NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	351 (a) Biologics License Application (BLA)
Application Number(s)	BLA 761467
Priority or Standard	Priority
Submit Date(s)	January 23, 2025
Received Date(s)	January 23, 2025
PDUFA Goal Date	September 23, 2025
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	See attached electronic signature page
Established Name	Pembrolizumab and berahyaluronidase alfa-pmph
(Proposed) Trade Name	KEYTRUDA QLEX
Pharmacologic Class	Combination product of pembrolizumab, a programmed death-ligand 1 (PD-L1) blocking antibody, and berahyaluronidase alfa, an endoglycosidase
Code name	MK-3475A
Applicant	Merck Sharp & Dohme LLC
Formulation(s)	•Each KEYTRUDA QLEX 2.4 mL single-dose vial contains 395 mg of pembrolizumab and 4,800 units of berahyaluronidase alfa-pmph, and histidine (0.7 mg), histidine hydrochloride monohydrate (4.1 mg), methionine (3.6 mg), polysorbate 80 (0.5 mg), sucrose (168 mg), and Water for Injection, USP. •Each KEYTRUDA QLEX 4.8 mL single-dose vial contains 790 mg of pembrolizumab and 9,600 units of berahyaluronidase alfa, and histidine (1.4 mg), histidine hydrochloride monohydrate (8.2 mg), methionine (7.2 mg), polysorbate 80 (1 mg), sucrose (336 mg), and Water for Injection, USP.
Dosing Regimen	790 mg pembrolizumab/9600 units berahyaluronidase alfa Q6W or 395 mg pembrolizumab/4800 units berahyaluronidase alfa Q3W
Applicant Proposed Indication(s)/Population(s)	All currently approved solid tumor indications for pembrolizumab IV (BLA 125514) for adults and pediatric patients 12 years and older.
Recommendation on Regulatory Action	Traditional Approval for all proposed indications except for tumor mutational burden-high cancers. This indication is approved under Accelerated Approval for KEYTRUDA and should also be approved under Accelerated Approval for KEYTRUDA QLEX.

Recommended Indication(s)/Population(s) (if applicable)	All solid tumor indications for pembrolizumab IV (BLA 125514) approved at the time of the BLA submission, for adults and pediatric patients 12 years and older.

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

Glossary

AC	advisory committee
ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOSI	adverse event(s) of special interest
ALK	anaplastic lymphoma kinase
APaT	All-Participants-as-Treated
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}3wks}$	area under the curve from 0 to 3 weeks
$AUC_{0\text{-}6wks}$	area under the curve from 0 to 6 weeks
BICR	blinded independent central review
BLA	biologics license application
BLQ	below the limit of quantification
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BTC	biliary tract cancer
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
C_{max}	maximal concentration
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSF	colony stimulating factor
CSR	clinical study report
CSS	Controlled Substance Staff
C_{trough}	trough concentration
CV	coefficient of variation
DDI	drug-drug interaction
DHM2	Division of Hematologic Malignancies 2
DILI	drug-induced liver injury
DMC	data monitoring committee

DMF	Drug Master File
dMMR	deficient mismatch repair
DO2	Division of Oncology 2
DOR	duration of response
E-R	exposure-response
EGFR	epidermal growth factor receptor
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EOC	Executive Oversight Committee
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30
EQ-5D-5L	EuroQol 5-dimension 5-level Questionnaire
ETASU	elements to assure safe use
F	bioavailability
FA	final analysis
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDARA	Food and Drug Administration Reauthorization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
GC	gastric cancer
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GLP	good laboratory practice
GM	geometric mean
GMR	geometric mean ration
GRMP	good review management practice
HER2	human epidermal growth factor receptor 2
HNSCC	head and neck squamous cell carcinoma
HR	hazard ration
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG4	immunoglobulin G, subclass 4
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous(ly)
Ka	absorption rate constant
KM	Kaplan-Meier

M&S	modeling and simulation
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSI-H	microsatellite instability-high
NAb	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PRV	priority review voucher
PS	performance status
PSUR	Periodic Safety Update report
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumor
REMS	risk evaluation and mitigation strategy

ROS1	c-ros oncogene 1
RSD	Reference Safety Dataset
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	safety dataset
SGE	special government employee
$t_{½}$	half-life
TB	total bilirubin
TEAE	treatment emergent adverse event
T_{max}	time to reach maximum concentration
TMB-H	tumor mutational burden-high
TNBC	triple negative breast cancer
TPS	tumor proportion score
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale
Vc	central volume of distribution
Vd_{ss}	volume of distribution at steady state

1 Executive Summary

1.1 Product Introduction

Pembrolizumab and berahyaluronidase alfa-pmph（MK-3475A) injection, for subcutaneous (SC) use which will also be referred to as “pembrolizumab SC” or “pembro SC” throughout this review), is a biological product which contains two active ingredients, pembrolizumab (MK-3475) and berahyaluronidase alfa-pmph (MK-5180). Pembrolizumab is a humanized monoclonal IgG4 kappa antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

The pembrolizumab SC product offers patients a different route of administration than intravenous pembrolizumab (which will be referred to as “pembrolizumab IV” or “pembro IV” throughout this review), reduced patient chair time, and shortened physician and nurse time needed to administer the product. Other aspects that differ between pembro SC and pembro IV include:

- Pembrolizumab is in combination with berahyaluronidase alfa for the pembro SC product
- Administration of pembro SC by a healthcare professional in the thigh or abdomen takes approximately 1 to 2 minutes. Pembro IV is administered over a 30-minute infusion.

The recommended dose of pembro SC for adults and pediatric patients 12 years and older who weigh greater than 40 kg is:

- Every 3-week dosing (395 mg/4,800 units): Inject 2.4 mL subcutaneously in the abdomen or thigh over 1 minute.
- Every 6-week dosing (790 mg/9,600 units): Inject 4.8 mL subcutaneously in the abdomen or thigh over 2 minutes.

Pembro SC is not currently approved in the United States (U.S.) or any other part of the world. The Applicant is requesting approval of pembro SC for all adult and pediatric (12 years and older) solid tumor indications which were approved for pembro IV at the time of the original BLA submission.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The marketing application was submitted by the Applicant on January 23, 2025, and is intended to support approval of pembro SC for all adult and pediatric (12 years and older) solid tumor indications which were approved for pembro IV (BLA 125514) at the time of the original BLA submission.

The Applicant submitted the results of Study MK-3475A-D77, a randomized, open-label, active-controlled, parallel-group, multiregional clinical trial comparing the pharmacokinetics (PK),

efficacy, and safety of pembrolizumab SC to pembrolizumab IV in patients with treatment-naïve metastatic NSCLC. A total of 377 patients were randomized (2:1) to pembrolizumab SC 790 mg Q6W in combination with chemotherapy (n=251) or pembrolizumab IV 400 mg Q6W in combination with chemotherapy (n=126). Patients with squamous NSCLC received carboplatin with investigator's choice of a taxane (paclitaxel or nab-paclitaxel) and patients with non-squamous NSCLC received pemetrexed with investigator's choice of a platinum (cisplatin or carboplatin) followed by pemetrexed maintenance. Randomization was stratified by ECOG performance status (0 vs. 1), PD-L1 TPS (<50% vs. ≥50%), histology (squamous vs. non-squamous), and region (East Asia vs. North America/Western Europe/Australia/New Zealand vs. Rest of the World).

This trial had dual primary PK endpoints of Cycle 1 $AUC_{0\text{-}6\ weeks}$ and Cycle 3 (i.e., Steady State) C_{trough}. Overall response rate (ORR) by blinded independent central review (BICR), progression-free survival (PFS) by BICR, and overall survival (OS) were included as secondary endpoints. Safety was an additional secondary endpoint.

The trial met the dual primary endpoints of PK exposure of pembro SC compared to pembro IV. Both PK endpoints met the pre-specified criteria with the lower bound of the 90% CI of the geometric mean ratio (GMR) at 0.8 or above, i.e., GMR for Cycle 1 $AUC_{0\text{-}6weeks}$ was 1.14 (96% CI: 1.06, 1.22) and GMR for Cycle 3 C_{trough}, was 1.67 (94% CI: 1.52, 1.84).

The secondary, descriptive efficacy analysis of ORR per RECIST 1.1 by BICR for patients treated with pembrolizumab SC plus chemotherapy was 45% (95% CI: 39, 52) and was 42% (95% CI: 33, 51) for patients treated with pembrolizumab IV plus chemotherapy. Based on descriptive analyses, no notable differences in PFS or OS were observed between patients who received pembrolizumab SC and pembrolizumab IV.

The safety profile of pembrolizumab SC was compared with the safety profile of pembrolizumab IV. Local injection site reactions was the only newly identified safety signal for pembrolizumab SC.

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Substantial evidence of effectiveness for all the proposed indications for pembrolizumab SC at the dosages of 395 mg Q3W or 790 mg Q6W in adult and pediatric (12 years and older) patients was established based on a demonstration of comparable PK exposure, and comparable ORR, DOR, PFS, and OS in descriptive efficacy analyses, between pembrolizumab SC and pembrolizumab IV in Study MK-3475A-D77; and supportive analyses. The efficacy of MK-3475A SC across solid tumor indications for adult and pediatric (12 to <17 years old) patients is extrapolated from the pembrolizumab IV indications, based on the following:

- Demonstration of comparability of PK exposure of MK-3475A SC to pembrolizumab IV when administered in combination with platinum-based chemotherapy in adult patients with previously untreated metastatic NSCLC.

- The PK are predicted to be comparable between the Q6W dosing regimen at 790 mg SC and the Q3W dosing regimen at 395 mg SC based on modeling and simulation data and supported by available data for the 395 mg Q3W dosing regimen in patients with melanoma in Study MK-3475A-C18.
- The PK of the two proposed SC dosages (i.e., 790 mg Q6W and 395 mg Q3W) is predicted to be comparable between the adult and pediatric patients (12 years and older), based on modeling and simulation. This prediction is supported by the PK comparability observed between adults and pediatric patients (12 to <17 years old) for the approved IV dosages.
- Extrapolation of the SC dosages to other solid tumor indications is supported by PK comparability of SC and IV dosages based on results from the pivotal trial MK-3475A-D77, combined with the demonstrated PK comparability across all approved solid tumor indications for pembrolizumab IV.

  The development approach of pembrolizumab SC is consistent with FDA Guidance on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", which states the following: "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form." When being applied to different doses, regimens, or dosage forms, the above FDA Guidance states that "it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of PK data without an additional clinical efficacy trial".

  In the current application, PK data, together with descriptive analyses of efficacy endpoints (i.e., ORR, PFS, and OS) from Study MK-3475A-D77 can bridge to establish efficacy results between pembrolizumab SC and pembrolizumab IV. Currently approved dosage and administration schedules for pembrolizumab IV are pembrolizumab 200 mg IV Q3W or pembrolizumab 400 mg IV Q6W. Given that the PK comparability of pembrolizumab SC to pembrolizumab IV has been demonstrated based on results of Study MK-3475A-D77 and PK is comparable among approved IV dosages of pembrolizumab, the data support approval of pembrolizumab SC 395 mg/4,800 units Q3W or pembrolizumab 790 mg/9600 units Q6W for solid tumor indications for adult and pediatric patients 12 years and older (who weigh greater than 40 kg) approved for pembrolizumab IV administered as a single agent or as part of combination therapy, at the time of the original BLA submission. The well-established efficacy and safety profile of pembrolizumab IV also supports approval of pembrolizumab SC for the indications not studied in Study MK-3475A-D77. The submitted evidence for pembrolizumab SC (pembrolizumab 395 mg/ berahyaluronidase alfa-pmph 4,800 units Q3W and pembrolizumab 790 mg/ berahyaluronidase alfa-pmph 9600 units Q6W injection) provides substantial evidence of effectiveness and meets the statutory evidentiary standard for approval.

Based on a favorable risk-benefit assessment, the review team recommends traditional approval of pembrolizumab SC for the proposed indications in adult and pediatric (12 years and older) patients, except for tumor mutational burden-high cancers; pembrolizumab IV is approved for tumor mutational burden-high cancers under accelerated approval and pembrolizumab SC should also be approved under accelerated approval for this indication. An accelerated approval postmarketing requirement (PMR) will be issued, using the verbatim language from the existing PMR for pembrolizumab IV under BLA 125514, for the indication for tumor mutational burden-high (TMB-H) cancers.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Pembrolizumab is a humanized monoclonal IgG4 kappa antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Intravenous pembrolizumab (which will be referred to as "pembrolizumab IV" or "pembro IV" throughout this review) is FDA-approved for over 40 oncologic indications for the treatment of adult patients and pediatric (12 years and older) patients in over 18 tumor types.

Berahyaluronidase is an endoglycosidase that can increase the dispersion and absorption of other injected drugs. Berahyaluronidase alfa (human hyaluronidase variant) temporarily breaks down the extracellular matrix of subcutaneous tissue and enhances permeation of the drug, pembrolizumab.

Intravenous administration of pembrolizumab may present challenges for patients with difficult venous access or patients with poor renal or cardiac function who cannot tolerate larger infusion volumes. Intravenous infusions also generally require longer administration times compared to subcutaneous (SC) administration of the same drug. Pembrolizumab and berahyaluronidase alfa-pmph injection (which will also be referred to as "pembrolizumab SC" or "pembro SC" throughout this review), is being developed as a co-formulation to allow for SC administration of pembrolizumab and offers patients an alternative route of administration compared to pembrolizumab IV.

This application is based on results of Study MK-3475A-D77 (NCT05722015), a randomized (2:1), open-label, active-controlled, parallel-group, multiregional clinical trial of pembrolizumab SC 790 mg every 6 weeks (Q6W) in combination with chemotherapy compared to pembrolizumab IV 400 mg Q6W for patients with treatment-naïve metastatic non-small cell lung cancer (NSCLC), in whom there were no EGFR, ALK, or ROS1 genomic tumor aberrations. The dual primary endpoints were Cycle 1 $AUC_{0\text{-}6weeks}$ and Cycle 3 (steady state) C_{trough}. Analyses of the secondary efficacy endpoints of overall response rate (ORR) and progression-free survival (PFS) per RECIST v1.1 by blinded independent central review (BICR), and overall survival (OS) were all descriptive. Safety was an additional descriptive secondary endpoint.

The dual primary endpoints of PK exposure of pembrolizumab SC compared to pembrolizumab IV were both met. Both PK endpoints met the pre-specified criteria with the lower bound of the 90% CI of the geometric mean ratio (GMR) at 0.8 or above, i.e., GMR for Cycle 1 $AUC_{0\text{-}6weeks}$ was 1.14 (96% CI: 1.06, 1.22) and GMR for Cycle 3 C_{trough}, was 1.67 (94% CI: 1.52, 1.84). Based on a descriptive analysis, the confirmed ORR was 45% (95% CI: 39, 52) in the pembrolizumab SC + chemotherapy arm and 42% (95% CI: 33, 51) in the pembrolizumab IV + chemotherapy

arm. The median PFS was 8.1 months (95% CI: 6.3, 8.3) for pembrolizumab SC + chemotherapy versus 7.8 months (95% CI: 6.2, 9.7) for pembrolizumab IV + chemotherapy, with a hazard ratio of 1.05 (95% CI: 0.78, 1.43). At the time of the original BLA submission, with a data cutoff (DCO) date of July 12, 2024, the OS data were immature with only 26% of patients having experienced OS events. Based on an updated analysis of OS with a DCO date of June 3, 2025, 49% of patients had experienced OS events; the median OS was 19.4 months (95% CI: 17.2, NR) for MK-3475A + chemotherapy versus 17.7 months (95% CI: 13.9, NR) for pembrolizumab IV + chemotherapy, with a hazard ratio of 0.92 (95% CI: 0.68, 1.25). There were no notable differences in PFS or OS observed in patients who received pembrolizumab SC compared to patients who received pembrolizumab IV in Study MK-3475A-D77.

The evaluation of safety for pembrolizumab SC was primarily based upon safety data from Study MK-3475A-D77. In this trial, 251 patients received pembrolizumab SC in combination with chemotherapy in the study arm and 126 patients received pembrolizumab IV in combination with chemotherapy in the control arm. Among the 251 patients treated on the pembrolizumab SC in combination with chemotherapy arm, the most common adverse reactions (≥20% and excluding laboratory abnormalities) were nausea (25%), fatigue (25%), and musculoskeletal pain (21%). Serious adverse reactions occurred in 39% of patients who received pembrolizumab SC in combination with chemotherapy. Serious adverse reactions in ≥1% included pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%), musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%), and anemia (1.2%). Fatal adverse reactions occurred in 10% of patients who received pembrolizumab SC in combination with chemotherapy including pneumonia (3.2%), neutropenic sepsis (2%), death not otherwise specified (1.6%), respiratory failure (1.2%), parotitis (0.4%), pneumonitis (0.4%), pneumothorax (0.4%), pulmonary embolism (0.4%), neutropenic colitis (0.4%), and seizure (0.4%).

Permanent discontinuation of pembrolizumab SC due to an adverse reaction occurred in 16% of patients. Adverse reactions which resulted in permanent discontinuation of pembrolizumab SC in ≥2% of patients included pneumonia (3.2%) and pneumonitis (2.4%). Dosage interruptions of pembrolizumab SC due to an adverse reaction occurred in 45% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia (16%), anemia (8%), thrombocytopenia (8%), pneumonia (4.8%), rash (2.8%), and increased aspartate aminotransferase (2%).

The overall safety profile of pembrolizumab SC was similar to the known safety profile of pembrolizumab IV and similar to other anti-PD-(L)1 antibodies. Safety issues identified as significant and serious during the BLA review were immune-related adverse events, which are adequately addressed by the information in the Warnings and Precautions section included in product labeling. Local injection site reactions was the only newly identified safety signal for pembrolizumab SC, compared to pembrolizumab IV, observed in Study MK-3475A-D77. In total, 2.4% of patients treated with pembrolizumab SC had local injection site reactions leading to inclusion in the USPI of “local injection site reactions” as a clinically relevant adverse reaction in <10% of patients who received pembrolizumab SC in Study MK-3475A-D77.

For pediatric patients 12 years to <17 years old, the Applicant submitted a modeling and simulation report of a molecularly targeted pediatric investigation in pediatric patients, 12 years and older and who weigh at least 40 kg, with melanoma, Merkel cell carcinoma, microsatellite instability high, and tumor mutation burden high tumors, to support approval of MK-3475A in these indications for pediatric patients 12 years to <17 years old. Modeling and simulation data to predict whether PK data are comparable between pembrolizumab SC 790 mg Q6W and pembrolizumab SC 395 mg Q3W, and observed data for the 395 mg SC Q3W dosing regimen in patients with melanoma in Study MK-3475A-C18, were also used to support approval of pembrolizumab SC 395 Q3W. Extrapolation of the SC dosages to other solid tumor indications is supported by PK comparability of SC and IV dosages based on results from Study MK-3475A-D77, combined with the demonstrated PK comparability across all approved solid tumor indications for pembrolizumab IV.

The incidence of antidrug antibody (ADA) to pembrolizumab were generally low and comparable between SC (1.4%) and IV (0.9%) formulations. The ADA incidence (3.6%) for berahyaluronidase alfa was also low, as compared to other approved SC formulations using hyaluronidase (e.g., 5.4% for atezolizumab and 8.8% for nivolumab).

In summary, the FDA review teams consider the PK, efficacy, and safety results of Study MK-3475A-D77, and supportive modeling and simulation data and data from trials of pembrolizumab IV, to meet the evidentiary standard for approval of pembrolizumab SC. The results of Study MK-3475A-D77 demonstrate substantial evidence of effectiveness for pembrolizumab SC, and the overall data support approval of pembrolizumab SC 790 mg Q6W and 395 mg Q3W in adults and pediatric patients (12 years and older). The well-established efficacy and safety profile of pembrolizumab IV also supports approval of pembrolizumab SC for the indications not studied in Study MK-3475A-D77. Based on a favorable risk-benefit assessment, the FDA review teams recommend traditional approval of pembrolizumab and berahyaluronidase alfa-pmph for subcutaneous injection for adult and pediatric (12 years and older) solid tumor indications approved for the intravenous formulation of pembrolizumab at the time of the original BLA submission, except for tumor mutational burden-high cancers; pembrolizumab IV is approved for tumor mutational burden-high cancers under accelerated approval and pembrolizumab SC should also be approved under accelerated approval for this indication. An accelerated approval postmarketing requirement (PMR) will be issued, using the verbatim language from the existing PMR for pembrolizumab IV under BLA 125514, for the indication for tumor mutational burden-high (TMB-H) cancers.

One indication for perioperative pembrolizumab IV for patients with resectable head and neck squamous cell carcinoma (HNSCC) was approved under BLA 125514 after the current original BLA 761467 for pembrolizumab SC was submitted; therefore, this indication for pembrolizumab SC will not be approved under BLA 761467 (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Anti-PD-(L)1 antibodies have demonstrated efficacy across multiple solid tumor types, including melanoma, non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), head and neck squamous cell cancer (HNSCC), urothelial cancer, microsatellite instability-high or mismatch repair deficient cancer, microsatellite instability-high or mismatch repair deficient colorectal cancer (CRC), gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), biliary tract cancer (BTC), Merkel cell carcinoma (MCC), renal cell carcinoma (RCC), endometrial carcinoma, tumor mutational burden-high (TMB-H) cancer, cutaneous squamous cell carcinoma (cSCC), and triple negative breast cancer (TNBC). o While the malignancies have different risk factors, growth patterns, and treatment regimens, they are all solid tumor malignancies that are serious and life threatening.	Anti-PD-(L)1 antibodies have demonstrated efficacy for the treatment of numerous solid tumor cancers that are serious and life-threatening diseases.
Current Treatment Options	• Pembrolizumab IV is approved either as a single agent or as part of combination therapy for indications across the following solid tumors: o Melanoma o NSCLC o MPM o HNSCC o Urothelial cancer o Microsatellite instability-high or mismatch repair deficient cancer o Microsatellite instability-high or mismatch repair deficient colorectal cancer o Gastric cancer o Esophageal cancer o Cervical Cancer	• Pembrolizumab IV is FDA approved as a single agent and in multiple combinations and lines of therapy for patients with multiple tumor types. • Pembrolizumab IV has demonstrated efficacy and safety for the specific FDA approved indications. • A rationale exists for the development of a pembrolizumab formulation that improves the convenience of administration for patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ HCC ○ BTC ○ MCC ○ RCC ○ Endometrial carcinoma ○ TMB-H cancer ○ cSCC ○ TNBC • Pembrolizumab IV is administered intravenously as 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) as a 30-minute intravenous infusion.	
Benefit	• Pembrolizumab SC provides patients with a different route of administration compared to pembrolizumab IV. • Study MK-3475A-D77 evaluated pembrolizumab SC 790 mg Q6W in combination with chemotherapy compared to pembrolizumab IV 400 mg Q6W in patients with treatment-naïve metastatic NSCLC. Study MK-3475A-D77 met its dual primary endpoints of Cycle 1 $AUC_{0\text{-}6weeks}$ and Cycle 3 steady state C_{trough}. The geometric mean ratio (GMR) for Cycle 1 $AUC_{0\text{-}6weeks}$ was 1.14 (96% CI: 1.06, 1.22) and GMR for Cycle 3 C_{trough} was 1.67 (94% CI: 1.52, 1.84). The lower limits of the GMR (96% and 94%) for both $AUC_{0\text{-}6weeks}$ and C_{trough} were above the pre-specified threshold of 0.8 to demonstrate PK exposure comparability for pembrolizumab SC and pembrolizumab IV. • Study MK-3475A-D77 included secondary, descriptive analyses of ORR, PFS, and OS. The ORR for patients treated with pembrolizumab SC + chemotherapy was 45% (95% CI: 39, 52) and 42% (95% CI: 33, 51) in the pembrolizumab IV + chemotherapy arm.	• The PK exposure of pembrolizumab SC and pembrolizumab IV are comparable. • Based on exploratory analyses, no differences in ORR and PFS per RESIST 1.1 by BICR, and OS were observed for pembrolizumab SC and pembrolizumab IV in Study MK-3475A-D77. • Pembrolizumab SC offers patients another route of administration to receive the anti-PD-1 antibody therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• No differences in PFS and OS were observed between pembrolizumab SC and pembrolizumab IV in Study MK-3475A-D77. • Modeling and simulation data in pediatric patients, 12 years and older and who weigh at least 40 kg, with melanoma, Merkel cell carcinoma, microsatellite instability high, and tumor mutation burden high tumors, support approval of MK-3475A in these indications for pediatric patients 12 years to <17 years old. • Modeling and simulation data to predict the PK exposure of pembrolizumab SC 395 mg Q3W compared to pembrolizumab SC 790 mg Q6W, and observed data in patients with melanoma who received pembrolizumab SC 395 Q3W in Study MK-3475A-C18, also supported approval of pembrolizumab SC 395 Q3W.	
Risk and Risk Management	• The primary safety population in Study MK-3475A-D77 included 251 patients who received pembrolizumab SC in combination with chemotherapy in the experimental arm and 126 patients who received pembrolizumab IV in combination with chemotherapy in the control arm. • For patients on the pembrolizumab SC arm, serious adverse reactions (≥1%) included pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%), musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%), and anemia (1.2%). • Fatal adverse reactions occurred in 10% of patients in the pembrolizumab SC plus chemotherapy arm compared to 9.5% among patients in pembrolizumab IV plus chemotherapy arm. • Local injection site reactions occurred in 2.4% of patients receiving pembrolizumab SC.	The observed safety profile of pembrolizumab SC was similar to the known safety profile of pembrolizumab IV. Safety issues identified as significant and serious during the BLA review were immune-related adverse events, which are adequately addressed by the information in the Warnings and Precautions section included in product labeling. Local injection site reactions was the only newly identified safety signal, compared to pembrolizumab IV, observed in Study MK-3475A-D77. There were no significant safety concerns identified during the review of this application warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure the safe use of pembrolizumab SC.

1.4 Patient Experience Data

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

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

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Immunotherapy, in particular pembrolizumab as monotherapy or in combination with chemotherapy or other agents, has changed the treatment paradigm for numerous cancers. Since the initial exploration of pembrolizumab in advanced/metastatic melanoma and NSCLC, its use has been evaluated in numerous other malignancies across a broad spectrum of settings including early stage disease, where it has been found to be efficacious and to improve long-term outcomes. Landmark studies in advanced/metastatic melanoma and NSCLC have shown 5-year and 10-year OS improvement over previously available therapies [1] [2] [3] [4].

The currently approved regimen for treatment with pembrolizumab is administration by IV infusion over 30 minutes, often for extended periods of time (ie, 1 to 2 years), which requires substantial time for patients and health care resources. SC products are advantageous to patients because they offer increased convenience, time savings, and improved psychological and emotional impacts while providing clinical benefits comparable to IV products.

In an open-label randomized study of the preference for SC or IV administration of trastuzumab in patients with HER2-positive early breast cancer, 216 of 236 participants preferred SC administration to IV administration [5]. The 2 main reasons reported for preferring SC administration were time savings (195 of 216 participants) and less pain and discomfort (88 of 216 participants). Participants also reported convenience and ease of administration (35 and 33 participants, respectively) as reasons for preferring SC administration. Most participants reported their overall preference for SC administration as "very strong" (67.4% [95% CI: 61.0, 73.3] SC vs 3.4% [95% CI: 1.5, 6.6] IV). Similar results were reported among patients with CD20+ diffuse large B-cell lymphoma or follicular lymphoma receiving rituximab SC and for patients with HER2-positive early breast cancer receiving the fixed-dose combination of pertuzumab and trastuzumab SC [6] [7].

