment 9 of lung. On (b) (6) 349 days after the first administration of tepotinib, the participant developed a serious tumor hemorrhage (Grade 5). The event was considered serious as it was fatal. On (b) (6) the patient was found lying unconscious on the floor of the bathroom in a pool of blood and bleeding from her mouth and nose. The emergency doctor attempted to resuscitate, however asystole persisted, and resuscitation was terminated after twelve minutes. While we acknowledge that this patient had imaging demonstrating progressive disease, the patient was still receiving tepotinib (last dose: (b) (6) (b) (6) at the time of TEAE. The patient had a prior history of hemoptysis and essential thrombocythemia and was on aspirin. Therefore, FDA agrees it is reasonable to assess that this fatal TEAE was most likely not related to tepotinib.

Patient (b) (6) Physician assisted suicide

A 78-year-old male diagnosed with NSCLC on (b) (6). He underwent treatment but on (b) (6) a computed tomography scan with contrast showed primary recurrent target lesion at left upper lobe of the lung with metastatic lesion in the brain. The patient first dose of tepotinib was (b) (6). On (b) (6) the same day after the most recent administration and 317 days after the first administration of tepotinib, the patient felt depressed about the lung cancer condition with increased dyspnea and decided to have palliative sedation at home. The patient was not hospitalized to receive palliative sedation and on the same day, the patient committed assisted suicide (physician assisted suicide).

Patient (b) (6) Disease progression followed by general health deterioration

An 88-yearold male diagnosed with NSCLC in (b) (6) with stage IB and underwent surgery of segmentectomy of right upper lobe in December 2018 without any prior chemotherapy or radiotherapy. At Screening on (b) (6) a CT scan with contrast showed two primary recurrent target lesions in lung and on (b) (6) he received tepotinib. On (b) (6) a CT scan showed new lesion in pleural cavity. On (b) (6) a CT scan showed anew lesion in the right lung. The last dose of tepotinib was (b) (6) On (b) (6) and 391 days after the first administration of tepotinib, the patient presented to the emergency room with fatigue and poor general condition and was subsequently hospitalized for treatment and observation. The event was considered serious as it required hospitalization and was fatal. The laboratory test result showed C-reactive protein at 137.69 mg/L (normal range: < 5) and the participant was diagnosed with nonserious C-reactive protein increased (Grade 2) and nonserious respiratory tract infection (Grade 2). The participant reported diarrhea due to Clostridium difficile toxin during admission. The patient died on (b) (6) and an autopsy was not performed.

Patient (b) (6) Covid-19 pneumonia death

On (b) (6) a 77year-old male was diagnosed with metastatic NSCLC. The patient received chemotherapy with carboplatin and paclitaxel and durvalumab. Radiotherapy was also administered at the chest wall. On (b) (6) the patient received the first dose of tepotinib. On (b) (6) the patient tested positive for COVID-19. On (b) (6) (b) (6) (282 days from initial tepotinib dose) the diagnosis of COVID-19 pneumonia worsened to Grade 3 and was considered serious as it required hospitalization. The patient died on (b) (6) (b) (6) due to COVID-19 pneumonia.

Patient (b) (6) Disease progression followed by general health deterioration

A 68-year-old female was diagnosed with metastatic NSCLC on (b) (6). On (b) (6) (b) (6) the patient received her first dose of tepotinib. On (b) (6) the patient with

preexisting condition of pleural effusion (left) presented to the hospital due to dyspnea and was reported with serious pleural effusion (Grade 3) and was subsequently hospitalized for elective video-assisted thoracoscopic surgery due to recurrent fluid in the left pleural cavity. (b) (6) and (b) (6) the patient underwent elective video-assisted thoracoscopic surgery for increasing pleural effusion of the left lung. It was reported that the surgery was complicated by acute renal failure, respiratory failure, and hypotonia. On (b) (6) a CT scan of the femur, chest, abdominal cavity, and pelvis showed a small left sided pneumothorax. A large emphysema in the soft tissues of the left chest wall was observed which was extended to the soft tissues of the abdominal wall, pelvis, and soft tissues of the left arm. Fluid accumulation was noted in right pleural cavity and infiltrative lesions in the right lung were observed. The left supraclavicular lymph nodes and mediastinal lymph nodes were enlarged and the lymph nodes in the anteroinferior mediastinum were increased in size. Nodular lesions associated with the parietal and mediastinal pleura were seen in the left, another nodular lesion was observed in the left apex, and infiltrative and atelectatic lesions were noted in the left lung. The patient died on (b) (6) (b) (6) due to general physical health deterioration and an autopsy was not performed. The Investigator indicated progressive disease and/or disease related condition as the primary cause of death.

Patient (b) (6): Worsening and clinical deterioration from Parkinson's disease

A 78-year-old male with a history of Parkinsonism since (b) (6) was diagnosed with metastatic NSCLC on (b) (6) A computed tomography scan with contrast showed target lesions primary recurrence type at lung and metastatic type at left adrenal gland and right adrenal gland. The patient received his first dose of tepotinib on (b) (6). On (b) (6) (248 days after the first administration of tepotinib), the patient pre-existing condition of Parkinson's disease worsened. On (b) (6) the patient experienced clinical deterioration and died due to progression of Parkinson's disease and an autopsy was not performed. The event was considered serious as it was fatal.

Patient (b) (6) Worsening and clinical deterioration following pneumonia and iatrogenic infection following thoracentesis puncture and effusion drainage

A 71-year-old male with an history of Afib was initially diagnosed with metastatic NSCLC on (b) (6) (b) (6) Screening on (b) (6) a computed tomography scan with contrast showed primary recurrent target lesion at lung, and metastatic target lesion in soft tissue. On (b) (6) (b) (6) the patient received tepotinib. On (b) (6) (134 days after the first administration of tepotinib), the patient was admitted to the emergency department with abdominal pain and fever. On (b) (6) re-examination of chest CT showed pleural effusion on the right side and atelectasis of the right lower lobe. There was no CT or cytologic

evidence to suggest that this pleural effusion was related to disease progression. On (b) (6) (b) (6) the patient underwent percutaneous right thoracentesis and pleural drainage; however, post operation the participant developed high fever (body temperature not reported), cough, chest tightness, and received unspecified symptomatic treatment. On (b) (6) and 377 days after the first administration of tepotinib, the participant developed a fever with serious pneumonia (Grade 3). On (b) (6) the patient had respiratory and cardiac arrest and an autopsy was not performed. The Investigator considered concomitant procedures (pleural effusion puncture and drainage) as possible cause of the pneumonia. Because the death was related to a procedure to treat a TEAE that was possibly related to tepotinib this death cannot be ruled out as being unrelated to tepotinib. Pneumonia was considered the fatal TEAE and is listed in the USPI.

Patient (b) (6): Disease progression followed by general health deterioration and death

An 82-year-old male was diagnosed with metastatic NSCLC on (b) (6). The patient received chemotherapy with carboplatin from (b) (6) and gemcitabine from (b) (6) (b) (6). On (b) (6) a computed tomography scan showed primary or recurrent lesions at lungs, right upper lobe of lung, kidney, and nodal lesion at subcarinal lymph node. The patient received the first dose of tepotinib on (b) (6). On (b) (6) (b) (6) a spiral computed tomography with contrast showed target lesions at right upper lobe of lung, subcarinal lymph node, right upper lobe of lung, and right renal lesions. Tumor assessment of nontarget lesions showed multiple bone metastatic lesions, mediastinal nodes lesions, multiple lung metastasis, and pleural effusion lesions at pleural cavity, both with unequivocal progression. On (b) (6) magnetic resonance imaging scan ruled out brain metastases of nontarget lesions; however, the overall response was assessed progressive disease. The patient received chemotherapy with atezolizumab, 1200 mg once intravenously and was reported that the participant's condition deteriorated rapidly after the chemotherapy. The clinical presentation and vitals at the time of deterioration were not specified. On (b) (6) (131 days after the first administration of tepotinib), the patient died, and no symptoms were reported prior to the event. An autopsy was not performed, and the specific cause of death was not reported.

Patient (b) (6) Rapid health deterioration due to infection/sepsis

A 69-year-old female diagnosed with NSCLC on (b) (6) with stage IB. The patient received chemotherapy (cisplatin and pemetrexed) and atezolizumab from. The patient then underwent surgery of right lower lobectomy of lung with mediastinal lymph node dissection on (b) (6) (b) (6) At screening on (b) (6) a computed tomography scan with contrast showed primary recurrent target lesion and nodal lesion at lung and metastatic lesion at bone. The patient received her first dose of tepotinib on (b) (6). On (b) (6) on the same day of most recent administration and 358 days after the first administration of tepotinib,

the patient reported with serious sepsis. On (b) (6) the patient developed fever and urine color became dark and was admitted to the hospital on (b) (6). On (b) (6) (b) (6) the SPO2 was not maintained, and ECG was confirmed as asystole. A cardiopulmonary resuscitation (CPR) was performed for more than 30 minutes; however, the participant died. An autopsy was not performed. As the patient was still receiving tepotinib, the fatal TEAE of sepsis could not definitively be determined to be unrelated to tepotinib.

