CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761467Orig1,Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 161465

MEETING MINUTES

Merck Sharp & Dohme LLC
Attention: Janice Kim, PharmD, MS
Director, Global Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY34-A2014
Rahway, NJ 07065

Dear Dr. Kim:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-3475A.

We also refer to the video conference between representatives of your firm and the FDA on January 6, 2025. The purpose of the meeting was to discuss a proposed original Biologics License Application (BLA) submission for MK-3475A, a novel hyaluronidase as a permeation enhancer administered by subcutaneous injection for all currently approved adult and pediatric solid tumor indications approved within BLA 125514 for intravenous administration of pembrolizumab.

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

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

If you have any questions, please contact me via email at Ashley.Lane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ashley Lane, MS
Senior Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	January 6, 2025; 9:00 AM – 10:00 AM, EST
Meeting Location:	FDA will provide a CALL-IN NUMBER AND PASSCODE
Application Number:	IND 161465
Product Name:	MK-3475A
Indication:	All currently approved adult and pediatric (12-17 years old) solid tumor indications for intravenous pembrolizumab
Sponsor Name:	Merck Sharp & Dohme LLC
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Timil Patel, MD
Meeting Recorder:	Ashley Lane, MS

FDA ATTENDEES (tentative)

Paz Vellanki, MD, PhD, Acting Supervisory Associate Director, Division of Oncology 2 (DO2)
Timil Patel, MD, Cross Disciplinary Team Lead, DO2
Satinder (Mona) Choudhary, PharmD, Clinical Analyst, DO2
Xiaoxue Li, PhD, Statistical Team Lead, Division of Biometrics V (DBV)
Qingyu (Sophia) Chen, PhD, Statistical Reviewer, DBV
Hong Zhao, PhD, Master Pharmacokineticist, Division of Cancer Pharmacology II (DCP II)
Xiulian Du, PhD, Clinical Pharmacology Reviewer, DCP II
Da Zhang, PhD, Pharmacometrics Reviewer, Division of Pharmacometrics
Idara Ojofeitimi, Chief, Project Management Staff, Division of Regulatory Operations (DRO)
Ashley Lane, Senior Regulatory Health Project Manager, DRO

SPONSOR ATTENDEES

Sunita Zalani, PhD, Vice President, Global Regulatory Affairs
Robert Kester, MS, Executive Director, Global Regulatory Affairs
Janice Kim, PharmD, Principal Scientist, Global Regulatory Affairs
M. Catherine Pietanza, MD, Vice President, Clinical Research-Oncology
Greg Lubiniecki, MD, Vice President, Clinical Research-Oncology
Renata Eiras, MD, Senior Director, Clinical Research-Oncology
Mallika Lala, PhD, Senior Director, Quantitative Pharmacology and Pharmacometrics - Immuno/Oncology (QP2-IO)

Azher Hussain, PhD, Associate Vice President, Quantitative Pharmacology and Pharmacometrics -Immuno/Oncology (QP2-IO)
Gina Song, PhD, Director, Quantitative Pharmacology and Pharmacometrics - Immuno/Oncology (QP2-IO)
Anshu Marathe, PhD, Quantitative Pharmacology and Pharmacometrics - Immuno/Oncology (QP2-IO)
Yue Shentu, PhD, Executive Director, Biostatistics
Todd Gruber, MD, Associate Vice President, Drug Safety

BACKGROUND

Meeting Purpose

On November 8, 2024, the FDA received a Type B Pre-BLA meeting request from Merck to discuss the proposed submission of an original Biologics License Application (BLA) for MK-3475A. This product is a fixed-dose combination of two active ingredients, pembrolizumab (MK-3475) and berahyaluronidase alfa (MK-5180), designed for subcutaneous (SC) administration. Merck is seeking approval for all adult and pediatric (ages 12 to 17) solid tumor indications that are currently approved under BLA 125514 for the intravenous (IV) administration of pembrolizumab.

