CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214096Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 128073

MEETING MINUTES

EMD Serono Research and Development Institute
Attention: Virginia Vetter, M.S., RAC
Director, Global Regulatory Affairs, Immuno-Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Vetter:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for

We also refer to the teleconference between representatives of your firm and the FDA on May 4, 2020. The purpose of the meeting was to discuss and reach agreement on the content and format of your proposed New Drug Application (NDA) for tepotinib for the treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition factor gene (*MET*) exon 14 (*MET*ex14) skipping alterations (b) (4)

A copy of the official minutes of the teleconference meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1] 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.

If you have any questions, call me at 301-796-4803.

Sincerely,

{See appended electronic signature page}

Stacie Woods, Pharm.D.
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases 2
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 4, 2020, 12 PM – 1 PM ET
Meeting Location: Teleconference

Application Number: IND 128073
Product Name: tepotinib

Indication: treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition factor gene (*MET*) exon 14 (*MET*ex14) skipping alterations, (b) (4)

Sponsor Name: EMD Serono Research and Development Institute, Inc.
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

Meeting Chair: Adnan Jaigirdar, M.D.
Meeting Recorder: Stacie Woods

FDA ATTENDEES

Office of Oncologic Diseases (OOD)
Division of Oncology 2 (DO2)
Harpreet Singh, M.D., Division Director
Paz Vellanki, M.D., Clinical Reviewer
Adnan Jaigirdar, M.D., Clinical Team Leader (Acting)
Janice Kim, Pharm.D., Clinical Reviewer
Katie Chon, Pharm.D., Clinical Reviewer
Sujay Shah, M.D., Clinical Reviewer

Division of Hematology Oncology Toxicology (DHOT)
Stephanie Aungst, Ph.D., Nonclinical Reviewer
Whitney Helms, Ph.D., Nonclinical Team Leader

Office of Biostatistics (OB)
Division of Biostatistics V (DBV)
Pourab Roy, Ph.D., Statistical Reviewer
Pallavi Mishra-Kalyani, Ph.D., Statistical Reviewer Team Leader

Office of Clinical Pharmacology (OCP)
Division of Cancer Pharmacology (DCPII)
Krithika Arun Shetty, Ph.D., Clinical Pharmacology Reviewer
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader

Office of Product Quality (OPQ)
Olen Stephens, Ph.D., Product Quality Reviewer

Office of Regulatory Operations (ORO)/Oncologic Disease (OD)
Stacie Woods, Pharm.D., Regulatory Health Project Manager

Center for Devices and Radiologic Health (CDRH)
Abdelrahmman Abukhdeir, Ph.D., Reviewer

SPONSOR ATTENDEES
Virginia Vetter, MS, RAC, Global Regulatory Affairs, EMD Serono Research and Development Institute, Inc.
Georgios Amexis, PhD, RAC, Global Regulatory Affairs, Merck Healthcare KGaA
Praveen Marapaka, PhD, Global Regulatory Affairs, EMD Serono Research and Development Institute, Inc.
Ilhan Celik, MD, Global Program Lead, Global Clinical Development, Merck Healthcare KGaA
Andreas Johne, MD, Global Clinical Development, Merck Healthcare KGaA
Karl Maria Schumacher, MD, Global Clinical Development, Merck Healthcare KGaA
Tim Demuth, MD, Global Clinical Development, Merck Healthcare KGaA
Klaus Edvardsen, MD, Global Clinical Development, Merck Healthcare KGaA
Barbara Ellers-Lenz, Global Biostatistics, Merck Healthcare KGaA
Anja von Heydebreck, Global Biostatistics, Merck Healthcare KGaA
Anup Kalapur, MD, Global Patient Safety, Merck Healthcare KGaA
Rainer Strotmann, Translational Medicine, Clinical Pharmacology Expert Team Lead, Merck Healthcare KGaA
Dennis Merkle, Translational Medicine, Companion Diagnostics, Merck Healthcare KGaA
Svetlana Mukhina, Global Regulatory Affairs Translational Medicine and Devices, Merck Healthcare KGaA
Christopher Stroh, Translational Innovation Platform Oncology, Translational and Biomarker Research, Merck Healthcare KGaA
Ioanna Bethani, Global Medical Writing, Merck Healthcare KGaA
Katrin Bender-Golden, CMC Development, Merck Healthcare KGaA
Dina Oksen, Global Epidemiology, Merck Healthcare KGaA
Dagmar Kottig-Roth, PhD, Global Clinical Sciences, Merck Healthcare KGaA

BACKGROUND

Regulatory

- A separate pre-NDA meeting was held for nonclinical questions. Written Responses were issued on April 13, 2020.

- A separate pre-NDA meeting was held for CMC. The meeting was held on January 28, 2020. The Meeting Minutes were issued on February 28, 2020.

- On November 8, 2019, EMD Serono submitted an Amended Agreed Initial Pediatric Study Plan (Amended Agreed iPSP-2) for tepotinib for the treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors harbor MET exon 14 (METex14) skipping alterations. FDA issued an Amended Agreed iPSP Agreement on December 17, 2019.

- On September 10, 2019, breakthrough therapy designation was granted for tepotinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors harbor MET exon 14 skipping alterations (METex14) and who progressed following platinum-based cancer therapy.

CMC

The tepotinib hydrochloride hydrate is a small molecule new molecular entity. The drug product is a film-coated oral tablet, formulated to have a 225 mg strength on the basis of the tepotinib free base.

Clinical Pharmacology

Capsule formulations containing (b) (4) (CF1) and (b) (4) (CF2) drug substance (tepotinib hydrochloride hydrate), and three tablet formulations (TF1, TF2-100 and 500 mg strengths and TF3 -100 and 250 mg strengths) have been used during the clinical development of tepotinib. The VISION study initially utilized the TF2 formulation; however, patients are currently being transitioned to the TF3 formulation. TF3 is the proposed commercial formulation, provided as film-coated tablets containing 250 mg of (b) (4) tepotinib hydrochloride hydrate drug substance. TF3 (2 x 250 mg tablets) was found to be bioequivalent to TF2 (1 x 500 mg tablet) in a dedicated BE study, MS200095-0044.

The proposed clinical dosing regimen of tepotinib in adults is 500 mg of tepotinib hydrochloride hydrate once daily, administered orally with food. EMD Serono proposes a single dose reduction level of 250 mg in patients with NSCLC harboring *MET*ex14 mutations, which is based on the clinical experience with 300 mg and 200 mg dose reduction levels previously used in the VISION study, translational PK/PD modeling, and exposure-response analyses performed to date. The 250 mg dose was also

selected as it represents the tablet strength of the proposed commercial TF3 formulation.

Clinical pharmacology has previously reviewed and agreed to both these proposals as documented in the Type C meeting Final Written Response dated September 12, 2019.

EMD Serono states that the clinical pharmacology and pharmacometrics package in the NDA submission will consist of data from 14 clinical studies, population PK modeling and exposure-response modeling with pharmacodynamic, efficacy and safety endpoints.

Clinical

EMD Serono proposes to submit an original NDA based on the results of Study MS200095-002, referred to as VISION, for the treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring *MET* exon 14 skipping (*MET*exon14) mutations with tepotinib.

VISION Study

VISION is an ongoing, parallel-cohort, open-label study investigating tepotinib for the first and beyond first line treatment of patients with advanced NSCLC harboring *MET*ex14 alterations or *MET* amplification. After screening, eligible patients were assigned to either cohort A (if harboring *MET*ex14 tumor alterations), cohort B (for tumors with *MET* amplification), or cohort C (a confirmatory cohort for patients with *MET*ex14 tumor alterations). Data from the following cohorts are proposed to support the NDA:

- Cohort A will provide the key efficacy data for tepotinib for the proposed indication with a minimum follow-up of 9 months for patients.
- Efficacy results from cohort C as of the data cutoff date will only be presented in the VISION Clinical Study Report. Enrollment for cohort C is ongoing and as of the data cutoff date, 29 of expected ≥100 patients are enrolled.
- Data from cohorts A and C are proposed to provide the safety data for the NDA.

The *MET*ex14 skipping alterations were identified either in tumor tissue or plasma circulating tumor DNA (ctDNA) by liquid biopsy. The protocol defined three primary analysis sets for efficacy based on results from patients screened using tumor tissue (T+), liquid biopsy (L+), or both.

The primary endpoint is overall response rate (ORR) as determined by an independent review committee (IRC) per RECIST v1.1. Secondary endpoints include ORR per Investigator assessment, duration of response (DOR) per IRC, DOR per Investigator, and overall survival (OS).

Results from cohort A

As of the data cutoff date of January 1, 2020, 152 patients on cohort A have received treatment with tepotinib. However, only 100 patients have follow-up greater than 9 months, the minimum amount of time specified in the protocol for the primary analysis. In total, 99 patients will be evaluable for efficacy as there was insufficient *MET*ex14 alteration data for one patient. Additionally, as per the request from the FDA, all patients with an objective response (N=99) had 6 months of follow-up after onset of response. Therefore, the evaluation of efficacy in the NDA will focus on this population.

An ORR of 47% (95% CI: 36, 57), associated with a median DOR of 11 months (95% CI: 7, Not Estimable [NE]), was observed in the combined analysis set (L+ and/or T+). Of the 46 patients who had a response, 29 (63%) had a DOR ≥6 months. A consistent proportion of responders was observed across lines of therapy or prior platinum use, with ORRs ranging from 44% to 53% in the combined analysis set. The proportion of patients with a DOR ≥6 months was also consistent regardless of whether patients had received prior anticancer treatment for advanced or metastatic NSCLC or not.