Patient (b) (6): Death at home without known cause

A 70-year-old male initially diagnosed with metastatic NSCLC on (b) (6). He received tepotinib on (b) (6), died at home without known symptoms preceding the death. On (b) (6) the same day of the most recent administration and 123 days after the first administration of tepotinib, a CT scan of chest, abdomen, and pelvis showed new nodules and consolidated shadows in the right lung and the participant was diagnosed with serious pneumonia (Grade 2). On (b) (6) a CT scan of chest, abdomen, and pelvis showed a decrease in right lower lobe paraspinal consolidation with persistent pneumonia and on (b) (6) a CT scan of chest, abdomen, and pelvis showed no significant changes compared to the CT scan performed on (b) (6). On the same day, the event pneumonia improved to Grade 1 and became nonserious. The patient was noted to have stopped tepotinib on (b) (6); however, the reason for the discontinuation was unknown. On (b) (6) (b) (6) 348 days after the first administration of tepotinib, the participant died at home without known symptoms preceding the death. An autopsy was not performed. According to the death certificate, the cause of the death was disease progression or disease-related condition (lung cancer) leading to multiple organ failure. As the reason for tepotinib discontinuation, and the temporal relationship between tepotinib discontinuation and onset of the adverse event leading to death remain unknown, this fatal TEAE of unknown cause could not definitively be determined to be unrelated to tepotinib.

Serious Adverse Events

Data:

In VISION Cohorts A + C, 159 (50.8%) participants had at least 1 serious TEAE and 49 (15.7%) participants had at least 1 treatment-related serious TEAE (refer to VISION CSR DCO 20 Nov 2022 Tables 15.3.1.4 and 15.3.1.6). The most common serious TEAEs were pleural effusion (6.1%), pneumonia (5.4%), disease progression (4.2%), general physical health deterioration (3.8%), dyspnea (3.5%), and peripheral edema (3.2%). Serious TEAEs assessed as treatment-related by the Investigator in ≥ 2% of participants were pleural effusion (3.2%) and peripheral edema (2.9%).

The Applicant's Position:

The SAE profile mostly reflected the severity of the underlying disease.

The FDA's Assessment:

All-causality serious adverse events occurred in 51% of patients who received tepotinib in the VISION study. Serious adverse reactions in > 2% of patients included pleural effusion (6%), pneumonia (6%), edema (5%), general health deterioration (3.8%), dyspnea (3.5%), musculoskeletal pain (2.9%), and pulmonary embolism (2.2%).

Table 11 (FDA): All-causality serious adverse events occurring in > 2% of patients in VISION Study

	VISION N = 313 %
Total patients with at least one SAEs	**51**
Pneumonia	6
Pleural effusion	6
Edema (GT)	5
General Health Deterioration	3.8
Dyspnea	3.5
Musculoskeletal pain	2.9
Pulmonary embolism	2.2

Group Pneumonia (GT) includes PT terms PNEUMONIA, PNEUMONIA BACTERIAL, PNEUMONIA ASPIRATION,
Group Dyspnea (GT) includes PT terms DYSPNOEA,
Group Oedema (GT) includes PT terms OEDEMA PERIPHERAL, GENERALISED OEDEMA, OEDEMA,
Group Musculoskeletal Pain (GT) includes PT terms BACK PAIN, ARTHRALGIA, MUSCULOSKELETAL
Source: ADSL (Subject-Level Analysis Dataset) - 2023-04-25, ADAE (Adverse Events AD) - 2023-04-25. Variables used: USUBJID, TRT01A, SAFFL, AARM, TRTEMFL, AEDECOD, AETOXGR, AEACN, AEBODSYS, AESPINT, AESER

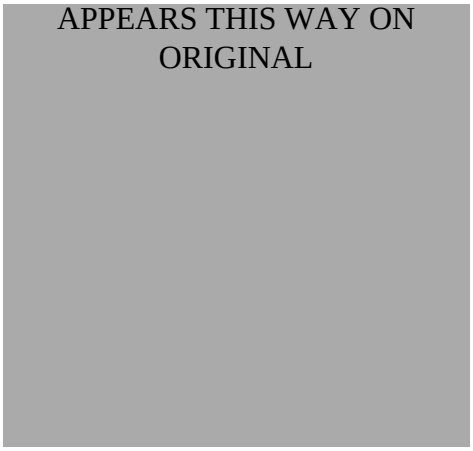
Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Enrollment of 313 METex14 NSCLC participants was completed with last participant first dose on 20 May 2021. At the time of the 20 Nov 2022 DCO, these VISION Cohorts A + C participants were at least 18 months followed-up from start of treatment (*Figure 2*).

At the DCO, 48 (15.3%) patients in VISION Cohorts A + C were still on treatment (refer to VISION CSR DCO 20 Nov 2022 Figure 4). 265 (84.7%) patients were permanently discontinued from treatment mainly due to disease progression (55%), AEs (16.4%) or death (7%).

In VISION Cohorts A + C, most of the events leading to permanent discontinuation of tepotinib were consistent with the tepotinib safety profile and the underlying disease. The incidence of TEAEs leading to permanent discontinuation of tepotinib treatment was 24.9% (78 participants; see *Table 15*). The incidence of treatment-related TEAEs leading to permanent discontinuation



was 14.7%. The TEAE leading to permanent discontinuation in ≥ 2% of participants was peripheral edema (5.4%; refer to VISION CSR DCO 20 Nov 2022 Table 15.3.1.14). All cases of peripheral edema leading to permanent discontinuation were considered treatment-related by the Investigator (refer to VISION CSR DCO 20 Nov 2022, Table 15.3.1.15).

The Applicant's Position:

Disease progression was the main reason for treatment discontinuation as anticipated considering the underlying aggressive cancer. In VISION Cohorts A + C, the incidence of treatment-related TEAEs (14.7%) leading to permanent discontinuation demonstrated an overall good tolerability for tepotinib. 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:

Permanent discontinuation due to an adverse reaction occurred in 25% of patients who received tepotinib. The most frequent adverse reactions (> 1%) leading to permanent discontinuations of tepotinib were edema (8%), pleural effusion (1.6%), and general health deterioration (1.6%).

Table 12 (FDA): All-causality adverse events leading to treatment discontinuation > 1%

	TEPOTINIB 500MG N = 313 (%)
Study treatment - drug withdrawn - due to AEs	**25**
Edema (GT)	8
Pleural Effusion	1.6
General Physical Health Deterioration	1.6

Source: ADSL (Subject-Level Analysis Dataset) - 2023-04-25, ADAE (Adverse Events AD) - 2023-04-25. Variables used: USUBJID, TRT01A, SAFFL, AARM, TRTEMFL, AEDECOD, AETOXGR, INTERRUPTED, REDUCED, WITHDRAWN, AEBODSYS, AESER
Group Oedema (GT) includes PT terms OEDEMA PERIPHERAL, OEDEMA, GENERALISED OEDEMA, LOCALISED OEDEMA, OEDEMA GENITAL, FACE OEDEMA, PERIORBITAL OEDEMA, SCROTAL OEDEMA, EYE OEDEMA

Dose Interruption/Reduction Due to Adverse Effects

Data:

TEAEs led to temporary discontinuation of study treatment in 165 (52.7%) participants.

Peripheral edema in 62 participants (19.8%) and blood creatinine increased (18, 5.8%) were the most common TEAEs leading to temporary discontinuation. All other TEAEs leading to temporary discontinuation occurred in < 5% of participants (refer to VISION CSR DCO 20 Nov 2022 Table 15.3.1.12). The incidence of treatment-related TEAEs leading to temporary discontinuation was 43.1% (see *Table 15*). Most peripheral edema cases were considered treatment-related by the Investigator (56 out of 62 participants); 17 out of 18 cases of blood creatinine increased were considered treatment-related by the Investigator.

The Investigators reduced the dose in 113 participants (36.1%) due to a TEAE. The most common TEAEs leading to dose reduction were peripheral edema (15.7%), generalized edema (3.2%), blood creatinine increased (2.9%), edema (2.6%), and pleural effusion (2.2%; refer to VISION CSR DCO 20 Nov 2022 Table 15.3.1.10). Nearly all these TEAEs were considered treatment-related by the Investigator.

The Applicant's Position:

In VISION Cohorts A + C, TEAEs leading to temporary discontinuation or dose reduction 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:

Dosage interruptions due to an adverse reaction occurred in 53% of patients who received tepotinib. Adverse reactions which required dosage interruption in > 2% of patients who received tepotinib included edema (28%), increased blood creatinine (6%), pleural effusion (3.5%), nausea (3.2%), increased ALT (2.9%), pneumonia (2.6%), decreased appetite (2.2%), and dyspnea (2.2%). Dose reductions due to an adverse reaction occurred in 36% of patients who received tepotinib. Adverse reactions which required dose reductions in > 2% of patients who received tepotinib included edema (22%), increased blood creatinine (2.9%), fatigue (2.2%), and pleural effusion (2.2%).

