CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215383Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 137354

MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Yuan Xue, PhD
Director, Global Regulatory Affairs
One Merck Dr., PO Box 100
Whitehouse Station, NJ 08889

Dear Dr. Xue:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-6482.

We also refer to the teleconference between representatives of your firm and the FDA on November 12, 2020. The purpose of the meeting was to discuss whether the data from the phase 2 study MK-6482-004 (formerly known as Study PT2977-202) entitled "*An Open-Label Phase 2 Study to Evaluate PT2977(MK-6482) for the Treatment of VHL Disease-Associated RCC*" are sufficient to permit submission of an NDA for MK-6482, for the treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma, not requiring immediate surgery.

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

If you have any questions, call Jeannette Dinin, Regulatory Project Manager, at 240-402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette Dinin
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Chana Weinstock, MD
Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 12, 2020; 4:00 – 5:00 pm
Meeting Location:	Teleconference
Application Number:	137354
Product Name:	MK-6482
Indication:	For the treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma (RCC) with non-metastatic renal cell carcinoma tumors less than 3 cm in size, unless immediate surgery is required
Sponsor Name:	Merck Sharp & Dohme Corporation
Regulatory Pathway:	505(b)(1)
Meeting Chair:	Chana Weinstock, MD
Meeting Recorder:	Jeannette Dinin

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Acting Director, DO1
Amna Ibrahim, MD, Deputy Director, DO1
Nam Atiqur Rahman, PhD, Director Pharmacology, DCP V
Daniel Suzman, MD, Clinical Team Leader, DO1
Chana Weinstock, MD, Clinical Team Leader, DO1
Jaleh Fallah, MD, Clinical Reviewer, DO1
Daniel Lee, MD, Clinical Reviewer, DO1
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP V
Huiming Xia, PhD, Clinical Pharmacology Reviewer, DCP V
Sara Dorff, PhD, Genomics Reviewer, DCP V
Rosane Charlab Orbach, Genomics Team Leader, DCP V
Lijun Zhang, PhD, Biometrics Reviewer, DBV
Banu Zolnik, PhD, Biopharmaceutics Team Leader, ONDP
Mathew John, PhD, Biopharmaceutics Reviewer, ONDP
Anamitro Banerjee, PhD, Branch Chief, ONDP
Xiao H. Chen, PhD, ONDP Pre-Marketing Lead QAL/CMC-Lead, OPMA, OPQ
Oscar Cano, MD, Regulatory Scientist, OIR/CDRH
Donna Roscoe, PhD, Molecular Genetics Branch Chief, OIR/CDRH
Jeannette Dinin, Regulatory Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD)

SPONSOR ATTENDEES
Rodolfo Perini, MD, Executive Director, Clinical Research
Eric Park, MD, Director, Clinical Research
Peter Kang, MD, Associate Vice President, Clinical Research
Scot Ebbinghaus, MD, Vice President, Clinical Research
Yuan Xue, PhD, Director, Regulatory Affairs
Layne Chaya, VMD, MS, RA/QA, Associate Director, Regulatory Affairs
Margaret McCann, DVM, Ph.D., Associate Vice President, Regulatory Affairs
Scott Korn, MD, Vice President, Regulatory Affairs
Ananya Roy, PhD, Principal Scientist, Biostatistics
Christine Gause, PhD, Executive Director, Biostatistics
Chuka Anude, MD, Executive Director, Drug Safety
Oswaldo Bracco, MD, Associate Vice President, Drug Safety
Eunkyung Kauh, MD, PhD, Executive Director, Translational Pharmacology
Cathy Anne Pinto, PhD, Director, Epidemiology
Ajay Acharya, PhD, Director, Regulatory Affairs CMC
James DiNunzio, Ph.D., Director, Pharmaceutical Sciences
Dhananjay Marathe, PhD, Principal Scientist, Quantitative Pharmacology and Pharmacometrics

Additional Attendees

(b) (4)

1.0 BACKGROUND

Merck has requested this type B pre-NDA meeting to discuss the proposed NDA submission of MK-6482 for the treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma (RCC) with non-metastatic renal cell carcinoma tumors less than 3 cm in size, unless immediate surgery is required.

MK-6482 is an oral, first-in-class small-molecule inhibitor of HIF-2α which impairs hypoxic and pseudohypoxia signaling in cancer cells and blocks the transcription of several genes involved in oncogenesis. HIF-2 α is important in oncogenesis in the VHL pathway; VHL disease is a hereditary cancer syndrome associated with VHL gene inactivation that results in accumulation of HIF molecule and associated increased tumor growth and invasion. Patients with VHL disease are at risk of developing RCCs, renal cysts and non-renal tumors including pheochromocytomas, pancreatic cysts, neuroendocrine tumors, CNS hemangioblastomas, retinal angiomas, inner ear tumors, and epididymal and broad ligament cystadenomas. There is currently no FDA approved systemic treatment for VHL-associated RCC in the non-metastatic setting.

The Sponsor conducted a single arm study (MK-6482-004) entitled, *A Phase 2 Study of PT2977 for the Treatment of Von Hippel Lindau Disease-Associated Renal Cell Carcinoma* to investigate the efficacy and safety of MK-6482 in patients with VHL-

associated RCC not in immediate need of surgical resection. Based on the preliminary clinical data (data cut-off date as March 29, 2020) presented to FDA at the EOP2 meeting, FDA granted breakthrough therapy designation to MK-6482 on July 27, 2020. On October 14, FDA acknowledged the Sponsor's plan to request a waiver of the requirement for the assessment of MK-6482 in all pediatric age groups because MK-6482 is not a relevant target in a pediatric tumor.

The Sponsor presents the topline updated clinical data (cut-off date of June 1, 2020) from the MK-6482-004 study. Based on the current plan, the Sponsor expects rolling NDA submissions on December 15, 2020 and January 15, 2021, respectively.

Summary of efficacy results from MK-6482-004 [median duration of follow-up of 15.8 (range: 4.2-24.1) months, Date of Data Cut-off: June 1, 2020]:

RCC tumors:

- Confirmed ORR: 22/61 (36.1%, 95% CI: 24.2, 49.4) CR: 0%, PR: 36.1%, SD: 62.3%
- Median DOR: not reached (DOR range: 11.9+, 62.3+ weeks)
- Median time to response: 31.1 weeks (Mean: 30.7, range: 11.6, 61.0 weeks)
- PFS (95% CI) at week 52: 98.3% (88.6, 99.8)
- Number of patients undergoing surgery: 1/61 (1.6%), median time: not reached

Pancreatic lesions:

- Confirmed ORR: 39/61 (63.9%)
- PD/death: 1/61 (1.6%)
- Median DOR: not reached (DOR range: 11.1+, 71.0+ weeks)

CNS hemangioblastoma:

- Confirmed ORR: 13/43 (30.2%)
- PD/death: 0
- Median DOR: not reached (DOR range: 11.9+, 72.4+ weeks)

Retinal lesions:

- Improved: 11/16 (68.8%, 95% CI: 41.3, 89.0)
- Stable: 4/16 (25.0%, 95% CI: 7.3, 52.4)
- PD: 0

Linear Growth Rate:

RCC tumors:

- Median LGR before treatment: +3.6 mm (range: -3.5 to +33.1 mm/year)
- Median LGR after treatment: -4.5 mm (range: -12.8 to +5.1 mm/year)

Pancreatic tumors:

- Median LGR before treatment: +1.6 mm (range: -7.4 to +10.7 mm/year)
- Median LGR after treatment: -6.6 mm (range: -23.7 to +3.3 mm/year)

Summary of safety results:

MK-6482-004:

- Median duration of treatment: 68 weeks
- Any AE: 61/61 (100%)
- Any AE ≥grade 3: 15/61 (25%); Grade 4 AE: 1/61; Grade 5 AE (death): 1/61
    - (No drug-related Grade 4 or 5 events were reported)
- Any SAE: 9/61 (15%)
- AE leading to treatment discontinuation: 2/61 (3%)
- AE leading to dose reduction: 8/61 (13%)
- AE leading to dose interruption: 24/61 (39%)
- 55/61 (90%) had anemia (grade 3: 4/55, no grade 4-5)
- 1/61 (1.6%) had hypoxia (grade 3)

MK-6482-001:

- MK-6482 was well tolerated at the RP2D of 120 mg QD in participants with RCC. MK-6482 was not associated with cardiovascular AEs or other AEs typical of the anti-VEGF class of agents. The most common grade 3 AEs in participants receiving MK-6482 were anemia and hypoxia.

To help contextualize results of the single-arm clinical study MK-6482-004, the Sponsor is also conducting a retrospective natural history study of growth kinetics and surgical patterns for patients with VHL disease-associated RCC using data registered by the NCI in a Hereditary Database, with plans to include study results in the NDA. In addition, a comprehensive summary of the published literature on natural history of the VHL disease also will be presented to support the evaluation of the natural history of the VHL disease.