FDA sent Preliminary Comments to Merck and January 2, 2025.

Regulatory

On December 14, 2022, the FDA issued a "Study May Proceed" letter for the clinical protocol titled, "A Phase 3 Randomized, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab Co-formulated With Hyaluronidase (MK-3475A) Versus IV Pembrolizumab, Administered With Chemotherapy, in the First-Line Treatment of Participants With Metastatic Non-Small Cell Lung Cancer."

On March 4, 2024, FDA provided a written response to Merck's Type C meeting request, offering feedback on the content and format of a planned BLA for the SC fixed-dose combination of pembrolizumab and berahyaluronidase alfa (MK-3475A). FDA generally agreed with the proposed presentation of safety data and the Integrated Summary of Safety (ISS). FDA also advised Merck to include a list of preferred terms for defining local injection site reactions in the marketing application and indicated that narratives should be provided for all reported deaths, not clearly due to disease progression.

On March 15, 2024, FDA held a Type D meeting with Merck to discuss their approach for addressing pediatric requirements in the original application. During the meeting, FDA advised that providing results from modeling and simulation studies to support dosing in adolescent patients could be an appropriate course of action.

On June 14, 2024, FDA issued an Agreed Initial Pediatric Study Plan (iPSP) letter, granting a partial waiver in pediatric patients <12 years of age and deferral of a molecularly-targeted pediatric cancer investigation in pediatric patients 12 to <17 years of age. Additionally, FDA stated that Merck may be exempt from conducting a molecularly-targeted pediatric cancer investigation if they complete the modeling and simulation studies to support the licensure of MK-3475A in adolescents.

On October 25, 2024, Merck submitted notification to use a rare pediatric disease priority review voucher (PRV) for this application.

Nonclinical

MK-3475A is a co-formulation of the PD-1 blocking antibody, pembrolizumab, and the human recombinant hyaluronidase, MK-5180 (berahyaluronidase alfa), intended for SC administration. MK-5180 is a novel variant of mature wild-type human hyaluronidase, PH20. Nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies supporting IV administration of pembrolizumab were previously reviewed under BLA 125514. To support a new BLA for SC administration of MK-3475A, Merck has conducted in vivo IV and SC PK studies with MK-5180 and pembrolizumab; a single-dose SC local tolerance study with pembrolizumab in rabbits; repeat-dose SC toxicology studies with MK-5180 up to 26-weeks duration in rats and up to 4-weeks duration in cynomolgus monkeys; a 1-month repeat-dose SC local tolerability study with MK-3475A in cynomolgus monkeys; a fertility study with SC MK-5180 in rats; embryofetal development studies with SC MK-5180 in rats and rabbits; a pre- and postnatal development toxicity study with SC MK-5180 in rats; and an in vitro immunogenicity assessment with MK-5180. In the proposed new BLA for SC MK-3475A, Merck proposes to cross-reference BLA 125514 for nonclinical studies conducted to support the approval of IV pembrolizumab, and to submit nonclinical studies evaluating the SC administration of pembrolizumab, MK-5180, and MK-3475A in Modules 2.4, 2.6, and 4 of the original BLA submission.

Clinical

Merck intends to submit a BLA for MK-3475A supported by one pivotal study (MK-3475A-D77) and three supporting studies listed below for approval of all adult solid tumor indications that are currently approved under BLA 125514 for the IV administration of pembrolizumab. Merck also intends to use modeling and simulation analyses to support approval of MK-3475A in pediatric patients 12 to 17 years of age.

Supporting Studies

- **Study MK-3475A-C18 (NCT05017012):** This is a single-arm bioavailability and safety study of MK-3475A in patients with advanced or metastatic

melanoma, non-small cell lung cancer (NSCLC), or renal cell carcinoma (RCC) to support the dosage selection for the pivotal study and to provide a preliminary assessment of whether measuring the anti-berahyaluronidase alfa antibodies in the pivotal study is necessary. The combined data from Study MK-3475A-C18 (Arms 1 to 3) with that from Study MK-3475A-D77 are being used to update the combined SC and IV population PK model. The data from Study MK-3475A-C18 (Arm 4) are used to validate the model for simulation of PK endpoints and dosage regimen extrapolation from every six weeks (Q6W) to every three weeks (Q3W).