Likewise, more healthcare professionals reported preferring SC administration (73.8% SC vs 1.9% IV; 24.3% expressed no preference for route of administration) [5]. SC oncologic therapies require less healthcare professional time for preparation and administration than IV agents; a systematic literature review reported reductions in patient total therapy time, use of consumables, drug wastage, and healthcare system costs for SC compared to IV administered oncology therapies [8].

In 2022, there were an estimated 20.0 million new cancer cases and approximately 9.7 million cancer deaths globally. The incidence of cancer is expected to rise, increasing the global burden 77% to an estimated 35 million new cases by 2050 [9]. Further, as immunotherapy has transformed cancer care, more patients are living with their cancers and receiving infusions in the clinic. The introduction of an SC version of pembrolizumab has the potential to decrease treatment bottlenecks and improve clinic efficiency with safety and efficacy similar to IV, which

is demonstrated by the totality of PK, safety, and efficacy data from studies evaluating MK-3475A.

The FDA's Assessment: FDA agrees with the Applicant's position that pembrolizumab IV is approved for numerous indications across tumor types. Additionally, FDA acknowledges that pembrolizumab SC provides an alternative route of administration, with the potential for increased convenience and time saving while providing clinical benefits comparable to pembrolizumab IV.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Currently, pembrolizumab is approved for IV administration in the US at 200 mg Q3W or 400 mg Q6W dosing regimens for more than 40 indications in over 18 different tumor types including several high-prevalence cancers such as NSCLC, melanoma, RCC, UC, TNBC, in both early and metastatic disease settings, and tumor agnostic indications (for tumors that are MSI-H/dMMR or TMB-H). An additional dosing regimen of 2 mg/kg Q3W (up to a maximum of 200 mg) is approved for pediatric patients with certain tumor types.

The development of a subcutaneous version of pembrolizumab is based on the extensive pembrolizumab IV program, including the breadth of accumulated clinical data when used as monotherapy or in combination with other agents (eg, chemotherapy, multi-targeted kinase inhibitors). These data have indicated that both PK and immunogenicity are generally consistent across tumor types, stages of disease, and between monotherapy and combination treatment. Furthermore, the exposure-response relationships of pembrolizumab for both efficacy and safety have been well-established based on 8 randomized dose comparisons in melanoma and NSCLC and are shown to be flat in the clinically studied >5-fold dose/exposure range from 2 mg/kg Q3W to 10 mg/kg Q2W. A consistent, flat exposure response relationship has also been observed for other indications (eg, HNSCC, cHL, UC, GC, PMBCL, and MSI-H cancers) based on a pooled analysis of data from treatment arms across trials.

The pivotal study MK-3475A-D77 was designed with PK primary endpoints to evaluate the noninferiority of pembrolizumab administered SC compared to IV. MK-3475A-D77 included a population that comprised adult participants with treatment-naïve metastatic NSCLC. The Applicant chose to study lung cancer in this pivotal study for the following reasons: lung cancer remains the most common malignancy in the world, with an estimated incidence in 2022 of 2.5 million and an associated 1.8 million deaths [10]; despite significant progress, the 5 year relative survival rates remain dismal at a mere 8.9% for those diagnosed with advanced/metastatic disease [11]; and pembrolizumab, administered as monotherapy or in combination with chemotherapy, has changed the treatment paradigm for patients with NSCLC. Establishing the PK noninferiority of MK-3475A plus chemotherapy to pembrolizumab IV plus chemotherapy, as well as comparable efficacy and safety in NSCLC, allows bridging to all other approved pembrolizumab indications.

As the pharmacological activity of mAbs is mediated through direct interaction with a specific target, target saturation can be used as a surrogate for maximal pharmacologic and therapeutic activity [12]. The active ingredient in MK-3475A is identical to the approved pembrolizumab IV

product; as such, demonstration of noninferiority of the systemic drug exposure after SC administration as MK-3475A, relative to 400 mg Q6W IV, as characterized by AUC at Cycle 1 and C_{trough} at steady state (Cycle 3) would provide evidence that efficacy similar to pembrolizumab IV will be maintained. A lower C_{max} at steady state is expected after SC administration compared with IV administration and would therefore be expected to have a similar systemic safety profile to that of the currently approved IV product.

The FDA's Assessment: FDA agrees with the Applicant's position that pembrolizumab IV is approved for more than 40 indications in over 18 different tumor types including several high-prevalence cancers such as NSCLC, melanoma, RCC, UC, TNBC, in both early and metastatic disease settings, and tumor agnostic indications (for tumors that are MSI-H/dMMR or TMB-H).

3 Regulatory Background

U.S. Regulatory Actions and Marketing History

The Applicant's Position:

This is the first marketing application for MK-3475A, a fixed dose combination of pembrolizumab (MK-3475) and berahyaluronidase alfa (MK-5180), a variant of human hyaluronidase as a permeation enhancer, for subcutaneous administration. For a full list of approved KEYTRUDA® indications, refer to the current USPI.

The FDA's Assessment: FDA agrees with the Applicant's position.

3.1 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Regulatory guidance was obtained from the FDA during the development of MK-3475A. A summary of key interactions during the MK-3475A clinical development program is presented in [].

Table 1: Applicant – Key Regulatory Interactions for MK-3475A Development

Date	Type of Meeting/ Correspondence	Comments
30-JUN-2022	Type B Pre-IND Meeting	Meeting requested to gain alignment on overall development plan, including nonclinical program as well as design of pivotal trial MK-3475A-D77. FDA was in general agreement with the development plan. FDA generally agreed with the study design of MK-3475A-D77 and the use of data from this study to support bridging MK-3475A approval to all approved adult solid tumor indications. DO2 recommended the Applicant to meet with DHM2 for specific requirements to bridge to cHL and PMBCL. During post meeting discussions with the Agency, FDA agreed to pembrolizumab 400 mg Q6W IV as the control arm for the MK-3475A-D77 study.
12-JUN-2023	Type C Meeting	The Applicant requested a Type C meeting with DO2 to obtain agreement on a Phase 2 patient preference study (MK-3475A-F11), including key design elements and statistical analysis plan. Preliminary comments reflected general agreement on the study design and the use of the Patient Preference Questionnaire. The Applicant formally submitted responses to FDA's preliminary comments and cancelled the meeting.

Date	Type of Meeting/ Correspondence	Comments
14-AUG-2023	Type B Pre-IND Meeting	The Applicant requested this Type B pre-IND meeting with DHM2 to discuss the ability of MK-3475A-D77 to support bridging to hematologic malignancies. The division indicated that a separate prospective study in patients with hematologic malignancies to collect clinical PK and safety will be required to obtain approval of the MK-3475A formulation for the treatment of hematologic malignancies.
4-MAR-2024	Type C Meeting (WRO)	The Applicant received FDA's written response to the request for a Type C Meeting (Written Response Only) to gain feedback and alignment on the content and format of an original BLA application for a subcutaneous fixed dose combination of pembrolizumab and berahyaluronidase alfa. The FDA generally agreed to the Applicant's proposed content and format with the exception of recommending that all treatment emergent serious adverse event narratives be included for MK-3475A-D77.
15-MAR-2024	Type D Meeting	FDA held a Type D meeting with the Applicant to discuss the submitted iPSP. FDA stated that the requirement under FDARA is for a molecularly targeted pediatric cancer investigation, in this circumstance FDA would consider releasing this obligation. FDA was receptive to a waiver in patients less than 12 years of age and modeling and simulation to support dosing for pediatric patients (12 to less than 17 years of age).
15-OCT-2024	Alignment with FDA PM on RSD via email	The Applicant aligned with the FDA, via email, to submit a more comprehensive RSD instead of the previously used RSD in Module 2.7.4 and ISS of the proposed MK-3475A BLA submission. Additionally, FDA requested to include a flag for those patients who were enrolled in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010 in order for FDA to perform a safety analysis for the previously used pembrolizumab monotherapy RSD (N=2799).
25-OCT-2024	Notification of PRV Use	The Applicant submitted notification to use a rare pediatric disease PRV for this application, along with supporting material documenting acquisition and transfer to the Applicant of the PRV. PRV User Fee was paid on 22-NOV-2024.
6-JAN-2025	Type B Pre-BLA Meeting	A pre-BLA meeting with the FDA was held to discuss and align on the acceptability of submitting an original BLA on the basis of the results of MK-3475A-D77 and other supportive studies. FDA generally agreed to the Applicant's bridging proposal, eCTD outline and SUR proposal.

The FDA's Assessment: FDA agrees with the Applicant's timeline of regulatory interactions.

One indication for perioperative pembrolizumab IV for patients with resectable head and neck squamous cell carcinoma (HNSCC) was approved under BLA 125514 after the current original BLA 761467 for pembrolizumab SC was submitted. (b) (4)

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

4.1 Office of Scientific Investigations (OSI)

Two clinical investigators, Dr. Ignacio Casarini (Site #1001), and Dr. Dariusz Kowalski (Site #2800), as well as the Applicant, Merck Sharp & Dohme LLC (henceforth, Merck), were inspected during the review cycle. Please refer to the Clinical Inspection Summary uploaded to DARRTS dated June 13, 2025, for a full discussion of clinical inspections.

Inspections of Drs. Casarini and Kowalski, and the Applicant, Merck, did not find significant concerns regarding study conduct, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance.

Based on these inspections, Study 3475A-D77 appears to have been conducted adequately, and the data generated by the inspected clinical investigators and submitted by the Applicant appear acceptable in support of the proposed indication.

4.2 Product Quality

Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) is a fixed-dose combination of two active ingredients: pembrolizumab (MK-3475) and berahyaluronidase alfa (MK-5180), that increases the permissible volume of subcutaneous pembrolizumab delivery and enhances its dispersion. Pembrolizumab (MK-3475) is a humanized IgG4 kappa monoclonal antibody (mAb) that binds to the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor on T cells, thereby inhibiting T cell proliferation and cytokine production. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection. Berahyaluronidase alfa (MK-5180), a novel variant of human hyaluronidase PH20, is included to enhance dispersion and allow for subcutaneous (SC) administration of pembrolizumab. Keytruda

Qlex is supplied as a fixed dose combination of pembrolizumab and berahyaluronidase alfa in a single-use vial as a solution for injection for SC administration. The drug product formulation is 165 mg/mL pembrolizumab and 2000 U/mL berahyaluronidase alfa in (b)(4) mg/mL (b)(4) histidine, (b)(4) mg/mL (b)(4) histidine hydrochloride monohydrate, (b)(4) mg/mL (b)(4) methionine, (b)(4) mg/mL sucrose, and (b)(4) mg/mL polysorbate 80, at a pH of 5.3-5.9. The overall control strategy for Keytruda Qlex manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, as well as release and stability testing ensure process consistency and the manufacture of drug substance and drug product that have appropriate quality and are free of adventitious agents.

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of BLA 761467 for Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph) manufactured by Merck Sharp & Dohme. The data submitted in this application are adequate to support the conclusion that the manufacture of Keytruda Qlex is well-controlled and leads to a product that is pure and potent for the duration of the shelf-life. It is recommended that this product be approved for human use under conditions specified in the package insert. Refer to the OPQ Executive Summary dated September 15, 2025, for full details.

4.3 Clinical Microbiology

Not applicable for this application as no clinical microbiology data or information were provided in this application.

4.4 Devices and Companion Diagnostic Issues

There was no device or companion diagnostic test reviewed as part of this application.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

MK-3475A is a co-formulation of the programmed death receptor-1 (PD-1) blocking antibody pembrolizumab (MK-3475) and berahyaluronidase alfa (MK-5180, previously ALT-B4), a novel recombinant human hyaluronidase (i.e., not approved as a stand-alone or as part of any FDA-approved drug products), intended for subcutaneous (SC) administration in patients with cancers for which intravenous (IV) pembrolizumab (KEYTRUDA) is an approved treatment option. The established pharmacological class of MK-3475A is a combination of pembrolizumab, a PD-1-blocking antibody, and berahyaluronidase alfa, an endoglycosidase. Pembrolizumab is a humanized monoclonal IgG4 antibody that blocks the PD-1/PD-L1 interaction, leading to T-cell activation and increased immune response in the tumor microenvironment. Berahyaluronidase alfa is an endoglycosidase variant of human hyaluronidase (PH20) that temporarily and locally breaks down hyaluronan, a polysaccharide found in the extracellular matrix, to increase the permeability of SC tissue. Berahyaluronidase alfa is a dispersion agent intended to increase the absorption of co-administered SC pembrolizumab.

The Applicant cross-referenced BLA 125514 (submitted by Merck Sharp & Dohme LLC on November 22, 2013) for nonclinical studies (pharmacology, pharmacokinetics, toxicology) conducted to support the approval of IV pembrolizumab (KEYTRUDA). The nonclinical development program for the co-formulation, MK-3475A, was limited to a 4-week repeat-dose toxicology study of once weekly SC administration of MK-3475A in monkeys. The Applicant also conducted pharmacology, pharmacokinetic (PK), and toxicology (general and a complete battery of reproductive) studies with MK-5180. The 26-week toxicology and reproductive animal studies were not warranted for the current BLA application.

In in vitro studies, berahyaluronidase alfa, MK-5180, exhibited low immunogenicity potential and in a separate study showed approximately a 2-fold increase in catalytic activity compared to rHuPH20. In vivo, MK-5180 increased dye dispersion in mice with greatest efficacy seen when MK-5180 was administered intradermally 1 minute before dye administration.

Secondary pharmacology studies of the hyaluronidase MK-5180 were not conducted as effects are expected to be localized based on the mechanism of action. Safety pharmacology testing of MK-5180 included GLP-compliant respiratory and neurological function studies in rats and cardiovascular function studies in monkeys, all with unremarkable findings. PK evaluation of SC MK-5180 in rats indicated rapid clearance compared to MK-5180 administered intravenously, indicating low systemic availability.

The Applicant conducted GLP-compliant repeat-dose toxicology studies evaluating once weekly SC administration of 0, 0.04, 0.2, or 2 mg/kg hyaluronidase MK-5180 as a single agent in rats (up to 6 months duration) and monkeys (up to 1 month duration). Findings were generally minimal and limited to the high dose group of 2 mg/kg with target organs of injection site, lung,

and kidney. Injection site findings included minimal to mild mixed cell inflammation and hemorrhage in monkeys and minimal to moderate perivascular inflammation in rats. Consistent with its mechanism of action, SC administration of MK-5180 resulted in minimal systemic exposure in rats and monkeys following treatment for 1 or 6 months; however, anti-drug antibodies (ADA) affected exposure in the 6-month rat study. In the 4-week rat study, definitive MK-5180 exposure was only seen at the high dose level.

Although not warranted to support the approval of the co-formulation MK-375A per ICH S9, the Applicant conducted a GLP-compliant 6-month repeat-dose toxicology study in rats with SC hyaluronidase MK-5180 including 13-week and 26-week necropsy endpoints. In this study there were three early deaths at doses ≥ 0.2 mg/kg, with findings of moderate kidney necrosis, mild hemorrhage of the thymus, and/or autolysis of multiple organs. It is unclear whether these deaths were definitively related to MK-5180. Clinical observations included hypersensitivity to touch. Histopathology examinations at the end of the 13- or 26-week treatment periods showed mononuclear cell infiltration of the pancreas and injection site, fibrosis of the kidney, atrophy of the pancreas, and decreased cellularity of the thymus at 2 mg/kg MK-5180. Toxicokinetics indicated low systemic exposure after repeat-dosing and extensive ADA formation. Potential target organs included the kidney, thymus, pancreas, lung, and injection site.

At the recommended doses of 395 mg pembrolizumab/4800 units MK-5180 every 3 weeks and 790 mg pembrolizumab/9600 U MK-5180 every 6 weeks, patients with a body weight of 60 kg receive 80 U/kg and 160 U/kg MK-5180, respectively. FDA calculated animal-to-human dose ratios on a body-weight basis (U/kg) using the 160 U/kg human dose of MK-5180 to convey the lowest margin.

To assess local toxicity of the MK-3475A co-formulation, the Applicant conducted a GLP-compliant 4-week repeat-dose toxicology study in cynomolgus monkeys evaluating once weekly SC administration of vehicle or MK-3475A [50 mg/kg pembrolizumab plus 4.1 µg/kg MK-5180 (~575 U/kg based on a specific activity of 140,000 U/mg)]. Notably, the dose of MK-3475A given to monkeys contained the same concentrations of pembrolizumab (165 mg/mL) and berahyaluronidase alfa (2000 U/mL) as KEYTRUDA QLEX. Consistent with local injection site findings in patients administered KEYTRUDA QLEX, findings related to MK-3475A included minimal hemorrhage and infiltration at the injection site. Minimal increased neutrophilic cellularity in the paracortical area of the draining lymph nodes was also observed. On Day 15, MK-3475A exposure to pembrolizumab was approximately 2.5-fold greater than Day 1 based on AUC and C_{max}, indicating accumulation in monkeys following once weekly administration of MK-3475A.

Genetic toxicology studies were not conducted because MK-3475A consists of two large molecules not expected to elicit genotoxicity.

Reproductive toxicology studies with MK-5180 (fertility and early embryonic development, embryo-fetal development, and prenatal and postnatal development) reported no adverse reproductive or developmental toxicity at clinically relevant doses; however, the label for

KEYTRUDA includes warnings for embryo-fetal developmental toxicity and contraception guidelines are provided during and after treatment.

Although not warranted to support the use of the co-formulation MK-3475A in the currently proposed indication, the Applicant conducted a fertility and early embryonic development study in which male and female rats were administered daily SC injections of MK-5180. Males were dosed for 9 weeks prior to mating and throughout mating to termination. Females were dosed for 2 weeks prior to mating, throughout mating, and up to gestation day 7. Treatment with ≥6 mg/kg (840,000 U/kg) MK-5180 (>5,200 times higher than the human dose) resulted in an increased incidence of abnormal sperm morphology (added to Section 13.1 of the KEYTRUDA QLEX label), however, there were no adverse effects on mating, fertility, or embryogenesis at doses up to 18 mg/kg (2,520,000 U/kg; >15,000 times higher than the human dose). MK-5180 did not induce dose-related adverse findings in reproductive organs in the 4-week monkey general toxicology study with SC MK-5180. In the 4-week rat general toxicology study with SC MK-5180, individual high dose animals exhibited minimal seminiferous epithelium degeneration/atrophy in the testis and increased cell debris in the epididymis at 2 mg/kg (280,000 U/kg; > 1,750 times higher than the human dose). The recovery of these findings was not assessed. Since findings in the testis and epididymis were only noted in 1 out of 10 animals, and unilateral or bilateral testicular degeneration/atrophy are known low-incidence background findings in rats (Creasy D, 2012), these findings were not added to Section 13.1 of the KEYTRUDA QLEX label.

The Applicant conducted GLP-compliant embryo-fetal development studies with MK-5180 in rats and rabbits. There were no adverse embryo-fetal findings in pregnant rats administered daily SC injections of MK-5180 at doses up to 2,520,000 U/kg (>15,000 times higher than the human dose) during the period of organogenesis (gestation day 6 to 17). In the rabbit embryo-fetal development study, MK-5180 caused delayed fetal development (decreased crown-rump length and fetal weight) at doses ≥ 2.88 mg/kg (403,200 U/kg, which is >2,500 times higher than the human dose); this correlated with decreased gravid uterine weight (20%) compared to controls. Increased post-implantation loss and visceral malformation (supernumerary fissure lung lobe) were observed at 1,209,600 U/kg MK-5180, which is >7,500 times higher than the human dose.

In a prenatal and postnatal development study, there were no MK-5180-related adverse effects in rats administered daily SC injections up to 18 mg/kg (2,520,000 U/kg, which is >15,000 times higher than the human dose. Overall, there was low systemic exposure of MK-5180 in the conduced reproductive studies as expected, and adverse findings were seen at doses much higher than patients are expected to receive at the recommended dose of KEYTRUDA QLEX.

The Applicant did not conduct embryofetal development studies or risk assessment with the MK-3475A co-formulation because pembrolizumab can cause fetal harm based on its mechanism of action. The KEYTRUDA QLEX label includes the warning for embryo-fetal toxicity, recommended duration of contraception (during treatment and for 4 months after the last dose in females), and recommendation to not breastfeed during treatment and for 4 months after the last dose that are included in the KEYTRUDA (IV) label. Additional new data for MK-5180 (berahyaluronidase alfa) has been added to the label.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of KEYTRUDA QLEX for the proposed oncology indications.

5.2 Referenced NDAs, BLAs, DMFs

The nonclinical development program to support the current application for MK-3475A, an SC administered version of a fixed dose combination of pembrolizumab and berahyaluronidase alfa (MK-5180) leverages the comprehensive nonclinical package (including pharmacology, pharmacokinetic/toxicokinetic, and toxicology) from the KEYTRUDA BLA 125514, supplemented with studies conducted with MK-5180 and MK-3475A, summarized below.

The FDA's Assessment:

FDA agrees with the Applicant's position.

5.3 Pharmacology

Primary pharmacology

The Applicant's Position:

While the nonclinical characterization of pembrolizumab was described in the KEYTRUDA BLA 125514, studies with MK-5180 alone were carried out to support this application. MK-5180 was evaluated for its immunogenicity potential in vitro and results indicated that MK-5180 has low potential to elicit immunogenicity. In an enzyme kinetic assay, the Morgan-Elson assay, MK-5180 had approximately 2 times higher catalytic efficiency compared to rHuPH20. In a dye dispersion study performed in mice, diffusion of Trypan Blue improved with increasing doses of MK-5180 or when the dye was sequentially administered with minimal delay after the MK-5180 SC injection. The dispersion study also showed that the effect of MK-5180 was temporary, lasting 24 to 48 hours post SC injection.
No primary pharmacodynamic studies were conducted with MK-3475A.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. In the Trypan blue dispersion study in mice (Study # PD002MK5180), when Trypan blue was administered one minute after intradermal administration of MK-5180 or vehicle, the low dose of 100 U/mL (2 U total) MK-5180 increased dye dispersion about 2-fold compared to vehicle administration (148 mm^2 compared to 70 mm^2) and was comparable to simultaneous administration of a co-mixture of 5000 U/mL (100 U total) MK-5180 + Trypan blue (146 mm^2) (). Although these data indicate that sequential (1 minute) administration of 100 U/mL MK-5180 increases dye dispersion compared to administration of a co-mixture, the data also suggest that administration of a co-mixture (i.e., MK-3475A) increases

dye dispersion at clinically relevant (2000 U/mL) concentrations of MK-5180 compared to vehicle control.

Table 2: FDA – Summary of In Vivo Dye Dispersion Study Results for Mice Administered MK-5180 Intradermally

Cohort #	Admin.	ALT-B4 Conc. (U/mL)	Time between ALT-B4 and trypan blue	0 min		2.5 min		5 min		20 min	
				AVG (mm^2)	SEM	AVG (mm^2)	SEM	AVG (mm^2)	SEM	AVG (mm^2)	SEM
1	Co-mix	0	0 min	30.7	2.1	74.5	3.8	94.9	8.5	110.4	4.9
2	Seq.		1 min	49.3	1.3	53.7	1.9	59.0	2.7	70.1	5.4
3	Co-mix	100	0 min	29.6	2.0	63.2	3.1	81.3	4.9	102.7	3.9
4		500		35.0	0.9	16.3	3.7	91.4	4.6	125.5	7.3
5		5000		31.9	1.2	87.7	4.2	107.8	6.9	145.6	5.1
6	Seq.	100	1 min	56.6	3.3	98.5	3.5	118.0	2.5	147.8	5.3
7		100	20 min	56.6	2.4	98.8	5.0	107.7	4.5	123.1	4.9
8		100	4 h	49.3	2.7	90.8	4.8	102.4	6.1	119.3	5.8
9		100	24 h	41.3	1.6	76.0	3.0	90.9	5.1	106.1	5.0
10		100	48 h	36.6	1.9	67.9	4.2	78.0	5.1	97.2	7.0

SEM, standard error of the mean.

Source: Applicant Table reproduced from Study # PD002MK5180

Secondary Pharmacology

The Applicant's Position:

No secondary pharmacology studies were conducted with MK-5180 or MK-3475A.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Safety Pharmacology

The Applicant's Position:

Safety pharmacology endpoints were included in the repeat-dose toxicity studies with pembrolizumab and described in KEYTRUDA BLA 125514.
Potential effects of MK-5180 on critical organ functions (ie, neurobehavioral, respiratory, and cardiovascular) systems were evaluated in stand-alone safety pharmacology studies or as components of repeat-dose toxicity studies. No MK-5180-related effects were observed in any of these studies up to the highest dose tested.
No safety pharmacology studies were conducted with MK-3475A.

The FDA's Assessment:

FDA generally agrees with the Applicant's conclusions. In the respiratory safety pharmacology study, rats were administered a subcutaneous injection of 0, 0.04, 0.2, or 2 mg/kg MK-5180 for a single dose and respiratory function was measured over 24 hours. The findings were

unremarkable, indicating that MK-5180 was tolerated up to ~280,000 U/kg (based on a specific activity of 140,000 U/mg) in rats, which is ≥1750 times greater than the dose of MK-5180 (up to 9600 U or 160 U/kg) included in the recommended dose of MK-3475A.

5.4 **ADME/PK**

The Applicant's Position:

Absorption

Pembrolizumab
A single-dose IV PK study in cynomolgus monkeys was conducted in support of the development of pembrolizumab for IV administration and described in KEYTRUDA BLA 125514.
Subsequent evaluation of pembrolizumab SC PK parameters in male Sprague Dawley rats and male cynomolgus monkeys used the same formulation as is used for IV clinical administration. In both rats and monkeys, the elimination phases of the pembrolizumab concentration time profiles following IV (in-study reference arm) or SC administration were comparable. Pembrolizumab showed a dose proportional increase in serum exposure when administered SC over the dose range of 8 to 50 mg/kg in rats and 4 to 8 mg/kg in monkeys. High bioavailability was observed after SC administration in rats (83% to 94%) and in monkeys (93% to 101%).
In monkeys, an additional study arm evaluated the SC PK of pembrolizumab in a similar set of formulation components as the clinical formulation of MK-3475A, but without MK-5180. Under these conditions, pembrolizumab also showed high SC bioavailability (93% to 111%).
MK-5180
Single-dose PK studies for MK-5180 were performed in rats and monkeys using an assay that measured hyaluronidase activity.
After a single IV administration of MK-5180 to Sprague Dawley rats at a dose of 1 mg/kg (124,000 U/kg), the systemic $t_{½}$ was 7 minutes with CL of 4.3 mL/(min×kg), slower than the liver blood flow rate in rats (55.2 mL/[min×kg]). The Vd_{ss} was 34.6 mL/kg, less than the total body water content in rats (668 mL/kg). These results indicate that transition of MK-5180 to the tissues was low.
After a single IV administration of MK-5180 at doses of 0.3, 3, 15, or 30 mg/kg in cynomolgus monkeys, the $t_{½}$ of MK-5180 in the 3- to 30- mg/kg dose groups was between 0.3 and 0.87 hours, indicating rapid elimination from systemic circulation.
After SC administration of MK-5180, higher than endogenous concentrations of hyaluronidase were only observed at the highest dose of 30 mg/kg. At 1 hour (T_{max}), the maximal MK-5180 concentration was approximately 3-fold above the average hyaluronidase endogenous concentration observed prior to dosing across dose groups in the IV arm of the study. This effect was not observed in the 3- or 10- mg/kg dose groups. Before SC injection, blood samples were not collected (absence of measurement of hyaluronidase endogenous concentrations). Overall, MK-5180 administered by SC injection was quickly absorbed and rapidly eliminated. Compared with IV dosing, MK-5180 bioavailability was negligible after SC injection due to rapid CL.
MK-3475A

Single-dose PK studies of the combination product MK-3475A have not been conducted.