Table 13 (FDA): All-causality adverse events requiring dose interruption by preferred term (> 2%)

	TEPOTINIB 500MG N = 313 (%)
Study Treatment - drug interrupted - due to AEs	**53**
Edema (GT)	28
Blood Creatinine Increased	6
Pleural Effusion	3.5
Nausea	3.2
Alanine Aminotransferase Increased	2.9
Pneumonia (GT)	2.6
Decreased Appetite	2.2
Dyspnea (GT)	2.2

Source: ADSL (Subject-Level Analysis Dataset) - 2023-04-25, ADAE (Adverse Events AD) - 2023-04-25. Variables used: USUBJID, TRT01A, SAFFL, AARM, TRTEMFL, AEDECOD, AETOXGR, INTERRUPTED, REDUCED, WITHDRAWN, AEBODSYS, AESER
Group Oedema (GT) includes PT terms OEDEMA PERIPHERAL, OEDEMA, GENERALISED OEDEMA, LOCALISED OEDEMA, OEDEMA GENITAL, FACE OEDEMA, PERIORBITAL OEDEMA, SCROTAL OEDEMA, EYE OEDEMA,
Group Dyspnea (GT) includes PT terms DYSPNOEA, DYSPNOEA EXERTIONAL, DYSPNOEA AT REST,
Group Pneumonia (GT) includes PT terms PNEUMONIA, PNEUMONIA BACTERIAL, PNEUMONIA ASPIRATION, PNEUMONIA CHLAMYDIAL, LOWER RESPIRATORY TRACT INFECTION.

Table 14 (FDA): All-causality adverse events requiring dose reduction by preferred term (>2%)

	TEPOTINIB 500MG N = 313 (%)
Study Treatment - drug reduced - due to AEs	**36**
Edema (GT)	22
Blood Creatinine Increased	2.9
Fatigue (GT)	2.2
Pleural Effusion	2.2

Group Oedema (GT) includes PT terms OEDEMA PERIPHERAL, OEDEMA, GENERALISED OEDEMA, LOCALISED OEDEMA, FACE OEDEMA, OEDEMA GENITAL, PERIORBITAL OEDEMA, SCROTAL OEDEMA, EYE OEDEMA
Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA

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.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Overview of TEAEs

In VISION Cohorts A + C, 99.0% of participants had ≥ 1 TEAE, 64.9% had Grade ≥ 3 TEAEs, and 50.8% had serious TEAEs (see *Table 15*). Although most participants (91.7%) had treatment-related TEAEs, treatment-related Grade ≥ 3 TEAEs and treatment-related serious TEAEs were reported with lower incidences of 34.8% and 15.7%, 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 14.7%. TEAE leading to death was seen in 41 participants (13.1%), including 3 participants with a TEAE documented as treatment-related (for details on the deaths, see Section 8.2.4 Deaths).

Table 15: Overview of TEAEs

Event	VISION Cohorts A + C (N = 313) n (%) Patients with Events n (%)
Any TEAE	310 (99.0)[b]
TEAE, NCI CTCAE Grade ≥ 3	203 (64.9)
Related TEAE	287 (91.7)
Related TEAE, NCI CTCAE Grade ≥ 3	109 (34.8)
TEAE leading to treatment dose reduction	113 (36.1)
Related TEAE leading to treatment dose reduction	105 (33.5)
TEAE leading to temporary treatment discontinuation	165 (52.7)
Related TEAE leading to temporary treatment discontinuation	135 (43.1)
TEAE leading to permanent treatment discontinuation[a]	78 (24.9)
Related TEAE leading to permanent treatment discontinuation	46 (14.7)
Serious TEAE	159 (50.8)
Related serious TEAE	49 (15.7)
TEAE leading to death	41 (13.1)
Related TEAE leading to death	3 (1.0)

Source: SCS 20 Nov 2022 DCO Table 12.6.1.1.1.

NCI CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, TEAE = treatment-emergent adverse event.

a The number reflects information from the adverse event eCRF page, resulting in a difference to the number of participants with an AE as primary reason for treatment discontinuation, which is based on the disposition eCRF page.

b Participant (b) (6) had a worsening of lipase increase on the start day of study treatment recorded as “before treatment”. This event is not a TEAE and has now been corrected. Since this participant does not have any other TEAEs, the overall number of "Participants with at least 1 TEAE" has decreased to 310 participants.

Most common TEAEs

The most frequently affected SOCs or PTs in VISION Cohorts A + C are consistent with the previously observed pattern that is in line with other MET inhibitors or with the underlying disease.

Participants had TEAEs belonging most often to the following SOCs > 50% (including PTs > 10%) (SCS 20 Nov 2022 DCO Table 12.6.2.1.1):

- General disorders and administration site conditions (99.0%), with the most frequent PTs being peripheral edema (72.5%), fatigue (15.7%), asthenia (14.1%), and pyrexia (10.2%)

- Gastrointestinal disorders (65.5%), with the most frequent PTs being nausea (31.0%), diarrhea (28.8%), constipation (19.2%), and vomiting (14.4%)
- Investigations (58.1%), with the most frequent PTs being blood creatinine increased (29.1%), ALT increased (18.2%), AST (13.7%), amylase increased (11.5%), and blood alkaline phosphatase increased (11.2%)
- Metabolism and nutrition disorders (55.0%), with the most frequent PTs being hypoalbuminemia (32.9%), decreased appetite (21.4%), and hypocalcemia (11.2%)
- Respiratory, thoracic and mediastinal disorders (52.1%), with the most frequent PTs being dyspnea (22.0%), cough (14.7%), and pleural effusion (14.4%)

Peripheral edema was the most frequently reported TEAE.

See Section 8.2.5 for details on edema, blood creatinine increased, hypoalbuminemia, diarrhea, and nausea.

The most common Grade ≥ 3 TEAEs were peripheral edema (11.8%), hypoalbuminemia (6.4%), disease progression (4.2%), pneumonia (4.5%) and pleural effusion (4.2%) (SCS 20 Nov 2022 DCO Table 12.6.6.1).

Adverse Reactions

Risks associated with tepotinib were identified with a comprehensive analysis based on predefined medical concepts, 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. The identified and potential risks shown in *Table 16* are described for the 313 participants with *MET*ex14 NSCLC in VISION Cohorts A + C with 20 Nov 2022 DCO based on the SCS Tables 12.6.2.1.1, 12.6.25.1.1.1, 12.6.25.1.2.1, 12.6.25.2.1.1, 12.6.25.2.3.1, 12.6.26.2.8.1.1, and 12.7.8.2.1.

The assessment of adverse reactions is provided in Section 8.2.5.

Table 16: Overview of Identified and Important Potential Risks (SAF)

Event	Tepotinib 500 mg qd VISION Cohorts A + C (N = 313) n (%)
Participants with at least 1 TEAE	310 (99.0)
Identified Risks	
Interstitial lung disease[a]	8 (2.6)
Oedema[a]	255 (81.5)
Creatinine increase[a]	95 (30.4)
Hypoalbuminemia[a]	106 (33.9)
Lipase/amylase increase[a]	50 (16.0)
ALT and/or AST increase[a]	62 (19.8)
ALP increased	35 (11.2)
Diarrhea	90 (28.8)
Nausea	97 (31.0)
Vomiting	45 (14.4)
Important Potential Risks	
Pleural effusion	45 (14.4)
QT prolongation[a]	20 (6.4)
Severe hepatotoxicity[a]	8 (2.6)

Sources: SCS DCO 20 Nov 2022 Table 12.6.25.2.1.1 and 12.6.25.1.3.1.

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; SAF = safety analyses set; TEAE = treatment-emergent adverse event.

a Incidences are based on composite search terms (refer to SCS DCO 20 Nov 2022, Table 1) and independent panel assessment for ILD events with DCO 1 January 2020. The independent panel assessment of ILD events, including re-reading of the radiology images or review of imaging reports and clinical data, concluded that 3 of 11 ILD events identified by broad composite term search from VISION Cohorts A + C are not consistent with an ILD event.

The Applicant's Position:

The most frequently affected SOCs or PTs in VISION Cohorts A + C are consistent with AEs reported with other MET inhibitors or with the underlying diseases. Peripheral edema is the AE reported in 72.5% of participants; it is also the most frequent severe AE.

For adverse reactions, see Section 8.2.5

The FDA's Assessment:

All-causality adverse events reported in > 10% of patients in VISION and the incidence of Grade 3-4 AEs are presented in the table below. The most common adverse events reported with an incidence of ≥ 20% in patients treated with tepotinib were edema, nausea, fatigue, musculoskeletal pain, diarrhea, dyspnea, decreased appetite, and rash.

Alopecia was noted to occur in 12% of patients; however, the majority of cases (18 of 21) were noted to be Grade 1; therefore, the review team determined it was reasonable to not include this as an adverse reaction in the USPI.

Table 17 (FDA): Adverse Reactions in ≥ 10% of Patients with NSCLC with METex14 Skipping Alterations Who Received TEPMETKO in VISION

Adverse Reactions	TEPMETKO (N=313)	
	All Grades* (%)	Grades 3 to 4* (%)
General disorders and administration-site conditions		
Edema[a]	81	16
Fatigue[b]	30	1.9
Gastrointestinal disorders		
Nausea	31	1.3
Diarrhea	29	0.6
Abdominal Pain[c]	19	0.6
Constipation	19	0.3
Vomiting[d]	15	1
Increased Amylase	11	2.9

Adverse Reactions	TEPMETKO (N=313)	
	All Grades* (%)	Grades 3 to 4* (%)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain[e]	30	3.2
Respiratory, thoracic, and mediastinal disorders		
Dyspnea[f]	24	2.6
Cough[g]	18	0.3
Pleural effusion	14	4.2
Metabolism and nutrition disorders		
Decreased appetite	21	1.9
Skin and Subcutaneous Tissue Disorders		
Rash[h]	21	1.3
Alopecia	12	0
Infections and Infestations		
Pneumonia[i]	12	3.8

* Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[a] Edema includes eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, peripheral swelling, periorbital edema, and scrotal edema.
[b] Fatigue includes asthenia and fatigue.
[c] Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, and hepatic pain.
[d] Vomiting includes retching and vomiting.
[e] 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.
[f] Dyspnea includes dyspnea, dyspnea at rest, and dyspnea exertional.
[g] Cough includes cough, and productive cough.
[h] Rash includes rash, palmar-plantar erythrodysaesthesia syndrome, rash maculo-papular, eczema, exfoliative rash, rash erythematous, rash pustular, skin exfoliation, dermatitis acneiform, drug eruption, dermatitis, rash pruritic, dermatitis bullous, toxic skin eruption.
[i] Pneumonia includes pneumonia, pneumonia aspiration, and pneumonia bacterial.