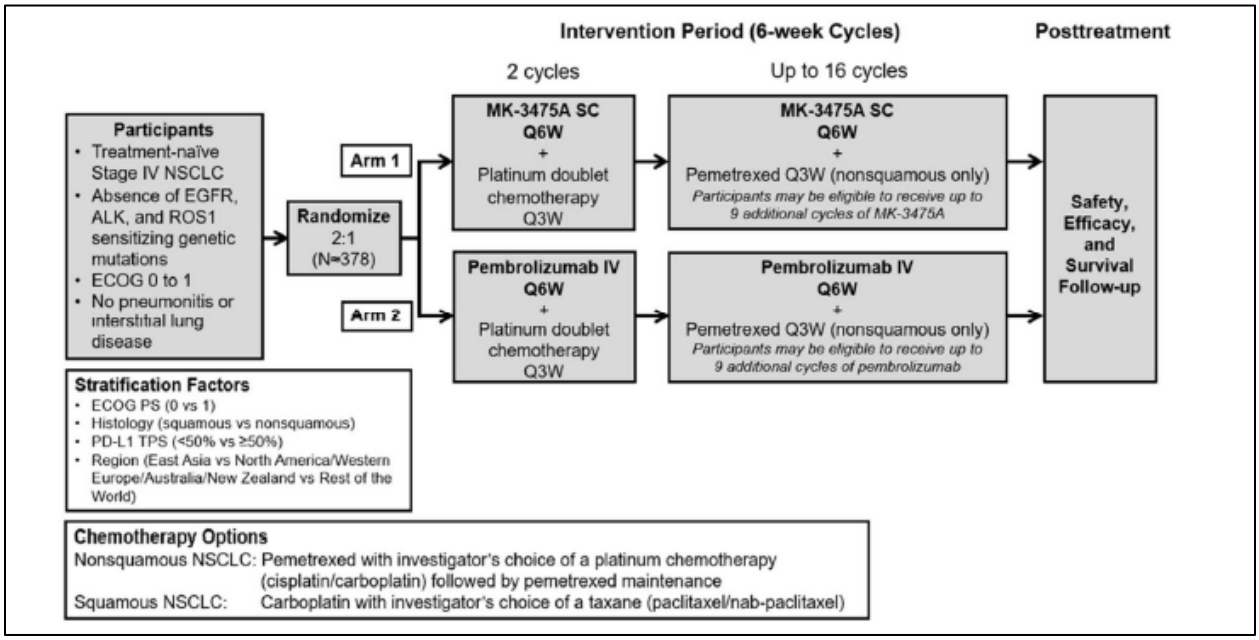
- **Study ALT-BB4-01 (NCT05232175):** This is a single-arm, single dose study of MK-5180 (berahyaluronidase alfa) in healthy volunteers to evaluate the tolerance, safety, and PK of MK-5180 (also referred to as ALT-B4).
- **Study MK-3475-AF11 (NCT06099782):** This is a randomized, open-label, two-arm crossover, patient preference study of MK-3475A to demonstrate the safety of switching from one route of administration to another.

Pivotal Study MK-3475A-D77

This is a randomized, open-label, active-controlled, parallel-group, multiregional trial to evaluate the PK and safety of MK3475A versus pembrolizumab IV, administered with histology-based platinum doublet chemotherapy, for the first-line treatment of patients with metastatic non-squamous or squamous NSCLC. Patients with EGFR, ALK, or ROS-1 sensitizing genetic alterations were excluded from the trial.