Distribution, Metabolism, and Excretion

As both pembrolizumab and MK-5180 are expected to be degraded into small peptides and amino acids via endogenous catabolic pathways, classical biotransformation studies as performed for small molecule pharmaceuticals are not needed. To monitor the lack of Fab-arm exchange in pembrolizumab which contains a mutation of S228P, a metabolism study was conducted in mice and described in KEYTRUDA BLA 125514. However, nonclinical distribution and excretion studies for pembrolizumab have not been conducted. Likewise nonclinical distribution, metabolism, and excretion studies have not been conducted for MK-5180 or MK-3475A.

The FDA's Assessment:

FDA generally agrees with the Applicant's conclusions.

5.5 Toxicology

5.5.1. General Toxicology

The Applicant's Position:

A comprehensive toxicology program was conducted in support of the development of pembrolizumab for IV administration and described in KEYTRUDA BLA 125514. Toxicology studies were conducted to support the nonclinical safety of MK-5180 and MK-3475A.
The safety of MK-5180 was evaluated in pivotal 1-month, repeat-dose toxicity studies in rats and cynomolgus monkeys and a 6-month, repeat-dose toxicity study in rats when administered SC at doses of 0.04, 0.2, or 2 mg/kg/dose once weekly in each study. There were no findings of toxicologic significance and the NOAEL in all 3 studies was 2 mg/kg/dose.
In light of the existing nonclinical and clinical data for pembrolizumab and the lack of toxicity of MK-5180 due to negligible systemic exposure, nonclinical evaluation of the drug product, MK-3475A, was limited to a 4-week SC tolerability study in monkeys. Monkeys were administered MK-3475A at a dose containing 50 mg/kg pembrolizumab and 4.1 µg/kg (approximately 600 U/kg) MK-5180. MK-3475A was well tolerated with acceptable local tolerability at the SC injection sites and draining lymph nodes. The MK-3475A formulation, used in the 4-week, once weekly SC monkey study, contained 165 mg/mL pembrolizumab and 13.8 µg/mL (2000 U/mL) MK-5180, which is equivalent to the maximum concentration for pembrolizumab and >1000-fold of MK-5180 concentration in the proposed clinical formulation. Importantly, once weekly SC dosing in repeat-dose animal studies is more frequent than the planned clinical dosing regimen (once every 3 or 6 weeks) for MK-3475A.
In monkeys, pembrolizumab systemic exposures achieved following SC administration of MK-3475A were within the ranges of systemic exposures achieved following pembrolizumab IV administration, for which the toxicological profile has been well characterized. The safety and

tolerability of MK-3475A is acceptable and considered comparable to the safety of pembrolizumab administered IV.

The FDA's Assessment:
FDA generally agrees with the Applicant's conclusions; however, FDA does not determine NOAEL values in general toxicology studies submitted to support oncology indications.

The Applicant requested revision to their statement that the concentration of MK-5180 in the 4-week study of MK-3475A SC once weekly was greater than 1000-fold the concentration in the proposed clinical formulation to: "The MK-3475A formulation used in the once weekly SC monkey 4-week study, contained 165 mg/mL pembrolizumab and 13.8 µg/mL (2000 U/mL) MK-5180, which is equivalent to the maximum concentrations for both pembrolizumab and MK-5180 in the proposed clinical formulation." FDA agrees with this statement. The dose ratios of MK-5180 were 3.6- to 7.2-fold greater in monkeys compared to humans (574 U/kg in monkeys based on a specific activity of 140,000 U/mg compared to a proposed 80 U/kg and 160 U/kg in humans, respectively) (see below for review).

FDA's assessments of the 4-week SC MK-3475 study and the 6-month SC MK-5180 study are presented below.

General Toxicology

Study title/ number: MK-3475A: Four-Week Subcutaneous Tolerability Study in Cynomolgus Monkeys / TT #21-1002

Key Study Findings

- There were no mortalities.
- There was ~2.5-fold accumulation in pembrolizumab on Day 15 compared to Day 1.
- SC injection of MK-3475A did not substantially affect hyaluronidase activity.
- Target organs included the injection site and lymph node.

GLP Compliance	Yes
Methods: A co-formulation of MK-3475 and MK-5180 or vehicle was administered subcutaneously once weekly for 4-weeks. A new injection site within the interscapular region was used for each dose. Due to the age of the animals and extended time housed in pairs, animals were assigned to the study in pairs established prior to study start. Each dose group was comprised of 2 pairs of animals or one pair of animals and 2 animals that were each paired with a companion animal.	
Dose and Frequency of Dosing	MK-3475A = 50 mg/kg pembrolizumab (165 mg/mL) + 4.1 µg/kg MK-5180 (2000 U/mL) co-administered once weekly
Route of Administration	Subcutaneous injection; interscapular cranial left and right, and interscapular caudal left and right
Formulation/Vehicle	(b) (4) mg/mL (b) (4) histidine, (b) (4) mg/mL (b) (4) histidine monohydrochloride monohydrate, (b) (4) mg/mL (b) (4) methionine, (b) (4) mg/mL sucrose, (b) (4) mg/mL, and water with a pH of 5.5
Species/Strain & Age	Cynomolgus monkey; 3-5 years
Number/Sex/Group	4/sex/group (16 total)
Study Design	Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, and anatomic pathology evaluations of the injection sites and associated lymph nodes.

Deviations affecting interpretation of results	None of significance
Observations and Results	
Mortality	None
Clinical Signs	Unformed feces in 2 monkeys and injection site scab/crust on the back of one monkey. Alopecia and skin/fur scabs were observed slightly more frequently in MK-3475A-treated monkeys compared to controls.
Body Weights and Feed Consumption	Unremarkable
Gross Pathology	One monkey dosed with MK-3475A exhibited red discoloration of the pons (brain), which did not correlate with any histologic findings. Additional findings included decreased size of thyroid gland (1 male), red discoloration of the kidney (1 female), and red discoloration of the left caudal injection sites.
Histopathology Adequate battery: Limited to 4 SC injection sites (interscapular cranial left and right, and interscapular caudal left and right) and axillary lymph nodes	In the draining lymph nodes of two monkeys dosed with MK-3475A, there was minimally increased neutrophilic cellularity limited to the paracortical area. MK-3475A induced minimal hemorrhage and infiltration at the injection sites.
Toxicokinetics	*Accumulation:* Yes, ~2.5-fold in pembrolizumab on Day 15 compared to Day 1 *Sex differences:* None Hyaluronidase activity (MK-5180 and endogenous hyaluronidase) was similar between control and MK-3475A-treated monkeys following dosing on Days 1 and 15 (data not shown), suggesting minimal MK-5180 systemic exposure.

Table 3: FDA – Summary of MK-3475 (Pembrolizumab) Toxicokinetics (4-Week SC Study; Monkeys)

Day	Dose (mg/kg)	C_{max} (µg/mL)		$AUC_{0\text{-}168hr}$ (µg·hr/mL)		T_{max} (hr)	
		M	F	M	F	M	F
1	50 mg/kg MK-3475 + 4.1 µg/kg MK-5180	578	568	82,800	84,600	73.5	78
15		1,540	1,370	224,000	188,000	37.5	48

Study title/ number: MK-5180: 26-Week Subcutaneous Injection Toxicity and Toxicokinetics Study in Rats with 4-Week Recovery/891-0017-TX

Key Study Findings

- Three early deaths at doses ≥ 0.2 mg/kg/week.
- Anti-drug antibodies were noted in all animals at the end of the treatment phase, which may have impacted maximum serum concentration (a ~3-fold decrease was noted for high-dose males).

GLP Compliance	Yes

Methods: Rats were administered 0, 0.04, 0.2, or 2 mg/kg MK-5180 once weekly for either 13- or 26-weeks in 10/sex/group or 15/sex/group, respectively. An additional 6/sex/group for control and high-dose animals were designated for a 4-week recovery phase after 26-weeks of treatment. Necropsies at 13-, 26-, and 30-weeks included histopathology examinations of adequate battery.	
Dose and Frequency of Dosing	0, 0.04, 0.2, or 2 mg/kg MK-5180 once weekly
Route of Administration	Subcutaneous injection; dorsal area
Formulation/Vehicle	MK-5180 formulation (b) (4) mM histidine and (b) (4) mM (b) (4) with a pH (b) (4)
Species & Age	Rat; 7-8 weeks
Number/Sex/Group	10/sex/group (13-weeks treatment) 15/sex/group (26-weeks treatment) 6/sex/group for 0 mg/kg and 2 mg/kg study (26-weeks treatment + 4 weeks recovery)
Study Design	Necropsies were conducted on Day 92 (interim), Day 183 (end of treatment phase), and Day 211 (end of recovery phase).
Deviations affecting results	None of significance
Observations and Results	
Mortality	Three early deaths were noted on Days 31, 150, and 161 for a 0.2 mg/kg male, a 0.2 mg/kg female, and a 2 mg/kg male, respectively. One early death male administered 0.2 mg/kg MK-5180 exhibited moderate kidney necrosis of the proximal tubule, mild hemorrhage of the thymus, and autolysis of the gastrointestinal tract, brain, and eyes. One early death female administered 0.2 mg/kg exhibited red liquid in the abdominal cavity and autolysis of multiple organs. The high dose preterm decedent exhibited abnormal respiratory sounds on Day 161 prior to being found dead, but no remarkable pathologic or histologic findings. The pathologist could not determine a cause of death; however, contributing toxicity from MK-5180 cannot be ruled out.
Clinical Signs	Clinical observations included an increase in the incidence of hypersensitivity to touch in individual treatment-group males compared to controls, with evidence of reversibility. Hypersensitivity to touch was also noted once in a single control-group female. This finding may be related to MK-5180 due to the frequency of findings in males treated with MK-5180 compared to controls.
Body Weights and Feed Consumption	Findings were unremarkable.
Ophthalmoscopy	Findings were unremarkable.
Hematology	Findings were unremarkable.
Clinical Chemistry	There was a statistically significant decrease (2%) in mean serum chloride on Day 92 and a statistically significant increase (up to 15%) in mean potassium on Day 183 in females dosed with ≥ 0.04 mg/kg compared to controls. Both findings showed evidence of reversibility during the recovery phase.
Urinalysis	Findings were unremarkable.
Gross Pathology	A single subcutaneous mass in the mammary gland was noted in one 0.2 mg/kg female on Day 92. Multifocal, pale discoloration of the lungs with mainstem bronchi and focal dark red discoloration of the pituitary gland were noted for a single 0.2 mg/kg male and female on Day 183, respectively.

Organ Weights	On Day 92, males administered 2 mg/kg exhibited a statistically significant increase in mean pituitary gland weight relative to brain weight compared to controls (+18%). On Day 183, males administered 2 mg/kg exhibited a statistically significant decrease in mean pituitary gland weight relative to brain weight compared to controls (-16%). There were no correlating histopathology or clinical chemistry findings and the changes noted to pituitary gland weight may not be related to MK-5180.
Histopathology Adequate battery: Yes	**0.2 mg/kg:** A benign mammary gland adenoma was noted in a single female, which correlated with the gross pathology finding of SC mass at 13-weeks. At 26-weeks, mild alveolar foamy macrophage was noted in the lungs of a single male, and mild hemorrhage of the pituitary gland was noted in a single female. **2 mg/kg:** At 13-weeks, a single male and female were noted with minimal mononuclear cell infiltrate of the pancreas and injection site, respectively. At 26-weeks, findings included minimal fibrosis of the kidney for a single female, mild atrophy of the pancreas in a single male, and mild decreased cellularity of the thymus for a single male. All findings noted during the treatment phase showed evidence of reversibility during the recovery phase.
Toxicokinetics	*Systemic exposure:* Systemic exposure was limited. Definitive evidence of systemic exposure was only observed at 2 mg/kg. Analysis on Day 176 was limited to male high-dose animals. C_{max} values for high-dose males decreased ~3-fold on Day 176 compared to Day 1. *Dose proportionality:* Yes *Sex differences:* There were no significant sex differences on Day 1.

Table 4: FDA – Summary of Toxicokinetics (26-Week Study; Rats)

Day	Dose (mg/kg)	C_{max} (ng/mL)		AUC_{0-24hr} (ng·hr/mL)		T_{max} (hr)	
		M	F	M	F	M	F
1	0.2	3.18	2.41	N/A	N/A	0.5	0.5
	2	24.5	25.6	29.1	42.6	0.5	0.5
176	2	8.66	N/A	N/A	N/A	0.5	N/A

N/A = Not applicable

General Toxicology; additional studies

The Applicant evaluated the same MK-5180 dose levels (0.04, 0.2, and 2 mg/kg) in the 4-week SC toxicology studies in rats (Study # 891-0004-TX / tt207838) and cynomolgus monkeys (Study # tt207837 / 20219234) as the 26-week SC toxicology study in rats. Systemic exposure of MK-5180 as a single agent administered SC was minimal in these studies, with definitive exposure only seen at the high dose level in the 4-week rat study. There were no mortalities or severe toxicities in the 4-week toxicology studies. MK-5180 induced histologic injection site findings in both species including inflammation. There were no findings of erythema, edema, or eschar formation at the injection sites. In the rat study, one high dose animal exhibited light yellow focal discoloration of the kidney, which correlated histologically with moderate focal

cortex fibrosis. Treatment with MK-5180 resulted in minimal histologic findings in individual high dose rats including osseous metaplasia in the lung, hyperplasia in the mammary gland, seminiferous epithelium degeneration/atrophy in the testis, and increased cell debris in the epididymis (recovery not assessed). In the monkey study, dark red discoloration and/or dark red focus in the colon of high dose male monkeys correlated histologically with mild hemorrhage. Minimal mixed cell infiltration and granulomatous inflammation was seen in the lung. There were no adverse findings in reproductive organs in the 4-week monkey study.

5.5.2. Genetic Toxicology

The Applicant's Position:

No genetic toxicology studies were conducted with pembrolizumab, MK-5180, or MK-3475A in accordance with ICH S6(R1).

The FDA's Assessment:

FDA agrees that no genotoxicity studies are needed as the formulation intended for patients consists of a combination of two large molecule amino acid based drugs.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies were conducted with pembrolizumab, MK-5180 or MK-3475A.

The FDA's Assessment:

FDA agrees that carcinogenicity studies with pembrolizumab, MK-3475A, or MK-5180 are not needed.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:
No developmental or reproductive toxicity studies have been conducted with pembrolizumab. Pembrolizumab-related risks on pregnancy (potential for fetal harm), lactation (potential for severe adverse reaction in breastfed children), as well as risk mitigation for females of reproductive potential (pregnancy testing and contraception use) have been identified (described in KEYTRUDA BLA 125514). Therefore, no reproductive and developmental toxicity studies were conducted with MK-3475A.
In reproductive toxicity studies in rats, MK-5180 had no adverse impact on fertility or prenatal or postnatal development and was not teratogenic up to a dose of 18 mg/kg/day (NOAEL), which is >9000-fold of the clinical dose. In a rabbit embryo-fetal development study, MK-5180-related findings were limited to delayed fetal development (reduced mean fetal weight, crown-rump length, and associated reduced maternal gravid uterine weight at ≥2.88 mg/kg/day and increased

incidence of associated skeletal variations at 8.64 mg/kg/day) and a visceral abnormality at 8.64 mg/kg/day. The NOAEL for embryo-fetal developmental toxicity in rabbits was 0.99 mg/kg/day, which is >700-fold of the clinical dose.
Overall, the developmental and reproductive toxicity risks associated with administration of MK-3475A are the risks on pregnancy and female reproductive potential associated with pembrolizumab mechanism of action (described in KEYTRUDA BLA 125514) and are communicated in the USPI.

The FDA's Assessment:

Fertility and Early Embryonic Development
Fertility and early embryonic development studies are not needed to support the use of MK-375A in the currently proposed indication per ICH S9; however, the Applicant conducted a fertility and early embryonic development study with MK-5180 in rats. FDA generally agrees with the Applicant's conclusions. FDA's assessment is below.

Study title/number: MK-5180: Subcutaneous Injection Dose Study on Fertility and Early Embryonic Development to Implantation in Rats/891-0011-DR
Key Findings:

- Systemic exposure was limited.
- Abnormal sperm morphology was noted at ≥ 6 mg/kg/day MK-5180.
- There were no adverse effects on mating, fertility, or early embryonic development.

GLP Compliance	Yes
Methods: This study was intended to analyze effects on the estrous cycle, tubal transport, implantation, and development of pre-implantation stages of the embryo, as well as male functional effects of the male reproductive organs.	
Dose and Frequency of Dosing	0, 2, 6, or 18 mg/kg/day MK-5180
Route of Administration	Subcutaneous injection
Formulation/Vehicle	MK-5180 (b) (4) mM histidine, (b) (4) mM (b) (4) pH (b) (4)
Species	Rat
Number/Sex/Group	24/sex/group (main study) 8/sex/group (TK treatment); 4/sex (TK control) 5 males/11 females (satellite)
Study Design	*Males:* Treated starting 9 weeks prior to mating and throughout mating to termination. *Females:* Treated starting 2 weeks prior to mating and throughout mating up to gestation day (GD) 7.
Deviations affecting results	None of significance
Observations and Results	
Parameters	**Major findings**
Mortality	**6 mg/kg:** 1 mortality on Day 27 **18 mg/kg:** 1 mortality on Day 56 Gross findings included red discoloration of the thymus, lungs, mandibular lymph node, and/or salivary glands.
Clinical Signs	Findings were unremarkable
Body Weights and Food Consumption	Findings were unremarkable

Reproductive Parameters	*Sperm Parameters:* Statistically significant increase (≥ 3.32%) in the incidence of abnormal sperm morphology was noted at ≥ 6 mg/kg/day MK-5180 compared to controls. At 18 mg/kg/day there was a statistically significant decrease (5%) in the percentage of rapid sperm compared to controls. *Reproductive performance:* All males and females mated successfully; two mated females/treatment group were not pregnant at termination.

Table 5: FDA – Summary of Sperm Analysis

Dose (mg/kg)	0	2	6	18
Sperm concentration (N/g*108)	5.14	5.60	5.44	4.90
Rapid sperm (%)	59	59	57	54*
Medium sperm (%)	1	1	1	2
Slow sperm (%)	23	24	24	27
Motile sperm (%)	83	84	82	81
Static sperm (%)	17	16	18	19
Abnormal sperm (%)	2.44	2.54	3.32*	3.43*

Sperm concentration = sperm count per cauda/weight of cauda epididymis (g);
*p≤0.01 (ANOVA & Dunnett's test)

Table 6: FDA – Male Reproductive Performance

Dose (mg/kg)	0	2	6	18
Group size	24	24	24	24
No. Males confirmed mating	24	24	24	24
No. Males cohabitated	24	24	24	24
No. Males impregnating a Female	24	22	22	22
Male Mating Index (%)	100	100	100	100
Male Fecundity Index (%)	100	91.7	91.7	91.7
Male Fertility Index (%)	100	91.7	91.7	91.7

No. = number; Mating index % = (Number of males confirmed mating / Number of males cohabitated) x 100
Fecundity index % = (Number of males impregnating a female / Number of males confirmed mating) x 100
Fertility Index % = (Number of males impregnating a female / Number of males cohabitated) x 100

Table 7: FDA – Female Reproductive Performance

Dose (mg/kg)	0	2	6	18
Group size	24	24	24	24
No. Females confirmed mating	24	24	24	24
No. Females cohabitated	24	24	24	24
No. Pregnant Females	24	22	22	22
Female Mating Index (%)	100	100	100	100
Female Fecundity Index (%)	100	91.7	91.7	91.7
Female Fertility Index (%)	100	91.7	91.7	91.7
Estrous Cycle Length (days)	5.3	6.1	5.3	6.1
Pre-Coital Interval (days)	3	3	3	3

No. = number; Mating index % = females confirmed mating/females cohabited x 100
Fecundity Index % = Pregnant females/females with confirmed mating x 100
Fertility Index % = Pregnant females/females cohabited x 100

Necropsy findings	*Ovarian and Uterine Examinations:* Findings were unremarkable *Gross Pathology:* Findings were unremarkable *Organ Weights:* Findings were unremarkable *Histopathology:* Not conducted

Table 8: FDA – Ovarian and Uterine Examinations (Fertility Study; Rats)

Dose (mg/kg)	0	2	6	18
# Pregnant	24	22	22	22
Mean # corpora lutea	19	18	19	19
Mean # implants	16	15	15	15
Mean # of viable embryos	14	14	14	14
Mean # of non-viable embryos	1	2	1	1
Mean pre-implantation loss (%)	18.6	13.2	16.7	22.4
Mean post-implantation loss (%)	8.4	10.7	10.7	7.4

Pre-implantation loss % = (No. corpora lutea-No. implants)/No. corpora lutea x 100
Post-implantation loss % = (No. implants-No. viable embryos)/No. implants x 100

Toxicokinetics: Exposure was limited after repeat-dosing and only noted for the mid- and high-dose females after two weeks of treatment and for high-dose males at the end of the study.

Table 9: FDA – Summary of Toxicokinetics (Fertility Study; Rats)

Day	Dose (mg/kg/day)	Cmax (ng/mL)		Tmax (hr)	
		M	F	M	F
1	2	23.5	47.6	0.5	0.5
	6	149	116	0.5	0.5
	18	263	222	1	0.5
14	2	N/A	BLQ	N/A	N/A
	6	N/A	7.2	N/A	1
	18	N/A	27.7	N/A	2
63	2	BLQ	N/A	N/A	N/A
	6	BLQ	N/A	N/A	N/A
	18	89	N/A	2	N/A

BLQ=below limit of qualification: N/A=not applicable

Embryo-Fetal Development

FDA generally agrees with the Applicant's conclusions. FDA's review of the embryo-fetal development studies is provided below.

Study Title: Subcutaneous Injection Dose Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rats/891-0013-DR

Key study findings:

- No teratogenicity or embryo-fetal toxicity at doses up to 18 mg/kg/day.
- Systemic exposure decreased on GD 17 compared to GD 6

Methods: Mated females were treated with subcutaneous MK-5180 once daily from GD 6-17 and sacrificed on GD 21; ovaries and uteri were examined by C-section for litter data, and live fetuses were collected for visceral and skeletal examination.	
GLP compliance: Yes	
Dose and Dose Frequency	0, 2, 6, or 18 mg/kg/day
Route of Administration	Subcutaneous injection

Formulation/Vehicle	MK-5180 formulation (b) (4) mM histidine, (b) (4) mM (b) (4) pH (b) (4)
Species	Rat
Number/sex/group	25 mated females/group (main study) 8 mated females/group (treatment-group TK); 4 mated females (control TK) 32 females/50 males (satellite)
Study Design	See Methods
Deviations Affecting Results	None of significance
Observations and Results	
Parameters	**Major findings**
Mortality	No drug-related mortalities
Clinical Signs	Findings were unremarkable
Body Weights and Food Consumption	Findings were unremarkable
Gravid Uterine Weights	Findings were unremarkable
Necropsy findings	*Gross Pathology* Findings were unremarkable

Table 10: FDA – Cesarean Section Findings (Embryo-Fetal Development Study; Rats)

Dose (mg/kg/day)	**0**	**2**	**6**	**18**
# Mated females	25	25	25	25
# Pregnant (%)	24 (96%)	24 (96%)	23 (92%)	24 (96%)
# Dams with live fetuses (%)	24 (96%)	24 (96%)	23 (92%)	24 (96%)
Mean # corpora lutea	19	18	19	19
Mean # implants	15	16	16	15
Mean % pre-implantation loss	16%	11.6%	15.6%	19.8%
Mean % post-implantation loss	2.8%	4.5%	3.7%	3.5%
Mean # embryonic resorptions	0	1	1	1
Mean # early resorptions	0	0	0	0
Mean # embryonic resorptions	0	1	1	1
Mean # dead fetuses	0	0	0	0
Mean # non-viable fetuses	0	1	1	1
Mean # live fetuses	15	15	15	14
Mean fetal body weight (g)	5.40	5.44	5.36	5.55
Mean fetal body weight, adjusted^ (g)	5.40	5.80	5.72	5.55
Mean fetal crown-rump length (mm)	41.3	41.2	41.0	41.6
Mean fetal sex ratio (% males)	56.3	51.4	50.6	50.5

% pre-implantation loss = (No. of corpora lutea/litter – No. of implantations/) / No. of corpora lutea/litter x 100; % post-implantation loss = (No. of implantations-No. of live fetuses) / No. of implantations x 100; ^ = covariate-adjusted for litter size (treated litter size/control litter size)*fetal body weight (calculated by reviewer)

Necropsy findings **Offspring**	External malformations: At 18 mg/kg a single fetus (1/345) was observed with right hindlimb hyperextension malformation, which was within the historical control range at the testing facility (up to 5% of litters). Skeletal malformations: At 18 mg/kg four fetuses (4/179) from one litter were noted with skeletal malformations of 13th rib absent (4/4), 13th thoracic vertebra absent (4/4), and/or split

	sternebra (1/4). Values were within the historical control range at the testing facility.

Table 11: FDA – Fetal Malformations and Variations (Embryo-Fetal Development Study; Rats)

Dose (mg/kg)	0	2	6	18
# Fetuses examined externally	358	369	344	345
# Fetuses examined viscerally	175	180	165	165
# Fetuses examined skeletally	182	189	179	179
# of Litters examined	24	24	23	24
Total # fetuses with malformations (% of litters)^	3 (4.2%)	1 (4.2%)	0	5 (8.3%)
External malformations: # of fetuses affected (% of litters)				
Hindlimb-hyperextension-right	0	0	0	1 (4.2%)
Total # fetuses with external malformations (% of litters) $	1 (4.2%)	0	0	1 (4.2%)
Visceral variations: # of fetuses affected (% of litters)				
Ureter-dilated-left or right	2 (8.3%)	1 (4.2%)	2 (8.7%)	1 (4.2%)
Total # of fetuses with visceral variations (% of litters)$	2 (8.3%)	1 (4.2%)	3 (13%)	1 (4.2%)
Skeletal malformations: # of fetuses affected (% of litters)				
Rib/thoracic vertebra- absent (13th)	0	0	0	4 (4.2%)
Sternebra- split	0	0	0	1 (4.2%)
Total # of fetuses with skeletal malformations (% of litters)	0	0	0	4 (4.2%)
Skeletal variations: # of fetuses affected (% of litters)				
Sternebra- unossified	1 (4.2%)	6 (25%)	7 (26%)	3 (14%)
Skull-incomplete ossification	0	0	0	1 (4.2%)
Total # of fetuses with skeletal variations (% of litters)$	83 (96%)	81 (96%)	62 (87%)	93 (100%)

% of litters = (Total # of litters with malformation or variation / Total # of litters) x 100; ^ = Calculated by Reviewer; $ = Includes findings not shown in this table

Toxicokinetics	*Dose proportionality:* Yes *Accumulation:* No *Sex differences:* N/A

Table 12: FDA – Summary of Toxicokinetics (EFD, Rats)

Dose (mg/kg/day	Gestation Day	C_{max} (ng/mL)	AUC_{0-24h} (h*ng/mL)	T_{max} (h)
GD 6	2	25.3	41.9	1
	6	79.2	150	0.5
	18	276	738	0.5
GD 17	2	6.2	N/A	1
	6	17.5	57.2	2
	18	61.5	282	4

N/A=not applicable

Study Title: Subcutaneous Injection Dose Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rabbits/891-0021-DR

Key study findings:

- Delayed fetal development at ≥ 2.88 mg/kg/day MK-5180 (reduced mean fetal weight, crown-rump length, and associated reduced maternal gravid uterine weight at ≥2.88 mg/kg/day and increased incidence of associated skeletal variations at 8.64 mg/kg/day).
- Increased post-implantation loss, visceral malformation (supernumerary lung fissure), and external malformation were noted at 8.64 mg/kg.
- The incidence of litters with malformations was 1.3-fold and 2.2-fold greater at 2.88 mg/kg/day and 8.64 mg/kg/day, respectively, compared to controls.
- Systemic exposure decreased on GD 19 compared to GD 6.