Laboratory Findings

Data:

All laboratory parameters were evaluated as part of the ongoing safety monitoring. Changes in laboratory parameters have been reviewed in conjunction with laboratory findings reported as TEAEs.

Abnormal laboratory findings were reported as AEs if they were associated with clinical signs and symptoms, led to treatment discontinuation, or were considered otherwise medically important by the Investigator.

Hematology

No treatment-related clinically meaningful changes in hematology parameters were observed in VISION Cohorts A + C.

As per the study protocol, participants 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 (worsening from baseline) and an incidence ≥ 5% was low lymphocytes (14.6%) (refer to SCS 20 Nov 2022 DCO Tables 12.7.3.1.1 and 12.7.3.2.1).

Irrespective of the 14.6% incidence of Grade ≥ 3 low lymphocytes as a laboratory parameter, the incidence of TEAEs of lymphopenia (2 participants; 0.6%) and lymphocyte count decreased (6 participants; 1.9%) was very low with 1 lymphopenia, and 3 lymphocyte count decreases, respectively being Grade ≥ 3 (refer to SCS 20 Nov 2022 DCO Tables 12.6.2.1 and 12.6.6.1).

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Biochemistry

Apart from the adverse events that are based on biochemistry parameters, no other clinically meaningful changes in biochemistry parameters were observed in VISION Cohorts A + C (refer to SCS 20 Nov 2022 DCO Tables 12.6.2.1, 12.6.6.1, 12.7.8.1.1, and 12.7.8.2.1). Biochemistry parameters with worsening on-treatment values to Grade ≥ 3 and an incidence of ≥ 5% were low creatinine clearance (12.6%), low albumin (9.2%), low sodium (9.4%), high gamma-glutamyl transferase (5.5%), and high lipase (5.3%).

The Applicant's Position:

No clinically meaningful changes in hematology parameters were observed with tepotinib. Hematological and clinical chemistry abnormalities reported post baseline were predominantly Grade 1 or 2.

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 ≥ 20% of patients in receiving tepotinib VISION. Of note, CTCAE v4.03 was not used for grading of creatinine shifts as any increase in creatinine would lead to a laboratory abnormality for this parameter, even if value is within normal limits. Instead, CTCAE v5 was used for grading of this lab. This strategy was consistent with the strategy used in product labeling at the time the accelerated approval for tepotinib was granted. See Section 8.2.5.4 for more detail.

Table 18 (FDA): Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients Who Received TEPMETKO in VISION

Laboratory Abnormalities	TEPMETKO*	
	Grades 1 to 4** (%)	Grades 3 to 4** (%)

Laboratory Abnormalities	TEPMETKO*	
	Grades 1 to 4** (%)	Grades 3 to 4** (%)
Chemistry		
Decreased albumin	81	9
Increased creatinine	60	1
Increased alkaline phosphatase	52	1.6
Increased alanine aminotransferase	50	4.9
Increased aspartate aminotransferase	40	3.6
Decreased sodium	36	9
Increased gamma-glutamyl transferase	29	6
Increased potassium	26	1.9
Increased amylase	25	5
Increased lipase	21	5
Hematology		
Decreased lymphocytes	57	15
Decreased hemoglobin	31	3.6
Decreased leukocytes	25	1.9
Decreased platelets	24	0.6

* The denominator used to calculate the rate varied from 268 to 309 based on the number of patients with a baseline value and at least one post-treatment value.
** Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Vital Signs

Data:

There were no clinically meaningful findings in the vital signs measurements (refer to VISION CSR 20 Nov 2022 DCO, Section 5.2.4).

The Applicant's Position:

Review of vital signs did not reveal any new safety observation.

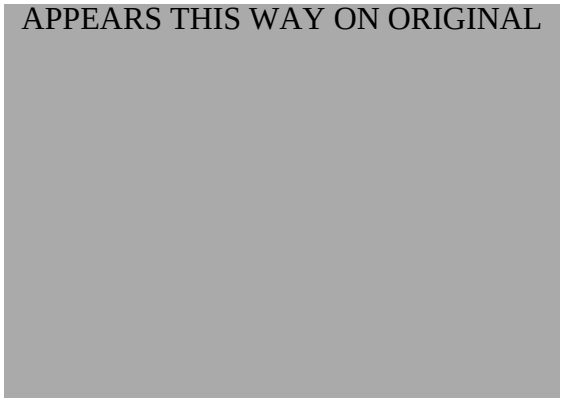
The FDA's Assessment:
FDA review of the Applicant's submitted CSR section 5.2.4 with vital signs, weight, BMI, systolic and diastolic blood pressure revealed no specific pattern in the change of temperature, pulse, blood pressure, or respiratory rate in patients treated with tepotinib.

Electrocardiograms (ECGs)/QT

Data:

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. 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 ΔQTcF at the mean C_{max} did not exceed the threshold of 10 msec at the approved clinical dose of 500 mg tepotinib or the highest administered dose of 1,400 mg.



No events of arrythmia (including Torsade de Pointes) secondary to the prolongation of the QTc were reported. Events of syncope (n = 2), seizure (n = 1) and loss of consciousness (n = 1) were reported but were not associated with QT prolongation.

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. Exposure-QTc analyses (integrated across studies and in VISION based on the 19 July 2019 cutoff) 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 ΔQTcF 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.

QT prolongation findings in VISION Cohorts A + C were asymptomatic, non-severe and non-serious. In few patients, multiple episodes of QT prolongation occurring on-treatment were reported without conclusive alternative explanations to these observations. No pattern is observed regarding time to occurrence and some events had a late onset. In patients who reported an event of syncope/loss of consciousness, the event did not involve QT prolongation.

For the patient who experienced cardio-respiratory arrest with fatal outcome, the event was confounded with medical history of fibrillo-flutter and use of citalopram. In most patients, confounders or alternative explanations for events were available. 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 assessment.

Immunogenicity

Data:

N/A

Applicant's Position:

N/A

The FDA's Assessment:

Not Applicable.

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8.2.5. Analysis of Submission-Specific Safety Issues

Data:

The description of the identified or potential risks associated with tepotinib includes a comprehensive analysis based on predefined medical concepts (for definitions, see *Table 6*), 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. The adverse reactions of tepotinib are presented in *Table 15*.

This section focuses on VISION Cohorts A + C as the relevant dataset for the proposed labeling.

8.2.5.1. Interstitial Lung Disease

Data:

ILD or ILD-like adverse reactions were reported in 8 participants (2.6%) with advanced NSCLC with *MET*ex14 skipping alterations who received tepotinib monotherapy at the recommended dosage regimen (n = 313), including 1 fatal case. Serious cases of ILD occurred in 4 participants (1.3%), including the 1 fatal case (refer to SCS Tables 12.6.25.1.2, 12.6.25.2.3 and 12.6.25.1.3.1 integrating independent panel assessment of ILD events).

Patients should be monitored for pulmonary symptoms indicative for ILD-like reactions. Tepotinib should be withheld, and patients should be promptly investigated for alternative diagnosis or specific etiology of ILD. Tepotinib must be permanently discontinued if ILD is confirmed, and the patient be treated accordingly.

The Applicant's Position:

ILD-like events are considered an important identified risk for tepotinib in patients with NSCLC. 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.

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 independent panel summarized that in

some cases an exacerbation of preexisting chronic-fibrosing idiopathic interstitial pneumonia or radiation fibrosis was observed with tepotinib, which is consistent with what is described in the literature (Gemma 2014). However, as per Applicant's opinion, the number of cases with ILD is too small to draw reliable conclusions on pre-existing ILD or fibrosis as a specific risk factor for tepotinib induced ILD.

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 506 patients, ILD/pneumonitis occurred in 2% of patients. This included one patient experiencing a Grade 3 or higher event; this event resulted in death. Five patients (1%) discontinued tepotinib due to ILD/pneumonitis.

8.2.5.2. **Edema**

Data:

Events of edema were the most frequent events and were reported in 255 (81.5%) participants. Among those edema events, the most frequent TEAE was peripheral edema (227 [72.5%] participants), followed by edema (26 participants; 8.3%), and generalized edema (21 participants; 6.7%). Although generalized edema had a much lower frequency than peripheral edema, it often develops based on peripheral edema.

Edema was mostly mild to moderate in severity (Grade 1 to 2) and 49 (15.7%) participants had Grade ≥ 3 edema TEAEs.

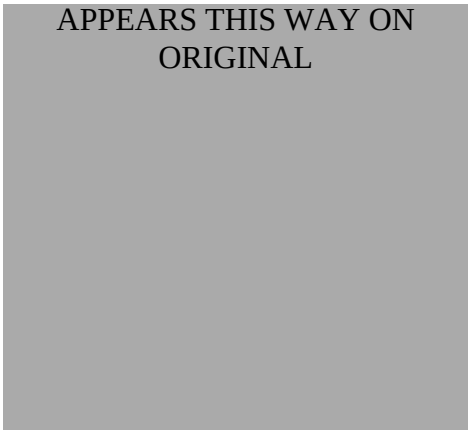
8 out of 21 participants experienced severe generalized edema; 8 participants had a Grade ≥ 3 event.