The dual primary endpoints of the trial are to compare Cycle 1 $AUC_{0\text{-}6\ weeks}$ and steady-state (Cycle 3) C_{trough} for MK-3475A SC vs pembrolizumab IV with every six weeks (Q6W) dosing regimens. The PK comparability was evaluated with the geometric mean ratio (GMR) of MK-3475A SC over pembrolizumab IV at each primary PK endpoint that is not less than 0.8. Secondary efficacy endpoints were descriptive and included overall response rate (ORR), progression free-survival (PFS) and duration of response (DOR) per RECIST v.1.1 as assessed by Blinded Independent Central Review (BICR); overall survival (OS); and patient reported outcomes (PROs). Figure 1 describes the study schema.

Figure 1: Study Schema MK-3475AD77



Source: Sponsor meeting package, page 21

Adult patients were randomized in a 2:1 ratio to one of two treatment arms:

- Arm 1 (MK-3475A 790 mg subcutaneously Q6W plus chemotherapy) or
- Arm 2 (pembrolizumab 400 mg IV Q6W plus chemotherapy).

Patients with squamous NSCLC received four cycles of carboplatin combined with a taxane (either paclitaxel or nab-paclitaxel). Patients with nonsquamous NSCLC received four cycles of pemetrexed paired with a platinum-based agent (cisplatin or carboplatin), followed by pemetrexed maintenance therapy.

MK-3475A SC and pembrolizumab IV were both administered Q6W for up to 18 cycles. Cross over was not permitted. Randomization was stratified by ECOG performance status (0 vs 1), histology (squamous vs non-squamous), tumor PD-L1 expression levels (TPS <50% vs ≥50%), and geographic region (East Asia vs North America/Western Europe/Australia/New Zealand vs Rest of the World).

Merck reports that, as of the data cutoff (DCO) on July 12, 2024, a total of 377 patients were randomized: 251 to the MK-3475A plus chemotherapy arm and 126 to the pembrolizumab IV plus chemotherapy arm. Table 2 describes the baseline patient characteristics.

Table 1 – MK-3475AD77, Baseline Patient Characteristics (Intent to Treat Population)

	MK-3475A plus Chemotherapy N=251	Pembrolizumab IV plus Chemotherapy N=126
Male	73%	68%
Median Age	65	66
Race		
White	63%	62%
Asian	30%	29%
Black	2%	4%
Ethnicity		
Hispanic/Latino	30%	33%
Non-Hispanic/Latino	70%	67%
Geographic Region		
East Asia	29%	29%
North America/Western Europe/New Zealand	5%	6%
Rest of World	67%	66%
PD-L1 Status		
TPS <1%	40%	45
TPS 1-49%	32%	27
TPS ≥50%	9%	20
Unknown	9	8
Histology		
Non-Squamous	67%	66%
Squamous	33%	34%
Never Smoker	15%	18%

Source: Adapted from Sponsor briefing document, page 24

Study Results

Merck reports that the noninferiority criterion was met based on the following PK analyses in the per-protocol population, which included patients with evaluable PK data (245 in the MK-3475A plus chemotherapy arm and 126 in the pembrolizumab IV plus chemotherapy arm):

- For Cycle 1 $AUC_{0\text{-}6\ weeks}$, the geometric mean ratio (GMR) was 1.14 (96% CI: 1.06, 1.22; one-sided p-value < 0.00001), meeting the noninferiority threshold with the originally assigned alpha of 0.02.
- For steady-state (Cycle 3) model-based C_{trough}, the GMR was 1.67 (94% CI: 1.52, 1.84; one-sided p-value < 0.00001), meeting the noninferiority threshold with the originally assigned alpha of 0.03.

The incidence of treatment-emergent anti-drug antibodies (ADA) was 1.4% in the MK-3475A plus chemotherapy arm and 0.9% in the pembrolizumab IV plus chemotherapy arm.