Methods: Mated females (24/group main study) were treated with subcutaneous MK-5180 once daily from GD 6-19 and sacrificed on GD 29; ovaries and uteri were examined for litter data, and live fetuses were collected for visceral and skeletal examination.	
GLP compliance: Yes	
Dose and dose frequency	0, 0.99, 2.88, or 8.64 mg/kg/day
Route of administration	Subcutaneous injection
Formulation/vehicle	MK-5180 (b) (4) mM histidine, (b) (4) mM (b) (4) pH (b) (4)
Species	New Zealand white rabbit
Number/sex/group	25 mated females/group (main study) 5 mated females/group (TK) 2 mated females (satellite)
Study Design	See methods
Deviations affecting results	None of significance
Observations and Results	
Parameters	**Major findings**
Mortality	**2.88 mg/kg:** A female was found dead GD 29 with no abnormal clinical signs or changes in body weight. **8.64 mg/kg:** A female was found dead on GD 26 with red material in the bedding and reduced feces on GD 15-20 with no other noted abnormal findings. Necropsy of these animals included gross pathology with no gross lesions noted in either early death animal.

Clinical Signs	**0.99 mg/kg:** Thinness, alopecia, scab, material in bedding **2.88 mg/kg:** Alopecia, thinness **8.64 mg/kg:** Scab, material in bedding, thinness, abscess Thinness was the only finding noted with dose-dependence (increase in number of days observed)
Body Weights and Food Consumption	**0.99 mg/kg:** Compared to controls, a 4.7% reduced body weight gain was noted on GD 12, correlating with a statistically significant 33.8% reduction in food consumption compared to controls. **2.88 mg/kg:** Compared to controls, a 3.9% reduction in body weight gain was noted on GD 29. **8.6 mg/kg/day:** Compared to controls, a 5.6% reduction in body weight gain was noted on GD 29. Reduced body weight gain was statistically significant on GD 6-9. Reduced food consumption was statistically significant on Days 6-7 and 18-19.
Gravid Uterine Weights	**0.99 mg/kg:** Gravid uterine weight decreased 4%, mean fetal weight decreased 4%, and the number of live fetuses decreased 3% compared to controls. **2.88 mg/kg:** Gravid uterine weight decreased 16%, mean fetal weight decreased 8%, and the number of live fetuses decreased 9%. **8.64 mg/kg:** Gravid uterine weight decreased 20%, mean fetal weight decreased 7%, and the number of live fetuses decreased 18%. Post implantation loss was 15.6% and outside the range of historical control data.
Necropsy findings	*Gross Pathology* Findings were unremarkable

Table 13: FDA – Cesarean Section Findings- Main Study (Embryo-Fetal Development Study; Rabbits)

Dose (mg/kg/day)	0	0.99	2.88	8.64
# Mated females	24	24	24	24
# Pregnant (%)	22 (92%)	22 (92%)	18 (75%)	21 (88%)
# Dams with live fetuses (%)	21 (88%)	21 (88%)	16 (67%)	19 (79%)
Mean # corpora lutea	12.6	12.3	12.6	12.1
Mean # implants	9.4	9.5	9.1	8.3*
Mean % pre-implantation loss	23.9%	20.3%	27.8%	29.3%
Mean % post-implantation loss	10.8%	14.6%[&]	11.0%	15.6%[&]
Mean # early resorptions	0.5[&]	0.7[&]	1.0[&]	1.0[&]
Mean # late resorptions	0.1	0.4	0.1	0.1
Mean total resorptions	0.6	1.1[&]	1.1[&]	1.1[&]
Mean # dead fetuses	0	0	0	0
Mean # live fetuses	8.7	8.5	7.9	7.2
Mean fetal body weight (g)	44.67	42.70	41.06*	41.48**
Mean fetal body weight, adjusted^ (g)	44.67	41.72	37.28	34.33
Mean fetal crown-rump length (mm)	101.35	99.34	97.82**	97.55***
Mean fetal sex ratio (% males)	44.1	47.3	53.8	52.9

% pre-implantation loss = (# of corpora lutea/litter - # of implantation sites/litter) / # of corpora lutea/litter x 100; % post-implantation loss = (# of dead fetuses/litter + resorptions/litter) / # of implantation sites/litter x 100]; * p<0.05, ** p<0.01, *** p<0.001 vs. control; [&] = Value not within range of historical control values at the testing facility; ^ = covariate-adjusted (treated litter size/control litter size)*fetal body weight (calculated by the reviewer)

Necropsy findings **Offspring**	**0.99 mg/kg:** A total of 5 fetuses were noted with malformations. One fetus each at 0.99 mg/kg and 2.88 mg/kg exhibited omphalocele of the abdomen, but this finding was not seen at the high dose level. **2.88 mg/kg:** Three fetuses were noted with visceral malformations, including supernumerary fissure of the lung lobes and a dilated lateral ventricle of the brain. A total of 6 fetuses were noted with malformations. **8.64 mg/kg:** One fetus was noted as having cyclopia of the eyes, a misshapen mouth, absent lower jaw, and small upper jaw. Two fetuses were noted as having supernumerary fissure of the lung lobes. A fused 3rd-5th sternabra was noted as well as absent 1st lumbar arch/centrum vertebra. A total of 12 fetuses were noted with malformations.

Table 14: FDA – Fetal Malformations and Variations (Embryo-Fetal Development Study; Rabbits)

Dose (mg/kg)	0	0.99	2.88	8.64
# Fetuses examined externally	192	186	135	144
# Fetuses examined viscerally	190	183	134	141
# Fetuses examined skeletally	101	96	71	77
# of Litters examined	21	21	16	19
Total # fetuses with malformations (% of litters)^	4 (19.0%)	5 (23.8%)	6 (25.0%)	12 (42.1%)
External malformations: # of fetuses affected (% of litters)				
Eye-cyclopia	0	0	0	1 (5.3%)[&]
Face-lower jaw, absent	0	0	0	1 (5.3%)
Face-upper jaw, small	0	0	0	1 (5.3%)
Face-mouth, misshapen	0	0	0	1 (5.3%)
Face-naris, absent	0	0	0	1 (5.3%)
Face-naris, fused	0	0	0	1 (5.3%)
Head-misshapen	0	0	0	1 (5.3%)
Trunk-abdomen, omphalocele	0	1 (4.8%)	1 (6.3%)[&]	0
Total # of fetuses with external malformations (% of litters)[$]	2 (9.5%)	3 (14.3%)	1 (6.3%)	3 (15.8%)
Visceral malformations: # of fetuses affected (% of litters)				
Brain-lateral ventricle, dilated	0	0	2 (6.3%)[&]	0
Lung-lobe, supernumerary fissure	0	0	1 (6.3%)[&]	2 (10.5%)[&]
Lung-lobe, absent	1 (4.8%)	1 (4.8%)	1 (6.3%)	2 (10.5%)
Gallbladder-absent	1 (4.8%)	1 (4.8%)	1 (6.3%)	2 (10.5%)
Total # of fetuses with visceral malformations (% of litters)	2 (9.5%)	2 (9.5%)	5 (25%)	6 (26.3%)
Visceral variations: # of fetuses affected (% of litters)				
Kidney-renal pelvis, dilated	0	0	0	1 (5.3%)
Total # of fetuses with visceral variations (% of litters)	0	0	0	1 (5.3%)
Skeletal malformations: # of fetuses affected (% of litters)				
Sternebra-3rd, fused	0	0	0	1 (5.3%)
Sternebra-4th, fused	0	0	0	1 (5.3%)
Sternebra-5th, fused	0	0	0	1 (5.3%)
Rib-1st costal cartilage, fused	0	0	0	1 (5.3%)
Rib-2nd costal cartilage, fused	0	0	0	1 (5.3%)
Vertebra-1st lumbar arch, absent	0	0	0	1 (5.3%)
Vertebra-1st lumbar centrum, absent	0	0	0	1 (5.3%)
Total # of fetuses with skeletal malformations (% of litters)	0	0	0	3 (15.8%)
Skeletal variations[$]: # of fetuses affected (% of litters)				
Sternebra-5th asymmetric	0	1 (4.8%)	0	2 (10.5%)[&]

	Sternebra-5th, incomplete ossification	13 (28.6%)	25 (66.7%)*	11 (25%)	8 (31.6%)
	Sternebra-5th, unilateral ossification	0	0	1 (6.3%)	0
	Sternebra-5th, unossified	4 (9.5%)	13 (38.1%)	9 (18.8%)	13 (31.6%)
	Rib-13th, short	4 (14.3%)	10 (33.3%)	4 (18.8%)	6 (31.6%)
	Rib-13th, unossified	0	0	1 (6.3%)	0
	Supernumerary Rib-thoracolumbar, short	50 (90.5%)[&]	53 (90.5%)[&]	36 (81.3%)	42 (94.7%)[&]
	Total # of fetuses with skeletal variations (% of litters)[$]	84 (100%)	102 (100%)	70 (100%)	78 (95%)
	% of litters = (Total # of litters with malformation or variation / Total # of litters) x 100; ^ = Calculated by Reviewer; [$] = Includes findings not shown in this table; [&] = Value not within range of historical control values at the testing facility; * = p≤0.05				

Toxicokinetics	*Dose proportionality:* Yes *Accumulation:* No *Sex differences:* N/A

Table 15: FDA – Summary of Toxicokinetics (EFD, Rabbits)

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	T_{max} (h)
GD 6	1	201	416	1
	2.9	492	1390	1
	8.6	1940	7430	1
GD 19	1	10.9	216	24
	2.9	4.0	6.7	0.8
	8.6	6.5	29.4	2

Exposure and maximum plasma concentration were affected by anti-drug antibodies (ADA), which were noted for all treatment group animals on Day 19 (samples were not analyzed for ADA on Day 6).

Prenatal and Postnatal Development: Study No. 891-0014-DR

Pre- and postnatal development studies are not needed to support the use of MK-375A in the currently proposed indication per ICH S9; however, the Applicant conducted a pre- and postnatal development study with MK-5180 in pregnant/lactating female rats (F0) and their offspring (F1) administered MK-5180 subcutaneously once daily from GD 6 to lactating day 21 (implantation through weaning) in 24 female rats/group for the main study at 0, 2, 6, or 18 mg/kg/day. FDA generally agrees with the Applicant's conclusions. Systemic exposure increased more than dose-proportionally in F0 with exposure in F1 below the limit of qualification, indicating no significant fetal exposure. No MK-5180-related adverse effects were noted on sexual maturation, learning and memory, or fertility for F1 animals. One toxicokinetic female at 6 mg/kg/day was found dead 4 minutes after drawing blood gestation day 6 (first day of dosing) with no clinical observations or findings in necropsy; all other female animals tolerated MK-5180 at doses up to 18 mg/kg/day from implantation to weaning. Systemic exposure of MK-5180 to fetuses during prenatal and postnatal development was minimal (below limit of quantification). One male offspring (F1) from a female at 18 mg/kg/day did not produce sperm and one female (F1)

offspring per dose level from females at 2 mg/kg/day, 6 mg/kg/day, and 18 mg/kg/day did not get pregnant; however, the fertility index for F1 animals were within the ranges noted in the historical control data.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Other nonclinical toxicology studies conducted with pembrolizumab including a T cell-dependent antibody response study in mice using a murine surrogate anti-PD-1 and tissue cross-reactivity studies in human and cynomolgus monkey tissues are summarized in KEYTRUDA BLA 125514.
MK-5180 was evaluated in a non-GLP, single-dose, range-finding tolerability study in which three 5-month-old male minipigs were dosed SC in the left, right, fore, and rear flanks. In minipigs, MK-5180 was well tolerated after SC injection at dose levels up to and including 2 mg/kg, which is >1000-fold of the planned clinical dose.
No other toxicology studies were conducted with MK-3475A.

The FDA's Assessment:

FDA agrees that no additional toxicology studies of MK-3475A are needed at this time. FDA generally agrees with the Applicant's conclusions from the single-dose local tolerance study of subcutaneous MK-5180 in minipigs. One low-dose animal exhibited slight erythema at the injection site on Day 2, which resolved after one day. SC injection of 2 mg/kg (280,000 U/kg) MK-5180 was tolerated, which is 1750-fold greater than the recommended dose of 160 U/kg.

(b) (4)
(b) (4)) was identified as an untargeted leachable in the Applicant's leachable study assessing the pembrolizumab drug product (DP; 790 mg) in contact with (b) (4) glass vials sealed with stoppers. The maximum patient exposure (MPE) of (b) (4) was calculated to be (b) (4) µg/day (b) (4) with an oral LD_{50} in rats of 12,000 mg/kg. In the ICH Q3C guidance, (b) (4) is listed as a solvent for which no adequate toxicological data were found to establish a PDE. According to the guidance, manufacturers should provide justification for residual levels of this solvent in their product. The Applicant justified the levels (b) (4) using a published toxicological evaluation including a calculated parental permitted daily exposure (PDE) of (b) (4) mg/day (b) (4) A PDE of (b) (4) mg/day has been previously used by the FDA to determine the safety of (b) (4) In a reproductive toxicity study, Sprague-Dawley rats (26/sex/group) were administered gasoline (G)/ (b) (4) via whole-body inhalation at doses of 2,000, 10,000 and 20,000 mg/m^3 for 6 hours/day, 7 days/week for one generation (b) (4) The literature report describing the reproductive study (b) (4) (b) (4) is a detailed report suitable for review. In this toxicity study, exposure to (b) (4) mg/m^3 G/ (b) (4) resulted in increased liver and kidney weights compared to controls. Thus, the No Observed Effect Level (NOEL) of G/ (b) (4) in rats was (b) (4) mg/m^3. Because (b) (4) was (b) (4)% of the generated vapor exposure concentration (b) (4) the NOEL for (b) (4) was (b) (4) mg/m^3. The calculated absorbed dose was then divided by the average maternal rat weight ((b) (4)

kg) in the study and then converted from discontinuous to a continuous exposure resulting in a NOEL of (b) (4) mg/kg/day. The PDE was calculated as follows:

PDE: NOEL x weight adjustment (50 mg) / F1 x F2 x F3 x F4 x F5
= ((b) (4) mg/kg x 50 kg) / (b) (4) = (b) (4) mg/day ((b) (4) µg/day)
(b) (4)
F1:
F2:
F3:
F4:
F5:

Since the systemic endpoint of reproductive toxicity was evaluated, it is acceptable to use a study by the inhalation route to set an acceptable limit for the parenteral route. (b) (4) is not genotoxic, but it was shown to be potentially carcinogenic in an oral rat study (b) (4) (b) (4) Thus, it can be considered a Class 2 solvent (non-mutagenic, animal carcinogen). Notably, the calculated PDE of (b) (4) mg/day is within the range of PDE values for other Class 2 solvents in ICH Q3C.

The MPE of (b) (4) in patients is (b) (4) µg/day, which is (b) (4)-fold lower than the calculated PDE of (b) (4) µg/day. The FDA review team also considered that patients will receive 790 mg pembrolizumab/9600 U MK-5180 once every 6 weeks. In conclusion, there are no safety concerns with a MPE of (b) (4) µg/day (b) (4) from the pharmacology/ toxicology perspective.

X _____ X _____

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

Pembrolizumab is a PD-1 blocking antibody currently approved for intravenous (IV) administration in adults for multiple indications, including HNSCC, melanoma, MPM, NSCLC, RCC, UC, TNBC, etc. Pembrolizumab IV is also approved in pediatric patients for certain cancer types (e.g., melanoma, MCC, MSIH/dMMR, TMB-H cancer, etc.).

In the current BLA submission, the Applicant is seeking approval of pembrolizumab/berahyaluronidase alfa in a fixed dose combination for subcutaneous (SC) administration in adults and pediatric patients (12 to <17 years old) for all the solid tumor indications approved for the pembrolizumab IV formulation. Berahyaluronidase alfa is a variant of hyaluronidase, an endoglycosidase that facilitates the SC absorption. The clinical pharmacology review of this BLA focused on the assessment of acceptability of the proposed SC (administered in thigh or abdomen) regimen of pembrolizumab (co-formulated with berahyaluronidase alfa) at the dosages of 395 mg every 3 weeks (Q3W) or 790 mg every 6 weeks (Q6W) in adult and pediatric (12 years and older) patients.

The primary evidence of PK comparability between the pembrolizumab SC and IV formulations was obtained from the pivotal randomized trial MK-3475A-D77 in adult patients with treatment-naïve metastatic squamous or non-squamous NSCLC.

The recommended dosages of pembrolizumab SC are supported by the evidence below:

- Dual primary PK endpoints of cycle 1 $AUC_{0\text{-}6weeks}$ and steady state (Cycle 3) C_{trough} exhibited PK comparability between SC dosage of 790 mg Q6W and IV dosage of 400 mg Q6W. Both PK endpoints met the pre-specified criteria with the lower bound of the 90% CI of the geometric mean ratio (GMR) at 0.8 or above, i.e., GMR for $AUC_{0\text{-}6weeks}$ was 1.14 (96% CI: 1.06, 1.22) and GMR for $C_{trough,cycle\ 3}$ was 1.67 (94% CI: 1.52, 1.84).
- PK data are predicted to be comparable between the Q6W dosing regimen at 790 mg SC and the Q3W dosing regimen at 395 mg SC based on the modeling and simulation and supported by available data for the 395 mg Q3W dosing regimen in patients with melanoma in Arm 4 of Study MK-3475A-C18.
- The PK at the two proposed SC dosages (i.e., 790 mg Q6W and 395 mg Q3W) is predicted to be comparable between the adult and pediatric patients (12 to <17 years old), based on modeling and simulation. This prediction is supported by the PK comparability observed between adults and pediatric patients (12 to <17 years old) for the approved IV dosages.
- Extrapolation of the SC dosages to other solid tumor indications is supported by PK comparability of SC and IV dosages based on results from the pivotal trial MK-3475A-D77, combined with the demonstrated PK comparability across all approved solid tumor indications for pembrolizumab IV.

The incidence of antidrug antibody (ADA) to pembrolizumab was generally low and comparable between SC (1.4%) and IV (0.9%) formulations. The ADA incidence (3.6%) for berahyaluronidase alfa was also low, as compared to other approved SC formulations using hyaluronidase (e.g., 5.4% for atezolizumab and 8.8% for nivolumab).

Recommendations
The Office of Clinical Pharmacology has reviewed the information contained in the BLA submission. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

Table 16: FDA – Key Clinical Pharmacology Review Issues, Recommendations, and Comments

Review Issues	Recommendations and Comments
Evidence of effectiveness	Additional descriptive efficacy assessments (i.e., overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)) come from the pivotal Study MK-3475A-D77 (NCT05722015). The confirmed ORR was 45% (95% CI: 39, 52) in the pembrolizumab SC (+ chemo) arm and 42% (95% CI: 33, 51) in the pembrolizumab IV (+ chemo) arm. No differences in PFS and OS were observed between the two arms. Refer to Section 8.1 for details.
General Dosing instructions	The recommended dosage in adult and pediatric patients aged >12 years who weigh >40 kg is 395 mg/4800 units Q3W or 790 mg/9600 units Q6W.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No clinically meaningful effect of age (37 to 87 years), sex, race (White [63%], Black [3%], Asian [28%]), or body weight (37 to 144 kg), tumor type, injection site (thigh or abdomen), mild to moderate renal impairment (eGFR ≥ 30 mL/min), and mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST). Based on simulations of pembrolizumab PK following MK-3475A SC administration in adult and pediatric (12 to <17 years old) populations, the exposure of pembrolizumab in pediatric patients 12 years and older who weigh at least 40 kg is predicted to be within range of exposure observed in adults at the same recommended dose of pembrolizumab SC.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Pivotal PK data are from the final analysis of MK-3475A-D77, a Phase 3 study evaluating the noninferiority of pembrolizumab PK exposures between MK-3475A administered subcutaneously and pembrolizumab administered intravenously. Additional supportive PK data are from MK-3475A-C18, an ongoing Phase 1 study supporting the MK-3475A dosing regimen, and ALT-BB4-01, a completed Phase 1 study of ALT-BB4, a drug product formulation containing ALT-B4 (also known as MK-5180) in healthy volunteers to provide data specific to MK-5180. The full list of clinical studies supporting this application are summarized in Section 7.1.

Clinical PK data and M&S analysis results show:

- The PK exposures assessed in MK-3475A-D77 as dual primary endpoints (Cycle 1 $AUC_{0\text{-}6wks}$ and steady-state [Cycle 3] C_{trough}) for pembrolizumab 790 mg Q6W administered SC as MK-3475A are noninferior to those for pembrolizumab 400 mg Q6W IV.
- The PK exposures (model-based Cycle 1 C_{trough} and C_{max} and steady-state [Cycle 3] $AUC_{0\text{-}6wks}$ and C_{max}; observed Cycle 1 C_{trough} and C_{max} and steady-state [Cycle 3] C_{max}) assessed in MK-3475A-D77 as secondary endpoints for pembrolizumab 790 mg Q6W administered SC as MK-3475A were generally consistent with those supporting pembrolizumab 400 mg Q6W IV. In addition, secondary PK endpoints of model-based Cycle 1 and steady-state (Cycle 3) C_{trough} at 790 mg Q6W SC were generally comparable to corresponding model-based Cycle 1 and steady-state (Cycle 6) C_{trough}, respectively, at 200 mg Q3W IV.
- The observed PK data in Arm 4 of MK-3475A-C18 validate model predictions of exposures at the 395-mg Q3W SC dosing regimen. PK exposures (model-based and observed Cycle 1 and steady-state C_{trough}, C_{max}, and AUC) of pembrolizumab 395 mg Q3W SC were generally consistent with those at 790 mg Q6W SC with both regimens administered as MK-3475A, confirming that 395 mg Q3W SC is expected to have similar efficacy and safety profile to 790 mg Q6W SC. In addition, the PK exposures (model-based Cycle 1 and steady-state C_{trough}, C_{max}, and AUC) at the 395-mg Q3W SC regimen are also generally consistent with those at the approved 200-mg Q3W IV regimen.
- The immunogenicity profile for pembrolizumab administered SC as MK-3475A is consistent with that for pembrolizumab IV.
- MK-5180 PK and immunogenicity evaluations showed that systemic absorption of MK-5180 after MK-3475A administration was negligible and MK-3475A had limited potential to elicit the formation of ADA to MK-5180.
- The equivalence of pembrolizumab PK exposures when administered SC as MK-3475A with pembrolizumab IV is applicable across indications based on the established, consistent PK and exposure-response of pembrolizumab IV across tumor types and treatment settings. Thus, it is expected that pembrolizumab 790 mg Q6W and 395 mg Q3W dosing regimens administered SC as MK-3475A are safe and efficacious across solid tumor indications for which pembrolizumab 400 mg Q6W IV and 200 mg Q3W IV are approved.

PK and immunogenicity for pembrolizumab and MK-5180 following MK-3475A SC administration are summarized below. Data supporting MK-3475A dosing regimens are in Section 6.2.2.1 and ADME properties are in Section 6.3.1. Conclusions supporting the applicability of these dosing regimens across approved solid tumor indications for pembrolizumab IV are in Section 6.3.2.

Pembrolizumab PK
Previously, extensive population PK modeling analyses have been performed to characterize the PK of pembrolizumab IV. A model including a time-dependency in CL was developed based on a pooled dataset from 5 Phase 1, 2, or 3 clinical studies (n=2993) in participants with melanoma or NSCLC.

MK-3475A-C18
The population PK analysis of pembrolizumab IV was expanded to characterize pembrolizumab PK after SC administration of MK-3475A using data from MK-3475A-C18. The MK-3475A-C18 data included Arms 1, 2, and 3 (650 mg Q6W SC as MK-3475A) and Arm 4 (395 mg Q3W SC as MK-3475A) (see Section 7.1 for study design details). The population PK analysis based on the combined SC and IV PK model showed that pembrolizumab when administered SC as MK-3475A had an estimated bioavailability of 61% (95% CI: 58% to 64%) and the observed median time to achieve maximum pembrolizumab serum concentration was estimated to be 4 days (range: 1 to 35 days).
MK-3475A-C18 evaluated 2 SC solution strengths of pembrolizumab (165 mg/mL and 130 mg/mL); both had similar absorption PK when administered as MK-3475A leading to 165 mg/mL being further developed. No demographic covariates were found to meaningfully impact SC absorption.
Observed PK data for MK-3475A 395 mg Q3W from Arm 4 were generally consistent with the model predictions, validating the model and supporting the 395 mg Q3W dosing regimen for MK-3475A (see Section 6.2.2).
MK-3475A-D77
At the final analysis of MK-3475A-D77, the combined SC and IV PK model was updated with a pooled Phase 1 (MK-3475A-C18 Arms 1, 2, and 3) and Phase 3 (MK-3475A-D77) dataset. The updated population PK model was able to adequately describe pembrolizumab PK after either IV or SC administration. SC bioavailability was 60% (95% CI: 58% to 62%), and median T_{max} was 4 days (range: 1 to 35 days). No clinically meaningful covariate on Ka and F was found.
The final model was used to estimate pembrolizumab exposures (C_{max}, C_{trough}, and $AUC_{0\text{-}6wks}$) after first dose (Cycle 1) and at steady state (Cycle 3 based on Q6W dosing) for participants in MK-3475A-D77 as primary and secondary endpoints in the study.

- The results for the dual primary endpoints demonstrated that pembrolizumab 790 mg Q6W administered SC as MK-3475A resulted in PK exposures (Cycle 1 $AUC_{0\text{-}6wks}$ and steady state [Cycle 3] C_{trough}) that are noninferior to pembrolizumab 400 mg Q6W IV, with respect to the noninferiority margin prespecified as 0.8.
    - The Cycle 1 $AUC_{0\text{-}6wks}$ GMR was 1.14 (96% CI: 1.06, 1.22; observed one-sided *p*-value <0.00001) [].