A partial association of edema with hypoalbuminemia was observed (Section 8.2.5.3).

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, peripheral swelling, periorbital edema, and scrotal edema. Within Cohorts A and C of VISION (n=313), edema occurred in 81% of patients (Grade 3-4 edema 16%). Edema led to interruption of tepotinib dosing in 28% of patients, dose reduction in 22% of patients, and permanent discontinuation of tepotinib in 8%. The incidence of edema as a serious adverse reaction was 5%. The events of edema were managed by drug interruption, dose reduction, or maintaining the tepotinib dose as appropriate. Given that events of edema were generally not considered severe and can be managed by dose reductions or interruptions as directed under "Other Adverse Reactions" in Section 2 of product labeling (Table 1 – Dose modifications), edema was not included in Section 5 (Warnings and Precautions).

8.2.5.3. **Hypoalbuminemia**

TEAEs of hypoalbuminemia were very common (106 [33.9%] participants). Most of these events were nonsevere (Grade < 3). Hypoalbuminemia appeared to be long lasting but did not lead to permanent treatment discontinuation (refer to VISION CSR Table 15.3.1.14). Dose reductions (5 participants, 1.6%) and temporary discontinuations (5 participants, 1.6%) were infrequent (refer to VISION CSR Tables 15.3.1.10 and 15.1.12).

Low albumin as a laboratory finding worsened on treatment in 28 (9.2%) participants to Grade ≥ 3.

A high proportion of participants had low albumin levels at baseline and on treatment, and overall, a broad overlap between low albumin levels and edema was observed. Low albumin as a potentially contributing factor for edema cannot be ruled out.

There was no evidence that hypoalbuminemia is secondary to liver dysfunction or renal loss.

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 non-severe, non-serious, long-lasting but did not lead to permanent treatment discontinuation. Dose reductions or temporary discontinuations were infrequent. The relationship between hypoalbuminemia and edema is unclear.

The FDA's Assessment:

The incidence of hypoalbuminemia in Cohorts A and C of VISION (n=313) was 81% (grade 3 to 4 hypoalbuminemia 9%). Dose reductions and interruptions of tepotinib due to hypoalbuminemia occurred in 1.6% of patients in Cohorts A and C (n = 313). There were two cases of serious adverse reactions due to hyopalbuminemia (0.6%). Although this TEAE was common, it did not frequently

lead to serious events, and was not included in Section 5 (Warnings and Precautions).

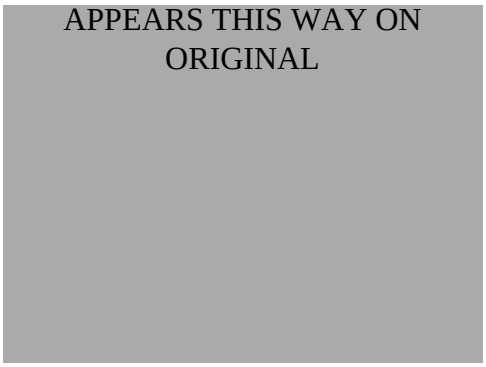
8.2.5.4. **Increased Creatinine**

Data:

TEAEs of increased creatinine were common (95 [30.4%] participants). These events were mostly mild or moderate (Grade 1 or 2). 2 participants discontinued treatment permanently due to creatinine increased (refer to VISION CSR Table 15.3.1.14). 18 (5.8%) participants temporarily discontinued treatment and for 9 (2.9%) participants a dose reduction was initiated due to increased creatinine (refer to VISION CSR Tables 15.3.1.10 and 15.1.12).

Based on laboratory values, a worsening from Baseline to Grade 1 or higher in creatinine was documented for 184 (59.9%) participants. 3 participants (1.0%) had worsening to a Grade 3 creatinine increase.

The observed increases in creatinine are thought to occur due to competition of renal tubular



secretion. Nonclinical studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins OCT2, MATE1, and MATE2. Creatinine is a substrate of these transporters, and the observed increases in creatinine may be the result of inhibition of active tubular secretion rather than renal injury. Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution considering this effect.

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:

In the VISION study, CTCAE version 4.03 was used for patient's safety assessment of creatinine. In this review, CTCAE version 5.0 was used instead to report for lab shift change for any Grade (as described by FDA above). Across Cohorts A and C of VISION, increased creatinine (all grades) occurred in 60% of patients, with grades 3 to 4 increased creatinine in 1% 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; generalized edema was reported in only 21 (7%) of 313 patients in Cohorts A and C of VISION, with Grade 3-4 events in 2.6% of patients. Given the relatively low incidence of generalized edema compared to the 60% incidence of increased creatinine, this was not considered to be a contributing factor for most cases of increased creatinine.

8.2.5.5. **Amylase and Lipase Increased**

Data:

TEAEs of amylase and lipase increases were generally asymptomatic and not associated with pancreatitis. The incidence of amylase increased was 11.5% (36 participants), lipase increased

was 9.3% (29 participants), and pancreatic enzymes increased was 0.3% (1 participant). Increases in amylase or lipase could be managed without dose reduction (refer to VISION CSR Tables 15.3.1.10, 15.1.12, and 15.3.1.14).

Based on laboratory values, a worsening from Baseline to Grade 1 or higher was observed for 75 (24.9%) participants for amylase and 64 (21.2%) participants for lipase. A worsening to Grade 3 or higher occurred in 16 (5.3%) participants for amylase and 16 (5.3%) participants for lipase.

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). Increases

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are manageable without dose reduction.

The FDA's Assessment:

Elevations in amylase and lipase levels occurred in patients treated with tepotinib. From the pooled safety population (n = 506), increased amylase and/or lipase occurred in 13% of patients treated with tepotinib. Furthermore, Grade 3 and 4 increased amylase and/or lipase occurred in 5% and 1.2% of patients, respectively. In VISION Cohorts A +C (n = 313), there were no permanent discontinuations of tepotinib due to increases in amylase or lipase. Dose interruptions due to increased lipase and amylase occurred in 1.6% and 1.6% of patients, respectively. There were no adverse reactions of pancreatitis noted.

As mentioned by the Applicant (above), pancreatic toxicity appears to be a class effect of drugs with MET inhibitor activity. Pancreatic toxicity is observed with brigatinib and capmatinib and included in Section 5 of the USPI for both drugs. Per current labeling practice, class effects should be included in Warnings and Precautions (section 5). The incidences noted from the pooled safety population (n=506) that experienced these adverse reactions are based on adverse event reporting and will be included in the USPI for tepotinib. The laboratory abnormality table in Section 6 of the USPI reflects incidence of increased amylase and lipase based on laboratory shift data.

8.2.5.6. **ALT and AST Increase and ALP Increase**

Data:

ALT and AST Increase

57 (18.2%) and 43 (13.7%) participants had TEAEs of ALT increased and AST increased, respectively. The events were mainly of low grade (Grade 1 or 2). ALT and/or AST increase infrequently led to permanent study drug discontinuation in 1 (0.3%) participant (ALT increased), to temporary discontinuation in 9 (2.9%) and 3 (1.0%) participants, and dose reduction in 2 (0.6%) and 1 (0.3%) participants, respectively (refer to VISION CSR Tables 15.3.1.10, 15.1.12, and 15.3.1.14).

Based on laboratory values, a worsening from Baseline to Grade 1 or higher was observed for 49.5% of participants for ALT and 39.9% of participants for AST. A worsening to Grade 3 or higher occurred in 4.9% of participants for ALT and 3.6% of participants for AST.

Liver enzymes (ALT and AST) and bilirubin should be monitored prior to the start of tepotinib treatment and thereafter as clinically indicated. If Grade 3 or higher increases occur, dose adjustment is recommended.

ALP Increase

35 (11.2%) participants had TEAEs of ALP increased. The events were mainly of low grade (Grade 1 or 2). Only 1 (0.3%) participant had a severe (Grade 3) event of ALP increase. There were no dose reductions and no temporary or permanent treatment discontinuation due to ALP increase (refer to VISION CSR Tables 15.3.1.10, 15.1.12, and 15.3.1.14).

Increases in ALP were mainly nonsevere and asymptomatic. ALP increase did not lead to any dose reductions, temporary discontinuation, or permanent discontinuation (refer to VISION CSR Tables 15.3.1.10, 15.1.12, and 15.3.1.14). The observed ALP increase was not associated with cholestasis. Based on laboratory values, a worsening from Baseline to Grade 1 or higher was observed for 51.6% of participants for ALP. A worsening to Grade 3 or higher occurred in 1.6% of participants.

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 did not indicate a risk of severe hepatotoxicity in patients treated with tepotinib.

Increase in transaminases and ALP are frequently observed with TKIs, including the MET inhibitor capmatinib (capmatinib US PI), but can be managed with treatment interruptions or dose reductions.