FDA sent Preliminary Comments to Merck on November 6, 2020.

2.0 QUESTIONS/RESPONSES

Question 1: At the EOP2 meeting on June 10, 2020, FDA requested Merck submit the topline results from Study MK-6482-004 for review before the NDA submission can be made. The clinical efficacy and safety data as of cut-off date 01-JUN-2020 are included in this briefing document. Does the Agency agree that the clinical efficacy data, including overall response rate (ORR), duration of response (DOR) and time to surgery, are of sufficient magnitude and duration to form the basis of the NDA submission and the proposed indication?

FDA Response: Yes. The safety and efficacy results submitted as topline results appear to support an NDA submission.

The wording of any indication will be a review issue.

Sponsor Response [submitted November 10, 2020]: The Sponsor acknowledges FDA's advice. No discussion is needed at the pre-NDA meeting.

Meeting Discussion: None.

Question 2: Does the Agency agree that the potential NDA submission can be considered for RTOR pilot?

FDA Response: Yes. With the proposed timeline for data submission, the NDA can be considered for the RTOR pilot.

As previously mentioned in the WRO meeting on October 23, 2020, we recommend submission of data from all manufacturing and testing sites in Wave 1 in order to facilitate the timely review of the NDA.

Sponsor Response [submitted November 10, 2020]: The Sponsor acknowledges FDA's advice and plans to submit the MK-6482-004 CSR as well as datasets (submission content as described in the briefing document) on ~November 20, 2020.

The Sponsor agrees to the FDA's request as made in the NDA Content and Format written responses. The Sponsor plans to submit the information (FEI, site contact, address, etc.) requested for the manufacturing and testing sites in the Wave 1 (December 15, 2020) submission.

Meeting Discussion: None.

Question 3: The Sponsor considers that the proposed NDA submission will clearly establish the clinical benefit of MK-6482 in the treatment of patients with VHL disease-associated RCC. The overall response rate and durability of responses seen for MK-6482 in RCC and non-RCC tumors are meaningful for the target patient population. In addition, the Sponsor plans to submit results of a natural history study of patients with VHL disease in the NDA dossier, which can be utilized to contextualize the data from Study MK-6482-004. Does the Agency agree that MK-6482 provides clinical benefit to the indicated patient population and supports consideration for regular approval?

FDA Response: Although the data submitted with the topline results suggest that MK-6482 appears promising, final decision about approval, including whether these data are appropriate for accelerated vs. regular approval, will be made upon review of the NDA; final decision about the indication population for any approval will also be a review issue.

Sponsor Response [submitted November 10, 2020]: The Sponsor acknowledges FDA's advice. No discussion is needed at the pre-NDA meeting.

Meeting Discussion: None.

Question 4: Does the Agency wish to schedule an Application Orientation Meeting with the Sponsor after the submission of the NDA?

FDA Response: Yes. An application orientation meeting (AOM) after the complete submission of the NDA is appropriate.

Sponsor Response [submitted November 10, 2020]: The Sponsor acknowledges FDA's advice, and will work with the FDA PM to schedule the AOM after NDA submission is completed. No discussion is needed at the pre-NDA meeting.

Meeting Discussion: None.

Question 5: At the EOP2 meeting on June 10, 2020, the Sponsor agreed to conduct a food effect study with the final market image formulation and a DDI study to investigate the impact of a strong CYP2C19 inducer on MK-6482 pharmacokinetics (PK). As summarized in the table below, the Sponsor currently anticipates the following timelines for these two studies and will submit the final CSRs when available. Does the Agency agree?

FDA Response: We recommend that you make your best effort to include the results of food effect and bioequivalence as well as drug interaction study results in the original NDA submission. In addition to your proposed food effect study, you should also establish the bioequivalence between to-be-marketed formulation and the formulation utilized in the pivotal study. If the results from the food effect for the to-be-marketed formulation and bioequivalence are not available for FDA review in the original NDA review cycle, only the formulation utilized in the pivotal study may be approved. In that case, the to-be-marketed formulation will be reviewed as an NDA supplement when the results of the food effect/bioequivalence study are available.

Sponsor Response [submitted November 10, 2020]: The Sponsor wishes to discuss this question with FDA at the pre-NDA meeting, but has provided a background on the food effect and prior BE strategy below.

To clarify the product history, only two formulations have been utilized in the clinical program for MK-6482 to date – both have been used in the pivotal Study MK-6482-004. The initial formulation was a fit-for-purpose (FFP) uncoated tablet. A subsequent presentation, the final market formulation (FMF), was developed with the addition of [redacted] (b) (4) film coat. A summary of the compositional

differences between the FFP and the FMF are provided in Table 1. These formulations were bridged using multi-media dissolution and also bridged in a comparative bioavailability study in healthy participants (Study MK-6482-006). The GMR [90% CI] for AUC0-inf (FMF/FFP) for 120 mg met BE criteria in this study (0.93 [0.88 - 0.98]) and the GMR [90% CI] for Cmax was 0.87 [0.77 - 0.99], as discussed previously with the Agency at the EOP2 meeting. The CSR of Study 006 will be included in the NDA submission.

A final market image (FMI), which is compositionally identical to the FMF, was developed to improve process efficiency. Minor process changes (i.e. (b) (4)) were bridged in alignment with SUPAC-IR using multi-media dissolution which demonstrated equivalence between the FMI and FMF. Based on the identical composition, nature of the process changes, and demonstrated in vitro equivalency, the Sponsor considers equivalency of the FMI and FMF to be sufficiently demonstrated.
As such, the Sponsor does not plan to conduct a BE study comparing FMF to FMI.

Table 1 – Composition of Formulations (Clinical Trials and Final Market Image)

Material	**Amount (mg/tablet)**		
	FFP	FMF	FMI
MK-6482	40.0	40.0	40.0
Hypromellose Acetate Succinate	(b) (4)		
Microcrystalline Cellulose			
Mannitol			
(b) (4) Silicon Dioxide			
Croscarmellose Sodium			
Magnesium Stearate			
(b) (4) Blue			
Tablet Weight	500.0	515.0	515.0

Further to the Agency's request, protocols for the food effect study (MK-6482-014) and rifampin DDI study (MK-6482-017) have been finalized, and site selection for both studies has been completed. Both studies are currently on schedule to be completed by late 1Q 2021, with the full CSR being available by July 2021, pending any unforeseen recruitment issues due to the COVID-19 pandemic.

As such, the final study results will not be available in the original NDA submission. However, the Sponsor intends to provide preliminary PK results from both studies to the Agency during the NDA review as they become available, approximately in April 2021mid.

Of note, the exposure-response analyses for efficacy and safety from the pivotal study (MK-6482-004) included a wide range of exposure (~7-fold AUC range) for 120 mg QD

from patients treated with both the FFP and FMF administered in the fasted state (study participants were transitioned from the FFP to FMF).

These data, along with results from the completed earlier food effect study (MK-6482-002) with the FFP formulation (where the GMR [fed/fasted] for AUC met BE criteria) and the demonstration of BE for AUC between the FFP and FMF in a comparative bioavailability study (MK-6482-006) support the recommendation that MK-6482 may be taken without regard to food.

FDA Response sent [November 12, 2020]: We recommend the food effect study should be conducted with to-be-market image formulation. If you do not want to do a bioequivalence study with the to-be-market image formulation, you should request a biowaiver. If you choose to do so, we may have further comments to relay at a later date.

Meeting Discussion: The Sponsor agreed that the food effect study will be conducted with FMI. The Sponsor stated that the process change is considered minor between FMF and FMI. FDA stated that bridging would be reviewed in the NDA.

The Sponsor does not plan to request a formal biowaiver in the NDA. The Sponsor agreed to submit the process change information for FMF and FMI under the IND for FDA feedback. The Sponsor will request feedback in the cover letter and notify the RPM by email.

Question 6: Does the Agency agree that the IRC data (e.g., ORR and DOR) from non-RCC tumors are adequate to support labeling in the Section 14 of the US Prescribing Information?

FDA Response: Possibly. We acknowledge your effort in collecting data on the efficacy of MK-6482 in non-RCC tumors. You should also submit the efficacy data for non-RCC tumors and analyses based on investigator assessment with the NDA. Inclusion of these data in Section 14 of the US Prescribing Information will be a review issue.

If you plan to submit data to support approval of MK-6482 in patients with non-RCC VHL, data on natural history of non-RCC lesions in patients with VHL should also be submitted.

Sponsor Response [submitted November 10, 2020]: The Sponsor acknowledges Agency's advice. No discussion is needed at the pre-NDA meeting. The upcoming NDA submission will contain a description of the published literature available for other VHL disease-associated neoplasms (non-RCC) and results of the Sponsor's natural history study of patients with VHL disease-associated RCC. (b) (4)

[redacted] (b) (4) plans to submit these data to the Agency at later date.