  - The steady-state (Cycle 3) model-based C_{trough} GMR was 1.67 (94% CI: 1.52, 1.84; observed one-sided *p*-value <0.00001) [].
  - The prespecified sensitivity analysis of observed steady-state (Cycle 3) C_{trough} was conducted to evaluate the robustness of steady-state (Cycle 3) C_{trough} results. Results were consistent with the primary analysis of model-based steady-state (Cycle 3) C_{trough}.
- The secondary PK endpoints of model-based Cycle 1 C_{trough}, Cycle 1 C_{max}, steady-state (Cycle 3) $AUC_{0\text{-}6wks}$, and steady-state (Cycle 3) C_{max} were also shown to be generally consistent between the SC and IV arms.
  - GM of C_{trough} at 790 mg Q6W SC was 58% higher than 400 mg Q6W IV in Cycle 1.
  - GM of $AUC_{0\text{-}6wks}$ at 790 mg Q6W SC was 32% higher than 400 mg Q6W IV at steady-state (Cycle 3).
  - GM of C_{max} at 790 mg Q6W SC was 50% lower in Cycle 1 and 33% lower at steady-state than 400 mg Q6W IV.
- The secondary PK endpoints of observed Cycle 1 C_{trough}, Cycle 1 C_{max}, and steady-state (Cycle 3) C_{max} were also evaluated and results were consistent with the model-based assessment of Cycle 1 C_{trough}, Cycle 1 C_{max}, and steady-state (Cycle 3) C_{max}.
- Model-based Cycle 1 and steady-state (Cycle 3) C_{trough} at 790 mg Q6W SC was also shown to be generally comparable with corresponding model-based Cycle 1 and steady-state (Cycle 6) C_{trough}, respectively, at 200 mg Q3W IV pembrolizumab.

MK-5180 PK

PK of MK-5180 was characterized using intensive sampling following a single dose of ALT-BB4 (a drug product formulation containing ALT-B4, also known as MK-5180) by SC injection in 23 healthy volunteers in ALT-BB4-01. The concentration was measurable (ie, higher than the quantification limit) in 2 participants, who also had predose samples with measurable concentrations. Given the concentration was comparable before and after MK-5180 administration, postdose concentration was not attributed to absorption of MK-5180.
Plasma MK-5180 concentrations were evaluated following SC administration of MK-3475A in MK-3475A-C18 and MK-3475A-D77. There were no participants in either study with postdose samples containing measurable MK-5180 concentrations (ie, above the detection level of the assay) in absence of positive predose samples following SC administration of MK-3475A, confirming negligible systemic absorption of MK-5180.

Pembrolizumab Immunogenicity

The clinical immunogenicity of pembrolizumab after SC administration as MK-3475A and pembrolizumab IV administration was assessed in MK-3475A-C18 and MK-3475A-D77.

The observed incidence of treatment-emergent ADA to pembrolizumab in the 127 evaluable participants from all arms of MK-3475A-C18 treated with MK-3475A or pembrolizumab IV, with or without standard of care therapy as appropriate for the indication, is 0.8%, based on 1 participant with confirmed treatment-emergent positive status, 2 with nontreatment-emergent positive status, and 124 with a negative immunogenicity status. The emergent positive participant had no antibodies with neutralizing capacity, resulting in a treatment-emergent neutralizing positive status of 0%.

In the 211 participants treated in the MK-3475A + chemo group in MK-3475A-D77, the observed incidence of treatment-emergent ADA to pembrolizumab is 1.4%, based on 3 treatment-emergent positive participants, 2 nontreatment-emergent positive participants, and 206 participants with negative immunogenicity status. One of the treatment-emergent positive participants had antibodies with neutralizing capacity, resulting in a treatment-emergent neutralizing positive incidence rate of 0.5%. Of 119 assessable participants in the pembro IV + chemo group, 5 were inconclusive for pembrolizumab immunogenicity analysis, resulting in 114 evaluable participants. Of these, 1 (0.9%) was treatment-emergent ADA positive. No participant was NAb positive.

To evaluate potential clinical risk, the impact of ADA positivity was analyzed on PK, efficacy, and safety for ADA positive participants in the MK-3475A + chemo group of MK-3475A-D77. Pembrolizumab immunogenicity was not associated with meaningful impact on PK, efficacy, or safety.

Collectively, the results confirm that pembrolizumab administered SC as MK-3475A in participants with advanced solid tumors has a limited potential to elicit the formation of ADA, with no meaningful clinical impact of immunogenicity on PK, efficacy, and safety in the cases where ADA formation occurred. These results are consistent with the low immunogenicity incidence in the participants treated with pembrolizumab IV plus chemotherapy in MK-3475A-D77 and well-characterized immunogenicity profile of pembrolizumab IV (ADA and NAb incidence of ~2% and ~0.5%, respectively, as reported in the KEYTRUDA USPI).

MK-5180 Immunogenicity

The clinical immunogenicity of MK-5180 following a single SC injection of ALT-BB4 was assessed in healthy volunteers in ALT-BB4-01 and following MK-3475A administration in patients with advanced solid tumors in MK-3475A-C18 and MK-3475A-D77. No neutralizing analysis was performed for MK-5180 ADA positive samples. No participant in ALT-BB4-01 was positive for MK-5180 ADA in the confirmatory assay.

Out of the 140 participants with MK-5180 ADA samples from MK-3475A-C18, 11 participants were not assessable, resulting in 129 evaluable participants. Of these, 3 (2.3%) participants were nontreatment-emergent ADA positive, 2 (1.6%) participants had a treatment-emergent ADA positive sample with very low titer value (<1) in each, and 1 (0.8%) participant had a treatment-boosted ADA positive sample with titer value 2-fold higher than baseline, which later returned to baseline value. Hence the detected ADA positive samples should be interpreted with caution, particularly given there was no systemic concentration of MK-5180 detected at all in these participants. No neutralizing analysis was performed for MK-5180 ADA positive samples.

Out of the 218 participants with MK-5180 ADA samples from MK-3475A-D77, 24 participants were not assessable, resulting in 194 evaluable participants. Of these, 7 (3.6%) had nontreatment-emergent ADA positive samples and 3 (1.5%) had ADA positive samples (1 treatment-emergent and 2 treatment-boosted). However, all 3 participants with ADA positive samples had very low titer values reported (<1, 1, and 2, respectively). Hence the detected ADA

positive samples should be interpreted with caution, particularly given there was no systemic concentration of MK-5180 detected in these participants. No neutralizing analysis was performed for MK-5180 ADA positive samples.

The effect of ADA status on MK-5180 exposure could not be evaluated as most sample concentrations were BLQ for all participants, including both ADA negative and ADA positive participants. The results confirmed that the emergence of MK-5180 ADA was minimal. Overall, there were no clinically meaningful effects of anti-MK-5180 antibodies on efficacy or safety.

Table 17: Applicant – Analysis of MK-3475A-D77 Primary Endpoint Cycle 1 $AUC_{0\text{-}6weeks}$ (Per Protocol Population)

Treatment	N [a]	Median (Range)	GM (95% CI)	Geometric percent CV	vs. pembro IV + chemo	
					GMR (96% CI)	p-value [b]
MK-3475A + chemo	245	1711.63 (234.65,3945.72)	1633.24 (1555.23,1715.15)	40.41	1.14 (1.06,1.22)	<0.00001
pembro IV + chemo	126	1450.73 (562.53,2858.42)	1437.58 (1373.68,1504.46)	26.23	---	---

[a] Number of Subjects with evaluable PK data.
[b] The one-sided p-value non-inferiority boundary is 0.02.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adpppm]

Table 18: Applicant – Analysis of MK-3475A-D77 Primary Endpoint Cycle 3 Model-Based C_{trough} (Per Protocol Population)

Treatment	N [a]	Median (Range)	GM (95% CI)	Geometric percent CV	vs. pembro IV + chemo	
					GMR (94% CI)	p-value [b]
MK-3475A + chemo	202	40.07 (10.89,120.82)	39.23 (37.04,41.55)	43.29	1.67 (1.52,1.84)	<0.00001
pembro IV + chemo	101	23.85 (4.82,53.75)	23.49 (21.61,25.54)	44.23	---	---

[a] Number of Subjects with evaluable PK data.
[b] The one-sided p-value non-inferiority boundary is 0.03.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adpppm]

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Selection of pembrolizumab SC dosages of 790 mg Q6W or 395 mg Q3W for the pivotal study was based on the comparable exposure to the pembrolizumab IV dosage of 400 mg Q6W or 200 mg Q3W observed previously in the KEYNOTE-189 study, along with support from modeling and simulation results. The bioavailability of pembrolizumab SC was estimated to be approximately 60% based on the combined SC and IV population PK model that incorporated the pooled data from SC pembrolizumab studies MK-3475-C18 and MK-3475-D77 to the previous IV only population PK model.

Pharmacokinetics
Comparative PK exposure (see , , ,) between SC (790 mg Q6W) and IV (400) arms was demonstrated based on results from the pivotal trial MK-3475-D77. Applicant's and show that the lower limit of 95% CI of the geometric mean ratio (GMR) for the primary endpoints of AUC and C_{trough} are above the prespecified non-inferiority criteria.

Table 19: FDA – Pharmacokinetics of Pembrolizumab SC vs. Pembrolizumab IV (Primary and Secondary PK Endpoints) From the Pivotal Study

PK Endpoints	**Geometric mean ratio (SC:IV)**
Primary PK Endpoints	
Model predicted $AUC_{0\text{-}6weeks}$ at Cycle 1	1.14 (96% CI: 1.06, 1.22) (SC: n=245, IV: n=126)
Model predicted steady state $C_{trough,}$	1.67 (94% CI: 1.52, 1.84) (SC: n=202, IV: n=101)
Secondary PK Endpoints	
Model predicted AUC at steady state	1.32
Model predicted $C_{trough.ss}$ at steady state	1.58

Additionally PK data are predicted to be comparable between the Q6W dosing regimen at 790 mg SC and the Q3W dosing regimen at 395 mg SC based on the modeling and simulation (see Section 19.4.2) and supported by available data for the 395 mg Q3W dosing regimen in patients with melanoma in Arm 4 of Study MK-3475A-C18.

Immunogenicity

Table 20: FDA – ADA Incidence of Pembrolizumab and Berahyaluronidase Across the Studies for SC Pembrolizumab

Studies	ADA incidence pembrolizumab	ADA incidence berahyaluronidase alfa
	% (number of evaluable patients)	% (number of evaluable patients)
MK-3475A-D77	SC: 1.4% (n=211)	3.6% (n=194)
	IV: 0.9% (n=114)	
MK-3475A-C18	SC: 0.8% (n=127)	2.3% (n=129)
ALT-BB4-01	N/A	0% (n=21)

Overall, ADA incidence for SC and IV pembrolizumab arms was low and also comparable between the two arms in the study MK-3475A-D77 (1.4% or 3/211 of patients for SC, 0.9% or 1/114 of patients for IV). Pembrolizumab PK between the ADA positive and ADA negative patients was also comparable for both the IV and SC arms. There were no major safety findings in ADA positive patients for pembrolizumab IV and SC. The clinical impact of ADA on pembrolizumab efficacy is unknown due to low ADA occurrence.

ADA incidence for berahylauronidase alfa for the pembrolizumab SC arm was low (3.6% or 7/194). The impact of ADA on MK-5180 levels were considered not evaluable because most concentrations were below the detection limit in both ADA-negative and ADA-positive subjects. Neutralizing analysis was not performed for MK-5180 ADA positive samples. Additionally, ADA incidence for berahylauronidase alfa, in general, was also considered low when compared to other approved hyaluronidase containing SC formulations (e.g. 5.4% for atezolizumab, 8.8% for nivolumab). Overall, berahyaluronidase is not expected to have a significant clinical impact on pembrolizumab PK, safety or efficacy.

Efficacy and Safety
The confirmed ORR in the pivotal study was 45% (95% CI: 39, 52) in the pembrolizumab SC (+ chemo) arm and 42% (95% CI: 33, 51) in the pembrolizumab IV (+ chemo) arm. No differences in PFS and OS were observed between the two arms. The safety profile including serious adverse effects (AEs) and Grade ≥3 AEs was comparable between the SC and IV arms.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A lead to generally consistent PK exposures with the approved IV doses of pembrolizumab 400 mg Q6W and 200 mg Q3W IV, confirming that both 790 mg Q6W and 395 mg Q3W are appropriate

dosing regimens for MK-3475A and are expected to maintain efficacy similar to IV, while also remaining within the known clinical safety margin.
PK exposure-matching principles are used to bridge the proposed dosing regimens pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A to the currently approved pembrolizumab IV dosing regimens across indications. This is based on pembrolizumab PK exposure comparison between MK-3475A and pembrolizumab IV based on data from MK-3475A-D77 and MK-3475A-C18.
Notably, the range of PK exposures for pembrolizumab 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 relationships for efficacy and safety have been well established. Hence the previously established exposure-response for pembrolizumab IV administration also applies to pembrolizumab SC as MK-3475A. Given the 5-fold margin at the upper end of exposures (up to 10 mg/kg Q2W IV), higher C_{trough} and AUC at the proposed 790 mg Q6W SC and 395 mg Q3W SC dosing regimens for MK-3475A compared to the approved pembrolizumab IV dosing regimens are not considered a safety concern. Additionally, C_{max} is lower in MK-3475A compared with pembrolizumab IV.

- Pembrolizumab 790 mg Q6W administered as MK-3475A leads to consistent PK exposure profiles with pembrolizumab 400 mg Q6W IV, supporting M&S analyses and confirming that 790 mg Q6W dosing regimen for MK-3475A is expected to maintain efficacy, while also remaining within the known clinical safety margin. See [], [], [], and Section 6.2.1.
- The simulations also indicated that 395 mg Q3W pembrolizumab administered SC as MK-3475A lead to generally consistent exposures as the 790-mg Q6W dose of pembrolizumab administered SC as MK-3475A. The model-based predictions of PK profiles for 395 mg Q3W SC were validated by observed data in Arm 4 of Study MK-3475A-C18. The PK exposures following pembrolizumab 395 mg Q3W administered SC as MK-3475A were generally consistent with corresponding exposures at 790 mg Q6W administered SC as MK-3475A as illustrated in [Figure 4], [Figure 5], and [Figure 6], confirming that both 395 mg Q3W and 790 mg Q6W dosing regimens for MK-3475A are expected to produce similar efficacy and safety.
- In addition, model-based PK exposures for 395 mg Q3W administered SC as MK-3475A were compared with those for the approved pembrolizumab IV dosing regimen 200 mg Q3W and found to be generally consistent as shown in [Figure 7], [Figure 8], and [Figure 9].

Figure 1: Applicant – Comparison of Model-based Pembrolizumab Cycle 1 and Steady-state (Cycle 3) C_{trough} After Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in MK-3475A-D77

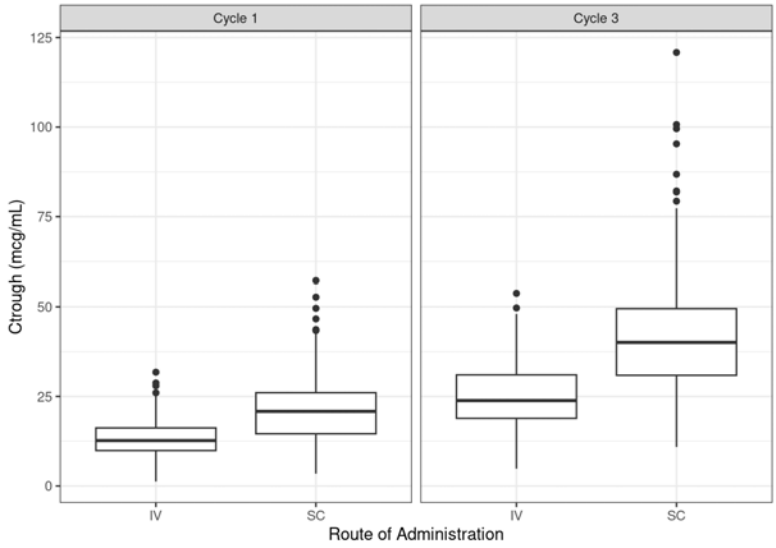
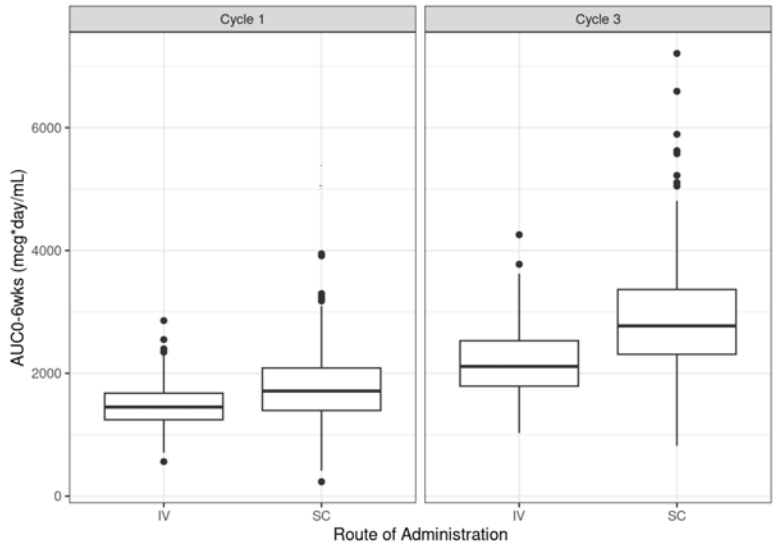
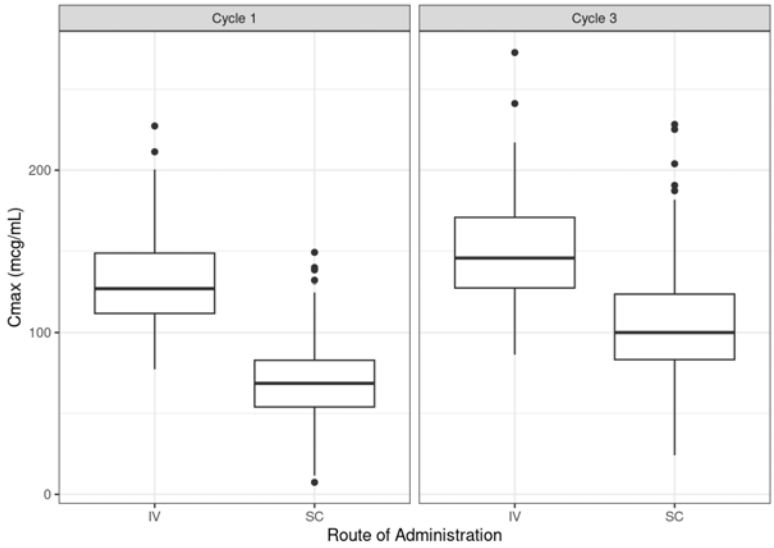


Figure 2: Applicant – Comparison of Model-based Pembrolizumab Cycle 1 and Steady-state (Cycle 3) $AUC_{0\text{-}6wks}$ After Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in MK-3475A-D77



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

Figure 3: Applicant – Comparison of Model-based Pembrolizumab Cycle 1 and Steady-state (Cycle 3) C_{max} After Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in MK-3475A-D77



Note (for , , and): Percentiles of the predicted PK exposure distribution based on Per Protocol Population set are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually. Source: [Ref. 5.3.5.3: 08QL4V]

Figure 4: Applicant – Comparison of Model-based Cycle 1 and Steady-state C_{trough} Between 395 mg Q3W SC and 790 mg Q6W SC Overlaid With Observed C_{trough} for 395 mg Q3W SC in MK-3475A-C18 Arm 4

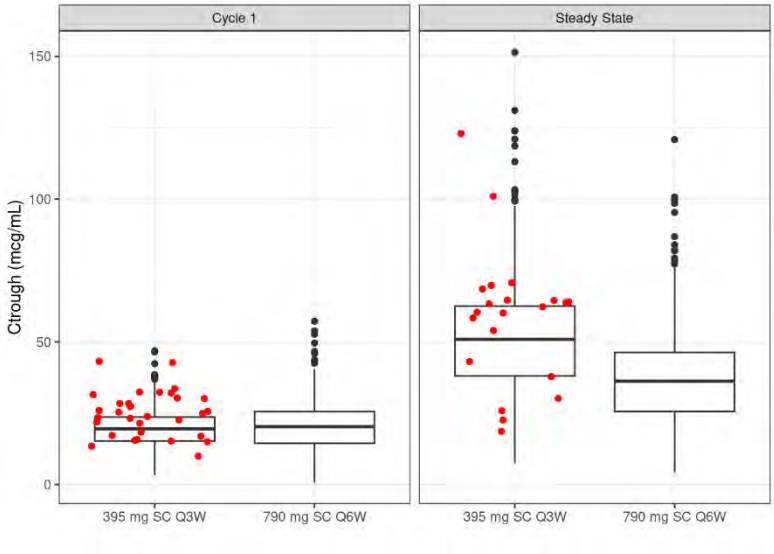


Figure 5: Applicant – Comparison of Model-based Cycle 1 and Steady-state C_{max} Between 395 mg Q3W SC and 790 mg Q6W SC Overlaid With Observed C_{max} for 395 mg Q3W SC in MK-3475A-C18 Arm 4

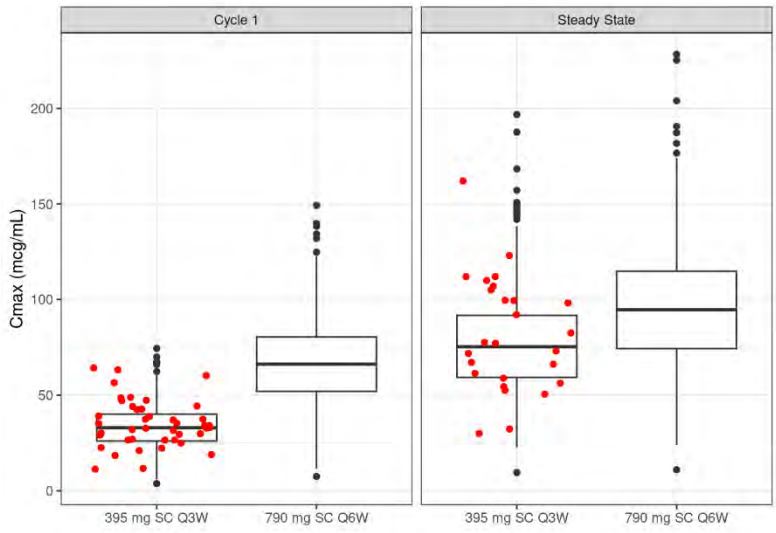
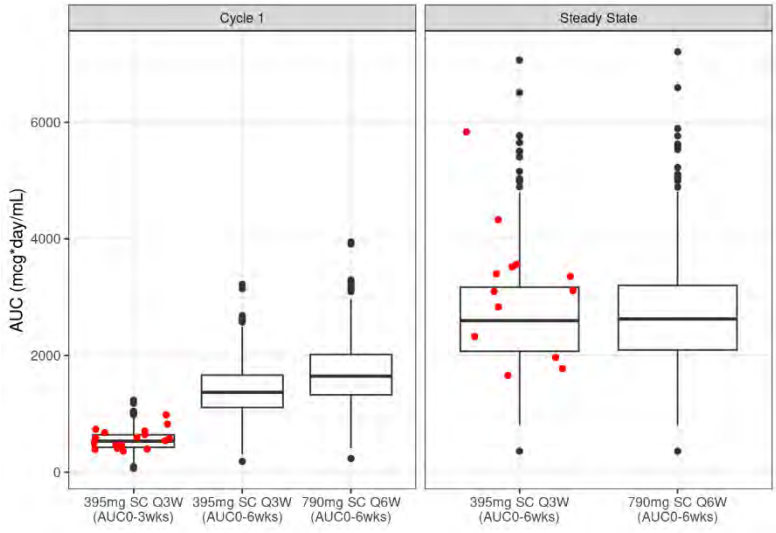


Figure 6: Applicant – Comparison of Model-based Cycle 1 and Steady-state $AUC_{0\text{-}3wks}$ for 395 mg Q3W SC and $AUC_{0\text{-}6wks}$ for 395 mg Q3W and 790 mg Q6W SC Overlaid With Observed $AUC_{0\text{-}3wks}$ for 395 mg Q3W SC in MK-3475A-C18 Arm 4



Note:
Figure 4: Red dots (Cycle 1 N=32; Cycle 6 N=21) are the observed PK exposures at 395 mg Q3W SC from MK-3475A-C18 Arm 4. C_{trough} in Cycle 1 was at Day 21 for observed and model-based 395 mg Q3W SC and at Day 42 for model predicted 790 mg Q6W SC. C_{trough} at steady-state was at Day 126 for observed Q3W SC and model-based Q3W SC and Q6W SC.