The FDA's Assessment:

Increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST) occurred in 18% of patients treated with tepotinib. Grade 3 or 4 increased ALT/AST occurred in 4.7% of patients. A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). Four patients (0.8%) discontinued tepotinib due to increased ALT/AST. The median time-to-onset of Grade 3 or higher increased ALT/AST was 47 days (range 1 to 262). Given the incidence of AST/ALT elevations and the occurrence of a fatal adverse reaction, hepatotoxicity will continue to be included in Section 5 (Warnings and Precautions) of product labeling for tepotinib.

8.2.5.7. **Diarrhea, Nausea, and Vomiting**

Data:

Diarrhea was one of the most frequent TEAEs; diarrhea occurred in 90 (28.8%) participants. Events were mostly mild to moderate in severity. 2 (0.6%) participants experienced a Grade 3 event, which was the most severe reported grade.

Nausea was 1 of the most frequent TEAEs; nausea occurred in 97 (31.0%) participants. It was mostly mild to moderate in severity. 4 (1.3%) participants had a Grade 3 event.

Vomiting was a frequent TEAE; vomiting occurred in 45 (14.4%) participants. It was mostly mild to moderate in severity. 3 (1.0%) participants had Grade 3 events, which was the most severe Grade reported.

The Applicant's Position:

Diarrhea, nausea and vomiting are non-serious and non-severe events with no relevant impact on dosing. Gastrointestinal disorders including vomiting and diarrhea were frequently observed in repeat-dose toxicity studies in dogs.

The FDA's Assessment:

Diarrhea occurred in 29% of patients in VISION Cohorts A and C (n= 313) and Grades 3 to 4 diarrhea occurred in 0.6% of patients. Nausea occurred in 31% of patients and Grades 3 to 4 nausea occurred in 1.3% of patients. Vomiting occurred in 15% of patients and Grades 3 to 4 vomiting occurred in 1% of patients.

8.2.5.8. **Pleural Effusion**

Data:

Pleural effusion was reported in 45 participants (14.4%). Grade ≥ 3 events were reported in 13 (4.2%) participants.

Pleural effusion is a known comorbidity in patients with NSCLC. However, it is unclear whether the observed incidence of pleural effusion is related to the underlying population with NSCLC harboring *MET*ex14 skipping alteration or part of a fluid retention syndrome, since edema (mainly peripheral but also generalized edema) is associated with tepotinib. Therefore, pleural effusion was classified as an important potential.

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 with tepotinib 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. Pleural effusion is manageable within clinical practice.

The FDA's Assessment:

Pleural effusion occurred in 14% of patients in VISION Cohorts A and C (n = 313) and Grades 3 to 4 pleural effusion occurred 4.2% of patients. Pleural effusion was categorized as a serious adverse reaction in 6% of patients and led to permanent discontinuation of tepotinib in 1.6% of patients. Dosage interruptions and dose reductions due to pleural effusion occurred in 3.5% and 2.2% 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.

8.2.5.9. QT Prolongation

See subsections ECG/QT under Section 8.2.4.

8.2.5.10. Severe Hepatotoxicity

To provide a comprehensive assessment of severe hepatotoxicity, a composite term consisting of SMQ of Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions (narrow) and SMQ of Hepatitis, noninfectious (narrow), was analyzed.

8 participants (2.6%) had an event belonging to the composite term severe hepatotoxicity. Only 2 of the 8 participants had a severe event: 1 participant with ascites and 1 participant with liver disorder.

1 participant who met Hy's Law criteria had acute hepatic failure for which a causal association to tepotinib cannot be ruled out. Regarding this outcome, the Investigator updated the serious criteria from fatal to life-threatening. The participant had documented disease progression (lung and brain metastasis), but the cause of death remains unclear; data were limited as this participant withdrew consent. Tepotinib was discontinued on Day 21 of the study. No new Hy's law cases were observed through the 20 Nov 2022 DCO.

The Applicant's Position:

Overall, hepatotoxicity observed with tepotinib is mainly reflected by asymptomatic and nonsevere elevation of the transaminases with no impact on treatment or benefit-risk balance.

There is insufficient evidence to confirm a causal association between tepotinib and severe hepatotoxicity. However, considering the clinical significance of this event, severe hepatotoxicity has been classified as an important potential risk.

The FDA's Assessment:

Hepatotoxicity occurred in patients treated with tepotinib. Please refer to section 8.2.5.6 above for additional information.

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 the PRO section 8.1.2 above.

8.2.7. Safety Analyses by Demographic Subgroups

Data and the Applicant's Position:

No new safety analyses by demographic subgroups have been performed.

The FDA's Assessment:

FDA performed safety analyses by age (≥65 years old vs <65 years old) and sex. Of 313 patients with METex14 skipping alterations in VISION who received 450 mg tepotinib once daily, 79% were 65 years or older, and 41% were 75 years or older. The table below provides an overview of adverse events observed in VISION by age groups. Given the smaller size of the population of patients aged < 65 years (n=66; 21%), comparisons to other age group should be interpreted with caution. Safety analysis by racial subgroup was not conducted due to the limited number of patients enrolled for the subgroups outside of White.

Table 19 (FDA): Overview of Adverse Events in VISION by Age

	>= 65 YEARS N = 247 N (%)	< 65 YEARS N = 66 N (%)
All-Grade TEAEs	99	100
Grade 3-4 TEAEs	51	41
Serious TEAEs (SAEs)	53	44
Study treatment - dose reduced - due to AEs	18	12

	>= 65 YEARS N = 247 N (%)	< 65 YEARS N = 66 N (%)
Study treatment - drug interrupted - due to AEs	45	41
Study treatment - drug withdrawn - due to AEs	19	9

The table below provides an overview of adverse events in VISION by sex. Overall, there were no major differences in the safety profile of tepotinib observed between males and females.

Table 20 (FDA): Overview of Adverse Events in VISION by Sex

	Males N = 154 N (%)	Females N = 159 N (%)
All-Grade TEAEs	49	50
Grade 3-4 TEAEs	24	28
Serious TEAEs (SAEs)	29	22
Study treatment - dose reduced - due to AEs	9	8
Study treatment - drug interrupted - due to AEs	23	22
Study treatment - drug withdrawn - due to AEs	10	8

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:
FDA agrees with the EMD Serono's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data and Applicant's Position:

For tepotinib, human carcinogenicity or tumor development studies were not conducted per ICH S6, ICH S1, and ICH S9.

The FDA's Assessment:

FDA agrees with the EMD Serono's position.

Human Reproduction and Pregnancy

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

There are no new updates or changes from original NDA submission for this topic.

Pediatrics and Assessment of Effects on Growth

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

Not Applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

1 potential overdose was reported in VISION Cohorts A + C. In addition, in VISION Cohorts A + C, 2 additional participants reported an event of accidental overdose of tepotinib (refer to SCS DCO 20 Nov 2022, CSR Table 15.3.1.3. There were no associated AEs with this observation.

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 the EMD Serono's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Tepotinib received the first regulatory approval in Japan in March 2020 and is now approved globally in more than 40 countries, including EU, Japan and US, for the treatment of patients with advanced or metastatic NSCLC harboring *MET*ex14 skipping alterations.

Based on the evaluation of safety data from postmarketing experience there are no new findings bearing on the established overall safety profile of tepotinib. Tepotinib was well tolerated and showed an acceptable safety profile that is consistent with the profile observed in the tepotinib clinical trials.

Applicant's Position:

Overall, postmarketing data did not alter the known safety profile of tepotinib.

The FDA's Assessment:
FDA agrees with EMD Serono's assessment.

Expectations on Safety in the Postmarket Setting

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

Major safety concerns beyond the risks conveyed in the proposed labeling are not expected. 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.

8.2.11. Integrated Assessment of Safety

Data:

The updated safety analyses of VISION study data from participants with a longer follow-up of at least 18 months after start of tepotinib treatment further substantiate that tepotinib, administered at an oral dose of 500 mg once daily, was associated with a tolerable and well manageable safety profile in patients with advanced NSCLC harboring *MET*ex14 skipping alterations. No new safety concerns were identified in the updated analysis, thus confirming the existing safety profile of tepotinib.

Adverse reactions of tepotinib include ILD (as important identified risk); edema; increased creatinine; hypoalbuminemia; increase in ALT, AST, and ALP; diarrhea; nausea; vomiting; and increase in amylase and lipase (as identified risks). Important potential risks include pleural effusion, QT prolongation, and severe hepatotoxicity.

In summary, the following AEs and laboratory parameter findings were observed in VISION Cohorts A + C:

- The incidence of ILD or ILD-like events is 2.6% (8/313 participants). This integrated assessment takes into account the independent panel conclusions and the current search results for this update.
- Peripheral edema was the most frequently reported TEAE (72.5%).
- Most participants experienced treatment-related TEAEs that were mild or moderate in severity.
- A total of 200 (63.9%) participants died. Most deaths were due to progression of the disease.

41 (13.1%) participants had TEAEs leading to death, including 3 treatment-related TEAEs: acute respiratory failure secondary to ILD, respiratory failure, and progressive disease or disease-related condition (lung cancer) leading to multiple organ failure (due to missing

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causality report, this event of multiple organ failure was considered as related in the analysis of causality).

- The most common Grade ≥ 3 TEAEs, regardless of causality, were peripheral edema (11.8%), hypoalbuminemia (6.4%), disease progression (4.2%), pneumonia (4.5%), and pleural effusion (4.2%).
- The incidence of TEAEs leading to permanent discontinuation of treatment (24.9%) indicates a good tolerability profile for tepotinib in this advanced cancer population. The most frequent TEAEs leading to permanent discontinuation were edema peripheral (5.4%). Most frequent TEAEs leading to dose reduction were edema peripheral (15.7%), generalized edema (3.2%), blood creatinine increased (2.9%), and edema (2.6%).
- Apart from the identified and potential risks described above, a review of clinical laboratory values, vital signs results did not reveal any additional safety findings.