Based on descriptive analyses, the ORR based on BICR per RECIST v.1.1 for MK3475A plus chemotherapy was 45.4% in the MK-3475A plus chemotherapy

arm, compared to 42.1% in the pembrolizumab IV plus chemotherapy arm, with an ORR ratio of 1.08 (95% CI: 0.85, 1.37). The median PFS was 8.1 months (95% CI: 6.3, 8.3) in the MK-3475A plus chemotherapy arm, compared to 7.8 months (95% CI: 6.2, 9.7) in the pembrolizumab IV plus chemotherapy arm. The PFS hazard ratio (HR) was 1.05 (95% CI: 0.78, 1.43).

Overall, the median duration of follow-up was 8.6 months (range: 0.2, 16.4), and the median OS was not reached in either intervention arm. The OS HR was 0.81 (95% CI: 0.53, 1.22).

Tables 2 and 3 describe the summary of safety based on a DCO date of July 12, 2024.

Table 2 – MK-3475AD77, Summary of Safety

	MK-3475A plus Chemotherapy N=251	**Pembrolizumab IV plus Chemotherapy N=126**
Any TEAE	99%	98%
Grade ≥3 TEAE	60%	65%
SAE	39%	41%
Fatal AE	10%	10%
TEAE Leading to Discontinuation of Any Study Treatment	25%	24%
TEAE Leading to MK-3475A or Pembrolizumab IV Discontinuation	16%	17%
TEAE Leading to Any Chemotherapy Discontinuation	23%	19%

Source: Adapted from Sponsor briefing document, page 37

Table 3 – Patients with Any Grade AE with ≥5% Difference Between Arms

	MK-3475A plus Chemotherapy N=251	**Pembrolizumab IV plus Chemotherapy N=126**
Anemia	59%	71%
Neutropenia	43%	33%
Decreased Appetite	11%	22%

Source: Adapted from Sponsor briefing document, page 37

In the MK-3475A plus chemotherapy group, six patients (2.4%) experienced an injection site reaction, all of which were grade 2 or less.

Merck proposes to submit a safety update report for MK-3475A-77A from a data lock of July 12, 2024, to a DCO date of November 6, 2024 (an additional 3.8 months from last DCO) within 60 days of the BLA submission.

Merck also considers the existing companion diagnostic (CDx) products would apply to the corresponding MK-3475A indications, without requiring updates to the CDx product labeling.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical/PK

1. Does the Agency agree that the totality of PK, efficacy, and safety data of MK-3475A Q6W from the pivotal study, MK-3475A-D77, along with data from supporting studies are sufficient to form the basis of the original BLA submission and to support the bridging of the approved adult and pediatric (12-17 years old) solid tumor indications of intravenous pembrolizumab?

FDA Response: Your proposal to submit an original BLA appears reasonable. However, please address the following issues:

a. For your secondary endpoint of duration of response, please also provide median estimates with corresponding 95% CI's.

Merck's Response Received via Email on January 3, 2025: The median estimates and corresponding 95% CIs for duration of response are available in the MK-3475A-D77 CSR section 11.2.7 and Module 2.5 section 4.1.3.

Discussion During Meeting: Discussion did not occur during the meeting.

b. Clarify what data will be included in the BLA under Module 5 Modeling & Simulation-PK and ADA for MK-5180 (5.3.5.3) as it is not clear if the PK and immunogenicity of MK-5180 (berahyaluronidase alfa) were adequately evaluated in Study MK-3475A-C18 and Study ALT-BB4-01, and if immunogenicity of MK-5180 was also assessed in Study MK-3475A-D77 to inform labeling.

Merck's Response Received via Email on January 3, 2025: Merck would like to clarify that the PK and immunogenicity of MK-5180 was evaluated in both phase 1 study MK-3475A-C18 and phase 3 study MK-3475A-D77. MK-5180 PK and ADA analysis reports for each study, MK-3475A-C18 and MK-3475A-D77, will be included in Module 5.3.5.3. The PK and immunogenicity of MK-5180 was also assessed in Study ALT-BB4-01 and the respective analysis report will be included in Module 5.3.1.1.