Figure 5: Red dots (Cycle 1 N=44; Cycle 6 N=26) are the observed PK exposures at 395 mg Q3W SC from MK-3475A-C18 Arm 4. C_{max} was during 0-3 weeks for observed and model-based 395 mg Q3W SC and during 0-6 weeks for model-based 790 mg Q6W SC.
Figure 6: Red dots (Cycle 1 N=17; Cycle 6 N=13) are the observed PK exposures at 395 mg Q3W SC from MK-3475A-C18 Arm 4. AUC is 0-3 weeks for observed and model-based 395 mg Q3W SC and 0-6 weeks for model-based 395 mg Q3W SC and 790 mg Q6W SC. Observed $AUC_{0\text{-}6wks}$ at steady-state for 395 mg Q3W SC is estimated by multiplying the observed $AUC_{0\text{-}3wks}$ at steady-state by 2.
For Figure 4, Figure 5, and Figure 6: Model-predictions for SC regimens were based on PK simulations using individual post-hoc estimates from pooled data from MK-3475A-C18 (Arms 1 to 3) and in SC arm in MK-3475A-D77 from the modeling analysis [Ref. 5.3.5.3. 08QL4V]. Percentiles of the predicted PK exposure distribution among 343 subjects at 395 mg Q3W SC and 790 mg Q6W SC given as MK-3475A are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whiskers extend from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually. Source: [Ref. 5.3.5.3: 08NTYM]

Figure 7: Applicant – Comparison of Model-based Cycle 1 and Steady-state C_{trough} for 395 mg Q3W SC as MK-3475A and Pembrolizumab 200 mg Q3W IV

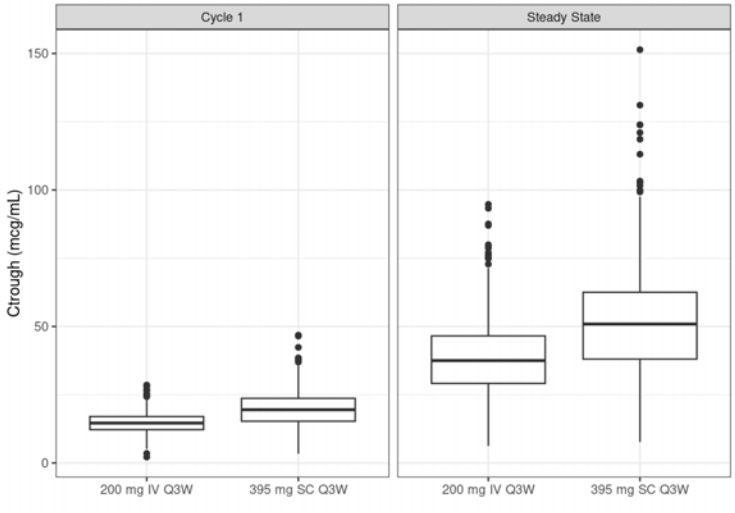


Figure 8: Applicant – Comparison of Model-based Cycle 1 and Steady-state C_{max} for 395 mg Q3W SC as MK-3475A and Pembrolizumab 200 mg Q3W IV

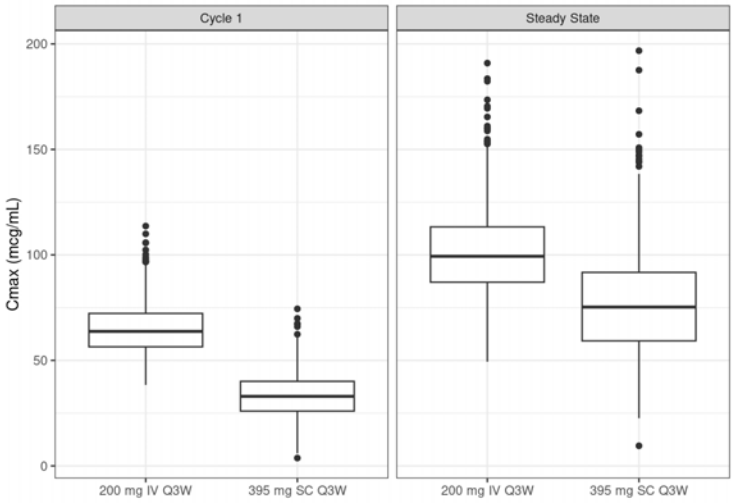
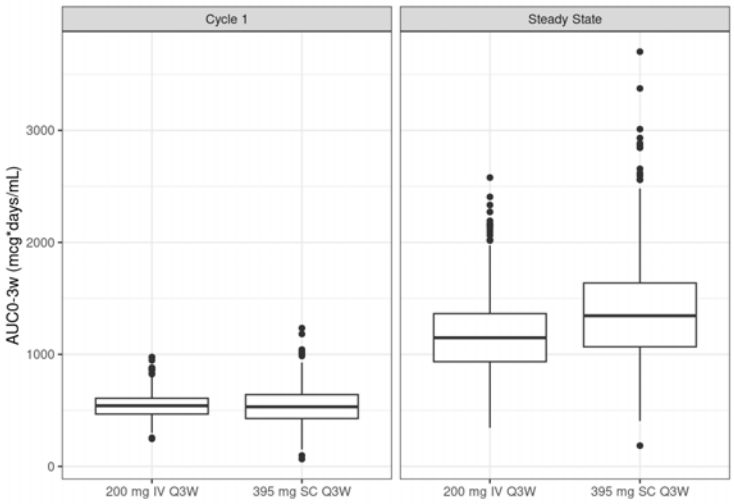


Figure 9: Applicant – Comparison of Model-based Cycle 1 and Steady-state $AUC_{0\text{-}3wks}$ for 395 mg Q3W SC as MK-3475A and Pembrolizumab 200 mg Q3W IV



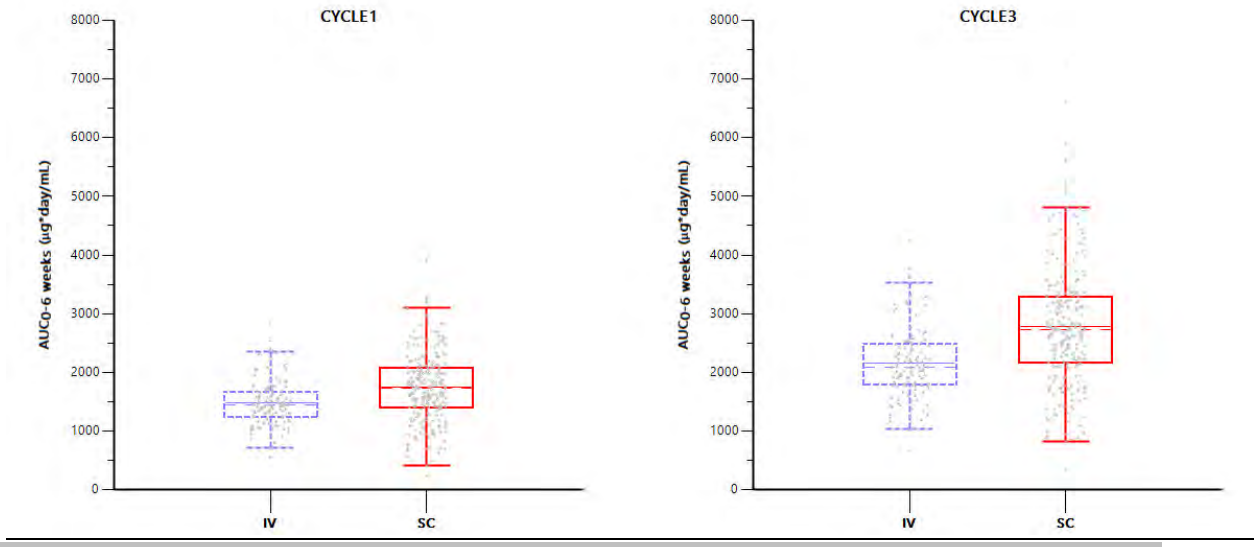
Note (for Figure 7, Figure 8, and Figure 9): Percentiles of the predicted PK exposure distribution among 343 participants at 395 mg Q3W SC given as MK-3475A and among 469 participants at 200 mg Q3W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whiskers extend from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually. Source: [Ref. 5.3.5.3: 08NTYM]

The FDA's Assessment:

FDA agrees with the Applicant's position on the proposed SC dosages of 790 mg pembrolizumab/ 9600 units berahyaluronidase Q6W or 395 mg pembrolizumab/ 4800 units berahyaluronidase Q3W. Overall, the PK exposure (model-based AUC in Cycle 1 and C_{trough} at steady state) are comparable between 790 mg SC Q6W and 400 mg IV Q6W (,) from the pivotal

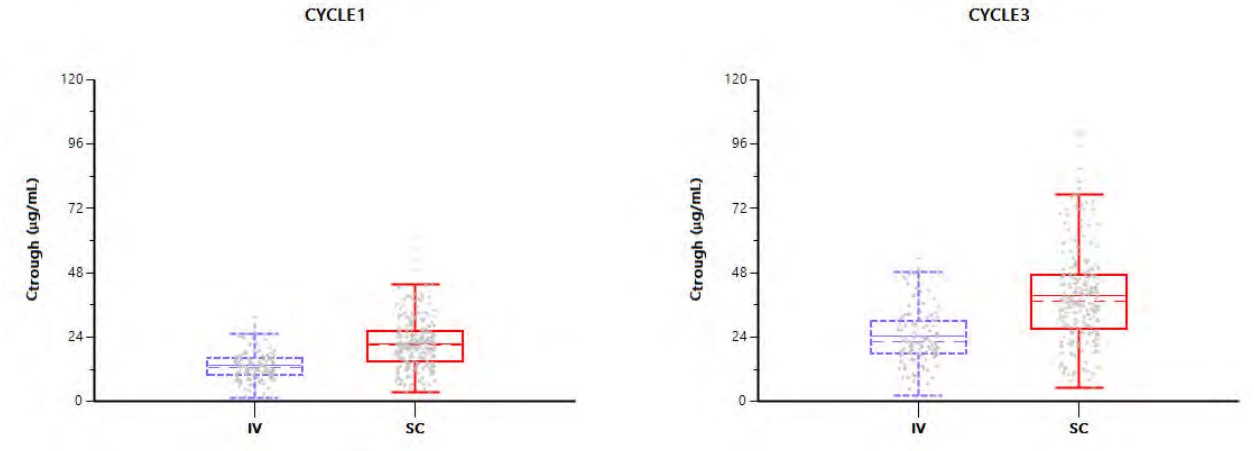
study, as well as between 395 mg SC Q3W and 790 mg SC Q6W (Figure 4, Figure 6) from arm 4 of study MK-3477A-C18. Additionally, model-based cross-comparison between 395 mg SC Q3W and 200 mg IV Q3W (Figure 7, Figure 9) showed comparable PK between the two SC dosing regimens.

Figure 10: FDA – Boxplots of $AUC_{0\text{-}6weeks}$ at Cycle 1 and Cycle 3 Comparing the IV and SC Pembrolizumab



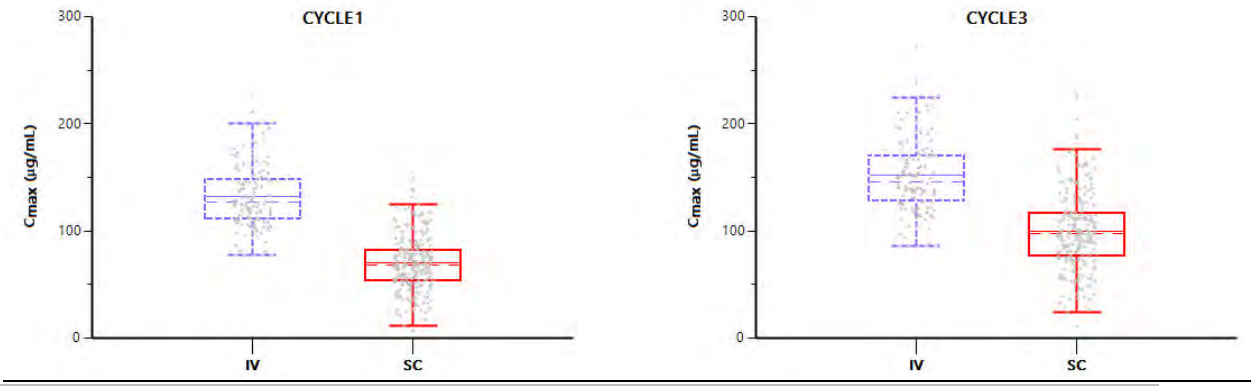
Source: FDA analysis based on Applicant's data.

Figure 11: FDA – Boxplots of C_{trough} at Cycle 1 and Cycle 3 Comparing the IV and SC Pembrolizumab



Source: FDA analysis based on Applicant's data.

Figure 12: FDA – Boxplots of C_{max} at Cycle 1 and Cycle 3 Comparing the IV and SC Pembrolizumab



Source: FDA analysis based on Applicant's data.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No specific dosing modifications are required or recommended based on intrinsic and/or extrinsic factors. See Section 6.3.1 for details.

The FDA's Assessment:
FDA agrees with the Applicant's assessment that there is no dose individualization of pembrolizumab SC required for adult and pediatric (12 to <17 years old) patients who weigh more than 40 kg. Based on the simulations conducted using integrated (SC and IV) population PK model, pembrolizumab exposures are predicted to be comparable between the pediatric (12 years and older with body weight > 40 kg) and adult (with the lowest body weight quartile) patients at the proposed pembrolizumab SC dosages of 790 mg Q6W SC and 395 mg Q3W. See Sections 10 and 19.4.2 for details.

6.2.2.3. Outstanding Issues

The Applicant's Position:

Not applicable

The FDA's Assessment:
There are no outstanding issues.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

An overview of the ADME properties and PK of pembrolizumab administered SC as MK-3475A are summarized below. This summary includes pembrolizumab IV data from KEYTRUDA BLA 125514 and additional data on SC administration of MK-3475A from the final analysis of MK-3475A-D77 (Section 6.2.1).

Absorption: Bioavailability of pembrolizumab administered SC as MK-3475A is 60% (CV: 14%) and T_{max} is 4 days (range: 1 to 35 days).

Distribution: Consistent with a limited extravascular distribution, the VD_{ss} of pembrolizumab is small (6.0 L; CV: 20%). As expected for an antibody, pembrolizumab is not expected to bind to plasma proteins in a specific manner.

Metabolism: Pembrolizumab is catabolized through nonspecific pathways; metabolism does not contribute to its CL.

Elimination: Pembrolizumab CL is approximately 23% lower (GM, 195 mL/day [CV: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean (CV) for the terminal $t_{1/2}$ at steady-state is 22 days (32%).

Pharmacokinetic Profile: The PK profile of pembrolizumab is consistent with that of other humanized mAbs, which typically have a low CL and a limited Vc. The estimates of between-subject variability are low-to-moderate and are within the range of historically reported variability levels for mAbs. In a review on mAbs, the between-subject variability range of 15% to 65% for CL and a median of 26% (range: 12% to 84%) for Vc was reported. Also, in context of SC administration, F and Ka are within the ranges reported for other mAbs (range, F: 50% to 80%) (range, Ka: 0.1/day to 0.5/day).

Steady-state concentrations of pembrolizumab are reached by 16 weeks of repeated dosing with a Q3W or Q6W regimen. The C_{max}, C_{trough}, and area under the plasma concentration-time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 mg/kg to 10 mg/kg Q3W IV.

Intrinsic Factors: The following factors had no clinically meaningful effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (89% White), tumor burden, renal impairment (estimated glomerular filtration rate ≥15 mL/min/1.73 m^2), or mild hepatic impairment (TB ≤ ULN and AST >ULN or TB between 1 and 1.5×ULN and any AST), or moderate hepatic impairment (TB >1.5-3×ULN and any AST). There is insufficient information to determine whether there are clinically important differences in the CL of pembrolizumab in patients with severe hepatic impairment (TB >3×ULN and any AST). The following factors had no clinically meaningful effect on the SC absorption (F or Ka) of pembrolizumab: age, sex, body weight, race, tumor type, injection site (thigh or abdomen).

The relationship between CL or Vc and body weight was determined by inclusion of an estimated allometric exponent (α) in the population PK model. As with other mAbs, body weight

was found to be related to pembrolizumab CL and Vc parameters, but the relationship between body weight and CL was weak (α estimates were close to 0.5 for both parameters). As such, either fixed or weight-based dosing provides similar control of PK variability.

Overall, no specific dosing modifications are required or recommended based on intrinsic factors.

Extrinsic Factors: As pembrolizumab is an IgG4 antibody administered SC as MK-3475A and cleared by catabolism, food and DDI are not anticipated to affect exposure. Therefore, no dedicated DDI studies have been performed. However, as systemic corticosteroids may be used to treat immune-mediated adverse reactions concomitant with pembrolizumab, the potential for a PK DDI with pembrolizumab as a victim was assessed. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure.

Corrected QT Interval: No clinically meaningful effects on QTc were identified in the analyses included in previous submissions (KEYTRUDA BLA 125514).

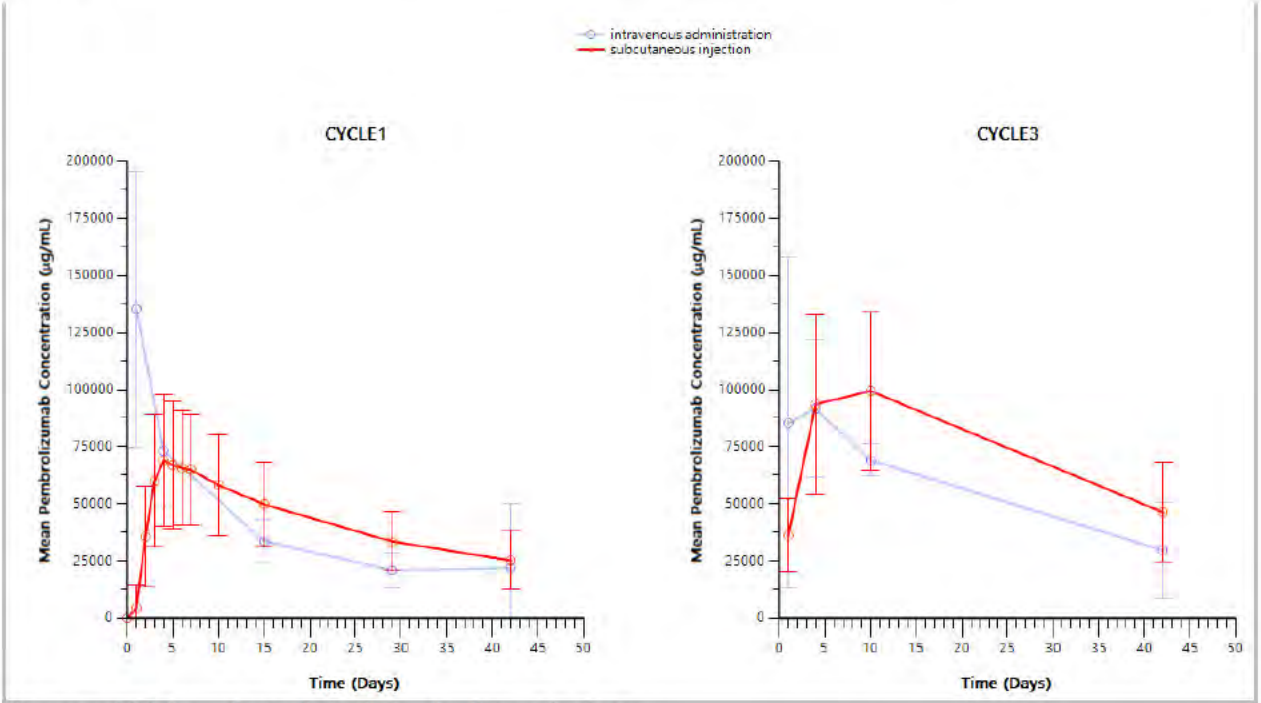
The FDA's Assessment:

FDA generally agrees with the Applicant's position on clinical pharmacology and PK characterization of pembrolizumab, i.e., the majority of the clinical pharmacology information is applicable to both IV and SC administrations. The PK characteristics (e.g., absorption and impacting covariates) of pembrolizumab SC were assessed with the PK data obtained from the pivotal trial and the updated population PK model.

The PK results from the pivotal study confirm that the selected dosage (790 mg Q6W) of pembrolizumab for SC administration provided comparable exposure to the approved IV dosage of 400 mg Q6W (, ,).

The population PK model from the previous studies with IV pembrolizumab was updated by adding the absorption process for the SC pembrolizumab. PK exposure comparisons were conducted across the different IV and SC dose regimens using simulated PK data, which demonstrated comparable PK between SC and IV dosages (). See Section 19.4.1 for details.

Figure 13: FDA – Concentration-Time Profiles of Pembrolizumab SC and IV: Cycle 1 and Cycle 3



Source: FDA analysis based on Applicant's data.

Table 21: FDA – Model-Predicted PK Comparison Between SC and IV Dosages

Dosage	**790 mg Q6W (SC) vs 400 mg Q6W (IV)**			**395 mg Q3W (SC) vs 200 mg Q3W (IV)**		
Ratio	$AUC_{0\text{-}6W}$	C_{max}	C_{trough}	$AUC_{0\text{-}3W}$	C_{max}	C_{trough}
First dose	1.07	0.65	1.32	1.02	0.49	1.32
Steady state	1.11	0.78	1.29	1.13	0.73	1.32

Source: FDA analysis based on Applicant's data.

6.3.2. Clinical Pharmacology Questions

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

The Applicant's Position:

Yes, the clinical pharmacology program provides supportive evidence of effectiveness.

As summarized in Section 6.2.1, results from the final analysis of MK-3475A-D77 demonstrated that pembrolizumab 790 mg Q6W administered SC as MK-3475A resulted in PK exposures (dual primary endpoints: Cycle 1 $AUC_{0\text{-}6wks}$ and steady-state [Cycle 3] C_{trough}) that are noninferior to pembrolizumab 400 mg Q6W IV in patients with previously untreated metastatic NSCLC [] []. Analysis of secondary PK endpoints showed that pembrolizumab exposures after MK-3475A administration were within range of the exposures after pembrolizumab IV administration. Because the pharmacological activity of mAbs is mediated through direct interaction with a specific target, target saturation can be used as a surrogate for maximal pharmacologic and therapeutic activity [12]. As such, noninferiority of pembrolizumab steady-state (Cycle 3) C_{trough} for pembrolizumab 790 mg Q6W administered SC as MK 3475A relative to pembrolizumab 400 mg Q6W IV infers that efficacy similar to pembrolizumab IV dosing will be maintained.

As summarized later in Section 8.1.2, results of MK-3475A-D77 demonstrate comparable efficacy based on ORR, PFS, OS, and DOR, between pembrolizumab 790 mg Q6W administered SC as MK-3475A and pembrolizumab 400 mg Q6W IV. Given similar PK and flat exposure-response across tumor types and treatment settings, any inferences on comparability of PK exposure and thereby efficacy, between SC and IV administrations are expected to apply across approved pembrolizumab indications and doses, using monotherapy and combination regimens.

The FDA's Assessment:
The secondary efficacy endpoints for the pivotal study include ORR, PFS, OS and duration of response. The descriptive analysis of the efficacy endpoints showed no clinically meaningful differences between SC and IV administration at the respective dosages. Refer to Section 8.1 of the Assessment Aid for details. Previous studies conducted with pembrolizumab IV have shown a flat exposure-efficacy relationship over 2 mg/kg Q3W to 10 mg/kg Q3W and the PK exposure following pembrolizumab SC 790 mg Q6W and 395 mg Q3W are within the above exposure range.

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

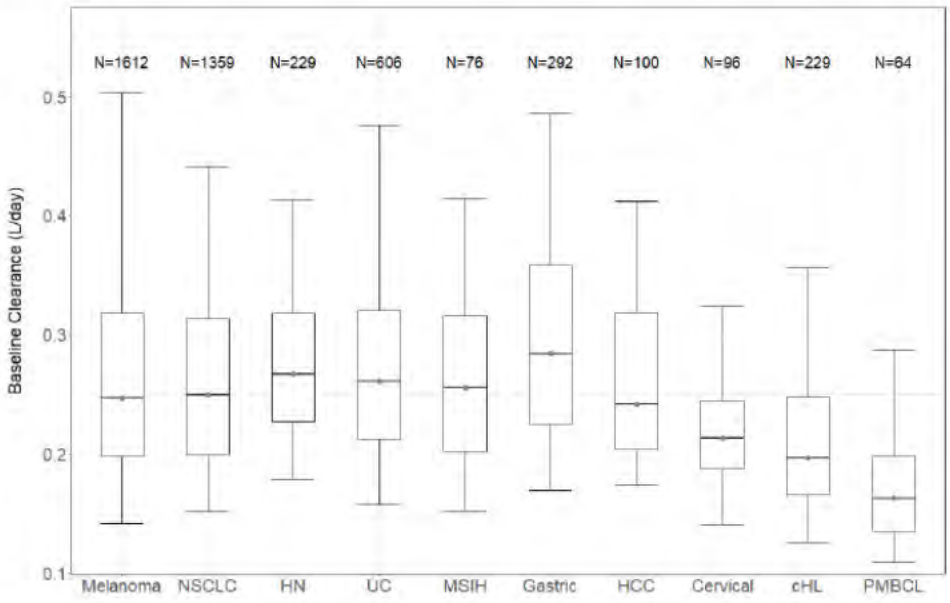
The Applicant's Position:

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought.
As summarized in Sections 6.2.1 and 6.2.2.1, data from MK-3475A-D77 and MK-3475A-C18 and population PK analyses demonstrated consistent PK exposures and immunogenicity profiles of pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A compared with the approved dosing regimens of 400 mg Q6W and 200 mg Q3W IV, leading to similar efficacy and safety profiles for the 2 SC dosing regimens.
The equivalence of pembrolizumab PK exposures when administered SC as MK-3475A with pembrolizumab IV is applicable across indications based on consistent PK and exposure-response of pembrolizumab IV across tumor types and treatment settings. Thus, it is expected

that pembrolizumab 790 mg Q6W and 395 mg Q3W dosing regimens administered SC as MK-3475A provide the same clinical benefit for all solid tumor indications for which pembrolizumab IV is approved for adults and pediatric patients 12 years and older.

The FDA's Assessment:
FDA agrees with the Applicant's position that the pembrolizumab SC dosages of 795 mg Q6W or 395 mg Q3W are appropriate for the general population for the proposed indications. The pivotal trial MK-3475A-D77 supporting the SC formulation demonstrated that the exposure of pembrolizumab SC at 790 mg and IV at 400 mg Q6W were comparable in the NSCLC population. A cross-indication comparison of pembrolizumab IV showed that clearance of pembrolizumab was comparable across indications (). Given the absorption of pembrolizumab SC is independent of solid tumor types, it is expected that the exposure of pembrolizumab following SC administration is comparable across all the solid tumor indications.

Figure 14: FDA – Similarity of Pembrolizumab Clearance Based on TDPK Model Across Indications



Note: Percentiles of the distribution of post-hoc estimated individual baseline clearance values among subjects per indication (number of subjects per indication shown above) are represented by the line (50^{th}), box (25^{th}-75^{th}) and whiskers (5^{th}-95^{th}). The sample size (N) per group is provided above each box-whisker plot.
Abbreviations: TDPK = time-dependent pharmacokinetic; NSCLC = non-small cell lung cancer; HN = head & neck squamous cell carcinoma; UC = urothelial cancer; MSIH = microsatellite instability high cancers; HCC = hepatocellular carcinoma; cHL = classical Hodgkin's lymphoma; PMBCL = primary mediastinal B-cell lymphoma

Source: Applicant's Summary of Clinical Pharmacology, Figure 2.7.2, Page 12.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

No specific dosing modification are required or recommended based on intrinsic factors.

The FDA's Assessment:
FDA agrees with the Applicant's position that no dosing modification is required based on the intrinsic factors including body weight, sex, age, race, ethnicity, mild to moderate renal impairment, or mild to moderate hepatic impairment.

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

The Applicant's Position:

There have been no dedicated clinical biopharmaceutical studies for food effect or drug-drug interactions given the route of administration and well-understood clearance mechanism for monoclonal antibody (ie, catabolism).

The FDA's Assessment:
FDA agrees with the Applicant's position given SC route of administration and low potential of drug-drug interactions with monoclonal antibodies.