Overall, the AEs observed were typical of the underlying NSCLC or were linked to the mode of action of tepotinib.

The Applicant's Position:

In conclusion, tepotinib administered as monotherapy at a dose of 500 mg once daily in the pivotal VISION study, was associated with a tolerable and well manageable safety profile in participants 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 Applicant 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:

FDA agrees that, in general, the additional safety follow-up data based on the DCO of November 20, 2022, are consistent with data previously reported in the original NDA submission. However, the additional safety signal of pancreatic toxicity was identified during the current review, with elevated amylase and lipase observed in the study population, and reflects a probable class effect with MET inhibitors. This newly identified safety signal of pancreatic toxicity was added to the Warnings and Precautions section of the USPI. Incidences of adverse reactions within the USPI of tepotinib were revised to reflect the increased safety population in VISION (n = 313) and the pooled safety population (n = 506). Additionally, updated safety data submitted as part of the 90-day safety update were reviewed and found to be consistent with the data included in the initial supplemental application. The overall safety profile of tepotinib is considered acceptable in the context of observed efficacy in the setting of a life-threatening disease.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

EMD Serono submitted data and results from the single-arm VISION study for the efficacy endpoints of ORR and DOR investigating tepotinib in patients with locally advanced or metastatic NSCLC with MET exon 14 (METex14) skipping alterations or MET amplification. Results were reported separately for the two subpopulations of treatment-naïve patients and previously treated patients, consistent with the efficacy characterization utilized for the application that supported the accelerated approval for the same indications. The observed ORR was 57% (95% CI: 49, 65) in treatment-naïve patients and 45% (95%CI: 37%, 53%) in previously treated patients. Due to a high proportion of informative censoring, the Kaplan Meier estimates for DOR are unreliable, as discussed below. The range for observed DOR in the treatment-naïve subpopulation was (1.3+, 56.6+), and in the previously treated subpopulation was (1.4+, 67.6+), where "+" indicates ongoing response at the latest DCO date (November 20, 2022).

Assessment of impact of Censoring for DOR

The Kaplan Meier estimates of the median duration of response were exaggerated, particularly in the subpopulation of treatment-naïve patients, due to a large proportion of censoring taking place prior to the median of the Kaplan-Meier (K-M) curve. The FDA sent IRs to EMD Serono requesting updated DOR data, additional information regarding the status of censored patients, and additional analyses to investigate the impact of censoring on the K-M estimate of DOR. The FDA further explored the nature of this censoring with its own sensitivity analyses. The reasons for censoring and sensitivity analyses are given below.

Sensitivity Analyses to explore the effect of censoring on K-M estimates for DOR per BIRC:

a. Censoring due to progression or death after 2 missed assessments.

   In the VISION study, 94 treatment-naïve patients had an objective response and were followed for DOR assessment. Of these, 20 patients (21%) had progression or death after two missed BICR assessments (according to the reason for censoring). Their DOR follow-up was censored at the last evaluable tumor assessment not showing progression. Death dates for 18 of these patients were known (13 deaths occurred within 20 months of response). Two main reasons for two or more missing BICR assessments for these patients appear to be (i) investigators calling progression before BICR or (ii) missed assessments due to adverse events. In the previously treated patient subgroup, out of the 67 responders followed for DOR, 14 patients were censored for progression or death after two missed assessments: 12 patients were known to have died (10 deaths occurred within 19 months

of response) and two patients had progression after missing two assessments.

FDA conducted a sensitivity analysis in the treatment-naïve population by assuming these 18 patients had no disease progression before death and their response ended only at the time of death. This confers the longest DOR for each of these patients. This analysis resulted in a median DOR of 17.3 months (95% CI: 10.8, 22.4).

Similarly, in the previously treated population, FDA conducted a sensitivity analysis assuming that the 12 patients identified had no disease progression before death and their response ended at time of death. For previously treated patients, the median DOR was 13.0 months (95% CI: 9.65, 19.3).

b. Censoring due to investigator assessed progression.

There were an additional 11 patients across both the treatment-naïve and previously treated subgroups who had progression per investigator but were censored by the BIRC due to lack of additional scans after the investigator called progression for the independent readers to review. The reason listed for censoring in the dataset for these patients was "no progression or death." The survival status for these patients is unknown.

FDA performed a sensitivity analysis for DOR by assuming the 11 patients with progression by investigator, and 34 patients who were known to have progressed or died following 2 missed assessments, had their response end at the time of censoring in the original analysis (i.e., at the last BIRC scan not showing progression). This is a conservative assumption on the observed DOR for these patients. For treatment-naïve patients, there were 64 events including events from 27 previously censored patients, and the median DOR was 10.34 months (95% CI: 7.12, 14.9) by K-M analyses. For previously treated patients, there 55 events, including events from 22 previously censored patients, and the median DOR was 9.32 months (95% CI: 6.89, 11.1) by K-M analyses.

The first sensitivity analysis suggests that the median DOR estimate in treatment-naïve patients (46.4 months) based on K-M method is likely a gross overestimate of actual DOR of the patients with a response in VISION study and could be misleading. The second analysis provides a conservative estimate of median DOR observed in the trial.

(b) (4)

Conclusions and Recommendations

The FDA's Assessment:

The accelerated approval of tepotinib for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations was based primarily on ORR results observed in 69 treatment-naïve patients and 83 previously treated patients enrolled in the VISION study. As part of the accelerated approval, postmarketing requirement (PMR) 4013-1 was issued for the submission of additional data from the ongoing VISION study, including at least 12 months of response follow-up for treatment-naïve patients and 6 months of response follow-up for previously treated patients, to be submitted to verify the clinical benefit of tepotinib in patients with metastatic NSCLC harboring MET exon 14 skipping alterations.

Based on the data from the VISION study as of a DCO date of November 20, 2022, tepotinib demonstrates substantial evidence of effectiveness in patients with NSCLC harboring MET exon 14 skipping alterations, including 164 treatment-naïve patients and 149 previously treated patients (of whom 84% were treated with prior platinum-based therapy). This assessment is based on the durability of responses observed with longer follow-up, including an additional approximately 28 months of follow-up time for the DOR data included in the original NDA, and is supported by the consistency of ORR results in each patient population with additional patients. The ORR observed in treatment-naïve patients was 57% (95% CI 49, 65) with an observed median DOR of 9.1 months (range 1.3+, 56.6+ months); 40% of responders had a DOR ≥12 months. The ORR observed in previously treated patients was 45% (95% CI 37, 53) with an observed median DOR of 8.4 months (range 1.4+, 67.6+ months); 36% of responders had a DOR ≥12 months. There is one other targeted therapy (capmatinib) with traditional approval for the treatment of patients with NSCLC with MET exon 14 skipping mutations. The traditional approval for capmatinib was also based on ORR and durable response rates.

The safety dataset included 313 patients with MET exon 14 skipping mutated NSCLC who were treated in the VISION study. The most common (≥ 20%) all-causality adverse events associated with tepotinib treatment were edema, nausea, fatigue, musculoskeletal pain, abdominal pain, diarrhea, dyspnea, decreased appetite, and rash. Most adverse events were Grade 1-2 in severity and were managed by dose reduction and/or interruption. Most adverse events were Grade 1-2 in severity and were managed by dose reduction and/or interruption. Serious adverse events occurred in 51% of patients who received tepotinib; however, the serious risks of treatment are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of tepotinib product labeling. This includes the addition of pancreatic toxicity, which was newly identified during the current review as a safety issue with tepotinib. Most treatment discontinuations were due to disease progression, and the rate of permanent discontinuation of tepotinib due to adverse events was 25%. The safety profile of tepotinib is acceptable when considered in the context of the observed clinical benefit and the life-threatening nature of metastatic NSCLC.

Given the rarity of NSCLC with MET exon 14 skipping mutations and the availability of currently approved therapies, the conduct of a randomized clinical trial enrolling a population reflective of the US patient population is considered infeasible. In this context, the submitted evidence meets the statutory evidentiary standard for traditional approval as it provides substantial evidence of effectiveness of tepotinib as a single agent for the treatment of patients with metastatic NSCLC harboring MET exon 14 skipping alterations in both the treatment-naïve and previously treated settings.

Approval of this sNDA fulfills PMR 4013-1 and verifies the clinical benefit of tepotinib.

Therefore, the reviewers recommend granting traditional approval to 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
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The FDA did not refer this supplemental application to an advisory committee as no major efficacy or safety issues were identified during the review that required external input for the proposed indication

10 Pediatrics

The Applicant's Position:

N/A

The FDA's Assessment:

FDA granted tepotinib orphan designation for treatment of NSCLC with MET genomic tumor aberrations on October 26, 2020. Because tepotinib has orphan drug designation for NSCLC, it is exempt from the requirements of the Pediatric Research Equity Act (PREA) to conduct studies for the treatment of NSCLC in pediatric patients. Conducting studies with tepotinib would be highly impracticable or impossible given the small number of pediatric patients with NSCLC whose tumors have a mutation that leads to MET exon 14 skipping alterations.