Meeting Discussion: None.

Question 7: Considering the high percentage of co-existing manifestations of multiple VHL associated neoplasms in patients with VHL disease, the common fundamental pathophysiology of VHL disease-associated neoplasms, the high unmet need for these patients, and the efficacy in non-RCC tumors in MK-6482-004, would the Agency consider a broader indication for VHL disease-associated neoplasm beyond RCC, not requiring immediate intervention, on the basis of these data?

FDA Response: Possibly. See response to Question 6. This will be a review issue.

Sponsor Response [submitted November 10, 2020]: The Sponsor acknowledges FDA's advice. No discussion is needed at the pre-NDA meeting.

Meeting Discussion: None.

Question 8: In light of the data from safety analyses of Study MK-6482-004, which are supported by MK-6482-001, the Sponsor believes that the risks associated with treatment using MK-6482 can be adequately managed with appropriate labeling and routine pharmacovigilance activities. Does the Agency agree that a REMS will not be required if MK-6482 is approved for the target patient population?

FDA Response: Based on the topline results submitted to the FDA, it appears that a REMS is not likely for MK6482. Final decision on whether a REMS is required will be made upon review after complete submission of the NDA. For more details, please refer to the FDA guidance for industry: https://www.fda.gov/media/100307/download

Sponsor Response [submitted November 10, 2020]: The Sponsor acknowledges FDA's advice. No discussion is needed at the pre-NDA meeting.

Meeting Discussion: None.

Additional Statistical Comment:

Please conduct a multi-level analysis using a mixed effect model to estimate LGR at the tumor-level and at the patient-level. If the study CSR is already finalized, you can submit this analysis report as a separate document. Please also submit the SAS program.

Sponsor Response [submitted November 10, 2020]: The Sponsor will conduct the requested analysis and prepare a separate report which will be included in the NDA dossier. The SAS program also will be submitted.

Meeting Discussion: None.

Additional Regulatory Comment:

As a reminder, please submit your completed multi-disciplinary and chemistry assessment aids in your January submission.

Sponsor Response [submitted November 10, 2020]: The preparation of multi-disciplinary and chemistry assessment aids is on track and will be included in the January submission (wave 2).

Meeting Discussion: None.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 3, 2020 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

In addition, we note that a chemistry pre-submission Written Response Only meeting document was sent on August 28, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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 505BI(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

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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. 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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, 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.[3]

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

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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 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.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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,* and the associated conformance guide, *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*.[8]

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:

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

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[10]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] 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/

JEANNETTE L DININ
12/03/2020 03:38:01 PM

CHANA WEINSTOCK
12/04/2020 02:24:53 PM

IND 137354

MEETING REQUEST-
WRITTEN RESPONSES

Merck Sharp & Dohme Corp.
Attention: Yuan Xue, PhD
Director, Global Regulatory Affairs
One Merck Dr., PO Box 100
Whitehouse Station, NJ 08889

Dear Dr. Xue:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-6482.

We also refer to your submission dated August 27, 2020, containing a meeting request. The purpose of the requested meeting to discuss the planned content and format of your upcoming NDA submission.

Further reference is made to our Meeting Granted letter dated September 3, 2020, wherein we stated 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 September 25, 2020, background package.

If you have any questions, call Jeannette Dinin, Regulatory Project Manager, at 240-402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette Dinin
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Chana Weinstock, MD
Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure: Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	Type B
Meeting Category:	pre-NDA; content and format
Application Number:	IND 137354
Product Name:	MK-6482
Proposed Indication:	MK-6482 is indicated for the treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma (RCC) with non-metastatic renal cell carcinoma tumors less than 3 cm in size, unless immediate surgery is required
Sponsor Name:	Merck Sharp & Dohme Corp.
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

Merck has requested this type B pre-NDA meeting to discuss the structure, content and format of the proposed NDA submission of MK-6482 for the treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma (RCC) with non-metastatic renal cell carcinoma tumors less than 3 cm in size, unless immediate surgery is required.

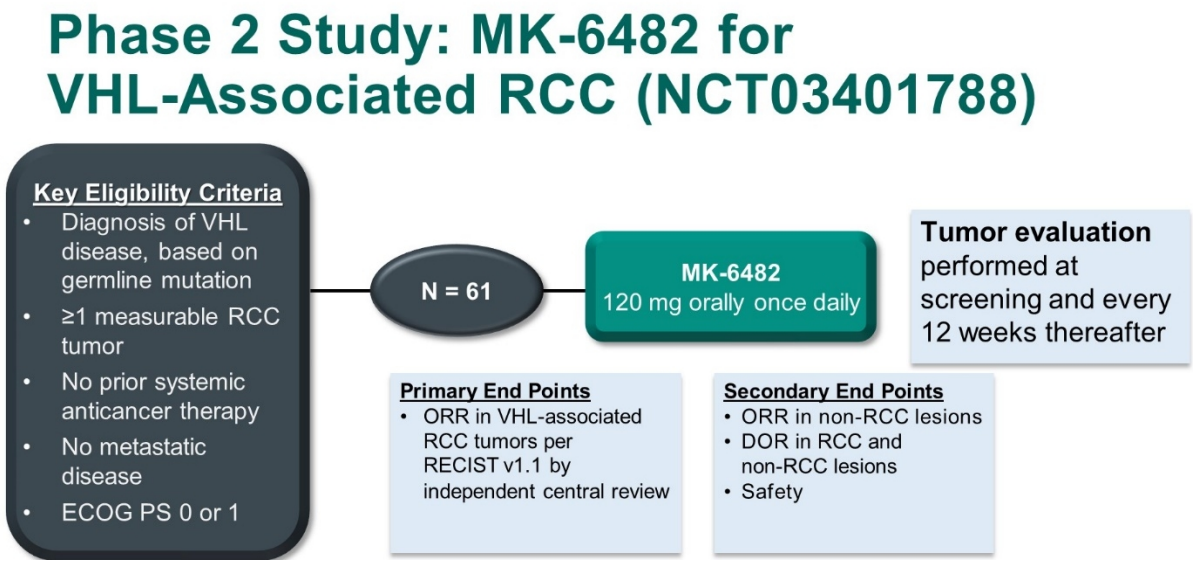
MK-6482 is an oral, first-in-class small-molecule inhibitor of HIF-2α which impairs hypoxic and pseudohypoxia signaling in cancer cells and blocks the transcription of several genes involved in oncogenesis. HIF-2 α is important in oncogenesis in the VHL pathway; VHL disease is a hereditary cancer syndrome associated with VHL gene inactivation that results in accumulation of HIF molecule and associated increased tumor growth and invasion. Patients with VHL disease are at risk of developing RCCs, renal cysts and non-renal tumors including pheochromocytomas, pancreatic cysts, neuroendocrine tumors, CNS hemangioblastomas, retinal angiomas, inner ear tumors, and epididymal and broad ligament cystadenomas. RCC occurs in up to 70% of those with VHL disease. Current management of VHL-disease associated RCC is active surveillance of the tumors and surgical resection if tumor ≥3 cm. However, new RCC tumors continue to emerge over time and repeated surgeries are associated with morbidity including risk of decreased renal function. There is currently no FDA approved systemic treatment for VHL-associated RCC in the non-metastatic setting.

The Sponsor conducted a single arm Phase 2 study (MK-6482-004) to investigate the efficacy and safety of MK-6482 in VHL-associated RCC not in immediate need of surgical resection. In terms of relevant regulatory history, the Sponsor presented the preliminary clinical data (data cut-off date as March 29, 2020) to FDA at an EOP2 meeting on June 10, 2020. FDA granted breakthrough designation to MK-6482 on

July 27, 2020 for the treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma with non-metastatic renal cell carcinoma tumors less than 3 cm in size, unless immediate surgery is required. A separate pre-NDA meeting is scheduled in November 2020 to discuss topline updated clinical data (cut-off date of June 1, 2020).

The proposed NDA submission will be based on the phase 2 Study MK-6482-004, with supportive data from the phase 1 Study MK-6482-001 which is being conducted in patients with advanced RCC.

The study schema for MK-6482-004 is presented below:



(Jonasch et al., ASCO 2020)

Patients were eligible for treatment as per schema above. Sixty-one patients were enrolled; median age was 41 years (range: 19-66), 52.5% were men, 82% had ECOG 0. There were 20 confirmed responses (ORR: 33%) with 20/20 responses ongoing and 5 additional patients having unconfirmed responses at the time of initial data cut off. Median duration of response was not reached (range: 12-49 months). Responses were also observed in VHL-disease-associated non-RCC tumors (confirmed ORR 25% in CNS hemangioblastoma and ORR 29% in pancreatic tumors). In terms of safety, there were 3% of patients with dose discontinuations, 13% dose reductions and 36% dose interruptions.

The Sponsor proposes to conduct a rolling submission of the NDA. As CMC data will be available later than clinical data, the Sponsor proposes to provide CMC modules later.