The ORR and DOR results by line of therapy or prior platinum-based therapy are further detailed below in the table submitted by the Sponsor:

Table 6 **Objective Response Rate and Duration of Response by Line of Therapy or Prior Platinum-based Therapy for Metastatic Disease (Independent Review), VISION Cohort A, ITT Patients with First Dose of Tepotinib Prior to 02 April 2019 – 01 January 2020 Data Cutoff**

	L+ N = 66	T+ N = 60	Combined (L+ and/or T+) N = 99
Overall			
ORR [a] n/N (%)	32/66 **(48.5)**	30/60 **(50.0)**	46/99 **(46.5)**
[95% CI] [b]	[36.0, 61.1]	[36.8, 63.2]	[36.4, 56.8]
mDOR months [c]	9.9	15.7	11.1
[95% CI] [d]	[7.2, ne]	[9.7, ne]	[7.2, ne]
DOR ≥ 6 months n/N (%)	22/32 (68.8)	17/30 (56.7)	29/46 (63.0)
1st line			
ORR [a] n/N (%)	15/29 **(51.7)**	11/27 **(40.7)**	19/43 **(44.2)**
[95% CI] [b]	[32.5, 70.6]	[22.4, 61.2]	[29.1, 60.1]
mDOR months [c]	ne	ne	ne
[95% CI] [d]	[5.8, ne]	[3.7, ne]	[5.8, ne]
DOR ≥ 6 months n/N (%)	9/15 (60.0)	6/11 (54.5)	12/19 (63.2)
2nd line			
ORR [a] n/N (%)	10/22 **(45.5)**	12/19 **(63.2)**	16/33 **(48.5)**
[95% CI] [b]	[24.4, 67.8]	[38.4, 83.7]	[30.8, 66.5]
mDOR months [c]	11.7	11.1	11.1
[95% CI] [d]	[4.4, ne]	[4.4, ne]	[5.6, ne]
DOR ≥ 6 months n/N (%)	8/10 (80.0)	8/12 (66.7)	11/16 (68.8)
≥ 3rd line			
ORR [a] n/N (%)	7/15 **(46.7)**	7/14 **(50.0)**	11/23 **(47.8)**
[95% CI] [b]	[21.3, 73.4]	[23.0, 77.0]	[26.8, 69.4]
mDOR months [c]	9.9	9.9	9.9
[95% CI] [d]	[3.6, ne]	[5.6, 15.7]	[5.6, ne]
DOR ≥ 6 months n/N (%)	5/7 (71.4)	3/7 (42.9)	6/11 (54.5)
No Prior Platinum-based Therapy for Metastatic Disease			
ORR [a] n/N (%)	16/32 **(50.0)**	12/29 **(41.4)**	20/47 **(42.6)**
[95% CI] [b]	[31.9, 68.1]	[23.5, 61.1]	[28.3, 57.8]
mDOR months [c]	9.7	ne	ne
[95% CI] [d]	[5.8, ne]	[5.7, ne]	[6.6, ne]
DOR ≥ 6 months n/N (%)	10/16 (62.5)	7/12 (58.3)	13/20 (65.0)
Prior Platinum-based Therapy for Metastatic Disease			
ORR [a] n/N (%)	16/32 **(50.0)**	18/29 **(62.1)**	26/49 **(53.1)**
[95% CI] [b]	[31.9, 68.1]	[42.3, 79.3]	[38.3, 67.5]
mDOR months [c]	11.1	12.4	11.1
[95% CI] [d]	[8.3, ne]	[5.6, ne]	[7.0, ne]
DOR ≥ 6 months n/N (%)	12/16 (75.0)	10/18 (55.6)	16/26 (61.5)

CI=confidence interval, DOR=duration of response, ITT=intention-to-treat, L+=liquid biopsy positive; mDOR=median duration of response, ne=not estimable, ORR=objective response rate, T+=tissue biopsy positive.

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.

Status of cohort C to confirm efficacy of tepotinib for NSCLC with METex14 alterations

Cohort C will enroll the same population of patients with NSCLC harboring *MET*ex14 skipping alterations and employ the same objectives, endpoints, and inclusion/exclusion criteria as in cohort A. At least 60 patients are to be enrolled in the L+ and T+ analysis sets each. Regardless of the material (LBx or TBx) used for inclusion into the study, ≥ 50 first line, ≥ 30 second line, and ≥ 20 third line patients will be enrolled. In addition to the study sites for cohort A, cohort C will also enroll patients from 20 new sites and four additional countries. Enrollment for cohort C is currently ongoing; as of January 1, 2020, 29 patients are enrolled.

Analysis of Safety

As of July 19, 2019, adverse reactions of tepotinib from 130 patients enrolled in VISION include edema (65%), diarrhea (31%), increased creatinine (24%), hypoalbuminemia (19%), increased amylase and lipase (12% and 8% respectively), and increased aspartate transaminase (AST) and alanine transaminase (ALT) (9% and 11%, respectively). An important identified risk is interstitial lung disease (ILD) occurred in 3.8% of patients.

Data from cohorts A and C of VISION up to the data cutoff of January 1, 2020 are intended to form the main basis for the safety evaluation of tepotinib for this NDA. However, to further characterize the safety profile of tepotinib at the clinical dose of 500 mg once daily, data from clinical studies for all cancer patients dosed with tepotinib monotherapy at 500 mg once daily will be pooled into a pooled safety analysis set (referred to as POOL). In total, 373 patients from 5 studies were included in the POOL, including cohorts A – C of VISION.

(b) (4)

(b) (4)

Clinical Trial Assays (b) (4)

Patients were screened for the VISION trial for *MET*ex14 alterations by testing tumor tissue or ctDNA from liquid biopsies using the clinical trial assays (CTAs) below:

- The Guardant 360® CDx Test was used to identify *MET*ex14 alterations in the form of single nucleotide variants and insertions/deletions from plasma.
- The Oncomine® Focus Assay was used to detect aberrant deletion of *MET*ex14 from RNA samples extracted from tumor tissue.
- In Japan, an RT-PCR based method was an optional CTA to detect *MET*ex14 alterations from fresh frozen tumor tissue.

(b) (4)

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the FDA agree that the data from the VISION study are adequate to support the filing of a marketing application for the proposed indication under the accelerated approval provisions of 21 CFR 314 subpart H?

   FDA Response: The current data from the VISION study for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) harboring *MET*ex14 skipping alterations do not demonstrate a meaningful advantage over available therapy for patients who are treatment-naïve for metastatic disease.

   For patients with disease progression on or after anti-PD-(L)1 therapy in combination with platinum-containing chemotherapy, we request data from additional patients in order to support a possible filing of a marketing application under 21 CFR 314 subpart H. In addition, please provide the exact numbers of patients, as well as ORR and duration of response, for patients who received prior platinum therapy. Please confirm that all patients have been followed for at least 6 months post onset of response. At this time, your proposed submission may be premature, given the limited numbers of patients in your proposed efficacy population.

   EMD Serono's response received via email on April 30, 2020: We appreciate the Agency's feedback on the potential submission to support the proposed indication. Please find below the requested information on the patients who received prior platinum therapy.

   As of the January 1, 2020 cut-off, out of the 151 patients in Cohort A with NSCLC MetEx14 skipping mutation, 99 patients[2] with at least 6 months follow-up from onset of response, 49 of whom have received prior platinum therapy for metastatic disease. The ORR for these patients is 53.1% [95% CI; 38.3, 67.5]; the median duration of response is 11.1 months (January 1, 2020 cut-off).

   In order to facilitate the Agency's review of the potential submission and in alignment with the previous FDA feedback (Type C WRO feedback received September 25, 2019, Reference ID 4497312), we have planned a July 2020 data-cut in order to provide updated data during the review of the application for the 146 patients with MetEx14 skipping mutation enrolled in Cohort A who will have been followed at least 6 months post onset of response, including the data

[2] In all but one patient, the duration of follow-up was at least 6 months after the onset of response. This patient experienced a late occurring response on Day 208 in October 2019 and therefore did not reach 6 months follow-up after start of response at the date of cutoff (01 Jan 2020). DOR for this patient was censored at the date of the last available tumor assessment before data cutoff. There were 4 additional patients with ongoing response whose DOR was censored at the date of the last available tumor assessment before data cutoff, occurring less than 6 months after start of response.

on approximately 72 patients who have received prior platinum therapy. The data from the January 2020 data cut-off in these patients (ORR 48.6% [95% CI; 36.7, 60.7]; DOR, the median duration of response is 11.1 months) is consistent with the observed ORR, DOR of the 49 patients.

Discussion during the May 4, 2020, meeting: FDA reiterated that the data on the 49 patients would not be adequate to support an approval. FDA agreed with the submission of an application with the current data set and an update of the 72 patients during the review of the application, who have received prior platinum therapy and will have at least 6 months of follow-up post onset of response. EMD Serono will consider Real-Time Oncology Review (RTOR) submission and will update with additional efficacy of these 72 patients when available.

Post Meeting Addendum: The proposed data submission in September 2020 would provide an update to the duration of response (DOR) since by September all responders among the 72 patients would have at least 6 months or greater follow-up past onset of response.

2. Does the FDA:

   a. support the use of tablet formulation 3 (TF3) as the commercial formulation?

   b. confirm their agreement with the definition of a dose reduction level of 250 mg in the US labeling information?