11 Labeling Recommendations

Data:

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	• Removal of accelerated approval statement and respective contingent condition upon fulfilling PMR 4013-1	• Revision accepted.
	• No changes proposed.	• Text added for clarity: Patients who have difficulty swallowing solids can disperse tablets in water *[see Dosage and Administration (2.3)]*. • Footnote added to Dosage Modification table to clarify

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.

		NCI CTCAE Version 5
5 WARNINGS AND PRECAUTIONS	5.1 Interstitial Lung Disease/Pneumonitis • Numbers updated	• Incidences of adverse reactions revised to reflect the safety population N= 506 *(previous safety population N=448).*
	5.2 Hepatotoxicity • Numbers updated and statement streamlined • 5.3 Pancreatic toxicity	• Incidences of adverse reactions revised to reflect the safety population N= 506 (previous safety population N=448). • Inclusion of text to report a fatal adverse reaction of hepatic failure. • Incidences reflect the proportion of the pooled safety population (n=506) that experienced pancreatic toxicity based on adverse event reporting.
6 ADVERSE REACTIONS	6.1 Clinical Trial Experiences • Safety information updated and revised based on updated analysis for VISION trial (18m follow-up)	• Incidences of adverse reactions observed in the VISION trial revised to reflect

		the safety population N= 313 (previously was N=255). • Inclusion of text to report a fatal adverse reaction of hepatic failure and to add dose reduction for fatigue. • Inclusion of 3 additional fatal TEAEs (pneumonia, sepsis, and death of unknown cause). • Included footnote under the adverse reaction and laboratory abnormality tables defining NCI CTCAE Version 4.03
8 USE IN SPECIFIC POPULATIONS	8.5 Geriatric Use • Numbers updated	• Geriatric Use was revised to reflect the incidences of adverse reactions observed in the VISION trial revised to reflect the safety population N= 313 (previously was N=255).

14 CLINICAL STUDIES	• Efficacy information for treatment naïve and previously treated patients with METex 14 skipping alterations updated and revised based on updated analysis for VISION trial (18m follow-up)	• The Clinical Studies section was revised to reflect the efficacy in the updated efficacy population N=164 (previously was N=69). Overall response rate and duration of response (DOR) were revised. (b) (4)

Patient Information

The current Patient Information for TEPMETKO is also revised. Updates are made to section '*What are the possible side effects of TEPMETKO*' of the Patient Information to align the current information on most common side effects with the information from the Full Prescribing Information.

The Applicant's Position:

All pertinent label sections will be updated as indicated above.

The FDA's Assessment:

The Applicant proposed text was reviewed and revised by FDA for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases.

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 provided in the US prescribing information (USPI). 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:

The clinical review team concludes that the post-marketing requirement (PMR) 4013-1 issued with the accelerated approval of tepotinib has been fulfilled. The additional data submitted in this supplement verifies the clinical benefit for tepotinib in patients with metastatic NSCLC haboring MET exon 14 skipping alterations and who are treatment-naïve or have previously received platinum-based chemotherapy.

Post-marketing commitment (PMC) 4013-4 remains outstanding. Details on the status of this PMC are described in Section 4. Fulfillment of this PMC is considered delayed based on the original projected final report submission of 01/2022.

PMC 4013-4: 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.

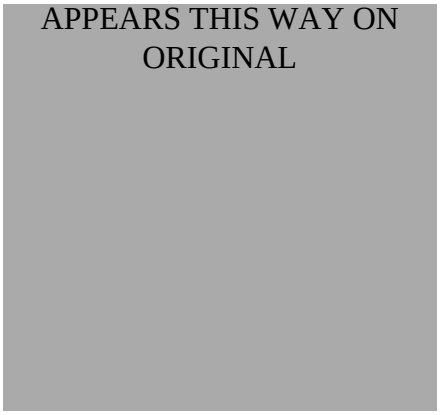
14 Division Director (DHOT) (NME ONLY)

X _____

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP)

X _____



16 Division Director (OB)

X _____

APPEARS THIS WAY ON ORIGINAL

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.

17 Division Director (Clinical)

X _____

APPEARS THIS WAY ON ORIGINAL

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 _____

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

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2. Schrock AB, Frampton GM, Suh J, Chalmers ZR, Rosenzweig M, Erlich RL, et al. Characterization of 298 patients with lung cancer harboring MET exon 14 skipping alterations. J Thoracic Oncology 2016;1493–502.

3. Sabari JK, Leonardi GC, Shu CA, Umeton R, Montecalvo J, Ni A, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncology 2018;29: 2085–91.

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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 1352 out of 1362 (99%) principal investigators and sub-investigators responded and provided study-specific financial disclosure forms. The 10 sub-investigators participating in the VISION study from whom a signed financial disclosure was not obtained 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 14 sub-investigators who participated in the VISION study from (b) (6) where (b) (6) patients were enrolled. The Applicant reports that (b) (6) was not the primary investigator at (b) (6) and his involvement with the study was limited. The Applicant also reports that (b) (6) (b) (6) to EMD Serono; however, (b) (6) 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 by (b) (6) (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, further reducing opportunity for bias.

Covered Clinical Study (Name and/or Number):* Study A2201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1362		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
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: 1 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (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:

Not Applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

Not Applicable.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

None.

Signatures – NDA (214096 S-003) – TEPMETKO (tepotinib)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Luckson Mathieu, MD	CDER/OOD/DO2	Sections: 1,2,3,4.4,7,8,9,10,11,12, 13	**Select one:** _X_ Authored ___ Approved
	Signature: Luckson Mathieu -S Digitally signed by Luckson Mathieu -S Date: 2024.02.15 11:20:25 -05'00'			
Clinical Team Leader	Gautam Mehta, MD	CDER/OOD/DO2	Sections: see CDTL below	**Select one:** ___ Authored ___ Approved
	Signature: see CDTL signature			
Statistical Reviewer	Michelle Marcovitz, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** ___X Authored ___ Approved
	Signature: Michelle S. Marcovitz -S Digitally signed by Michelle S. Marcovitz -S Date: 2024.02.15 11:02:36 -05'00'			
Statistical Team Leader	Anup Amatya, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** ___X Authored ___X Approved
	Signature: Anup K. Amatya -S Digitally signed by Anup K. Amatya -S Date: 2024.02.15 10:02:48 -05'00'			
Deputy Division Director (OB)	Pallavi Mishra-Kalyani, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** _ Authored _X_ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2024.02.15 10:06:16 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	Barbara Scepura	CDER/OOD	Sections: 11	**Select one:** ___ Authored x___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2024.02.15 12:37:56 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Gautam Mehta, MD	CDER/OOD/DO2	Sections: All	**Select one:** __ Authored X__ Approved
	Signature: Gautam U. Mehta -S Digitally signed by Gautam U. Mehta -S Date: 2024.02.15 12:34:34 -05'00'			

Signatures – NDA 214096 S-003 – TEPMETKO (tepotinib)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Stephanie Aungst, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** ___ Authored x Approved
	Signature: Stephanie L. Aungst -S Digitally signed by Stephanie L. Aungst -S Date: 2024.02.15 07:34:17 -05'00'			
Nonclinical Team Leader	Claudia P. Miller, PhD	CDER/OOD/DHOT	Sections: 5	**Select one:** ___ Authored x Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2024.02.15 07:59:26 -05'00'			

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/s/

GAUTAM U MEHTA
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ERIN A LARKINS
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Supervisory Associate Director, DO2, as designated signatory on behalf of Dr. Harpreet Singh

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214096Orig1s003

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 20, 2023
To:	Jacqueline Glen, MS Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, WOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Helen Young, MSN, MPH, CRRN, PHN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kelle Caruso, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TEPMETKO (tepotinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214096
Supplement Number:	S-003
Applicant:	EMD Serono, Inc.

1 INTRODUCTION

On April 25, 2023, EMD Serono, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 214096/S-003 for TEPMETKO (tepotinib) tablets. With this submission, the Applicant proposes to convert the indication for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations from accelerated approval to full approval based on completion of Study MS200095_022 and to update the Prescribing Information (PI) reflecting the current efficacy and safety information.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on October 18, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TEPMETKO (tepotinib) tablets.

2 MATERIAL REVIEWED

- Draft TEPMETKO (tepotinib) tablets PPI received on April 25, 2023, and received by DMPP and OPDP on December 13, 2023.
- Draft TEPMETKO (tepotinib) tablets Prescribing Information (PI) received on April 25, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 14, 2023
- Approved TEPMETKO (tepotinib) labeling dated March 23, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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KELLE E CARUSO
12/20/2023 08:49:00 AM

BARBARA A FULLER
12/20/2023 08:52:07 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 19, 2023

To: Jacqueline Glen, Regulatory Project Manager
Division of Oncology 2 (DO2)

Barbara Scepura, Associate Director for Labeling, DO2

From: Kelle Caruso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for TEPMETKO® (tepotinib) tablets, for oral use

NDA: 214096, S-003

Background:
In response to DO2's consult request dated October 18, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for supplement 003 for TEPMETKO® (tepotinib) tablets, for oral use. This supplement is for the fulfillment of PMR 4013-1 and to convert tepotinib to full approval from accelerated approval for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations and to update the USPI (mainly sections 5 and 6) to reflect the current efficacy and safety information.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 14, 2023, and our comments are provided below.

PPI
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Kelle Caruso at 301-796-5044 or Kelle.Caruso@fda.hhs.gov.

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/s/

KELLE E CARUSO
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