The results of PK and immunogenicity of MK-5180 in MK-3475A-C18, MK-3475A-D77, and ALT-BB4-01 are also summarized in the respective CSRs, Module 2.7.2 and Integrated Summary of Immunogenicity (ISI).

Discussion During Meeting: Discussion did not occur during the meeting.

c. Provide modeling and simulation data which may help support approval of MK-3475A in pediatric patients aged 12-17 years.

Merck's Response Received via Email on January 3, 2025: Modeling and simulation data to support approval of MK-3475A in pediatric patients aged 12-17 years will be included in the BLA. Modeling and simulation report supporting MK-3475A dosage in pediatric patients will be placed in Module 5.3.5.3 and Pediatric Rationale will be included as an Appendix for Module 2.5.

Discussion During Meeting: Discussion did not occur during the meeting.

2. Does the Agency agree that the data for MK-3475A Q3W dosing regimen from MK-3475A-C18 and MK-3475A Q6W dosing regimen from MK-3475A-D77, along with the modeling and simulation analyses to bridge both SC schedules, are sufficient to support Q3W dosing regimen for MK-3475A?

FDA Response: We generally agree that the totality of these PK data support filing of a BLA. The adequacy of the PK data to support an approval will be determined during the BLA review.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

Safety

3. Does the Agency agree with the sponsor's plan to provide a Safety Update Report?

FDA Response: Your proposal appears reasonable.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

Regulatory

4. **Does the Agency agree with the sponsor's proposal** [redacted] (b) (4)

FDA Response: No, FDA does not agree. [redacted] (b) (4)

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comment. [redacted] (b) (4) (b) (4)

Discussion During Meeting: FDA informed Merck [redacted] (b) (4)

5. A notification of intent to submit a rare pediatric disease priority review voucher (PRV) was submitted on October 25, 2024. Does the Agency anticipate any additional review materials that would assist the Agency during the priority review time period?

FDA Response: We agree with your proposal to submit an assessment aid at the time of the BLA submission. Although no additional review materials are requested at this time, we will notify you if we determine that additional materials are needed during the priority review period.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

6. Does the Agency agree with the eCTD outline of the original BLA submission of MK-3475A, the fixed dose combination of pembrolizumab and berahyaluronidase alfa?

FDA Response: The proposed eCTD outline for the MK-3475A original BLA submission appears reasonable.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

7. Does the Agency agree with the sponsor's proposal for labeling for indications that require the use of FDA-approved tests to identify patients for treatment?

FDA Response: We agree that current CDx approvals can be applied to the corresponding MK-3475A indications without necessitating updates to the CDx product labeling.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

Data Management

8. Does the Agency agree that the Study Data Standardization Plan will be acceptable to support the BLA submission?

FDA Response: The proposed Study Data Standardization Plan appears generally reasonable. We recommend you submit clinical pharmacology relevant data following FDA guidance, *Study Data Technical Conformance Guide*. Refer to Additional Clinical Pharmacology Comments for further details.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comment.

Discussion During Meeting: Discussion did not occur during the meeting.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

Additional Clinical Pharmacology Comments on the Proposed BLA Submission

9. 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". 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.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comments to additional comments 9-13. All requested documents, datasets, reports and analyses will be included in the original BLA submission.

Discussion During Meeting: Discussion did not occur during the meeting.

10. Address the following questions in the Summary of Clinical Pharmacology:
a. What is the basis for selecting the doses and dosing regimens used in the registration trials to support your marketing application?
b. What is the impact of immunogenicity on exposure, efficacy and safety?

Merck's Response Received via Email on January 3, 2025: See Merck's response for Question 9.

Discussion During Meeting: Discussion did not occur during the meeting.