FDA Response: Yes, FDA agrees with both proposals. The adequacy of the data in support of filing the NDA and labeling will be determined during the NDA review.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

3. Does the FDA agree that the clinical pharmacology and pharmacometric package, including exposure-Pd, exposure-efficacy and exposure-safety analyses is acceptable to support the filing of a marketing application for the proposed indication under the accelerated approval provisions of 21 CFR 314 subpart H?

FDA Response: FDA agrees that the proposed clinical pharmacology and pharmacometrics data package would support submission of a potential NDA. However, see clinical pharmacology additional comment 19. The adequacy of the

data in support of filing the NDA and labeling will be determined during the NDA review.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback; please also refer to the Company response for FDA Additional Comment 19.

Discussion during the May 4, 2020 meeting: No discussion occurred.

4. Does the FDA agree that a simple stability update may be submitted during the course of the NDA review?

FDA Response: Yes, in addition to 12 months of long-term stability data and 6 months of accelerated stability data for three registration batches for the drug substance and drug product of each strength, the three drug product batches should be manufactured from at least two different drug substance batches. FDA will accept stability updated during the course of a potential NDA review. Data received 30-days after the original NDA submission will be reviewed as resources allow.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

5. With regard to the inclusion (b) (4) in the NDA:

   a. Does the FDA confirm their agreement (b) (4)

   FDA Response: (b) (4)

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

b. Does the FDA agree (b) (4)

FDA Response: (b) (4)

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

6. With regards to the planned assessment of ILD:

a. Does the FDA agree with the proposed Sponsor assessment of ILD cases?

FDA Response: Your proposal seems reasonable. In addition, you should retrieve cases based on the preferred terms (PT) pneumonitis, acute interstitial pneumonitis, and immune-mediated pneumonitis.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

b. Does the FDA agree with the selection of cases to be reviewed by the expert panel and the plan to submit the expert panel review analysis with the 90-day safety update report?

FDA Response: Yes.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

7. Does the FDA confirm their agreement with the revised ISS-SAP?

   FDA Response: Yes.

   Please also note that the ISS SAP Section 18.3 states, “Only subjects with any post-baseline laboratory values will be included in the safety evaluation of laboratory data. The last measurement before study treatment will serve as the baseline measurement.” Generally, we request that only patients with a baseline and at least one post-baseline measurement and at least one grade on-treatment worsening be included in the laboratory analyses table.

   EMD Serono’s response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

   Discussion during the May 4, 2020 meeting: No discussion occurred.

8. Does the FDA agree with the proposed integrated analyses cutoff date and content for the 90-day safety update report?

   FDA Response: See response to FDA Question 1.

   EMD Serono’s response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback; please also refer to the Company position in response to Question 1.

   Discussion during the May 4, 2020 meeting: FDA agrees and refers to the meeting discussion in Question 1.

9. Does the FDA agree with submitting an update of efficacy data together with the 90-day safety update report?

   FDA Response: See response to FDA Question 1.

   EMD Serono’s response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback; please also refer to the Company position in response to Question 1.

   Discussion during the May 4, 2020 meeting: FDA agrees and refers to the meeting discussion in Question 1.

10. Does FDA agree with the plan for submission [redacted]?

FDA Response: [redacted]

[redacted]

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback and confirms discussions [redacted] are ongoing. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

11. Does the FDA agree with the proposed rolling submission?

FDA Response: See response to Question 1 regarding the acceptability of your data for submission.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback; please also refer to the Company position in response to Question 1.

Discussion during the May 4, 2020 meeting: Refer to meeting discussion in Question 1.

12. Does the FDA agree with the proposed content of the Study Data Standardization Plan?

FDA Response: Electronic study data files are required for adequate FDA review of all studies (pre-clinical, clinical pharmacology and clinical), provided in

the NDA submission. The lack of relevant data sets would represent an NDA filing issue. Please see additional clinical pharmacology comments 19 and 20.

EMD Serono's response received via email on April 30, 2020: EMD Serono confirms that for all relevant studies (pre-clinical, clinical pharmacology and clinical), which were initiated after December 2016, standardized study data will be provided as per previous discussion with the Agency (reference the Type C Written Response Only feedback received September 25, 2019, Reference ID 4497312).

Electronic study data for the clinical studies EMR200095-001, EMR200095-002, EMR200095-003, EMR200095-004, EMR200095-005, EMR200095-006, EMR200095-007 and EMR200095-012 will be included in the integrated analysis datasets for the ISS (in CDISC ADaM format) and/or Pop-PK analysis (ASCII / SAS transport files), as detailed in the Study Data Standardization Plan (SDSP). No individual electronic study data files are planned to be submitted for these studies. Study-level SDTM and ADaM packages will be provided for all other clinical studies included in the NDA submission: MS200095-0022 (01-Jan-2020 cut-off), MS200095-0028, MS200095-0030, MS200095-0032, MS200095-0038, MS200095-0039, MS200095-0044.

Discussion during the May 4, 2020 meeting: FDA recommends submission of individual electronic study data files for studies EMR200095-001 and EMR200095-007. The proposed plan for other clinical pharmacology studies appears acceptable but additional files might be requested during the course of NDA review. FDA reiterated the preliminary comments and acknowledges that ADaM data may not be available prior to Dec 2016. However, SDTM data sets will be submitted.

13. Does FDA agree with the proposed plan regarding the submission of BIMO data?

FDA Response: Your specified plan is acceptable. Please refer to detailed OSI requests as listed below for BIMO data submission.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

14. Does FDA agree that based on the available safety information from the studies included in the ISS (i.e., 152 patients in VISION cohorts A + C and 373 patients in the POOL, treated with 500 mg tepotinib monotherapy, as well as additional 194 patients treated with other tepotinib dose strengths or in combination with gefinitib), that submission of a Risk Evaluation and Mitigation Strategy (REMS) will not be required for the NDA submission (considering that EMD Serono's

proposed risk management strategy does not include a Medication Guide as part of the US product labeling)?

FDA Response: This proposal is acceptable. Also see response to Question 1 regarding the acceptability of your data for submission.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: There was no additional discussion. Refer to the discussion in Question 1.

15. Does FDA agree with the proposed Formal Communication Plan?

FDA Response: Yes.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion during the May 4, 2020 meeting: No discussion occurred.

16. EMD Serono considers the overall content and strategy meets the criteria to support the NDA submission. Does FDA agree?

FDA Response: No. See response to Question 1.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback; please also refer to the Company position in response to Question 1.

Discussion during the May 4, 2020 meeting: Refer to the discussion in Question 1.

17. Does FDA agree with the proposals outlined in the briefing package?

FDA Response: Please see FDA responses and additional comments in this preliminary response.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback; please also refer to the Company position in response to Question 1.

Discussion during the May 4, 2020 meeting: Refer to the discussion in Question 1.

ADDITIONAL COMMENTS

CMC

18. Section 4 of the meeting package suggests that the proposed strength representation for the drug product (b) (4) This strength representation is not consistent with current salt nomenclature practices. FDA refers you to The Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations (USP <1121>) and the FDA Guidance for Industry: "Naming of Drug Products Containing Salt Drug Substances" found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf
In the original NDA submission, include drug product labeling that complies with current nomenclature practices.

EMD Serono's response received via email on April 30, 2020: The drug substance of the medicinal product is tepotinib hydrochloride hydrate and the active moiety is tepotinib. EMD Serono, Inc. intends to represent the strength in the product label based on Example 1 in Appendix 2 of the referenced guidance as follows:
Each tablet contains:
Tepotinib.....225mg
(equivalent to 250 mg Tepotinib Hydrochloride Hydrate)

Discussion during the May 4, 2020 meeting: FDA acknowledges that EMD Serono will follow the established nomenclature practices for salt drug substances in drug products as described in the above guidance.

Clinical Pharmacology

Regarding the data standardization plan:

19. Per the Data Standardization Plan, electronic study data files will not be provided as part of the NDA submission for multiple clinical pharmacology studies which are identified as part of the clinical pharmacology data package. Electronic study data files are required to enable adequate FDA review of all studies relevant to the clinical pharmacology data package. The lack of relevant data sets might represent an NDA filing issue.

EMD Serono's response received via email on April 30, 2020: EMD Serono acknowledges the FDA feedback; please also refer to the Company position in response to Question 12 above.

Discussion during the May 4, 2020 meeting: Refer to the discussion under Question 12.

20. Please refer to the IRT website for additional information regarding QT data submission. When you submit your QT evaluation report, please include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt).

EMD Serono's response received via email on April 30, 2020: An integrated exposure-QTc analysis plan was submitted for QT-IRT review and was found reasonable to characterize the effect of tepotinib and its main circulating metabolite on the QT/QTc interval (reference IND 128073 Serial Number 0145 submitted on October 17, 2019 and the FDA feedback received February 6, 2020, Reference ID 4557437; further reference is made to the feedback received via email on February 13, 2020 in response to clarifying questions submitted on February 11, 2020). A further exposure-QTc analysis has been conducted for the pivotal VISION trial.