Rolling Submission Approximate Submission Timeline:

Wave 1 by December 15, 2020:

- Complete nonclinical modules 2.4, 2.6, and 4, along with additional bioanalytical reports,
- Clinical Modules 2.7, and 5 except the study report from the natural history study.

Wave 2 by January 15, 2021:

- Complete Quality & CMC modules 2.3, and 3,
- Clinical Module 2.5 and the study report of the natural history study,
- Module 1 (labeling and other administrative documents).

Additional proposed dates during NDA submission

- March 17, 2021- submission of the 12-month formal stability study data
- April 15, 2021- submission of safety and efficacy updates with a DCO of December 1, 2020 (additional 5 months follow-up for DOR).

The Sponsor proposes to pool safety data from Studies MK-6482-004 and MK-6482-001 and to submit this in the Integrated Summary of Safety (ISS). They propose to present the safety data as outlined below:

1. MK-6482-004
2. MK-6482-001
3. A safety data pool of all evaluable participants who received the target dose of 120 mg q.d. from both Studies MK-6482-004 and MK-6482-001.
4. A 2nd safety data pool consists of all patients who received MK-6482 irrespective of dose.

At the EOP2 meeting on June 10, 2020, FDA requested that the Sponsor collect family history and diagnosis methods from the patients in Study MK-6482-004. The Sponsor plans to collect the relevant information from the enrollment packets of the Study MK-6482-004, summarize such data as available for each patient in a table format and provide the information in Module 2.5.

2.0 QUESTIONS AND RESPONSES

Question 1: Does the Agency agree that the filing format and the layout of the proposed NDA, as shown in the draft table of contents, is adequate to support the review of the NDA?

FDA Response: Your proposed filing format provided in Appendix 1 appears to be acceptable. Final decision on whether the NDA is fileable will be made upon review after complete submission of the NDA.

Question 2: Does the Agency agree with the proposed rolling submission timelines of the NDA dossiers?

FDA Response: Yes. The proposed rolling submission timeline appears to be acceptable.

Question 3: To follow up the Type B CMC meeting on Aug 28, 2020 (written response only), the Sponsor plans to submit the 12-month formal stability study data on March 17, 2021. Does the Agency agree with the plan?

FDA Response: Yes. Your plan appears acceptable. To facilitate our timely review of your NDA, we recommend that you submit all manufacturing and testing sites in Wave 1.

Question 4: The Sponsor proposes to submit an Efficacy Update Report (containing the updated duration of response) at the time of submission of the Safety Update Report. The schedule and format for the planned Efficacy Update Report and Safety Update Report is proposed in the company position. Does the Agency find this proposal acceptable?

FDA Response: Yes. Your proposed timeline for submission of the efficacy update report appears to be acceptable. No additional responders should be identified at that point but updated response durations for previously-identified responding patients should be provided.

Question 5: Does the Agency agree with the proposed structure of the Integrated Summary of Safety and the Safety Update Report?

FDA Response: Yes. The proposed structure of the integrated summary of safety and the safety update report is acceptable. We reiterate that the adequacy of the submitted safety database to support review and approval of MK-6482 will be a review issue.

For the integrated safety dataset that includes patients dosed at multiple dose levels, the dose received by each included patient should be clearly indicated and named within the dataset itself.

As previously indicated, please provide a detailed assessment of hypoxia resulting from your drug administration in the NDA submission.

Question 6: At the EOP2 meeting on June 10, 2020, FDA requested the Sponsor to collect family history and diagnosis methods from the patients in Study MK-6482-004. The Sponsor plans to collect the relevant information from the enrollment packets of the Study MK-6482-004, summarize such data as available for each patient in a table format as below, and provide the information in Module 2.5. Does the Agency agree?

Table 10 Summary of family history and diagnosis methods

Subject #	Family History of VHL disease (Yes/No/Unknown)	1st Clinical Manifestation	Year of 1st Clinical Manifestation	Year of Genetic Testing

FDA Response: No. You should submit a report reviewing and summarizing this information and an associated dataset in Module 5. You should modify the above table to include the following additional information, and you should also provide an associated dataset with subject-level data including the information as proposed above and this additional information:

- **The specific VHL variants obtained from subjects' medical history and the ones identified through retrospective central testing. Include the variant classification (e.g., Pathogenic or Likely Pathogenic, Variants of Uncertain Significance).**

- **If available, you should also include data on sex of the relative, alive or not, age at death, reason for death, relationship to patients (1st, 2nd or 3rd gen relationship), the organs affected by VHL, interventions for VHL, and genetic testing method.**

Please also indicate the diagnostic partner for the test that will be FDA authorized for detection of VHL variants to determine therapeutic eligibility.

Question 7: The contents of the electronic submission package are outlined below. Does the Agency agree with the proposed electronic submission package to support the NDA submission?

FDA Response: **The proposed electronic submission package appears to be reasonable. Final decision will be made upon review of the NDA submission package.**

Question 8: The content of the OSI package is outlined below. Does the Agency agree with the proposed OSI package to support the NDA submission?

FDA Response: **Your proposed submission of the clinical site dataset and data listings by clinical site is acceptable. For both studies, please also include Clinical Study-Level Information in your OSI package based on the recently released Bioresearch Monitoring Technical Conformance Guide https://www.fda.gov/media/85061/download [see "OSI Requests in Section 3 (Additional Information) of this Written Response].**

Additional Genomics Comment

Submit a dataset supporting the report of the pharmacogenetic analysis results for both UGT2B17 and CYP2C19 poor metabolizers to be provided in the NDA submission. Include subject level genotype in addition to phenotype for UGT2B17 and CYP2C19. Also include a description of the methodology for determination of phenotypes from genotypes.

Additional Clinical Pharmacology Comments

1. **The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.**

2. **Address the following questions in the Summary of Clinical Pharmacology:**

    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.**

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

c. **What is the effect of MK-6482 on the QT/QTc interval?**

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

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.**

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?**

3. **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.**

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.**

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.**

i. **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.**

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

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

i. **Standard model diagnostic plots**

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

iii. **Model parameter names and units in tables.**

iv. **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.

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

   a. **SAS transport files (*.xpt) for all datasets used for model development and validation**

   b. **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**

   c. **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)**

5. **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.**

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 3, 2020 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

In addition, we note that a chemistry pre-submission Written Response Only meeting document was sent on August 28, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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

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

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. 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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, 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.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- A sample tool illustrating the format for Highlights and Contents, and

APPEARS THIS WAY ON ORIGINAL

- 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 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.

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 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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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[8] https://www.fda.gov/media/85061/download
[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] 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/

JEANNETTE L DININ
10/23/2020 07:26:45 AM

CHANA WEINSTOCK
10/23/2020 11:39:55 AM

IND 137354

MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Yuan Xue, PhD
Director, Global Regulatory Affairs
One Merck Dr., PO Box 100
Whitehouse Station, NJ 08889

Dear Dr. Xue:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-6482.

We also refer to the teleconference between representatives of your firm and the FDA on June 10, 2020. The purpose of the meeting was to discuss your proposed phase 3 trial for treatment of von Hippel-Lindau disease associated renal cell carcinoma.

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

If you have any questions, call Jeannette Dinin, Regulatory Project Manager, at 240-402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeannette Dinin
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Chana Weinstock, MD
Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: June 10, 2020; 11:00 – 12:00 pm
Meeting Location: Teleconference

Application Number: IND 137354
Product Name: MK-6482

Indication: Treatment of von Hippel-Lindau (VHL) disease associated renal cell carcinoma (RCC)
Sponsor Name: Merck Sharp & Dohme Corp.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Chana Weinstock, MD
Meeting Recorder: Jeannette Dinin

FDA ATTENDEES

Amna Ibrahim, MD, Deputy Director, Division of Oncology 1 (DO1)
Laleh Amiri-Kordestani, MD, Supervisory Associate Director, DO1
Chana Weinstock, MD, Clinical Team Leader, DO1
Daniel Suzman, MD, Clinical Team Leader, DO1
Jamie Brewer, MD, Clinical Reviewer, DO1
Michael Brave, MD, Clinical Reviewer, DO1
Elaine Chang, MD, Clinical Reviewer, DO1
Mitchell Anscher, MD, Clinical Reviewer, DO1
Mallorie Fiero, PhD, Acting Biometrics Team Leader, DBV
Lijun Zhang, PhD, Biometrics Reviewer, DBV
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP V
Huiming Xie, PhD, Clinical Pharmacology Reviewer, DCP V
Robert Schuck, PhD, Genomics Reviewer, DCP V
Rosane Charlab Orbach, Genomics Team Leader, DCP V
Jeannette Dinin, Regulatory Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD), Oncology 1 Group

SPONSOR ATTENDEES

Rodolfo Perini, MD, Executive Director, Clinical Research
Eric Park, MD, Director, Clinical Research
Peter Kang, MD, Associate Vice President, Clinical Research
Scot Ebbinghaus, MD, Vice President, Clinical Research
Yuan Xue, PhD, Director, Regulatory Affairs