X X

Primary Reviewer Team Leader

7 Sources of Clinical Data

7.1 Table of Clinical Studies

Table 22: Applicant – List of Clinical Trials Relevant to the BLA

Study Number (Status)	Design (Indication)	Dosage/Treatment Regimen	Study Population (N)	Primary Endpoint(s)
Pivotal Phase 3 Study				
MK-3475A-D77 (ongoing)	Randomized, active-controlled, parallel-group, multisite, open-label study of MK-3475A versus pembrolizumab IV, with chemotherapy (metastatic squamous or nonsquamous NSCLC)	**Arm 1**: MK-3475A 790 mg SC Q6W for up to 18 cycles in combination with platinum doublet chemotherapy[a] **Arm 2**: Pembrolizumab 400 mg IV Q6W for up to 18 cycles in combination with platinum doublet chemotherapy[a]	**Arm 1**: 251 randomized/ 251 treated Gender: 182 Male/69 Female Median age: 65.0 years **Arm 2**: 126 randomized/ 126 treated Gender: 86 Male/40 Female Median age: 66.0 years	• Cycle 1 $AUC_{0\text{-}6\ wks}$ • Steady-state (Cycle 3) C_{trough}
Supportive Studies				
MK-3475A-C18 (Phase 1, ongoing)	Nonrandomized, sequential, multicenter, bioavailability and safety study of MK-3475A (unresectable, advanced melanoma, metastatic	**Arm 1 (Q6W)**: Cycle 1: MK-3475A 650mg SC, Cycle 2: pembrolizumab 400mg IV, Cycle 3: 650 mg SC, Cycles 4-18: pembrolizumab 400 mg IV; with or without standard of care therapy, as appropriate for the indication[a,b,c]	**Arm 1**: 46 allocated/ 46 treated Gender: 33 Male/13 Female Median age: 61.0 years	**Arms 1 and 2**: • Ctrough • Cmax • Tmax • AUC • F

Study Number (Status)	Design (Indication)	Dosage/Treatment Regimen	Study Population (N)	Primary Endpoint(s)
	NSCLC, or advanced or metastatic RCC)	**Arm 2 (Q6W)**: Cycle 1: MK-3475A 650 mg SC, Cycle 2: pembrolizumab 400 mg IV, Cycle 3: 650 mg SC, Cycles 4-18: pembrolizumab 400 mg IV; with or without standard of care therapy, as appropriate for the indication[a,b,c]	**Arm 2**: 44 allocated/ 44 treated Gender: 26 Male/18 Female Median age: 66.5 years	
		Arm 3 (Q6W): Cycle 1: MK-3475A 790 mg SC with standard of care chemotherapy, Cycles 2-18: pembrolizumab 400 mg IV[a]	**Arm 3**: 6 allocated/ 6 treated Gender: 6 Male/0 Female Median age: 68.0 years	**Arm 3**: • Ctrough • Cmax • Tmax • AUC • Safety
		Arm 4 (Q3W): Cycles 1-35: MK-3475A 395 mg SC	**Arm 4**: 44 allocated/44 treated Gender: 22 Male/22 Female Median age: 60.0 years	**Arm 4**: • Ctrough • Cmax • AUC
ALT-BB4-01 (Phase 1, completed)	Tolerance, safety and pharmacokinetics of ALT-BB4 (a drug product containing ALT-B4, also known as MK-5180) (healthy volunteers)	**Part I**: Single dose of ALT-BB4 and comparator (0.9% NaCl) 0.02 mL **Part II-A**: Single dose of ALT-BB4 1 mL	**Part I**: 290 allocated/282 completed Gender: 96 Male/148 Female Median age: 34.0 years **Part II-A**: 23 allocated/23 completed Gender: 8 Male/15 Female Median age: 41.0 years	**Part I**: Incidence rate of drug allergy following ID injection of MK-5180 **Part II**: Safety and tolerability following SC injection of MK-5180

Study Number (Status)	Design (Indication)	Dosage/Treatment Regimen	Study Population (N)	Primary Endpoint(s)
		Part II-B: Single dose of ALT-BB4 (study group) or comparator (0.9% NaCl) (control group) 1 mL	**Part II-B**: Study group: 172 allocated/142 treated Gender: 62 Male/80 Female Median age: 34.0 years Control group: 87 allocated/72 treated Gender: 24 Male/48 Female Median age: 34.0 years	
MK-3475A-F11 (Phase 2, ongoing)	Randomized, cross-over, multicenter, open-label study of MK-3475A (resected Stage IIB, IIC, III melanoma, intermediate-high or high risk resected RCC, or newly diagnosed, untreated Stage IV NSCLC with a PD-L1 TPS ≥50%)	Treatment Crossover Period: **Arm A**: MK-3475A 395 mg SC Q3W for 3 cycles followed by pembrolizumab IV 200 mg Q3W for 3 cycles **Arm B**: pembrolizumab 200 mg IV Q3W for 3 cycles followed by MK-3475A 395 mg SC Q3W for 3 cycles	**Arm A**: 63 randomized/63 treated Gender: 39 Male/24 Female Median age: 61.0 years **Arm B**: 69 randomized/69 treated Gender: 44 Male/25 Female Median age: 65.0 years	Participant preference assessed by response of MK-3475A SC on PPQ question 1

Study Number (Status)	Design (Indication)	Dosage/Treatment Regimen	Study Population (N)	Primary Endpoint(s)
		Treatment Continuation Period: Participants continued their preferred intervention for up to a total of 17 cycles (for adjuvant melanoma and RCC participants) or 35 cycles (for metastatic NSCLC participants)		

AUC = area under the curve; $AUC_{0\text{-}6wks}$ = area under the curve from 0 to 6 weeks; C_{max} = maximal concentration; C_{trough} = trough concentration; F = bioavailability; ID = intradermally; IV = intravenous; Ka = absorption rate; NaCl = sodium chloride; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1; PPQ = Patient Preference Questionnaire; Q3W = every 3 weeks; Q6W = every 6 weeks; RCC = renal cell carcinoma; SC = subcutaneous; Tmax = time to reach maximum concentration; TPS = tumor proportion score.

[a] For participants with nonsquamous NSCLC, platinum doublet chemotherapy included 4 infusions of pemetrexed with investigator's choice of cisplatin or carboplatin, followed by pemetrexed maintenance until a discontinuation criterion was met. For participants with squamous NSCLC, platinum doublet chemotherapy included 4 infusions of carboplatin with investigator's choice of paclitaxel or nab-paclitaxel.

[b] For participants in Arm 1, MK-3475A concentration was 165 mg/mL. For participants in Arm 2, MK-3475A concentration was 130 mg/mL

[c] For participants with RCC, standard of care included axitinib; for participants with NSCLC, standard of care included platinum doublet chemotherapy (see footnote a)

The FDA's Assessment: FDA agrees with the Applicant's description of the clinical trials relevant to this application. The primary objective of MK-3475A-D77 was to demonstrate that pembrolizumab SC has comparable exposure to pembrolizumab IV based on PK endpoints. MK-3475A-D77 was the primary trial submitted by the Applicant to support this BLA. The patient preference Study MK-3475A-F11 was not reviewed during this review cycle as results from the final analysis were not submitted by the Applicant.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

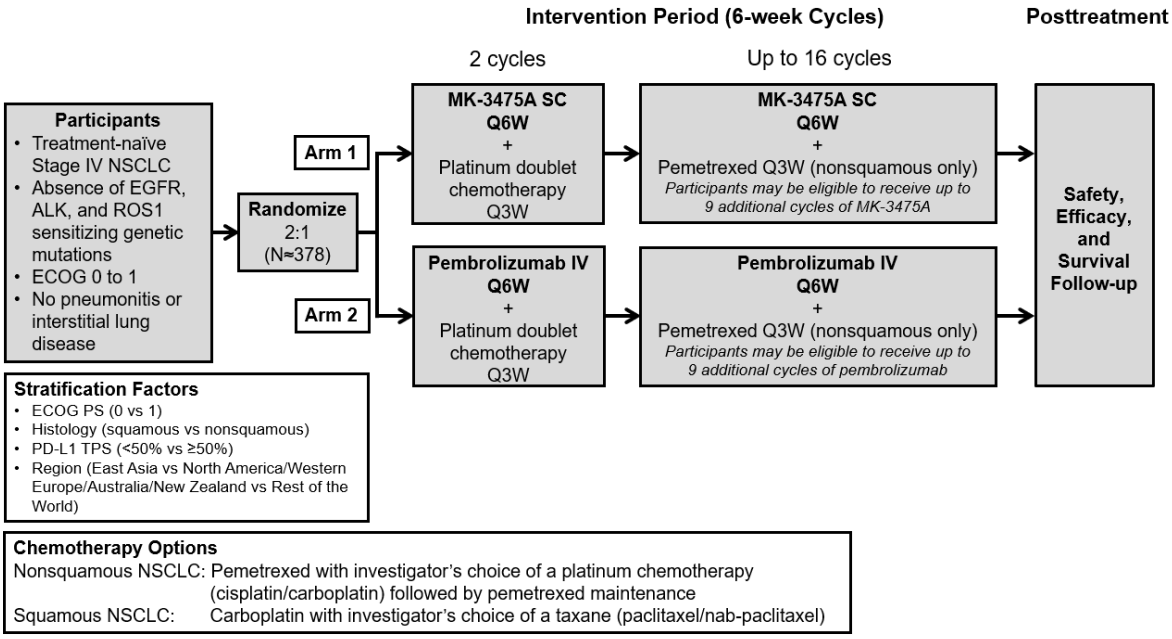
8.1.1. MK-3475A-D77

Trial Design

The Applicant's Description:

MK-3475A-D77 is a Phase 3, randomized, active-controlled, parallel-group, multisite, open-label study of pembrolizumab 790 mg Q6W administered SC as MK-3475A and histology-based platinum doublet chemotherapy (Arm 1 or MK-3475A + chemo) versus pembrolizumab 400 mg Q6W IV and histology-based platinum doublet chemotherapy (Arm 2 or pembro IV + chemo) in participants with treatment-naïve metastatic NSCLC. Participants were to have an ECOG PS of 0 to 1 and their NSCLC was to be untreated. The study design is shown in Figure 15.
The planned enrollment total for the global study was 378 participants.

Figure 15: Applicant – MK-3475A-D77 Study Design



ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; IV=intravenous; NSCLC=non-small cell lung cancer; PD-L1=programmed cell death ligand 1; PS=performance status; Q3W=every 3 weeks; Q6W=every 6 weeks; ROS1=c-ros oncogene 1; SC=subcutaneous; TPS=tumor proportion score

Trial Location: MK-3475A-D77 is an ongoing global study conducted at 110 centers in 16 countries. Three participants from the US were randomized.

Choice of Control Group: All participants received pembrolizumab administered with platinum doublet chemotherapy based on histology. The use of pembrolizumab IV as an active comparator ensured that participants received the approved formulation in the control arm.
Assignment to Treatment: Participants were randomly assigned in a 2:1 ratio to MK-3475A + chemo or pembrolizumab IV + chemo. Randomization was stratified by ECOG performance status (0 vs 1), PD-L1 TPS (<50% vs ≥50%), histology (squamous vs nonsquamous), and region (East Asia vs North America/Western Europe/Australia/New Zealand vs Rest of the World).
Blinding: This is an open-label study.
Dose Modification, Dose Discontinuation: Treatment with MK-3475A or pembrolizumab was withheld or discontinued based on guidelines described in the protocol which included treatment-related toxicities or life-threatening AEs. Dosing interruptions were permitted for situations other than treatment-related AEs. Discontinuation of MK-3475A or pembrolizumab was permitted. Dose modifications for chemotherapy components followed the recommendations detailed in the prescribing information for the relevant product.
Administrative Structure: An external DMC made recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. The DMC monitored data accumulated during the study and considered the overall risk and benefit to study participants and recommended to the EOC whether the study should continue in accordance with the protocol.
Procedures and Schedules: Screening procedures were to be completed within 28 days before the first dose of study treatment. MK-3475A or pembrolizumab was administered every 6 weeks (1 cycle) during the treatment period, with Cycle 1 beginning at Day 1 for up to 18 cycles (+9 cycles as second-course treatment, if eligible). Imaging was performed at screening and Weeks 6, 12, 18, and subsequently every 9 weeks. Participants who completed the protocol-required cycles of study treatment or who discontinued study treatment for a reason other than BICR-verified disease progression began efficacy follow-up to monitor disease status according to the schedule outlined in the protocol. Participants who completed all efficacy assessments and/or did not have further efficacy assessments entered survival follow-up. Participant survival follow-up status was assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurred first.
Concurrent Medications: All treatments that the investigator considered necessary for a participant's welfare could be administered at the discretion of the investigator in keeping with the community standards of medical care. If a participant required systemic antineoplastic chemotherapy, immunotherapy, radiation therapy, investigational vaccines, or biological therapy not specified in the protocol, all study interventions were to be discontinued.
Treatment Compliance: Participants received study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic was recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification were confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.
Rescue Medications: Participants received appropriate supportive care measures as deemed necessary by the treating investigator. Supportive care measures for the management of AEs with potential immunologic etiology were outlined in the protocol and consistent with the approved

labeling of pembrolizumab. Chemotherapy-related AEs were managed according to the label and local and international guidelines.

Participant Completion, Discontinuation, or Withdrawal: Participants may have withdrawn consent at any time for any reason. Participants may have also been discontinued from treatment by the investigator. A participant may have discontinued from all treatments, but continued to participate in the regularly scheduled activities, as long as the participant did not withdraw consent. A participant must have been discontinued from the study if the participant (or legal representative) withdrew consent. Participants who discontinued from study treatment or withdrew from the study were not replaced.

The FDA's Assessment:

FDA agrees with the Applicant's position. Study MK 3475A D77 (NCT05722015) was a randomized, multicenter, open-label, non-inferiority, active-controlled trial conducted in patients with treatment-naïve metastatic NSCLC, in whom there were no EGFR, ALK, or ROS1 genomic tumor aberrations. A total of 377 patients were randomized (2:1) to receive either KEYTRUDA QLEX 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa administered subcutaneously every 6 weeks with platinum doublet chemotherapy (n=251) or pembrolizumab 400 mg intravenously every 6 weeks with platinum doublet chemotherapy (n=126).

The chemotherapy regimens were as follows:

- Non-squamous NSCLC: pemetrexed 500 mg/m^2 and a platinum chemotherapy (cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min) intravenously every 3 weeks for 4 cycles, followed by pemetrexed 500 mg/m^2 intravenously every 3 weeks.
- Squamous NSCLC: carboplatin AUC 6 mg/mL/min and a taxane (paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle or paclitaxel protein-bound 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle) intravenously every 3 weeks for 4 cycles.

Randomization was stratified by ECOG performance status (0 vs. 1), histology (squamous vs. non-squamous), PD-L1 TPS (<50% vs. ≥50%), and geographic region (East Asia vs. North America/Western Europe/Australia/New Zealand vs. Rest of the World).

Treatment with pembro SC or pembro IV was continued until RECIST v1.1 defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 18 cycles (approximately 24 months). Treatment was permitted beyond RECIST-defined disease progression by BICR or beyond discontinuation of pemetrexed if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Study MK 3475A D77 was only powered for PK endpoints and the sample size calculation was not driven by an efficacy endpoint. All efficacy endpoints were descriptive in nature.

Eligibility Criteria

The Applicant's Description:

Key inclusion criteria included:

- Histologically or cytologically confirmed diagnosis of squamous or nonsquamous NSCLC (Stage IV: M1a, M1b, M1c, AJCC Staging Manual, version 8).
- In participants with nonsquamous NSCLC, confirmation that EGFR-, ALK-, or ROS1-directed therapy is not indicated as primary therapy (documentation of absence of tumor-activating *EGFR* mutations [eg, DEL19 or L858R] AND absence of *ALK* and *ROS1* gene rearrangements).
- Measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology.
- At least 18 years of age at the time of providing informed consent.
- An ECOG performance status of 0 to 1.
- A life expectancy of at least 3 months.
- Archival tumor tissue sample or newly obtained core, incisional, or excisional biopsy of a tumor lesion not previously irradiated for determination of PD-L1 status before randomization.
- Adequate organ function.

Key exclusion criteria included:

- Diagnosis of small cell lung cancer or, for mixed tumors, presence of small cell elements.
- Received prior systemic anticancer therapy for their metastatic NSCLC.
- Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
- Received prior radiotherapy within 2 weeks of start of study intervention or has radiation-related toxicity requiring corticosteroids.
- Received radiation therapy to the lung that is >30 Gray within 6 months of start of study intervention.
- Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy
- Known additional malignancy that is progressing or has required active treatment within the past 3 years.
- Known active central nervous system metastases and/or carcinomatous meningitis.
- Active autoimmune disease that has required systemic treatment in past 2 years.
- History of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

The FDA's Assessment: FDA agrees with the Applicant's description.

Study Endpoints

The Applicant's Description:

Primary Endpoint(s)	• Cycle 1 $AUC_{0\text{-}6\ wks}$ • Steady-state (Cycle 3) C_{trough} (model-based)

Secondary Endpoints	• For descriptive comparison to pembrolizumab 400 mg Q6W IV: o Cycle 1: C_{max}, C_{trough} o Cycle 3: $AUC_{0\text{-}6\ wks}$, C_{max} • For descriptive comparison to pembrolizumab 200 mg Q3W IV: o Model-based C_{trough} at Cycle 1 and steady state • ADA • ORR per RECIST 1.1 by BICR • PFS per RECIST 1.1 by BICR • OS • DOR • Safety and tolerability • PROs

The FDA's Assessment: FDA agrees with the Applicant's description of study endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Table 23: Applicant – Summary of Statistical Analysis Plan for MK-3475A-D77

Analysis Populations	• PK (primary): Per-protocol Set • Efficacy: ITT • Safety: APaT • PRO: PRO Full Analysis Set
Statistical Methods for Key Immunogenicity/ Pharmacokinetic Analyses	For both primary hypotheses of noninferiority of MK-3475A SC versus pembrolizumab IV with respect to Cycle 1 $AUC_{0\text{-}6\ wks}$ and Cycle 3 C_{trough}, the noninferiority margin with respect to the AUC and C_{trough} GMR of MK-3475A SC versus pembrolizumab IV is specified to be 0.8. Computation of the CIs of GMR will be calculated using Welch's t-test statistics (which does not rely on the assumption of equal variances for SC and IV) with the log-transformed AUC and C_{trough}.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen's method [13].
Interim Analyses	**Pharmacokinetics** There are no planned IAs for PK analysis in this study. One final analysis (FA) is planned to be performed when a minimum of 27 weeks follow-up is achieved after the last participant is randomized. This is expected about 16.2 months after first participant is randomized. The purpose of FA is for noninferiority of Cycle 1 $AUC_{0\text{-}6wks}$ and Cycle 3 C_{trough}. **Safety** The study plans 1 interim safety analysis, which will be performed approximately 7 months after first participant is randomized.
Multiplicity	The overall Type I error over the primary endpoints is strongly controlled at 0.05 (1-sided), with 0.02 initially allocated to Cycle 1 $AUC_{0\text{-}6\ wks}$ and 0.03 to Cycle 3 C_{trough}.

	By using the graphical approach of Maurer and Bretz [14], if 1 hypothesis is rejected, the alfa will be shifted to the other hypothesis.
Sample Size and Power	The planned sample size is approximately 378 participants. For the primary endpoint of Cycle 1 $AUC_{0\text{-}6\ wks}$, based on 318 participants with evaluable Cycle 1 $AUC_{0\text{-}6\ wks}$, the study has approximately >99.9% power to reject the null hypothesis (AUC GMR ≤0.8) under a true AUC GMR = 1.07 at the initially assigned 0.02 (1-sided) significance level. For the primary endpoint of Cycle 3 C_{trough}, based on 240 participants with evaluable Cycle 3 C_{trough} data, the study has approximately 99.8% power to reject the null hypothesis (C_{trough} GMR ≤0.8) under a true Cycle 3 C_{trough} GMR = 1.29 at the initially assigned 0.03 (1-sided) significance level.

The FDA's Assessment: FDA agrees with the Applicant's description.

For the PRO analysis population, the full analysis set (FAS) was defined as all randomized patients who received at least one dose of study intervention and had at least one PRO assessment available for the specific endpoint. As part of Protocol Amendment 03, PRO data from the Japan population were excluded, as documented in SAP Amendment #1. The EORTC QLQ-LC13 (lung cancer-specific module) was also removed, as it was not collected.

Protocol Amendments

The Applicant's Description:

Table 24: Applicant – Summary of Amendments to MK-3475A-D77 Protocol

Document	Date of Issue	Overall Rationale
Amendment 3[a]	06-FEB-2024	To add G-CSF as primary prophylaxis during the first 4 platinum-doublet infusions in both arms.
Amendment 2	19-OCT-2023	To update the assumptions and timing of the analyses in the SAP.
Amendment 1	10-APR-2023	To incorporate revisions based on health authority feedback.
Original Protocol	20-OCT-2022	Not applicable

[a] In response to an observed high rate of neutropenia and related events, which upon review were deemed chemotherapy-related, the Applicant issued a Dear Investigator Letter and implemented a protocol amendment requiring that all participants receive CSF as primary prophylaxis during the first 4 platinum-doublet infusions. At the time of the Dear Investigator Letter, 91.2% of participants were already randomized on the study and many had completed the first 4 platinum doublet infusions.

The FDA's Assessment: FDA agrees with the Applicant's presentation of the key protocol changes listed in the table above.

8.1.2. MK-3475A-D77 Study Results

Results are presented from the protocol-specified final analysis of the MK-3475A-D77 study with a data cutoff date of 12-JUL-2024.

Compliance with Good Clinical Practices

The Applicant's Position:

MK-3475A-D77 was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent, and the protection of human participants in biomedical research. The protocol and any amendments, information provided to participants, and any recruitment materials were reviewed and approved by the IECs (also referred to as an IRB, ERC, or any other ethics committee). The IEC(s) consulted for this study met the definition of an "IEC" as outlined in US CFR Title 21 Part 56, or equivalent country specific regulations. Informed consent was obtained and documented in accordance with the principles and provisions in Section 4.8 of the ICH E6 Guideline for Good Clinical Practice, US CFR Title 21 Part 50, Protection of Human Subjects, and/or local country/cultural consent practices and/or requirements where applicable. Informed consent was obtained from all participants before performing study related procedures or assessments.

The FDA's Assessment:

FDA agrees with the Applicant's description of compliance with Good Clinical Practices. The Applicant provided attestation that the study was conducted in accordance with good clinical practice.

Financial Disclosure

The Applicant's Position:

A financial disclosure review of MK-3475A-D77 has been conducted. See Section 19.2.

The FDA's Assessment: FDA agrees.

Patient Disposition

Data:

Table 25: Applicant – Disposition of Participants (ITT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
Status for Study Treatment in Trial				
Started	251		126	
Discontinued	116	(46.2)	66	(52.4)
Adverse Event	36	(14.3)	16	(12.7)
Clinical Progression	10	(4.0)	3	(2.4)
Lost To Follow-Up	0	(0.0)	2	(1.6)
Non-Compliance With Protocol	0	(0.0)	1	(0.8)
Physician Decision	1	(0.4)	0	(0.0)
Progressive Disease	61	(24.3)	41	(32.5)
Withdrawal By Subject	8	(3.2)	3	(2.4)
Participants Ongoing	135	(53.8)	60	(47.6)
Status for Trial				
Discontinued	63	(25.1)	38	(30.2)
Death	57	(22.7)	37	(29.4)
Lost To Follow-Up	1	(0.4)	0	(0.0)
Withdrawal By Subject	5	(2.0)	1	(0.8)
Participants Ongoing	188	(74.9)	88	(69.8)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Database Cutoff Date: 12JUL2024

Source: [PD77V01MK3475A: adam-adsl]

The Applicant's Position:

A total of 377 participants were randomly assigned to treatment, and comprised the ITT population. All participants in both the MK-3475A + chemo group (n=251) and pembro IV + chemo group (n=126) received at least 1 dose of study treatment []. The disposition of participants was generally comparable in the MK-3475A + chemo and pembro IV + chemo groups. As of the data cutoff date, the median duration of follow-up was 8.6 months (range: 0.2, 16.4 months).

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition. The overall discontinuation rates were similar at 46.2% for MK-3475A + chemo versus 52.4% for pembrolizumab IV + chemo. Rates of treatment discontinuation due to adverse events was comparable between the MK-3475A + chemo and pembrolizumab IV + chemo arms at 14.3% versus 12.7% respectively, suggesting similar tolerability profiles between formulations. Higher proportions of disease progression per RECIST (32.5% vs 24.3%) and mortality (29.4% vs 22.7%) were observed in patients receiving pembrolizumab IV + chemo versus those receiving MK-3475A subcutaneously + chemo.

Protocol Violations/Deviations

The Applicant's Position:

Protocol deviations were classified as per the ICH E3 classification of protocol deviations as important (those that may significantly impact the quality or integrity of key trial data or that may significantly affect a participant's rights, safety, or well-being) or not important. Important protocol deviations were further classified as either clinically important (deviations that may compromise critical data analyses pertaining to primary efficacy and/or safety endpoints or the participant's safety) or not clinically important.
There were 4 participants with important protocol deviations that were considered to be clinically important, all of which were related to administration of MK-3475A. MK-3475A was to be administered by a single subcutaneous injection in the participant's abdomen wall or thigh; however, these participants received a single dose split into 2 injections. All 4 participants were excluded from the per protocol population for PK analyses.
Important protocol deviations considered to be not clinically important were reported for 19 (7.6%) participants in the MK-3475A + chemo group and 8 (6.3%) participants in the pembro IV + chemo group.
No participants were excluded from efficacy analyses due to protocol deviations. No protocol deviations were classified as a serious GCP compliance issue. None of the important protocol deviations impacted the overall safety or integrity of the study.

The FDA's Assessment: FDA agrees with the description of protocol violations and deviations, and that they are not likely to have impacted the interpretability of the study results.

Table of Demographic Characteristics

Data:

Table 26: Applicant – Participant Characteristics (ITT Population)

	MK-3475A + chemo		pembro IV + chemo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	251		126		377	
Sex						
Male	182	(72.5)	86	(68.3)	268	(71.1)
Female	69	(27.5)	40	(31.7)	109	(28.9)
Age (Years)						
< 65	119	(47.4)	57	(45.2)	176	(46.7)
>= 65	132	(52.6)	69	(54.8)	201	(53.3)
Mean	64.7		64.8		64.8	
SD	9.6		8.5		9.2	
Median	65.0		66.0		65.0	
Range	39 to 87		37 to 83		37 to 87	

	MK-3475A + chemo		pembro IV + chemo		Total	
	n	(%)	n	(%)	n	(%)
Race						
American Indian Or Alaska Native	2	(0.8)	4	(3.2)	6	(1.6)
Asian	74	(29.5)	36	(28.6)	110	(29.2)
Black Or African American	5	(2.0)	5	(4.0)	10	(2.7)
Multiple	12	(4.8)	3	(2.4)	15	(4.0)
American Indian Or Alaska Native, White	8	(3.2)	1	(0.8)	9	(2.4)
Black Or African American, White	4	(1.6)	2	(1.6)	6	(1.6)
White	158	(62.9)	78	(61.9)	236	(62.6)
Ethnicity						
Hispanic Or Latino	74	(29.5)	41	(32.5)	115	(30.5)
Not Hispanic Or Latino	177	(70.5)	85	(67.5)	262	(69.5)
Geographic Region						
East Asia	73	(29.1)	36	(28.6)	109	(28.9)
North America/Western Europe/Australia/New Zealand	11	(4.4)	7	(5.6)	18	(4.8)
Rest of the World	167	(66.5)	83	(65.9)	250	(66.3)
PD-L1 Status						
TPS < 50%	181	(72.1)	91	(72.2)	272	(72.1)
TPS >= 50%	48	(19.1)	25	(19.8)	73	(19.4)
Unknown	22	(8.8)	10	(7.9)	32	(8.5)
PD-L1 Status						
TPS < 1%	101	(40.2)	57	(45.2)	158	(41.9)
TPS >= 1%	128	(51.0)	59	(46.8)	187	(49.6)
Unknown	22	(8.8)	10	(7.9)	32	(8.5)
PD-L1 Status						
TPS < 1%	101	(40.2)	57	(45.2)	158	(41.9)
TPS 1-49%	80	(31.9)	34	(27.0)	114	(30.2)
TPS >= 50%	48	(19.1)	25	(19.8)	73	(19.4)
Unknown	22	(8.8)	10	(7.9)	32	(8.5)
ECOG						
0	89	(35.5)	42	(33.3)	131	(34.7)
1	162	(64.5)	84	(66.7)	246	(65.3)
Histology						
Non-Squamous	167	(66.5)	83	(65.9)	250	(66.3)
Squamous	84	(33.5)	43	(34.1)	127	(33.7)
Metastatic Stage						
M1a	97	(38.6)	51	(40.5)	148	(39.3)
M1b	44	(17.5)	13	(10.3)	57	(15.1)
M1c	110	(43.8)	62	(49.2)	172	(45.6)
Overall Stage						

	MK-3475A + chemo		pembro IV + chemo		Total	
	n	(%)	n	(%)	n	(%)
IVA	141	(56.2)	64	(50.8)	205	(54.4)
IVB	110	(43.8)	62	(49.2)	172	(45.6)
Brain Metastasis Status at Baseline						
Yes	19	(7.6)	14	(11.1)	33	(8.8)
No	232	(92.4)	112	(88.9)	344	(91.2)
Liver Metastasis Status at Baseline						
Yes	46	(18.3)	15	(11.9)	61	(16.2)
No	205	(81.7)	111	(88.1)	316	(83.8)
Smoking Status						
Never Smoker	38	(15.1)	23	(18.3)	61	(16.2)
Former Smoker	142	(56.6)	62	(49.2)	204	(54.1)
Current Smoker	71	(28.3)	41	(32.5)	112	(29.7)
Prior Adjuvant/Neo-adjuvant Therapy						
Yes	5	(2.0)	6	(4.8)	11	(2.9)
No	246	(98.0)	120	(95.2)	366	(97.1)
Prior Radiation						
Yes	37	(14.7)	24	(19.0)	61	(16.2)
No	214	(85.3)	102	(81.0)	316	(83.8)
Prior Thoracic Radiation						
Yes	10	(4.0)	8	(6.3)	18	(4.8)
No	241	(96.0)	118	(93.7)	359	(95.2)

SD=Standard deviation.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl]

The Applicant's Position:

The demographics and baseline characteristics of the study participants were balanced across the intervention groups and representative of a patient population with treatment-naïve metastatic NSCLC []. Most participants were ≥65 years of age, male, and former or current smokers with an ECOG performance status of 1. The proportion of participants with PD-L1 TPS ≥50% was 19.4%, which is lower than the approximately 26% to 34% typically observed in pembrolizumab studies including participants with NSCLC [2] [3], but was balanced between the treatment arms.