We confirm as part of the submission package we will provide the completed QT Evaluation Report Submission Checklist. This will include references to:

- The ADaM-like pooled dataset that contains the data of the four studies used in the integrated QT analysis, and accordingly for the QT analysis of the VISION trial. Since the analysis was ongoing at the time of publication of the FDA guidance "*Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs*" (June 2019), the datasets are not fully compliant with the format described therein. The ADaM-like pooled datasets contain the data that are expected in the ADEG, ADPC and ADSL datasets according to the FDA guidance. The CDISC ADaM principles have been closely but not fully applied, and the datasets are not strictly conformant with CDISC ADaM standards as laid down in the ADaM implementation Guide 1.1. The package will contain a define.pdf and the datasets. To maintain traceability of the analyses, we propose not to change the format. This had been previously communicated to FDA (reference the Type C Written Response Only feedback received September 25, 2019, Reference ID 4497312), and no objection was received.

- Scans of the source paper ECGs from study EMR200095-001 and information about the ECG devices used. This follows recommendation 1 of the QT-IRT feedback (reference the FDA advice received February 6, 2020, Reference ID 4557437).

- Overview and raw data files from relevant non-clinical studies pertinent to the QT evaluation.

Discussion during the May 4, 2020 meeting: EMD Serono's QT data submission plan appears acceptable; the adequacy of the QT assessment will be determined during NDA review.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed during this meeting. In addition, we note that a chemistry pre-submission meeting was held on January 28, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a risk evaluation and mitigation strategies (REMS). Refer to FDA's response to question 14.

- Regarding the agreement for content of a complete application, the sponsor will consider the discussion in question number 1 and decide on the mechanism for submission (i.e., rolling submission or RTOR).

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020,

contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[3]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[4] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[5]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and

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[4] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[8]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[9]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[10]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and

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[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[10] 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.

DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated

Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications.[11]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[12]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[13]

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
None

[11] https://www.fda.gov/media/85061/download
[12] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[13] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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/

STACIE A WOODS
05/29/2020 02:27:26 PM

IND 128073

MEETING REQUEST-
WRITTEN RESPONSES

EMD Serono Research and Development Institute
Attention: Virginia Pappalardo, M.S., RAC
Director, Global Regulatory Affairs, Immuno-Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Pappalardo:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tepotinib.

We also refer to your submission dated February 27, 2020, containing a meeting request. The purpose of the requested meeting was to discuss and obtain feedback regarding the sufficiency of the proposed nonclinical data package to support a proposed New Drug Application (NDA) for tepotinib.

Further reference is made to our Meeting Granted letter dated March 3, 2020, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 27, 2020, background package.

[1] 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.

If you have any questions, call me at 301-796-4803.

Sincerely,

{See appended electronic signature page}

Stacie Woods, Pharm.D.
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases 2
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA (nonclinical)

Application Number: 128073

Product Name: tepotinib

Indication: for the treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition factor gene (*MET*) exon 14 (*MET*ex14) skipping alterations (b) (4)
Sponsor: EMD Serono Research & Development Institute Inc.
Regulatory Pathway: 505(b)(1)

BACKGROUND

Tepotinib is a reversible ATP- competitive inhibitor of the mesenchymal-epithelial transition factor (c-MET). EMD Serono states that the nonclinical safety testing strategy includes proof-of concept pharmacology studies, safety pharmacology studies, non-clinical pharmacokinetic studies, genotoxicity studies (in vitro and in vivo), phototoxicity tests, as well as studies on the major circulating human metabolite of tepotinib, MSC2571109A (in vitro and in vivo activity, in vitro safety pharmacology, and genotoxicity), and GLP-compliant repeat-dose toxicology studies of up to 26 and 39 weeks in rats and dogs, respectively. EMD Serono states that it also included a 28-day study in rats used to identify the MTD and plasma levels of MSC2571109A based on feedback from the FDA in the July 11, 2017 Type C meeting response due to lack of exposure or the use of the maximum tolerated dose or highest feasible dose in previous toxicology studies. EMD Serono states that two preliminary embryo-fetal development (EFD) study in rabbits showed evidence of teratogenicity at doses below doses that resulted in maternal toxicity; FDA agreed in the July 11, 2017 meeting correspondence that no additional EFD studies were needed. Carcinogenicity, fertility, and pre- and postnatal studies are not planned due to the intended patient population.

EMD Serono conducted all pivotal repeat-dose toxicity studies with (b) (4) drug substance, except for the last 4-week repeat-dose toxicity study in rats and a 14-day bridging study and the 39-week study in dogs, which were performed using (b) (4) drug substance. Use of the (b) (4) drug substance achieved exposure at the MTD or highest tested dose of 31% and 83% for total Cmax and 18% to 73% for total AUC, respectively, in rats and dogs as compared to human values at the clinical dose of 500 mg. In studies using the (b) (4) drug substance, total Cmax and total AUC values at the MTD or highest tested dose in rats and dogs were respectively in the

range of 4% to 12%, and 3% to 8%, respectively, compared to human values at the dose of 500 mg. EMD Serono states that when considering the differences in protein binding, the achieved exposure in rats and dogs at the MTD with (b) (4) drug substance was comparable or even slightly higher than that in human.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the nonclinical package, as proposed, is adequate to support the NDA filing?

   FDA Response: Yes, FDA agrees that the nonclinical package, as proposed, appears sufficient to support filing of an NDA. Final determination of the acceptability of the data to support a marketing application will be determined following review of the reports included in the original NDA submission.

2. In the FDA Type C Written Response Feedback (July 2017, Reference ID 4154974), the Agency requested further clarification on certain aspects of the nonclinical package (please see details in the Sponsor Position below). Does the Agency agree the clarifications provided are satisfactory?

   FDA Response: Yes, FDA agrees that the clarifications provided appear sufficient. Final determination of the data from these studies to support a marketing application will be determined following review of the reports included in the original NDA submission.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of

relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

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- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review

[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[9]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

[9] 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.
[10] https://www.fda.gov/media/85061/download

- RTOR[11]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[12]

[11] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[12] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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/

STACIE A WOODS
04/13/2020 09:09:14 AM

IND 128073

MEETING REQUEST-
WRITTEN RESPONSES

EMD Serono Research and Development Institute
Attention: Kathleen Andrade
Senior Manager, Global Regulatory Affairs, Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Andrade:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MSC2156119J, Tepotinib.

We also refer to your submission dated August 9, 2019, containing a meeting request. The purpose of the requested meeting was to obtain the Agency's guidance on product comparability to support introduction of a new product formulation during generation of confirmatory evidence.

Further reference is made to our Meeting Granted letter dated August 28, 2019, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your background package.

If you have any questions, call Shamika P. Brooks, PharmD, Regulatory Business Process Manager at 301-796-2888.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	Type C WRO
Meeting Category:	Pre-NDA
Application Number:	IND 128073
Product Name:	MSC2156119J, Tepotinib
Indication:	The treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors harbor *MET* exon 14 skipping alterations (*MET*ex14).
Applicant Name:	EMD Serono Research and Development Institute
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

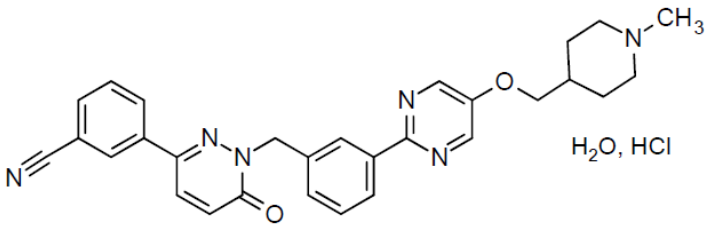
On July 12, 2019, EMD Serono Research and Development Institute submitted a meeting request to DOP2 for an OND Led meeting. On July 30,2019, the agency requested that the meeting be separated into a clinical and CMC meeting.

On August 9, 2019, EMD Serono Research and Development Institute submitted a Type C WRO meeting request for specific questions from the July 12 meeting request. The agency agreed to maintain the original WRO response date of September 25, 2019. The purpose of this meeting is to seek Agency input on product comparability to support introduction of a new product formulation during generation of confirmatory evidence.

The submission reports that MSC2156119J, Tepotinib is a reversible, Class I adenosine triphosphate (ATP)-competitive inhibitor of the receptor tyrosine kinase mesenchymal-epithelial transition factor (MET) for the treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors harbor *MET* exon 14 skipping alterations (*MET*ex14).

Tepotinib is a white to off-white powder and is very slightly soluble in water and practically insoluble in simulated gastric fluid and simulated intestinal fluid. The drug substance is (b) (4) used to manufacture clinical supplies (Tablet Formulation 2 – TF2 available in 100 mg and 500 mg strengths) and the intended commercial supplies (Tablet Formulation 3 – TF3 available in 100 mg and 250 mg strengths). The two tablet formulations differ slightly quantitatively and qualitatively. Both formulations are manufactured (b) (4) though TF3 is manufactured (b) (4)

[redacted](b) (4) TF2 and TF3 are film coated immediate release tablets.



$C_{29}H_{28}N_6O_2$ HCl H_2O
MW = 547.05 g/mol

Clinical Pharmacology Background:

A bioequivalence study (MS200095-0044) was conducted to evaluate the bioequivalence (BE) between TF2 and TF3 after a single 500 mg dose under fasted conditions, as well as the effect of food of TF2 and TF3 in separate arms in the same trial. A pooled BE analysis was performed to evaluate the BE between TF2 and TF3 under fasted and fed conditions. In the pooled analysis, the confidence interval of the geometric mean ratio of TF3/TF2 appears to be within 80-125%, showing BE for both conditions.