11. 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 PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the PK datasets should be consistent with the numbers used in the clinical datasets.
d. Provide all concentration-time and derived PK 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.
e. Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.

Merck's Response Received via Email on January 3, 2025: See Merck's response for Question 9.

Discussion During Meeting (11e): Merck inquired if it would be acceptable to provide datasets and information regarding dosage modifications for MK-34754A and pembrolizumab IV only, without providing data for chemotherapy. FDA stated that Merck should include an overall summary of dosage modifications for MK-3475A and chemotherapy in their submission, while data on individual dosage modifications may focus solely on MK-3475A.

12. Submit the following for the population PK analysis reports:
a. Standard model diagnostic plots
b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
c. Model parameter names and units in tables.
d. Summary of the report describing the clinical application of modeling results.
e. Refer to the pharmacometric data and models submission guidelines.

Merck's Response Received via Email on January 3, 2025: See Merck's response for Question 9.

Discussion During Meeting: Discussion did not occur during the meeting.

13. Submit the following information and data to support the population PK 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)

Merck's Response Received via Email on January 3, 2025: See Merck's response for Question 9.

Discussion During Meeting: Discussion did not occur during the meeting.

14. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the FDA comment (14 and 15). Notably, the range of PK exposures for pembrolizumab at the proposed dosing regimens 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A are well within the 5-fold range of exposures from 2 mg/kg Q3W to 10 mg/kg Q2W of pembrolizumab IV where flat exposure-response relationship for efficacy and safety have been well characterized and established. Hence the previously established exposure-response for pembrolizumab IV administration also applies to pembrolizumab SC as MK-3475A and the efficacy and safety was generally consistent between pembrolizumab SC administered as MK-3475A and pembrolizumab IV. This ER analysis will be discussed in the Module 2.7.2 and the cross-reference to the previous ER analysis will be provided in Section 2.3 in the Module 2.7.2. Given that Study MK-3475A-D77 showed a narrow exposure range at one dose level compared to the exposure range for IV, ER analysis for Study MK-3475A-D77 independently or pooling with IV data has limitations and does not add further information on well-established ER relationship of pembrolizumab and, therefore, is not planned to be submitted.

Discussion During Meeting: FDA indicated that the plan not to submit exposure-response (ER) data based on a single dose level of SC administration appears reasonable. However, if differences in efficacy or safety are observed between the SC and IV arms, FDA may request additional ER analyses.

15. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of

intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

Merck's Response Received via Email on January 3, 2025: See Merck's response for Question 14.

Discussion During Meeting: Refer to Discussion During Meeting under Question 14.

16. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Merck's Response Received via Email on January 3, 2025: Merck acknowledges the Agency's comments and a description of the pooled non-laboratory-based adverse reactions will be provided in the reviewer's guide. The variables that identify the maximum toxicity grade are included in adlb and adae and will be detailed in the reviewer's guide.

Discussion During Meeting: Discussion did not occur during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Reference the discussion on the contents of a complete application as captured in the above Meeting Minutes.

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

- FDA will make a final determination regarding the need for REMS during the review of the BLA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 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 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

[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
[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

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.

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.

SECURE EMAIL COMMUNICATIONS

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

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.

BIORESEARCH MONITORING INSPECTION PLANNING

Submit the data and information described in the guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of*

[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

Bioresearch Monitoring (BIMO) Inspections for CDER Submissions in your application. [8] The data and information will be used to plan BIMO inspections, facilitate the timely identification of sites for inspection, and ensure that field investigators from the Agency have the information needed to conduct the 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). The guidance should be used in conjunction with the *Bioresearch Monitoring Technical Conformance Guide*, or BIMO TCG, when preparing the required data and information. The BIMO TCG provides more specific directions related to formatting and is updated routinely to provide current specifications, recommendations, and general considerations for preparing the data and information.

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.[9] In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[10]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork

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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

Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[11] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

[11] https://www.fda.gov/media/124795/download

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/

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