Margaret McCann, DVM, PhD, Associate Vice President, Regulatory Affairs
Eunice Lee, PhD, Executive Director, Regulatory Affairs
Scott Korn, MD, Vice President, Regulatory Affairs
Julie Anne Zawisza, Director, Global Regulatory Policy
Ananya Roy, PhD, Director, Biostatistics
Christine Gause, PhD, Executive Director, Biostatistics
Chuka Anude, MD, Executive Director, Clinical Safety and Risk Management
Oswaldo L. Bracco, MD, Associate Vice President, Clinical Safety & Risk Management
Takayuki Tsuchiya, DVM, PhD, Director, Nonclinical Safety Assessment
Eunkyung Kauh, MD, PhD, Executive Director, Translational Pharmacology
Cathy Anne Pinto, PhD, Director, Pharmacoepidemiology
Murali Sundaram, Director, Outcomes Research
Dhananjay Marathe, PhD, Principal Scientist, Quantitative Pharmacology & Pharmacometrics

1.0 BACKGROUND

The Sponsor has requested this EOP2 meeting to discuss registration potential of MK-6482, a small molecule inhibitor of hypoxia-inducible factor (HIF)-2α, for the treatment of von-Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC) based on data from the open-label, single arm, phase 2 Study MK-6482-004, of MK-6482 administered at 120 mg daily.

The Sponsor proposes MK-6482 to be a treatment option for patients with VHL disease-associated RCC tumors that are less than 3 cm which would have otherwise been under active surveillance until tumors reached 3 cm or more in size. At that time, standard practice is generally surgical resection of tumors to prevent metastatic progression.

At the time of data cut-off (DCO) (12/6/19), enrollment was complete and 61 patients were enrolled on trial with treatment ongoing for 58 patients. All active patients had at least 36 weeks of follow up. There were three treatment discontinuations; due to death, adverse event, and patient decision (1 each).

At the DCO a confirmed ORR of 28% (95% CI: 17.1%, 40.8%) was observed. There are currently 6 patients with ongoing unconfirmed partial responses (PRs) and 2 additional patients with confirmed PRs at the time of submission of this briefing document. The median duration of response (DOR) was not reached by the December DCO (95% CI: 35.6 weeks, not estimable) and 16/17 RCC responders had ongoing responses. Investigator assessed treatment responses were also seen in other VHL-related lesions, with an ORR of 27% for CNS hemangioblastomas and 26% for pancreatic lesions. DOR for these other VHL related lesions were consistent with what was observed with the RCC analysis. Median PFS for RCC was not estimable at the time of DCO, however there were only 2 PFS events reported (1 progressive disease, 1

death) in the 61 patients enrolled. Similar results were seen in the CNS hemangioblastomas and pancreatic lesions.

The Sponsor also conducted an analysis of linear growth rate (LGR) of VHL disease-associated RCC tumors using available literature and a comparison of pre-treatment and post-treatment scans of patients enrolled on Study MK-6482-004. In Study MK-6482-004 the median LGR for all lesions before treatment was 3.30 (-3.06 to 17.33) mm/year which was consistent with the median growth rate of 3.5 to 4.5 mm/year observed in the literature. The median LGR for all lesions after treatment with MK-6482 was -6.40 (-23.32 to 4.48) mm/year.

All patients on study experienced a treatment emergent adverse event (TEAE) with the most common (≥20%) being anemia, fatigue, dizziness, headache, and nausea. The most common high grade TEAEs (>1 patient) were fatigue (n=3) and anemia (n=2). There was one Grade 4 TEAE of retinal detachment and one Grade 5 TEAE of fentanyl toxicity, neither considered related to study drug.

	MK-6482 N=61, n (%)
Grade ≥3 TEAEs	12 (20%)
Serious adverse events	7 (12%)
TEAE leading to death	1 (2%)
TEAE leading to discontinuation	2 (3%)
TEAE leading to dose interruption	20 (33%)
TEAE leading to dose reduction	7 (12%)

The Sponsor is also conducting a two-part phase 1 study with Parts 1A (dose escalation) and Part 1B (dose expansion) completed. Part 2 involves further dose expansion of specified solid tumors and is ongoing. There are an additional 55-58 patients from this study that received MK-6482 at the target dose 120 mg daily that the Sponsor proposes to include the pooled safety database.

The Sponsor proposes a DCO around June 1, 2020, which corresponds to a minimum of 14 months follow up in all responding patients for the NDA submission.

The only ongoing randomized phase 3 trial of MK-6482 in RCC is (b) (4)

Although there are no therapies specifically approved in this indication, other therapies including TKIs such as sunitinib and pazopanib have been studied in single-arm trials with response rates of ~30-40%.

FDA sent Preliminary Comments to Merck on June 5, 2020.

2.0 QUESTIONS/RESPONSES

Question 1: Does the Agency agree the completed, ongoing and planned nonclinical safety studies, will be sufficient to support a marketing application for the treatment of VHL disease-associated renal cell carcinoma?

FDA Response: Yes, we agree that the proposed nonclinical safety studies appear appropriate to support submission of a marketing application for the proposed indication. A final decision on the adequacy of the nonclinical safety data will be made following our review of a future NDA submission.

Sponsor Response [Submitted June 9, 2020]: Merck acknowledges Agency's advice. No discussion is needed at the EOP2 meeting.

Meeting Discussion: None.

Question 2: Does the Agency concur that the proposed clinical pharmacology development program is appropriate to support a marketing application for treatment of VHL disease-associated RCC?

FDA Response: Your proposal appears reasonable in general. Whether dedicated organ impairment studies are needed as post-marketing requirements will be determined during NDA review.

A dedicated drug interaction study should be conducted to evaluate the impact of strong inhibitors or inducers of CYP2C19 on pharmacokinetics of MK-6482. Furthermore, you should evaluate the effect of concomitant gastric acid-reducing agents on the pharmacokinetics of MK-6482, if MK-6482 is less soluble at pH 6.0–6.5 (with a solubility <clinical dose/250 mL) than at pH 1-2.

Sponsor Response [Submitted June 9, 2020]: Merck wishes to discuss this question with the Agency at the EOP2 meeting.

Organ impairment study:

As noted in the EOP2 background document, the Sponsor plans to conduct a single-dose ^{14}C-MK-6482 human mass balance study in 2H2020 and anticipates that the results from this trial will further inform on the need for dedicated organ impairment studies.

Impact of CYP2C19 strong inhibitor or inducers on the PK of MK-6482:

In vitro phenotyping studies indicated that MK-6482 is a substrate of both UGT2B17 and CYP2C19. Polymorphisms affecting enzyme activity have been described for both UGT2B17 and CYP2C19, and the prevalence of polymorphisms associated with decreased or absent enzyme activity are markedly higher in Asians compared to Caucasians. The Sponsor recently conducted an open-label, single-dose study in 49 healthy Japanese and Caucasian women of non-child bearing potential to assess the impact of UGT2B17 and CYP2C19 phenotype on MK-6482 pharmacokinetics (PK). Study participants included extensive, intermediate and poor metabolizers of CYP2C19. These data along with the extensive pharmacogenomic data for the metabolizer status of both these enzymes that is collected in the completed Phase 1 and Phase 2 trials will be evaluated for its impact on PK. The Sponsor will provide the results from this analysis in the NDA submission. Furthermore, the impact of CYP2C19 poor metabolizer status (i.e. no activity) on MK-6482 PK should represent the scenario of maximal inhibition due to a strong CYP2C19 inhibitor, and therefore, the above evaluation would address the Agency's recommendation to evaluate the impact of strong CYP2C19 inhibitors on MK-6482 PK. Regarding the recommendation to evaluate the impact of CYP2C19 induction on MK-6482 PK, the Sponsor considers that the likelihood of co-administration of MK-6482 with a strong CYP2C19 inducer (i.e. rifampin) to be low, and therefore the clinical relevance is uncertain. Nonetheless, the Sponsor proposes to [redacted (b) (4)], and these exposures will be further contextualized for clinical relevance within the overall exposure-response relationship for review at the time of filing.

Effect of concomitant gastric acid-reducing agents on the PK of MK-6482:

Regarding the comment on pH-dependent solubility of MK-6482, MK-6482 crystalline drug substance exhibits consistent solubility across the pH range (2 - 10) as summarized in Table 1 below. Furthermore, MK-6482 [redacted (b) (4)] which exhibits a pH-dependent solubility such that the material is more soluble at elevated pH. In this case, the solubility of profile of [redacted (b) (4)] would be more soluble at pH 6.0-6.5 than at pH 1-2. Overall, the Sponsor's position is that MK-6482 will not be less soluble at elevated pH and thus no evaluation of the effect of concomitant gastric acid-reducing agents on the pharmacokinetics of MK-6482 is warranted.