A change in the dose modification plan was proposed to allow for the recommended dose reduction level from 300 mg to 250 mg, i.e., to 1 tablet of the 250 mg TF3 dose strength rather than 3 tablets of the 100 mg TF3 dose strength. A translational PK/PD model was developed by EMD to justify the new dose modification plan. The simulation shows that after administration of either 300 mg or 250 mg dose levels, the target pharmacodynamic (PD) threshold is maintained in close to 90% of the total population. When considering the overall PK variability of tepotinib, there appears to be no clinically relevant difference between the 300 mg and 250 mg dose levels (approximately 20% change in exposure). In addition, EMD's pooled safety analysis across completed and ongoing clinical studies with 500 mg tepotinib QD, shows that dose reductions due to treatment emergent adverse events (TEAEs) were reported to occur in only 14.5% of patients.

2.0 QUESTIONS AND RESPONSES

Question 1a: Does the FDA agree that the Sponsor will administer the commercial product (Tablet Formulation 3) to patients enrolled in part 1 (Cohort A and Cohort B) as well as the confirmatory part 2 (Cohort C) of the VISION study (MS200095-0022)?

FDA Response to Question 1a: **FDA agrees with the proposal to administer the new commercial product (Tablet Formulation 3) to patients enrolled in part 1 (Cohort A and Cohort B) and part 2 (Cohort C) of the VISION study (MS200095-0022).**

Question 2: The Sponsor proposes to use 250 mg TF3 for dose modification in the ongoing VISION study (MS200095-0022).

FDA Response to Question 2: **FDA agrees that the dose modification plan appears acceptable based on EMD's reported dose reduction frequency across clinical studies of 14.5% for TEAEs at the 500 mg QD dosage. In addition, the proposal appears acceptable based on the less than 20% change (300 mg vs. 250 mg) for the initial dose reduction step in the proposed dose modification plan.**

Additional Comments:

1. **FDA refers you to the IND 106103 Type C CMC-only meeting conducted May 10, 2017 that discussed the selection of drug substance starting materials. The current IND submission does not address advice given during that meeting.**

2. **Identification testing is critical for drug product release. Refer to ICH Q6A for a discussion of this quality attribute. The identification test should include either one specific test, or two non-specific tests which are orthogonal to each other. The use of chromatographic retention time and UV absorbance maximum is not specific for determining identity. IR spectra or complete UV spectra obtained from HPLC/photodiode array testing may be appropriate, although other absolute tests may be used.**

3. **With regards to nomenclature of the product under development and strength representation, FDA refers you to The Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations (USP <1121>) and the FDA Guidance for Industry: "Naming of Drug Products Containing Salt Drug Substances" found at the link below. Confirm the strength representation in the product label and manufacturing process (batch formula, composition tables, and assay calculations) comply with the current practice described in the guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf**

4. **Refer to ICH Q1A(R2) and PDUFA VI for drug substance and drug product stability data needed at the submission of the original NDA.**

5. **The FDA has the following recommendations regarding the dissolution information (method and acceptance criterion) that should be provided in the submission.**

   a) **<u>Dissolution Method</u>: Provide in your submission the dissolution method development report supporting the selection of the proposed dissolution test evaluating the proposed drug product. Include the following information in the dissolution method development report:**

      1) **Solubility data of the drug substance over the physiologic pH range.**

      2) **Detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the apparatus, media, rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc.). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. Clearly specify the testing conditions associated with each method development study. The dissolution profile should be complete or whenever a plateau is reached (i.e., no increase over 3 consecutive time-points). It is recommended the use of at least twelve dosage units per testing variable and sampling time points (e.g., 10, 15, 20, 30, 45 60 min, etc.).**

      3) **Data supporting the discriminating ability of the selected dissolution method. In general, ensure that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± (b) (4) % change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.**

      4) **A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution.**

      5) **Supportive validation data for the dissolution methodology (bench testing) and analytical method used for assaying the dissolution samples (specificity, precision, accuracy, linearity/range, stability,**

robustness, etc. For general recommendations on method validation, refer to the USP Chapters "The Dissolution Procedure: Development and Validation" <1092> and "Validation of Compendial Methods" USP Chapter <1225>.

6) **Complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim). For the submission of the dissolution data, refer to data presentation below.**

b) **<u>Dissolution Acceptance Criterion:</u> For the selection of the dissolution acceptance criterion of the proposed drug product, consider the following:**

1) **Use the multi-point dissolution data from the clinical/PK drug product-batches and primary registration batches (throughout the stability program) for the setting of the dissolution acceptance criterion of the proposed drug product (i.e., sampling time points and limits).**

2) **Ensure that the in vitro dissolution profile is complete or if incomplete dissolution occurs, where the plateau of drug dissolved is reached (i.e., no increase over 3 consecutive time-points).**

3) **Base the dissolution acceptance criterion on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).**

4) **Select the sampling time point where Q = (b)(4) % dissolution occurs. However, if the drug product is a slow dissolving product, setting of acceptance limits at two or more sampling time points may be adequate. The first time point should include a dissolution range (e.g., (b)(4) % dissolution at 20 minutes) and the second time point should be where Q = (b)(4) % dissolution occurs.**

5) **Include a detailed discussion of the justification of the proposed dissolution acceptance criterion in the appropriate section of the eCTD.**

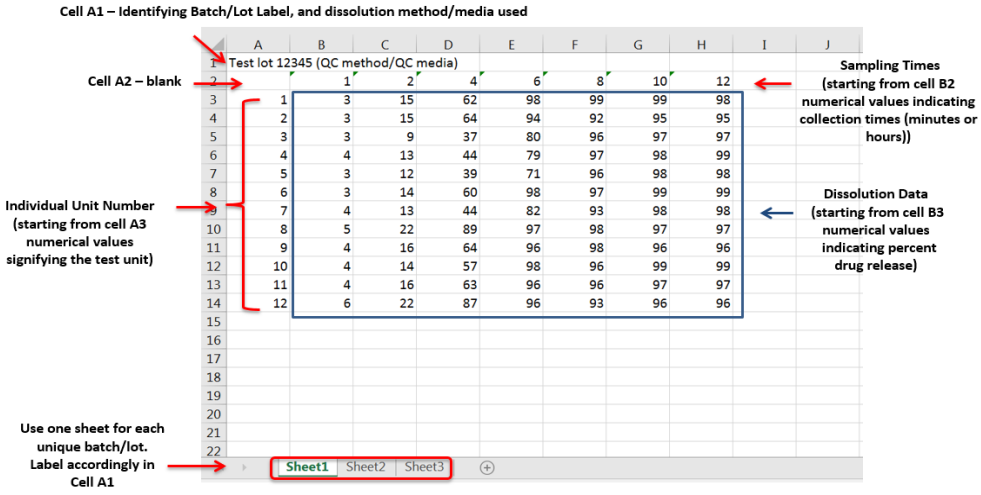
c) **<u>Dissolution Data Presentation:</u> In the dissolution method development report, present detailed experimental dissolution data as follows:**

1) **In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.**

2) **In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.**

3) **Provide in the NDA the dissolution data as described in the example below.**

Example - Reporting of individual vessel dissolution data



	A	B	C	D	E	F	G	H
1	Test lot 12345 (QC method/QC media)							
2		1	2	4	6	8	10	12
3	1	3	15	62	98	99	99	98
4	2	3	15	64	94	92	95	95
5	3	3	9	37	80	96	97	97
6	4	4	13	44	79	97	98	99
7	5	3	12	39	71	96	98	98
8	6	3	14	60	98	97	99	99
9	7	4	13	44	82	93	98	98
10	8	5	22	89	97	98	97	97
11	9	4	16	64	96	98	96	96
12	10	4	14	57	98	96	99	99
13	11	4	16	63	96	96	97	97
14	12	6	22	87	96	93	96	96

Follow the instructions provided in "Specifications for File Format Types Using eCTD Specifications" – updated March 2, 2017 (link below). https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf

3.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you

must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/

ANAMITRO BANERJEE
09/12/2019 10:29:00 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128073

MEETING MINUTES

EMD Serono Research and Development Institute
Attention: Kathleen Andrade
Senior Manager, Global Regulatory Affairs, Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Andrade:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tepotinib (MSC2156119J).

We also refer to the meeting between representatives of your firm and the FDA on August 8, 2018. The purpose of the meeting was to discuss the proposed data intended to support the submission of a marketing application seeking accelerated approval of tepotinib for the treatment of patients with (b) (4) metastatic (b) (4) non-small cell lung cancer who have MET exon 14 skipping alterations (METex14).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Rebecca Cohen, R.N., M.P.H., O.C.N.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
EMD Serono Slide Deck

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: Wednesday, August 8, 2018, 12:30 PM-1:30 PM (EST)
Meeting Location: WO 22 RM 1421

Application Number: 128073
Product Name: Tepotinib (MSC2156119J)

Indication: For the treatment of patients with (b) (4) metastatic (b) (4) non-small cell lung cancer (NSCLC) who have MET exon 14 skipping alterations (METex14)

Sponsor/Applicant Name: EMD Serono Research and Development Institute

FDA ATTENDEES (tentative)

Patricia Keegan	Division Director, OHOP/DOP2
Erin Larkins	Clinical Team Lead, OHOP/DOP2
Barbara Scepura	Clinical Reviewer, OHOP/DOP2
Whitney Helms	Nonclinical Team Lead, OHOP/DHOT
Elizabeth Spehalski	Nonclinical Reviewer, OHOP/DHOT
Hong Zhao	Clinical Pharmacology Team Lead, OHOP/DCPV
Edwin Chow	Clinical Pharmacology Reviewer, OHOP/DCPV
Pallavi Mishra-Kalyani	Statistics Team Lead, OB/DBVI
Rebecca Cohen	Regulatory Project Manager, OHOP/DOP2