Table 1 - Equilibrium Solubility of MK-6482 (crystalline drug substance)

Medium	Solubility (µg/mL)
50 mM phosphate buffer, pH 2.0	10.4
50 mM acetate buffer, pH 4.0	10.8
50 mM citrate buffer, pH 6.0	9.6
50 mM phosphate buffer, pH 8.0	9.4

50 mM carbonate buffer, pH 10.0	10.2

Overall, the Sponsor proposes the following plan:

- The need for specific organ impairment studies in the post-marketing setting can be discussed during the NDA review.
- An analysis of comprehensive genomics (metabolizer status) and PK data from the completed studies will be utilized to derive the impact of CYP2C19 inhibition on MK-6482 PK.
- (b) (4) this will be put in the context of exposure-response information to project clinical impact.
- The evaluation of effect of concomitant gastric acid-reducing agents on the PK of MK-6482 is not warranted based on the available information.

Meeting Discussion: The FDA acknowledged the Sponsor's plan regarding CYP2C19 inhibitors and acid-reducing agents. FDA strongly recommended the Sponsor conduct a DDI study with a strong CYP2C19 inducer. The Sponsor agreed. The FDA encouraged the Sponsor to submit the study report with the NDA submission.

The Sponsor will assess the role of CYP2C19 and UGT2B17 polymorphisms on MK-6482 PK and safety. The Sponsor indicated that patients will not be excluded based on genotype. If the Sponsor anticipates a safety issue for patients who are poor metabolizers for both enzymes, efforts should be conducted to identify these patients prospectively.

Question 3: Does the Agency agree that the results of the completed food effect study with the previous formulation, along with the results of the completed bio-comparability study between the previous formulation and the intended commercial tablet, provide sufficient information to support a recommendation for the administration of MK-6482 without regard to food?

FDA Response: No, you should conduct a formal food effect study with your to-be-marketed formulation. Without data, the food effect of formulation A may not be extrapolated to formulation B. Refer to the following FDA guidance for more details:

a. *Food-Effect Bioavailability and Fed Bioequivalence Studies*

b. *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations*

Sponsor Response [Submitted June 9, 2020]: Merck wishes to discuss this question with the Agency at the EOP2 meeting.

The Sponsor's position is as follows:

- As shown in [**Error! Reference source not found.**] in the briefing book, the two formulations are compositionally similar with only minor differences of addition of (b) (4) and film coating. These minor differences are not expected to alter drug release profile and thus the oral bioavailability of the product.

- The similarity of the two formulations is further supported by in vitro dissolution testing of Formulation A and Formulation B in 50mM phosphate buffer at pH 6.5 where both formulations provide drug release of at least 85% release in 15 minutes.

- Clinical PK data from the bio-comparability study provided data to confirm similarity in absorption profiles, with comparable C_{max} and AUC between the two formulations.

- Furthermore, preliminary exploratory exposure-efficacy and exposure-safety relationships based on available data do not indicate a strong relationship for efficacy and safety endpoints except for anemia. Therefore, a small variation in exposures (as observed in the food effect study with Formulation A) is not expected to alter efficacy and safety outcome. Based on previous food effect study there is potential of reduction in Cmax, while maintaining the AUC, when MK-6482 is administered with food. Therefore, no safety differences are expected even including for anemia when MK-6482 is administered with food.

- The Sponsor will include totality of these data in the submission and believes that these data provide adequate information to inform labeling recommendations with respect to administration with food.

Meeting Discussion: The FDA strongly suggested that the Sponsor conduct a formal food effect study with the "to-be-marketed" formulation. The Sponsor agreed and will make their best efforts to submit the study report with the NDA submission.

Question 4: Does the Agency agree that MK-6482-004 is considered a pivotal study to support the NDA submission in the proposed indication of VHL disease-associated RCC?

FDA Response: While the data you have described appear promising in this setting, the follow up provided is relatively short. You should provide updated data prior to NDA submission. Whether these data and MK-6482-004 in general are reasonable to submit in support of a NDA will be a review issue.

1. **We await further data on the patients with unconfirmed partial responses, as well as further data on DOR, in order to characterize the clinical benefit to enrolled patients in this setting.**

2. **The indication, should your data be sufficient for filing and review, will be a review issue.**

3. **As tolerability and delay of surgery are of primary importance in this population and are important factors when determining clinical benefit in this setting, you should provide all collected data and summaries on tolerability of a prolonged duration of treatment, other tolerability metrics (including patient-reported outcomes) and any known data on surgical procedures which these patients underwent due to progression. If feasible, provide real-world data on patients with VHL disease-associated RCC and expected rates of surgery in a similar setting in the absence of treatment. See also, response to Question 5.**

Sponsor Response [Submitted June 9, 2020]: Merck hereby provides responses below in responding to Agency's specific comments. Merck wishes to discuss this question with the Agency at the EOP2 meeting.

Study MK-6482-004 is a Phase 2, open-label efficacy and safety study of MK-6482 in participants with VHL disease-associated RCC. Patients received MK-6482 120 mg orally once daily. The latest clinical data are presented in this response letter based on cut-off as of 29-MAR-2020. 61 participants were enrolled in this study, with first patient enrolled on 31-MAY-2018 and enrollment completed on 29-MAR-2019. The study is ongoing. The data presented below are based on a snapshot, instead of a full database lock, of the cut-off on 29-MAR-2020. The comprehensive data and description are provided in Appendices 1 and 2. Patient-reported outcomes were not included in the study protocol.

Response to comment #1:

Merck considers that the data to be provided with the potential NDA (data cut-off on 01-JUN-2020) will enable the characterization of the clinical benefit of MK-6482 to patients in this setting. This would represent approximately a minimum of 14 months of follow-up for all active patients. In addition, Merck proposes to provide efficacy and safety update reports during the NDA review, with a corresponding cut-off date tentatively planned for November 2020. This would represent approximately 12 months duration of

response follow-up of these current 20 confirmed responders, from the onset of responses.

VHL disease-associated RCC

MK-6482 has demonstrated anti-tumor activity against VHL disease-associated RCC in the efficacy analysis population at the time of database cutoff, March 29, 2020. At the minimum follow-up of 52 weeks for all active patients, the confirmed ORR was 32.8% (95% CI: 21.3%, 46.0%) and the disease control rate (DCR) was 98.4% (Appendix 1: [Table 1] [Figure 1]). The waterfall plot shows that benefit extends beyond the patients who achieved a RECIST 1.1 defined response, as a total of 55 out of 61 (90.2%) of the participants had reduction in tumor size after treatment with MK-6482 (Appendix 1: [Figure 2]).

In comparing with data at prior cut-off dates, the ORR has continued to improve over time. As of 29-MAR-2020, an additional 3 subjects have had confirmed responses since the previous data cutoff of 06-DEC-2019, 5 subjects with unconfirmed PRs are awaiting subsequent confirmatory scans, the proportion of subjects with a reduction in tumor burden increased from 86.9% (53 out of 61) to 90.2%. Importantly, the lower bound of the 95% CI for ORR excluded 15%, a threshold considered by the Agency as clinically meaningful in previous scientific feedback (Correspondence between FDA and Peloton Therapeutics; pre-IND meeting on (b) (4)).

Objective responses were durable and all 20 of 20 RCC responders have ongoing responses, with the range of DOR (min 12.1 weeks+, max 49.4 weeks+). The median DOR, therefore, has not been reached and the lower bound of the 95% CI could not be estimated. (Appendix 1: [Figure 1] [Table 4] [Figure 3]). The median time to response (TTR) was 26.1 weeks (min 11.6, max 61.0) [Table 4]. With a prolonged TTR, ORR and DOR may underestimate the benefit achieved by these patients. The absence of meaningful tumor growth, as demonstrated by DCR, and changes in the growth kinetics of these tumors, as demonstrated by the negative post-treatment LGR, indicate that patients derive clinical benefit despite not having yet achieved a RECIST response - in that the need for surgery is prevented in patients who achieve arrested development or any reduction in tumor size. (Appendix 1: [Sec. 3.3]).

VHL disease-associated non-RCC tumors

MK-6482 also has shown clinical activity in VHL disease-associated CNS hemangioblastoma and pancreatic tumors with ORR of 24.5% (12/49) and 29% (9/31), respectively, similar to the ORR observed in RCC (Appendix 1: [Table 2]). Disease control rates in CNS hemangioblastoma and pancreatic tumors were also high, respectively 98% and 100%. No participant experienced disease progression in CNS hemangioblastoma or pancreatic tumors. In retinal hemangioblastomas, improvements from baseline in ≥50% of lesions were observed at Weeks 13, 25, 37, and 49 during treatment (Appendix 1: [Table 3]). There was no reported progression of retinal lesions.

These findings underscore the common underlying pathophysiology of these tumors and further support the benefit of MK-6482 in this patient population.