SPONSOR ATTENDEES

Donna Supko	Global Head Regulatory Affairs R&D
Georgios Amexis	Global Regulatory Affairs Lead
Kathleen Andrade	US Regulatory Affairs
Juergen Scheele	Medical Lead
Andreas Johne	Medical Expert
Karin Berghoff	Drug Safety Lead
Ilhan Celik	Program Lead
Patrice Verpillat	Epidemiologist
Josef Straub	Biomarker expert
Mark Walker	External expert – epidemiologist
Tim Demuth	Clinical Oncology
Alise Reicin Boiarsky	Global Clinical Development Expert
Armin Schueler	Biostatistics

BACKGROUND

Regulatory

On May 31, 2018, EMD Serono Research and Development Institute (EMD Serono) requested a meeting to discuss and seek FDA feedback on the data intended to support the proposed submission of a marketing application seeking accelerated approval of tepotinib for the treatment of patients with (b) (4) metastatic (b) (4) non-small cell lung cancer (NSCLC) who have MET exon 14 skipping alterations (METex14). The marketing application will rely primarily on the results from the VISION trial (Protocol ID MS200095-0022, entitled "A Phase II single-arm trial to investigate tepotinib in stage IIIB/IV adenocarcinoma of the lung with MET exon 14 (METex14) skipping alterations or MET amplification"). On June 12, 2018, FDA issued a letter granting the Type B meeting.

The proposed indication is:

> *Tepotinib is indicated for the treatment of patients with (b) (4) metastatic (b) (4) (b) (4) non-small cell lung cancer (NSCLC) whose tumors harbor MET Exon 14 skipping alterations (METex14).*

The clinical development for tepotinib was initiated in the U.S. under IND 106103.

On November 16, 2015, a pre-IND/end-of-Phase 2 meeting was held to discuss the clinical development program of tepotinib in support of two proposed indications:

- The proposed indication (b) (4) will be supported by the results of Study (b) (4) The design of a planned confirmatory trial was also discussed.
- The proposed indication (b) (4) will be supported by the results of Study (b) (4)

On February 11, 2016, IND 128073 was submitted to FDA for development of tepotinib (b) (4) The IND was allowed to proceed on March 11, 2016.

On March 18, 2016, FDA issued a letter containing the following advice:

- "We recommend that EMD Serono request a meeting to further discuss the clinical development plan for tepotinib in advanced non-small cell lung cancer, including plans for

confirmation of clinical benefit if the results of Study MS200095-0022 will be used to support accelerated approval.

- In the proposed protocol, consider including an exploratory exposure-response analysis for tepotinib and its active metabolites, if any, for measures of effectiveness, toxicity and pharmacological responses including pharmacodynamic biomarkers. Refer to the FDA Guidance for Industry entitled "Exposure-Response Relationships – Study Design,Data Analysis, and Regulatory Applications" found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.
- During the development of tepotinib, provide the calculated R values or ratios of the mean steady-state concentrations to the 50% maximal inhibitory concentration (IC_{50}) or to the enzyme inhibition constant K_i to determine the need for clinical pharmacokinetic drug interaction studies for Pgp, BRCP and OCT1. Refer to the FDA Draft Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf."

On May 9, 2017, FDA provided advice regarding archiving of tumor samples in Study EMR200095-022 and recommendations regarding the (b) (4)

On September 19, 2017, FDA issued Written Responses Only meeting minutes for a Type C meeting seeking FDA's feedback regarding the acceptability of the clinical pharmacology and nonclinical plans to support future marketing applications for the treatment of patients with (b) (4) (b) (4) harboring MET exon 14 (METex14) alterations and for the treatment of patients with (b) (4)

On February 5, 2018, FDA sent an electronic mail (e-mail) communication, providing clarification of a typographical error in the September 19, 2017 minutes and making the following request: Include net flux ratios for tepotinib and its active metabolite MSC2571109A as substrates for renal transporters MATE1, and MATE2K, to be compliant with the latest FDA draft drug interaction guidance entitled "In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies," available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf.

On March 5, 2018, a teleconference was held with EMD Serono to discuss the potential for breakthrough therapy designation (BTD). At that time, 31 patients had been treated, with 19 patients evaluable for response. The overall response rate (ORR) for the 19 evaluable patients was 58% (95% CI 34-80%). FDA informed EMD Serono that, given the small number of patients and limited duration of follow-up, a request for BTD was premature. FDA recommended that EMD Serono submit another request for preliminary BTD advice when they have data on approximately 30 patients and all responders (confirmed durable for ≥4 weeks) have been followed for at least 6 months from the onset of response. In such a future request for preliminary BTD advice, (1) the ORR results should be provided by line of therapy (1st line, 2nd

line, and 3rd line) with data for at least 10 evaluable patients per group with a minimum of 6 months of follow-up for responders from the onset of response; (2) the proportion of responders with duration of response ≥6 months (and if applicable ≥9 months and ≥12 months) based on observed durations of response rather than Kaplan-Meier estimates should be included; and (3) the request should contain characterization of the therapeutic and prognostic implications of METex14 skipping alterations in NSCLC. This should include any available information from clinical studies and the literature, regarding expected response to available standard therapy and the natural history of disease for these patients.

On May 24, 2018, EMD Serono cancelled the meeting scheduled for May 30, 2018, to discuss the bioequivalence study in a fed state that would support switching from formulation TF2 to TF3 at the time of commercialization without prior evaluation of TF3 in the ongoing VISION trial (MS200095-0022). This cancellation was based on the clarity of FDA's preliminary responses to the posed questions, issued to EMD Serono on May 22, 2018.

Nonclinical

Tepotinib is a reversible, ATP- competitive inhibitor of the mesenchymal-epithelial transition factor (c-MET). EMD Serono states that they have conducted repeat-dose toxicity studies in rats and dogs at durations up to 26 and 39 weeks, respectively, genotoxicity and phototoxicity studies, and two pilot embryo-fetal development studies in rabbits. In the Investigator Brochure, EMD Serono states that in the pilot embryo-fetal development studies, maternal deaths were observed at ≥50 mg/kg tepotinib per day, abortions observed at 0.5 mg/kg/day, and fetal malformations observed at ≥5 mg/kg/day. EMD Serono does not plan to conduct any additional embryo-fetal development studies or prenatal and postnatal development and carcinogenicity studies due to the intended indication of tepotinib in patients with advanced cancer.

Clinical

The prevalence of METex14 alterations across NSCLC histologies is approximately 3%. Approximately 15% of METex14 skipping alterations have concomitant MET gene amplification; however, MET amplification also occurs in the absence of METex14 skipping alterations. Both METex14 skipping alterations and MET amplifications appear to be equally distributed between gender and race. METex14 skipping alterations and MET amplifications are found more frequently in patients in their seventh decade and in those with a smoking history.

<u>VISION</u>
The VISION study, entitled "A Phase II single-arm study to investigate tepotinib in advanced (Stage IIIB/IV) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations", was initially designed as a single-arm, activity-estimating study in patients with Stage IIIB/IV non-small cell lung cancer (NSCLC) harboring MET exon 14 (METex14) skipping alterations. Patients received tepotinib 500 mg orally daily until disease progression or unacceptable toxicity.

The protocol was most recently amended (protocol version 5.0) and submitted to the IND on May 17, 2018. The revised protocol now includes an updated title (MET amplifications) and a new cohort (cohort B) enrolling patients with MET amplification, as shown below.

The amended protocol cohorts are:

Cohort A (METex14 skipping alterations)
Cohort A will consist of patients who tested positive for METex14 skipping alterations, regardless of MET amplification status

There are three primary analysis sets for Cohort A are:
- Tumor biopsy (TBx) or liquid biopsy (LBx) analysis set will include all patients who tested positive for METex14 skipping alterations irrespective of testing methodology
- The LBx analysis set will include all patients who tested positive for METex14 skipping alterations in plasma circulating tumor DNA (ctDNA)
- The TBx analysis set will include all patients who tested positive for METex14 skipping alterations in tumor tissue

Patients who tested positive in tumor tissue biopsy (TBx) and in plasma (Liquid Biopsy) (LBx) will be assigned to both analysis sets.

The primary endpoint will be independently reviewed ORR, the key secondary endpoints will be duration of response, disease control rate, progression free survival and overall survival. EMD Serono proposes that efficacy be evaluated when all enrolled patients have completed at least 12 months of follow-up. Approximately 70-90 patients are anticipated to be enrolled to ensure inclusion of at least 60 patients with METex14 skipping alterations by TBx or LBx; patients will be included in both analysis sets (TBx and LBx) if both tests are positive.

Since VISION is a single-arm study, EMD Serono proposes two methods to estimate effectiveness.

- Method 1 is to use external historical data from US databases to identify 30-40 patients with METex14 skipping alteration-positive NSCLC, regardless of treatment.
- Method 2 is to use the previous efficacy outcomes (i.e.,prior-line best-overall response (BOR) and PFS) in patients enrolled in VISION receiving tepotinib as 2nd (N=20-30) or 3rd line (N=20-30) treatment as the comparator for efficacy outcomes for patients receiving tepotinib as 1st line treatment in VISION

Cohort B (MET amplification)
Cohort B will consist of patients who tested positive for MET amplification and negative for METex14 skipping alterations.
There will be one primary analysis set for Cohort B:
- The LBx analysis set will include all patients who tested positive for MET amplification in plasma ctDNA irrespective of the tumor biopsy result

Two TBx analysis sets will be explored as well:
- Patients with gene copy number (GCN) gain of ≥ 4 and < 6 irrespective of LBx test result
- Patients with GCN gain of ≥ 6 irrespective of LBx test result.

At least 60 patients will be enrolled in Cohort B. The expected ORR is 40-50%. With at least 60 patients, the lower-bound of the Clopper-Pearson 95% CI will exceed 27.6% if the ORR is 40% or greater.

Preliminary results (Cohort A)
As of March 23, 2018, (cut-off for the data analysis presented in the briefing package submitted June 20, 2018), 1860 patients with NSCLC have been pre-screened for METex14 tumor status identifying 47 patients (2.5%) with METex14-positive NSCLC for participation on the VISION study. A total of 38 of these patients were treated with tepotinib as a single agent. EMD Serono states in the briefing package that, among these 38 patients, 82% had METex14 alterations identified in tumor tissue, 60% had METex14 alterations identified in plasma, and 45% had METex14 alterations identified in both plasma and tumor tissue. Demographic and other baseline variables were provided for the 38 patients enrolled but not the "efficacy evaluable" population.

EMD Serono provided efficacy results for an "efficacy evaluable" subgroup of 28 patients, comprising 74% of those enrolled in Cohort A. Twenty-two patients remain on treatment.

The table below is abstracted from the briefing package and presents ORR as assessed by independent review for the 28 patients enrolled in the VISION trial who received at least one

dose of tepotinib and had at least two post-baseline assessments or who discontinued for treatment prior to two post-baseline assessments for any reason.

Table 3 Efficacy: Overall Response by RECIST v1.1 - Independent Review*

Tepotinib 500 mg	L+ (n = 16)	T+ (n = 26)	Combined (T+ or L+) (N=28)
Best overall response, n (%)			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	9 (56.3)	11 (42.3)	12 (42.9)
Stable disease	2 (12.5)	6 (23.1)	6 (21.4)
Progressive disease	3 (18.8)	5 (19.2)	5 (17.9)
Non-evaluable	2 (12.5)	4 (15.4)	5 (17.9)
Objective response rate, n (%) [95% CI]	**9 (56.3) [29.9, 80.2]**	**11 (42.3) [23.4, 63.1]**	**12 (42.9) [24.5, 62.8]**
Objective response rate, n/N (%) by line of therapy, [95% CI]			
First-line	3/6 (50.0) [11.8, 88.2]	2/8 (25.0) [3.2, 65.1]	3/9 (33.3) [7.5, 70.1]
Second-line	3/4 (75.0) [19.4, 99.4]	5/8 (62.5) [24.5, 91.5]	5/9 (55.6) [21.2, 86.3]
Second or later line	6/10 (60.0) [26.2, 87.8]	9/18 (50.0) [26.0, 74.0]	9/19 (47.4) [24.4, 71.1]
Third or later line	3/6 (50.0) [11.8, 88.2]	4/10 (40.0) [12.2, 73.8]	4/10 (40.0) [12.2, 73.8]
Median duration of response (months, Kaplan-Meier estimate), [95% CI]	12.4 [3.71, 12.39]	12.4 [2.79, 15.74]	12.4 [2.79, 15.74]
Disease control rate, n (%) [95% CI]	11 (68.8) [41.3, 89.0]	17 (65.4) [44.3, 82.8]	18 (64.3) [44.1, 81.4]

* The efficacy analysis is restricted to patients who had at least two post-baseline assessments or who have discontinued treatment for any reason

L+ plasma
T+ tumor tissue

In the VISION study, the most frequent treatment emergent adverse events (TEAE) on the VISION study were peripheral edema (34%) and diarrhea (26%). Asymptomatic laboratory abnormalities included Grade 3 amylase (5.3%) and lipase (2.6%) elevations. Serious AE were interstitial lung disease, pneumonia, generalized edema, asthenia and dizziness.

Planned Safety Database to Support the Proposed NDA

EMD Serono reports that, at the time of the NDA submission, EMD Serono anticipates having safety data from approximately 450 patients. Table 6 is copied from the submission, and lists the number of tepotinib-treated patients by study as of the March 23, 2018 data cut-off.

Table 6 Overall subject exposure in tepotinib program (cut off 23rd March 2018)

Indication (Protocol)	Number of subjects	
	Tepotinib	Comparator
Solid tumors (EMR 200095-001)	149	-
Healthy volunteers (EMR 200092-002)	28	-
Solid tumors (EMR 200095-003)	12	-
1L HCC (EMR 200095-004)	72	44
2 L HCC (EMR 200095-005)	66	-
2L NSCLC (EMR 200095-006)	64	23
Healthy volunteers (EMR 200095-007)	27	-
Healthy volunteers (MS200095-0012)	24	-
2L METex14 NSCLC (MS200095-0022)	38	-
Total	**480**	**67**

Based on EMD Serono's breakdown of this population in the pre-meeting briefing package (below), there will be approximately 389 patients who received tepotinib as a single agent. EMD Serono stated that approximately half of the patients in the phase 2 trials and patients from regimen 3 in trial EMR200095-001 received tepotinib at the proposed dose for which approval will be sought (500 mg orally once daily).

- 90 patients with advanced or metastatic (stage IIIB/IV) NSCLC with MET exon 14 (METex14) skipping alterations receiving single agent tepotinib in single arm trials (MS200095-0022). EMD Serono anticipates that 70 patients will have exposure to tepotinib for ≥ 6 months and 50 patients with exposure of ≥12 months;
- 161 subjects with advanced solid tumors from US, Europe and Japan who received single agent tepotinib (EMR 200095-001 and 200095-003);
- 138 patients with HCC enrolled in US, Europe and Asia receiving single agent tepotinib (EMR 200095-004 and EMR 200095-005);
- 64 patients with NSCLC enrolled in Asia who received tepotinib in combination with gefitinib (EMR 200095-006).
- 79 healthy volunteers enrolled across three studies; healthy volunteers received between 1 and 3 doses of tepotinib.

Across 161 tepotinib-treated patients with solid tumors enrolled in completed trials, Studies EMR 200095-001 and 200095-003, the most frequent (>15%) TEAE were fatigue, decreased appetite, constipation, peripheral edema, nausea, vomiting, hypoalbumenia, and abdominal pain. The most frequent severe or life-threatening AEs (≥ Grade 3) were fatigue (7%) and pulmonary embolism (5%). Three patients (1.9%) permanently discontinued tepotinib due to TEAE; these were two patients with grade 4 increased lipase and one patient with grade 1 peripheral edema with grade 3 ALT increase. Of the two deaths on study, both were attributed to disease progression and not to tepotinib.

Across ongoing clinical trials, 4 deaths occurring on-study in trials of HCC (n=3) and NSCLC (n=1) were also attributed to disease progression and not to tepotinib.

Verification of Clinical Benefit

To confirm the clinical benefit of tepotinib, EMD Serono proposes (b) (4)

(b) (4)

The effectiveness of tepotinib will be assessed based on the events captured in the databases including:

- ORR
- DoR
- PFS
- time to next treatment
- death
- OS

The safety assessment will focus on a pre-defined list of selected adverse drug reactions of special interest. The results of this observational study on all included tepotinib-treated patients will be indirectly compared to the results from the historical control study performed to support the expedited approval and assess effectiveness of previous therapies considered as standard of care.

Companion Diagnostic

EMD Serono has held pre-submission meetings with the FDA to obtain input (b) (4) (b) (4)

On October 11th, 2017 (Q171331), FDA agreed that the design of the VISION study may support independent LBx and TBx claims if sufficient data will be generated with both LBx MRA and TBx MRA (subject to availability of material for the LBx CTA/LBx MRA and TBx CTA/TBx MRA bridging studies). FDA agreed that the isolated nucleic acid material tested for patient inclusion could be retested in the bridging study if its stability can be demonstrated.

The meeting package states that IDE approval has been granted for the OFA TBx assay and the GH360 LBx assay; the LC-SCRUM PCR test is not subject to IDE requirements.The data presented in the EMD Serono's Table 3 (above) were based on patients identified by LBx or TBx based testing.

Next generation sequencing tests used in the VISION study

Liquid / Plasma	Tumor Tissue
Guardant Health360v2.10 (GH360 LBx)	Oncomine Focus assay (OFA)
	Japanese Lung Cancer Consortium (LC-SCRUM)
	METex14 specific RT-PCR

Table 9 LBx and TBx CTAs for detection of METex14 skipping alterations

	LBx CTA: Guardant360 Health (G360v2.10)	TBx CTA: (OFA; ThermoFisher Scientific)	TBx CTA: LC-SCRUM Assay
Analyte	cfDNA	RNA	RNA
Specimen	Plasma	FFPE tissue	Fresh frozen tissue
Technology	NGS (Illumina)	NGS (Ion Torrent)	Real time PCR
Testing location	Central US laboratory	Central US laboratory	Central laboratory in Japan
Further details	IDE G170085	IDE G160111	n/a

Abbreviations:
LBx = liquid biopsy; CTA = clinical trial assay; TBx = tissue biopsy; OFA = Oncomine Focus Assay™; cfDNA; circulating cell-free DNA; FFPE = formalin-fixed paraffin-embedded; NGS = next generation sequencing; n/a = not available; IDE = investigational device exemption.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. Does the agency agree that clinical study MS200095-0022 (VISION study) in subjects with advanced stage IIIB/IV NSCLC whose tumors harbor METex14 skipping alterations will support an accelerated approval if the following conditions are met?