Response to comment #2:

Merck acknowledges Agency's advice.

Response to comment #3:

Merck proposes to provide cumulative safety data (pooled from Studies MK-6482-001 and -004; monotherapy with MK-6482) in the NDA submission. [Please refer to Company Response for Question 7]. These data, while encompassing patients both with advanced RCC (Study 001) and VHL-disease associated RCC (Study 004), will allow assessment of the tolerability of MK-6482 with prolonged treatment duration. Particularly in this setting, long-term tolerability will translate in durable clinical benefit. Merck will also provide information, in the potential NDA submission, on surgical procedures prior to study entry, as well as any surgical procedures patients underwent while on Study 004. From the current data, 42 of 61 (68.9%) patients had a history of renal surgical procedures, including kidney ablation, partial nephrectomy, nephrectomy, radical nephrectomy, tumorectomy (renal), renal tumor excision, and carcinoma excision (kidney). Of these, 32 of 61 (52.5%) patients had a history of partial nephrectomy prior to study entry. Regarding on-study surgeries/procedures (including cryotherapy and ablation), only 1 patient required surgery for RCC as of 29-MAR-2020. This patient enrolled into the study with 2 tumors (29.4 mm in the left and 29.8 mm in the right) identified by investigator as target lesions. By week 49, the left target tumor had decreased in size to 14.6 mm (~50% reduction) as assessed by the investigator. The right target tumor, however, grew 3 mm to 32.7 mm thus surpassing the 3 cm threshold and a right partial nephrectomy was performed. IRC also assessed this patient as having achieved SD as best response, until PD was reported at Week 61. As for on-study procedures/surgeries in other sites of disease, there were no procedures for pancreas tumors, one for CNS hemangioblastoma (cerebellar radiation), and one for retinal hemangioblastoma (vitrectomy for the patient who had Grade 4 retinal detachment, unrelated).

Merck will conduct a comprehensive literature review regarding patients with VHL disease-associated RCC and expected rates of surgery. Merck proposes to include the summary of literature review into the dossiers for NDA submission. In addition, Merck is evaluating the feasibility of conducting a real-world data study using electronic medical record data to evaluate the expected rates of surgery and surgical complications in a similar setting as the clinical trial in the absence of treatment. More broadly, the ability to report medication use including oncologic medication use and use of psychiatric medications, given the reported anxiety of patients with VHL patients, will also be explored.

Meeting Discussion: The Sponsor presented the updated data as of March 29, 2020. FDA stated that in light of the natural disease history of VHL, a longer follow up remains important. FDA noted that the Sponsor stated that all confirmed responders would have been followed for at least 6 months from initial response at that point and that they would provide further DoR update during the NDA review.

The FDA requested that topline data from the June DCO be provided prior to NDA submission and the Sponsor agreed. FDA clarified that the efficacy data update would have a data cutoff of November 2020; FDA will consider this data with updated DOR for review.

Question 5: Does the Agency agree that clinical efficacy data (including ORR, DCR and DOR) from 61 patients in MK-6482-004, with a minimum follow-up of 14 months on active patients, could serve as the primary analysis dataset to support a Regular Approval NDA pathway for treatment of VHL disease-associated RCC?

FDA Response: The adequacy of the sample size will depend on the effectiveness and safety profile of MK-6482 and the ability of your data to demonstrate clinical benefit in the proposed patient population. We note the 95% CI for the ORR at this time is wide.

Whether this trial can support an approval will be based on the benefit-risk assessment that includes magnitude of overall response rate, duration of response and the overall toxicity profile. See also response to Question 4.

The data cut-off date should allow a minimum of 6 months follow-up from initial response for all confirmed responders to ensure appropriate mature data for the duration of response endpoint.

Sponsor Response [Submitted June 9, 2020]: Merck wishes to discuss this question with the Agency at the EOP2 meeting.

As described in the response under Question 4, latest data from the March 29, 2020, cut-off show that the confirmed ORR was 32.8% (95% CI: 21.3%, 46. 0%) and all 20 of 20 RCC responders have ongoing responses, range (min 12.1 weeks +, max 49.4 weeks +) for the responses. The initial response for the latest of the confirmed responders occurred on November 27, 2019, thus data from an updated data cut-off of June 1, 2020 would allow for the requested minimum of 6 months follow-up from initial response for all 20 confirmed responders observed in the March 29, 2020, data cutoff. Merck believes that it is reasonable to utilize the data cut-off on June 1, 2020, as the basis for NDA submission.

In order to further support the benefit-risk assessment of MK-6482 in the target population, Merck proposes to provide efficacy and safety update reports during the

NDA review. The corresponding cut-off date is tentatively planned for November 2020, which would allow approximate 12 months follow-up of those 20 responders from the onset of responses. The efficacy update report can provide appropriate mature data to ensure the evaluation of the duration of response endpoint.

Meeting Discussion: See Meeting Discussion for Question 4.

Question 6: During the review of IND 137354, the Sponsor and Agency discussed a comparison of linear growth rate (LGR) of VHL disease-associated RCC before and after treatment to help contextualize the single arm trial results. The Sponsor has completed the LGR assessment in the Study MK-6482-004 as well as literature review on publications related to LGR. Does the Agency agree that the LGR assessment, and related published literature, supports the demonstration of clinical benefit and could support the proposed NDA?

FDA Response: The data provided from the literature and Study MK-6482-004 to demonstrate LGR in VHL disease-associated RCC lesions could be used as supportive data for the proposed NDA. Whether this data is sufficient to support demonstration of clinical benefit will be determined at the time of NDA review.

Sponsor Response [Submitted June 9, 2020]: Merck acknowledges Agency's advice. No discussion is needed at the EOP2 meeting.

Meeting Discussion: None.

Question 7: Does the Agency agree that the safety data pooled from Studies MK-6482-001 and MK-6482-004 are sufficient to support the NDA submission for treatment of VHL disease-associated RCC?

FDA Response: Your proposal generally appears reasonable. We are concerned that the single arm design of this trial may limit characterization of the safety profile of MK-6482, and that in this setting, tolerability and safety are key components of the risk/benefit analysis. Provide an assessment of cumulative toxicity of a prolonged duration of treatment. Also comment on the etiology and reversibility of hypoxia observed as an adverse reaction. Whether the submitted pooled data is sufficient will be a review issue.

Sponsor Response [Submitted June 9, 2020]: Merck wishes to discuss this question at the EOP2 meeting.

Summary on cumulative safety data from Study MK-6482-004:

Cumulative safety data from Study MK-6482-004 are presented below, based on the cut-off on 29-MAR-2020 representing a minimum of 52 weeks of follow-up for all active patients [Appendix 1: Sec. 4]. There are 56 out of 61 patients (91.8%) remaining on

therapy for at least 1 year. Additionally, 58 out of 61 (95.1%) have been on therapy for longer than 6 months.
All participants experienced AEs during the study [Table 2] [Appendix 1: Sec. 4; Table 9]. The most common AEs reported in ≥ 20% of participants were anemia, fatigue, dizziness, and headache, and nausea Table 24 in [Appendix 2].

Thirteen of 61 participants (21.3%) reported ≥ Grade 3 AEs [Table 2]. Fatigue in 3 participants (4.9%) considered related, anemia in 3 participants (4.9%) considered related, and hypertension in 2 participants (3.3%) both unrelated were the only individual AEs of ≥ Grade 3 severity reported by 1 participant Table 25 in [Appendix 2]. One Grade 4 event of retinal detachment and one Grade 5 event of toxicity to various agents (acute fentanyl toxicity) were reported, both considered unrelated to study treatment by the investigator Table 26 and Table 27 in [Appendix 2]. To date, the important identified risks of MK-6482 are erythropoietin (EPO) dependent anemia and hypoxia (54 participants had anemia and 1 participant had hypoxia in study MK-6482-004 Table 24 in [Appendix 2]).

Table 2
Overall Summary of Adverse Events
Safety Analysis Set

Category	PT2977 (N=61) n (%)
Number of adverse events	685
Subjects with any adverse events	61 (100.0)
Subjects with any treatment-related adverse events	60 (98.4)
Subjects with any adverse events of CTCAE Grade 3 and Above	13 (21.3)
Subjects with any serious adverse events	8 (13.1)
Subjects with any treatment-related serious adverse events	2 (3.3)
Severity grade (Refer to NCI-CTCAE V 4.03)[1]	
Mild(Grade 1)	17 (27.9)
Moderate(Grade 2)	31 (50.8)
Severe(Grade 3)	11 (18.0)
Life Threatening(Grade 4)	1 (1.6)
Death(Grade 5)	1 (1.6)
Related Severity grade (Refer to NCI-CTCAE V 4.03)[1]	
Mild(Grade 1)	27 (44.3)
Moderate(Grade 2)	26 (42.6)
Severe(Grade 3)	7 (11.5)
Subjects with adverse events leading to death	1 (1.6)
Subjects with adverse events leading to treatment discontinued	2 (3.3)
Subjects with adverse events leading to dose reduced	8 (13.1)
Subjects with treatment-related adverse events leading to dose reduced	6 (9.8)
Subjects with adverse events leading to dose interrupted	22 (36.1)
Subjects with treatment-related adverse events leading to dose interrupted	13 (21.3)

Adverse events up to 28 days of last dose are included.
[1] Adverse events by maximum severity grade for subject level.