   The lower limit of the corresponding exact two-sided 95% confidence interval (CI; according to Clopper-Pearson) for ORR exceeds:
   - >30% in all patients
   - > 20% in 2L+ patients
   - >10% in 3L+ patients

   and durability of responses can be demonstrated across treatment lines.

   FDA Response:
   The evaluation of the clinical significance of the ORR and the adequacy of the data to support accelerated approval will consider the magnitude and duration of the responses observed and the risk-benefit assessment during NDA review.

   Whether the available data would support the filing of an NDA should be discussed during the pre-NDA meeting that should be requested when the planned final analysis of Cohort A has been performed. This final analysis will occur when all enrolled patients (≥ 60 patients in the BTx and ≥ 60 patients in the LBx analysis sets) have completed at least 12 months of follow-up and all responding patients have been followed for a minimum of 6 months from the onset of response.

   It is unlikely that the proposed thresholds for the lower limit of the 95% CI for ORR as presented by EMD Serono would be adequate to support accelerated approval for a broad indication independent of line of therapy. FDA will assess whether the ORR with tepotinib and its associated 95% CI, by line of therapy, demonstrate an advantage over available therapy for each given line of therapy. For example, the inclusion of treatment-naïve patients in the planned indication would need to be supported by demonstration that the lower limit of the 95% CI of ORR in the treatment-naïve subpopulation of patients from the VISION trial exceeds the ORR for available first-line therapy at the time of submission of the NDA.

   Please provide the actual percentage (rather than Kaplan-Meier estimated percentage) of the 28 patients with responses in the VISION trial whose duration of response is ≥6, ≥9, ≥12, and ≥18 months.

   For additional information regarding the criteria for accelerated approval, please refer to the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics found at:
   https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

EMD Serono's Response dated 8/3/2018:
EMD Serono wishes to discuss Question 1.

Discussion During Meeting:
Refer to EMD Serono's slides 1-5. FDA acknowledged the updated information provided in the slides. FDA stated that with the small number of patients the appropriate duration of follow up should err on the side of having 6 months of follow up from onset of response in all responding patients. FDA noted that both durability of response and the lower limit of the confidence interval around the observed response rate will be considered in determining whether tepotonib is better than available therapy

2. Does the agency agree that the proposed methodologies are adequate to characterize the prognostic implications of METex14 alterations?

FDA Response:
FDA does not object to the use of external controls (methodology number 1), provided that the analysis plan for adjustment for imbalances in demographic and tumor prognostic characteristics is clearly described and appropriate to minimize bias. However, the proposal to use data from an external control population of only 30-40 patients is not acceptable; a population of this limited size may not be representative of the overall population of patients with METex14 skipping alteration-positive NSCLC. Therefore, a larger patient experience should be utilized and evidence should be provided to support that the external control is representative of the intended population. External control patients also should be similar to patients enrolled in the VISION trial with regard to demographic and important disease-related prognostic factors.

Regarding EMD Serono's proposal to use an internal historical control (methodology number 2), FDA does not agree with this approach. Therefore, FDA will rely solely on data obtained through approach methodology number 1.

EMD Serono's Response dated 8/3/2018:
EMD Serono wishes to discuss Question 2.

Discussion During Meeting:
Refer to EMD Serono's slides 6-7. FDA expressed concerns regarding the sample size as being representative of the patient population with METex14 NSCLC and urged EMD Serono to explore additional sources of data. FDA noted that such historical controls may provide insight into response rates but not PFS and OS. In the absence of an adequately sized external population FDA will rely on the experience in patients with unselected NSCLC.

FDA generally agreed with the proposed approach for data collection on slide 7.

3. Does the agency agree that NSCLC treatment options described below can be considered as the relevant available therapies against which ORR/DoR from the pivotal VISION can be compared to demonstrate a clinically relevant effect of tepotinib over available therapy to support accelerated approval?

EMD Serono's Response dated 8/3/2018:
EMD Serono wishes to discuss Question 3.

FDA Response:
Refer to EMD Serono's slides 8 and 9. Determination of available therapies will be based upon those therapies that are approved at the time a marketing application is received. In the absence of data demonstrating a differential treatment effect in this population, it is assumed that the subpopulation of patients with advanced (stage IIIB/IV) NSCLC whose tumors harbor METex14 skipping alterations would respond similarly to available therapy as the broader population of patients with advanced NSCLC.

For further information regarding determination of available therapy in the context of an application submitted under the provisions of accelerated approval, please see Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, see link provided in the response to question 1.

Discussion During Meeting:
FDA advised EMD Serono to consider the FDA's Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, specifically the subsection regarding available therapy, in assessing whether the data for patients receiving first line treatment have demonstrated an improvement over available therapy when additional data are available, please see
https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

4. Does the agency agree with the proposed (b) (4)

FDA Response:
This discussion is premature as the data intended to support accelerated approval has not yet been generated. However, it is unlikely that the proposal (b) (4)
supporting accelerated approval will suffice.

(b) (4)

(b) (4)

EMD Serono's Response dated 8/3/2018:
EMD Serono wishes to discuss Question 4.

Discussion During Meeting:
Refer to EMD Serono's slide 10. FDA is open to further discussions regarding real world experience. The sources of data chosen should consider the methodologic challenges with assessing the endpoints to be used. FDA further stated that the completeness of the data collected would be an issue. EMD Serono should present a plan for further feedback.

5. Does the agency agree (b) (4)

FDA Response:
No. Based on the currently available results, FDA does not agree (b) (4)

Discussion During Meeting:
No discussion occurred during the meeting

6. Does the agency agree that a safety database of more than 450 patients is sufficient to support accelerated approval?

FDA Response:
The pre-meeting briefing materials supplied are unclear as to the number of patients who received tepotinib at the proposed dose and schedule for which EMD Serono is seeking approval. FDA generally expects safety data on a minimum 300 patients who received the proposed recommended dosage regimen. If EMD Serono submits a data base with fewer than 300 patients, justification should be if the database is sufficient to make a risk-benefit assessment for the proposed population. A final determination of the adequacy of the database will be made at the time of review.

Discussion During Meeting:
No discussion occurred during the meeting

ADDITIONAL COMMENTS:

Clinical Pharmacology

7. Address the following questions in the Summary of Clinical Pharmacology provided in the planned NDA.

   a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

      Discussion During Meeting:
      No discussion occurred during the meeting

   b. What are the exposure-response relationships for efficacy, safety and biomarkers?

      Discussion During Meeting:
      No discussion occurred during the meeting

   c. What is the effect of tepotinib on the QT/QTc interval?

      Discussion During Meeting:
      No discussion occurred during the meeting

   d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

      Discussion During Meeting:
      No discussion occurred during the meeting

   e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.

      Discussion During Meeting:
      No discussion occurred during the meeting

   f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

      Discussion During Meeting:
      No discussion occurred during the meeting

8. Apply the following advice in preparing the clinical pharmacology sections of the original submission:

   a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

      Discussion During Meeting:
      No discussion occurred during the meeting

   b. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

      Discussion During Meeting:
      No discussion occurred during the meeting

   c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

      - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

      - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

      Discussion During Meeting:
      No discussion occurred during the meeting

   d. Submit the following for the population pharmacokinetic analysis reports:

      - Standard model diagnostic plots

      - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line

      - Model parameter names and units in tables.

      - Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Discussion During Meeting:
No discussion occurred during the meeting

e. Submit the following information and data to support the population pharmacokinetic analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation
- A description of each data item provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

Discussion During Meeting:
No discussion occurred during the meeting

f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

Discussion During Meeting:
No discussion occurred during the meeting

9. Submit the following items to FDA in the QT study report:

a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

Discussion During Meeting:
No discussion occurred during the meeting

b. Electronic copy of the study report

Discussion During Meeting:
No discussion occurred during the meeting

c. Electronic or hard copy of the clinical protocol

Discussion During Meeting:
No discussion occurred during the meeting

d. Electronic or hard copy of the Investigator's Brochure

Discussion During Meeting:
No discussion occurred during the meeting

e. Annotated case report forms (CRF)

Discussion During Meeting:
No discussion occurred during the meeting

f. A data definition file which describes the contents of the electronic data sets

Discussion During Meeting:
No discussion occurred during the meeting

g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses

Discussion During Meeting:
No discussion occurred during the meeting

h. Ensure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

Discussion During Meeting:
No discussion occurred during the meeting

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

Discussion During Meeting:
No discussion occurred during the meeting

j. Narrative summaries and case report forms for any:
   i. Deaths
   ii. Serious adverse events
   iii. Episodes of ventricular tachycardia or fibrillation
   iv. Episodes of syncope
   v. Episodes of seizure
   vi. Adverse events resulting in the subject discontinuing from the study

Discussion During Meeting:
No discussion occurred during the meeting

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

Discussion During Meeting:
No discussion occurred during the meeting

l. A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies –depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at http://cardiac-safety.org/ecg-database.

Discussion During Meeting:
No discussion occurred during the meeting

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

FDA acknowledges receipt of EMD Serono's Agreed Initial Pediatric Study Plan (iPSP) submitted on August 5, 2016, and refers to the September 2, 2016, letter confirming FDA's agreement to the Agreed iPSP-2 for the proposed (b) (4) [redacted]

However, please note that Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding

implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format.

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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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/

REBECCA L COHEN
08/09/2018