Date of Data Cut-off: 29MAR2020

Source: [P004V01MK6482: adam-adsl; adae]

Hypoxia as an observed AE:

Study MK-6482-004; data cut-off 29-MAR-2020:
With a minimum 52 weeks follow-up, 56 out of 61 patients are still active receiving treatment and only one patient with hypoxia was observed. This patient had Grade 3 hypoxia and evidence for restrictive lung disease pattern based on spirometry while CT was negative for pulmonary embolus. Medical history included hypertension and glaucoma. The patient was asymptomatic and never required supplemental oxygen. Oxygen saturation was 86% at the week 9 visit and 83% at week 13 at which point study drug was interrupted for 8 days. The subject has since been maintained at the reduced dose of 80mg q.d. and has not had any further hypoxic events with oxygen saturations ranging from 91% to 96% via pulse oximetry in subsequent follow-up visits.

Cumulative data from Study MK-6482-001, -003 and -004; data cut-off 6-SEP-2019:
As of 06 Sep 2019, 25 patients (25/185 pts, 13.5%) reported hypoxia in MK-6482 -001, -003 and -004 (Please note: MK-6482-003 is a Phase 2 single study of MK-6482 in combination with cabozantinib). No cases were fatal or life-threatening. 12 cases (12/25, 48%) were Grade 3 in severity, the remaining cases were Grade 2 in severity. 8 cases were serious (8/25, 32%). Of these 8 cases, 6 were assessed as related to MK-6482. 2 of these 6 cases (33% of related SAEs) were asymptomatic. The other 4 cases presented with contemporaneous symptoms including dyspnea, cough, fatigue, headache, vomiting.

Hypoxia is reversible and has been treated with supplemental oxygen therapy (17/25 cases, 68%), dose reduction (3/25 cases, 12%), dose interruption (8/25, 32%) and treatment for the concomitant acute co-morbid condition (e.g. antibiotics for pneumonia). 2 patients (2/25 cases, 8%) came off study for hypoxia. The median time to onset of hypoxia is 23 days.

Sponsor's assessment on etiology and reversibility of hypoxia:

Hypoxia is most often observed (23/25, 92%) in patients with concomitant acute co-morbid conditions (pneumonia, pleural effusion, bronchial hemorrhage, diastolic dysfunction, general anesthesia, pulmonary metastases, restrictive lung changes), or pre-existing co-morbid conditions (obesity, sleep apnea, extensive cardiac or pulmonary medical history). In 2 cases (2/25, 8%), the only pre-existing cardiac or pulmonary medical history was hypertension.

In patients treated with supplemental oxygen (17/25, 68%), no end date was reported for 4 events. For the remaining hypoxia events treated with supplemental oxygen, the estimated approximate median duration of supplemental oxygen treatment was 13 days (range: 1-57 days).

HIF-2α hypothetically plays a role in hypoxic pulmonary vasoconstriction (HPV). In normal physiology the HPV response is thought to minimize ventilation/perfusion (V/Q) mismatch in an area of the lung which is poorly ventilated. While the mechanism of hypoxia as observed in clinical experience has not been fully understood, it is hypothesized that MK-6482 may inhibit the HPV normal physiologic response in the setting of local ventilatory distress and potentially exacerbate the V/Q mismatch resulting in hypoxia.

Summary:

Based on the current data with a minimum of 52 weeks of follow-up, MK-6482 is well tolerated with the majority of AEs being mild to moderate with only one treatment related discontinuation and only 13% requiring dose reduction. There were no treatment related AEs of Grade 4 or 5. In addition to the current data above, Merck proposes to provide cumulative safety data (pooled from Studies 001 and 004; monotherapy with MK-6482) and a detailed assessment on hypoxia in the NDA submission.

Meeting Discussion: FDA stated that the proposal to provide pooled safety data from Study 001 and 004 appears reasonable, but ultimately will be a review issue.

Question 8: Does the Agency agree that the clinical efficacy data (ORR and DOR) from the Phase 2 clinical study MK-6482-004 demonstrates a sufficient magnitude of clinical benefit and could support an application for the Breakthrough Therapy Designation?

FDA Response: We have received your application for Breakthrough Therapy Designation and it is currently under review.

Sponsor Response [Submitted June 9, 2020]: Merck acknowledges Agency's comments. No discussion is needed at the EOP2 meeting.

Meeting Discussion: None.

Question 9: Based on clinical practice and retrospective verification of VHL disease diagnosis in the Study MK-6482-004 (Study PT2977-202), the Sponsor proposes that a companion diagnostic test is not needed for the safe and effective use of MK-6482 for VHL disease-associated RCC. Does the Agency concur?

FDA Response: Yes, we agree. The standard practice diagnosis of VHL is acceptable from a regulatory perspective in this setting. For each patient in study MK-6482-004 provide any relevant family history and the method of diagnosis of VHL disease in an NDA submission.

Post Preliminary Meeting Comment sent June 6, 2020: Although our response document on Friday June 5, 2020, indicated that a companion diagnostic device would not be needed for this application, discussions are presently ongoing and

we may provide you with updated information in the near future which may state otherwise.

Post Preliminary Meeting Comment sent June 9, 2020: You have identified a therapeutic target population that includes a requirement for a genetic test result. While the we agree that such testing is part of the diagnosis of VHL-disease-associated RCC, such tests are not harmonized or standardized with respect to the sequencing and interpretation of VHL candidate mutations.

We acknowledge the precedent example that you cited for RPE65, however, as you noted in the submission, the majority of VHL mutations are unique and therefore VHL-disease mutations require comprehensive genetic sequencing and interpretation. ClinVar has 1034 variant records for the VHL gene.

We recommend that you discuss with CDRH a plan forward for the availability of an FDA cleared/approved test for either the diagnosis of VHL-disease or as a companion diagnostic for selecting VHL-disease associated RCC for treatment with MK-6482 to ensure that an analytically valid test with, for example, an established list of rules for identifying pathogenic and likely pathogenic variants, and that such references are consistent with ClinVar.

Sponsor Response [Submitted June 9, 2020]: Merck acknowledges Agency's comments and will provide Agency-requested information in the NDA submission. No discussion is needed at the EOP2 meeting.

Meeting Discussion: None.

Post Meeting Comment: We recommend that you discuss with CDRH the regulatory path forward for a test for VHL variant detection for labeling. While CDRH recognizes some patients may be diagnosed in the absence of genetic testing, the current ITT population in your trial required a VHL genetic variant, almost all of which were unique. Therefore, an analytically validated comprehensive genetic panel with appropriate criteria for assigning pathogenicity should be available. CDRH believes the test is likely a candidate for the de novo process (i.e., class II). One option may be to partner with a laboratory capable of offering this test to expedite the availability of an analytically validated test.

Additional Comments:

1. **For an accelerated approval, there should generally be a confirmatory trial underway at the time of action. Provide trial design for confirmation of clinical benefit should the results of study MK-6482-004 lead to an accelerated approval. Justify the primary endpoint(s) you choose for the confirmatory trial.**

2. **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).**

Sponsor Response [Submitted June 9, 2020]:

Response to comment #1: Merck wishes to discuss the topic regarding confirmatory trial at the EOP2 meeting. Merck believes that a Regular Approval is warranted due to following rationale:

1) Available data from MK-6482-004 demonstrates meaningful response rate and durability of response, and high disease control rate in the target indication. This is further supported by meaningful responses observed from non-RCC tumors.

2) The target indication of VHL disease-associated RCC is a rare disease condition without systemic therapeutic option.

Response to comment #2: Merck acknowledges FDA's advice related to the QT evaluation report. No discussion is needed at the EOP2 meeting.

Meeting Discussion Comment 1: The decision of accelerated approval vs regular approval will be a review issue and will depend on data demonstrating clinical benefit.

Regarding labeling of off-target tumor responses: The Sponsor asked FDA about the feasibility of labeling responses in non-renal tumors. FDA stated that all relevant data should be provided and that this would be a review issue.

3.0 ADDITIONAL INFORMATION

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.[1]

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

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

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. 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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, 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.[2]

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.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] 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.

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[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[5]

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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.

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[6] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[7]

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]

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,* and the associated conformance guide, *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*

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[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download
[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

(BIMO) Inspections for CDER Submissions (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

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

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

- Assessment Aid[12]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None.

[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/

JEANNETTE L DININ
06/30/2020 05:02:06 PM

CHANA WEINSTOCK
07/01/2020 11:30:49 AM