The FDA's Assessment:

FDA agrees with the Applicant that the demographics and baseline characteristics of patients in Study MK-3475A-D77 were generally well balanced between the treatment arms. Only 2.7% of patients were Black or African American and 1.6% of patients were multiracial and were partly Black or African American, which underrepresents the proportion of patients with metastatic NSCLC who are Black or African American in the U.S. The demographic and baseline

characteristics of patients in the trial were otherwise generally representative of U.S. patients with treatment-naïve metastatic NSCLC.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Disease characteristics are provided in []. Participants represented a range of races and ethnicities, with 1.6% American Indian or Alaska Native, 29.2% Asian, 2.7% Black or African American, 4% multiple race categories, and 62.6% White; 30.5% were Hispanic or Latino and 69.5% were not Hispanic or Latino.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of race, region, and ethnicity. Black and African American patients were underrepresented in this trial compared to the actual proportion of Black and African American patients with metastatic NSCLC in the U.S.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Study interventions were administered in the clinic by qualified site personnel and recorded in the CRF. Concomitant medication was generally consistent between the MK-3475A + chemo group and the pembro IV + chemo group.

The FDA's Assessment: FDA agrees that the study interventions were administered in the clinic by qualified site personnel and recorded in the CRF. FDA noted that administration of concomitant medications was generally consistent between the pembrolizumab SC plus chemotherapy arm compared to pembrolizumab IV plus chemotherapy arm except for the following medications with >5% difference, as shown in table below:

Table 27: FDA – Concomitant Medications With >5% Difference in Arms MK-3475A-D77

Medication/Product	Pembrolizumab SC + Chemo	Pembrolizumab IV + Chemo
Tramadol Hydrochloride	21%	14%
Filgrastim	32.27%	26%
Acetylcysteine	18%	13%

Source: Applicant-provided analysis dataset adcm.xpt
Data cutoff Date: July 12, 2024

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

While MK-3475A-D77 was designed as a PK noninferiority study with PK primary endpoints, ORR, PFS, OS, and DOR were included as secondary endpoints to demonstrate comparable efficacy between SC and IV routes of administration and support totality of evidence to enable bridging across pembrolizumab IV indications. Efficacy analyses are presented below, in **Efficacy Results – Secondary and other relevant endpoints**. Results for the primary PK endpoints are presented in Section 6.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Data Quality and Integrity

The Applicant's Position:

Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. The clinical study program was conducted in accordance with GCP guidelines. Merck Research Laboratory Quality Assurance independently assessed quality through a comprehensive, risk-based audit program to ensure adherence with applicable GCP, Good Pharmacovigilance Practices regulations, and applicable company policies and procedures. No serious GCP compliance issues were identified for this study. Audit information is available on request. There are no potential issues concerning the submitted data quality or integrity that raise questions about the reported PK and efficacy results.

The FDA's Assessment: FDA agrees.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 28: Applicant – Summary of Secondary Efficacy Endpoints

	MK-3475A + chemo	pembro IV + chemo
Secondary Endpoints		
ORR (BICR per RECIST 1.1)		
% (95% CI)	45.4 (39.1,51.8)	42.1 (33.3,51.2)
Estimate (95% CI)[a]	3.47 (-7.01,13.69)	
PFS (BICR per RECIST 1.1)		
Median in months (95% CI)[b]	8.1 (6.3, 8.3)	7.8 (6.2, 9.7)
HR (95% CI)	1.05 (0.78, 1.43)	
3 month PFS Rate (95% CI)	80.3 (74.8, 84.7)	82.9 (75.0, 88.5)
6 month PFS rate (95% CI)	64.7 (58.4, 70.3)	65.0 (55.7, 72.8)
9 month PFS rate (95% CI)	38.3 (30.6, 45.8)	42.8 (32.4, 52.8)
OS		

Median in months (range)[b]	NR (NR, NR)	NR (NR, NR)
HR (95% CI)	0.81 (0.53, 1.22)	
3 month OS rate (95% CI)	91.6 (87.5, 94.5)	95.2 (89.7, 97.8)
6 month OS rate (95% CI)	82.4 (77.1, 86.6)	84.1 (76.5, 89.4)
9 month OS rate (95% CI)	76.8 (70.7, 81.7)	72.7 (63.4, 80.0)
DOR (confirmed CR or PR, BICR per RECIST 1.1)		
Number of participants with a response[c]	114	53
Median response duration in months (95% CI)[d]	9.1 (6.9, NR)	8.0 (7.4, NR)
% of participants with extended response duration ≥6 months	68.1	72.1
% of participants with extended response duration ≥9 months	52.8	49.5

BICR=blinded independent central review; CI=confidence interval; CR=confirmed response; DOR=duration of response; HR=hazard ratio; IV=Intravenous; NR=Not Reached; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; sSAP=supplemental statistical analysis plan.

[a] Based on Miettinen & Nurminen method stratified by ECOG (0 vs 1), Histology (squamous vs nonsquamous), PD-L1 status (TPS <50% vs ≥50%), and geographic region (East Asia vs North America/Western Europe vs Rest of the World) with small strata collapsed as pre-specified in the sSAP. Database Cutoff Date: 12JUL2024

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by ECOG performance status (0 vs 1), TPS (≥50% vs <50%), Histology (squamous vs nonsquamous) and Region (East-Asia vs North America/Western Europe/Australia/New Zealand vs Rest of the World).

[c] Includes participants with confirmed complete response or partial response.

[d] From product-limit (Kaplan-Meier) method for censored data.

Source: [Ref. 5.3.5.1: PD77V01MK3475A: Table 14.2-5] [Ref. 5.3.5.1: PD77V01MK3475A: Table 11-4] [Ref. 5.3.5.1: PD77V01MK3475A: Table 11-5] [Ref. 5.3.5.1: PD77V01MK3475A: Table 11-6]

The Applicant's Position:

Efficacy analyses are descriptive only. No type I error control is applied to efficacy analyses.
Objective Response Rate: The ORR for MK-3475A + chemo was comparable to pembro IV + chemo (45.4% vs 42.1%) with an ORR ratio of 1.08 (95% CI: 0.85, 1.37) []. The ORR difference estimate was 3.47 (95% CI: -7.01, 13.69) using the stratified Miettinen and Nurminen method. The ORR differences across prespecified subgroups were generally consistent with the ORR difference analysis in the ITT population.
Progression-free Survival: PFS, as assessed by BICR per RECIST 1.1, was comparable between treatment groups. The median PFS for MK-3475A + chemo was comparable to pembro IV + chemo (8.1 months vs 7.8 months) with an HR of 1.05 (95% CI: 0.78, 1.43) []. The PFS rates at 3 and 6 months are similar, with widely overlapping confidence intervals. The HRs for PFS by BICR across prespecified subgroups were generally consistent with the PFS analysis in the ITT population.
Overall Survival: OS was comparable between treatment groups. []. The OS HR was 0.81 (95% CI: 0.53, 1.22). The median OS was not reached in either intervention group. The OS rates at 3 and 6 months are similar, with widely overlapping confidence intervals. As of the data cutoff, the median duration of follow-up was 8.6 months (range: 0.2, 16.4), which is shorter than the median

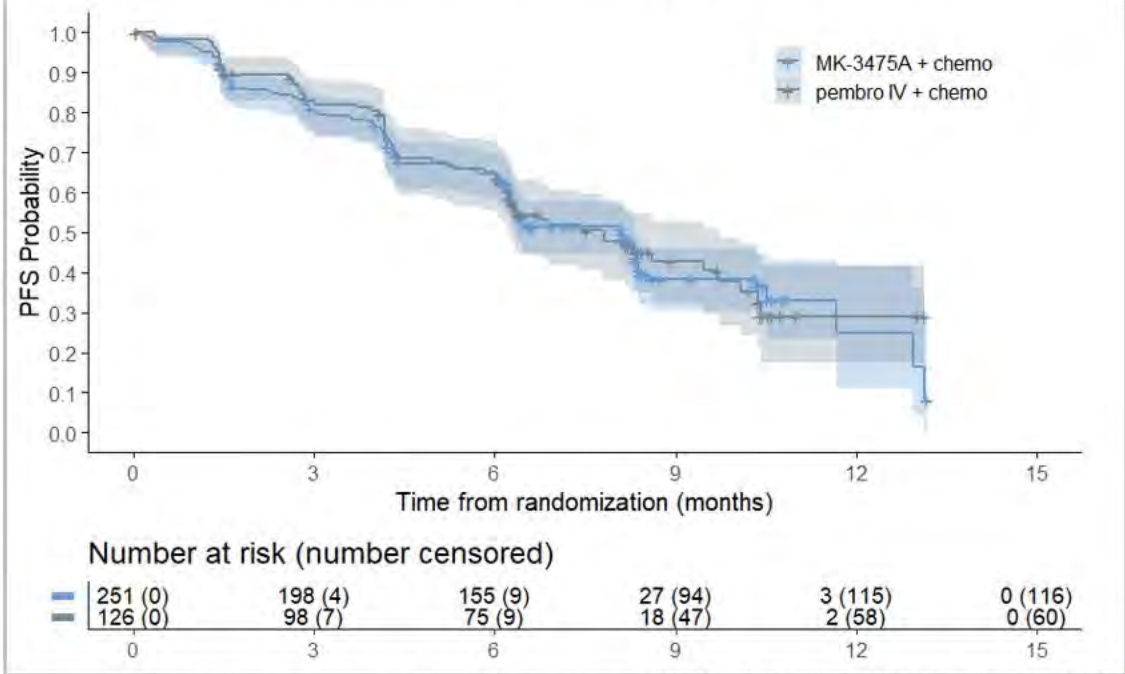
duration of follow-up in historic studies in NSCLC (KEYNOTE-189; KEYNOTE-407) [15] [16]; therefore, the OS data are considered immature.

Duration of Response: For DOR, the median time to response (both groups: 1.5 months) and response duration (MK 3475A + chemo: 9.1 months vs pembro IV + chemo: 8.0 months) for the MK-3475A + chemo group were comparable to pembro IV + chemo group []. Based on KM estimation, 68.1% and 72.1% of participants had responses lasting at least 6 months in the MK-3475A + chemo and pembro IV + chemo groups, respectively.

The FDA's Assessment:

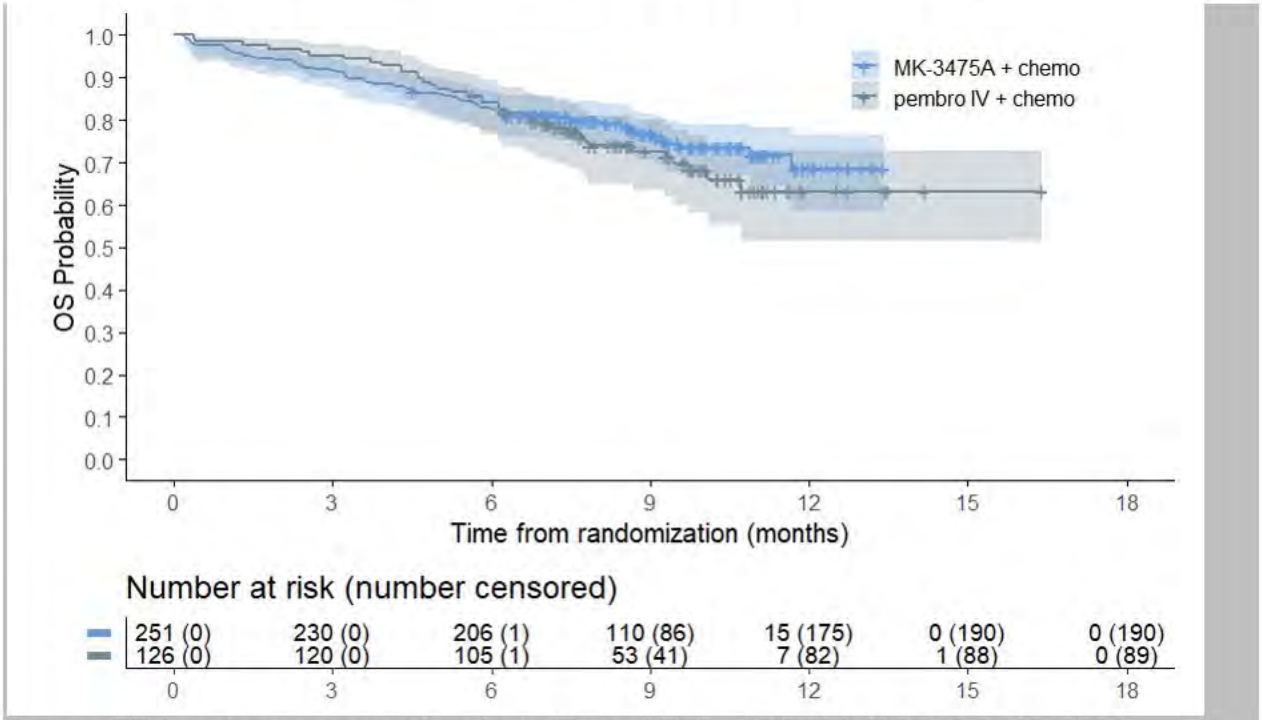
FDA generally agrees with the Applicant's summary of the results of the secondary endpoints, based on a data cutoff date of July 12, 2024, which were included in the original BLA submission. PFS events were observed in 135 (54%) patients in the MK-3475A + chemo arm and in 66 (52%) patients in the pembro IV + chemo arm. OS events occurred in 61 (24%) patients in the MK-3475A + chemo arm and in 37 (29%) patients in the pembro IV + chemo arm. No meaningful differences were observed between treatment arms for the secondary endpoints of ORR and PFS. With the original submission, OS data were immature, and the median OS was not reached in either group. The Kaplan-Meier curves for PFS and OS based on data provided at the time of the original BLA submission are presented below:

Figure 1617: FDA – Kaplan-Meier Curve for PFS by BICR in ITT on MK-3475A-D77



Source: FDA reviewer generated analysis (Data: ADSL, ADTTE), DCO: July 12, 2024

Figure 1819: FDA – Kaplan-Meier Curve for OS in ITT on MK-3475A-D77

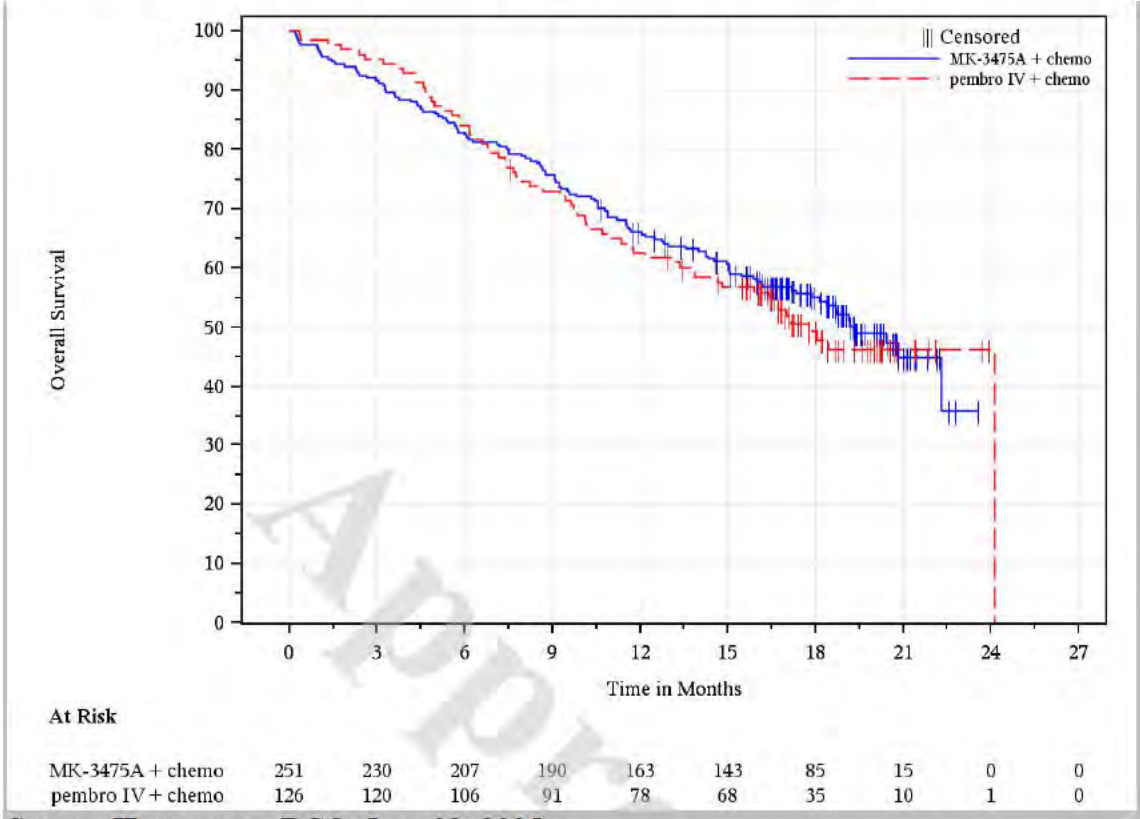


Source: FDA reviewer generated analysis (Data: ADSL, ADTTE), DCO: July 12, 2024

Due to the short follow-up duration, with only 26% of patients having OS events and compared to historic NSCLC studies, interpretation of the OS endpoint was limited based on data provided in the original BLA submission. Therefore, FDA requested additional OS data from the Applicant during the review. The Applicant provided updated OS data based on a DCO date of November 6, 2024. With 37% of patients having an OS event, the OS HR was 0.86 (95% CI 0.61, 1.23). While the OS data continued to demonstrate similar OS results between treatment arms, FDA sent an information request for the Applicant to provide additional OS results for a more mature estimate of OS. Based on a DCO date of June 03, 2025, OS events were observed in 120 (48%) patients in the MK-3475A + chemo arm and in 64 (51%) patients in the pembro IV + chemo arm. The median OS was now reached with 19.4 months (95% CI: 17.2, NR) for MK-3475A + chemotherapy versus 17.7 months (95% CI: 13.9, NR) for pembrolizumab IV + chemotherapy and with a hazard ratio of 0.92 (95% CI: 0.68, 1.25) the OS HR continues to approach one as the data maturity increases suggesting little difference between the arms. The

Kaplan-Meier curve for the updated OS data (DCO date of June 03, 2025) are shown below:

Figure 20: FDA – Kaplan-Meier Curve for OS in ITT on MK-3475A-D77



Source: IR response, DCO: June 03, 2025

As noted by the Applicant, follow-up was limited at the time of the original BLA submission, with a median duration of 8.6 months (range: 0.2, 16.4). According to KM analysis, the percentage of patients with extended response duration ≥ 9 months, was 52.8% (95% CI: 38.8, 65.0) for the MK-3475A + chemo arm and 49.5% (95% CI: 25.3, 69.7) for pembro IV + chemo arm.

Dose/Dose Response

The Applicant's Position:

Pembrolizumab 790 mg Q6W administered SC as MK-3475A in combination with chemotherapy is comparable to pembrolizumab 400 mg Q6W IV in combination with chemotherapy with respect to ORR, PFS, OS, and DOR, as summarized in the previous sections. There are no clinically significant exposure-response relationships for efficacy over a 5-fold dose/exposure range of 2 mg/kg Q3W IV to 10 mg/kg Q2W IV that includes exposures achieved at the recommended 790-mg Q6W SC and 395-mg Q3W SC dosing regimens for MK-3475A. Given similar PK and flat exposure-response across tumor types and treatment settings, any

inferences on comparability of PK exposure and thereby efficacy, between SC and IV administrations are expected to apply across approved pembrolizumab indications and doses, using monotherapy and combination regimens.

The FDA's Assessment:

FDA concurs with the Applicant's position that the exposure at the proposed pembrolizumab SC dosages of 790 mg Q6W are comparable to the pembrolizumab IV dosages of 400 mg Q6W based on the results (dual primary PK endpoints of cycle 1 AUC and steady state C_{trough} met the pre-specified criteria) from the pivotal trial in patients with NSCLC. The exposure is also predicted to be comparable between the Q6W dosing regimen (i.e., 790 mg SC or 400 mg IV) and the Q3W dosing regimen (i.e., 395 mg SC or 200 mg IV) based on modeling and simulation. Additionally, extrapolation of the SC dosages to other solid tumor indications is supported by the PK comparability of SC and IV dosages from the pivotal trial MK-3475A-D77, combined with the demonstrated PK comparability across all approved solid tumor indications for pembrolizumab IV. Furthermore, the PK comparability across the SC and IV dosages with regards to efficacy is supported by the flat exposure response relationship for efficacy with no increase in efficacy observed beyond the IV dosages of 2 mg/kg up to 10 mg/kg across the solid tumor types. See Section 6 of the Assessment Aid for additional details.

Durability of Response

The Applicant's Position:

Durability of response is discussed in the previous section for Efficacy Results – Secondary and other relevant endpoints (DOR).

The FDA's Assessment:

FDA agrees with the Applicant. Please refer to FDA's assessment on Efficacy Results – Secondary and other relevant endpoints section of the Assessment Aid.

Persistence of Effect

The Applicant's Position:

Persistence of Effect is discussed in the previous section for Efficacy Results – Secondary and other relevant endpoints (PFS, OS, and DOR).

The FDA's Assessment:

FDA agrees with the Applicant. Please refer to FDA's assessment on Efficacy Results – Secondary and other relevant endpoints section.

Efficacy Results – Secondary or supportive COA (PRO) endpoints

The Applicant's Position:

Overall, participants were observed to have maintained a similar HRQoL in the MK-3475A + chemo group compared with those in the pembro IV + chemo group, as assessed by the EORTC QLQ-C30 and the EQ-5D-5L-VAS.
The EORTC QLQ-C30 global health status/QoL score remained stable and was generally consistent between the 2 groups at Week 24. Similarly, both the EORTC QLQ-C30 physical and role functioning scores remained stable and were consistent between the 2 groups at Week 24.
A difference in the EORTC QLQ-C30 emotional and social functioning scores was observed between the MK-3475A + chemo and pembro IV + chemo groups with a mean change from baseline at Week 24 favoring participants in the MK 3475A + chemo group.
There were no observed differences between the MK-3475A + chemo and pembro IV + chemo groups for mean change from baseline to Week 24 in the EQ-5D-5L VAS score.

The FDA's Assessment:

FDA did not perform independent analysis of the PRO endpoint results given the descriptive and exploratory nature of this data. FDA agrees with the Applicant that there were no observed differences between arms on core PRO outcomes such as physical and role functioning. FDA does not agree with the Applicant regarding conclusions made on PRO domains outside of core outcomes, such as social function, emotional function, and global health score as these are subject to non-disease and non-treatment related factors.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analyses were conducted.

The FDA's Assessment: FDA agrees.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Study MK-3475A-D77 was a randomized, open-label clinical trial designed to evaluate the PK, efficacy, and safety of MK-3475A administered subcutaneously in combination with histology-based platinum doublet chemotherapy versus pembrolizumab IV in combination with histology-based platinum doublet chemotherapy, for the first-line treatment of patients with metastatic NSCLC. The trial met its dual primary endpoints of Cycle 1 $AUC_{0\text{-}6\ weeks}$ and Cycle 3 (i.e., Steady State) C_{trough}, demonstrating that the exposure of subcutaneous MK-3475A was comparable to intravenous pembrolizumab. See Section 6 of the Assessment Aid for a discussion of the PK primary endpoints and results. Study MK-3475A-D77 was not designed to formally compare the efficacy of MK-3475A SC and pembrolizumab IV. Secondary endpoints in the trial of ORR, DOR, PFS and OS were all descriptive.

Among the 251 patients treated with MK-3475A + chemotherapy, the ORR was 45% (95% CI: 39, 52) compared to 42% (95% CI: 33, 51) in the 126 patients treated with pembrolizumab IV + chemotherapy per RECIST 1.1 by BICR, demonstrating similar antitumor activity. The median DOR for MK-3475A + chemotherapy was 9.1 months (95% CI: 6.9, NR) compared to 8.0 months (95% CI: 7.4, NR) for pembrolizumab IV + chemotherapy. Both arms show similar DOR patterns with overlapping confidence intervals at all timepoints, suggesting comparable durability of responses.

The median PFS was 8.1 months (95% CI: 6.3, 8.3) for MK-3475A + chemotherapy versus 7.8 months (95% CI: 6.2, 9.7) for pembrolizumab IV + chemotherapy, with a hazard ratio of 1.05 (95% CI: 0.78, 1.43), indicating comparable treatment effects. At the time of the original BLA submission, with a DCO date of July 12, 2024, the OS data were immature with only 26% of patients having experienced OS events. Based on an updated analysis of OS with a DCO date of June 3, 2025, 49% of patients had experienced OS events; the median OS was 19.4 months (95% CI: 17.2, NR) for MK-3475A + chemotherapy versus 17.7 months (95% CI: 13.9, NR) for pembrolizumab IV + chemotherapy, with a hazard ratio of 0.92 (95% CI: 0.68, 1.25). These results suggest that there are no notable differences in PFS or OS for MK-3475A SC compared to pembrolizumab IV.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:

This is not applicable as the efficacy of MK-3475A is presented from 1 study (MK-3475A-D77).

The FDA's Assessment: FDA agrees.

Additional Efficacy Considerations

The FDA's Assessment: Not applicable.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

This is not applicable as the efficacy of MK-3475A is presented from 1 study (MK-3475A-D77).

The FDA's Assessment: Study MK-3475A-D77 was a randomized, open-label clinical trial designed to evaluate the PK, efficacy, and safety of MK-3475A administered subcutaneously in combination with histology-based platinum doublet chemotherapy versus pembrolizumab IV in combination with histology-based platinum doublet chemotherapy, for the first-line treatment of patients with metastatic NSCLC. The trial met its dual primary endpoints of Cycle 1 $AUC_{0\text{-}6\ weeks}$ and Cycle 3 (i.e., Steady State) C_{trough}, demonstrating that the exposure of subcutaneous MK-3475A 790 mg Q6W was comparable to intravenous pembrolizumab 400 mg Q6W. The geometric mean ratio

(GMR) for Cycle 1 $AUC_{0\text{-}6weeks}$ was 1.14 (96% CI: 1.06, 1.22) and the GMR for $C_{trough,cycle\ 3}$ was 1.67 (94% CI: 1.52, 1.84), meeting the pre-specified criteria of the lower bound of the 90% CI of the GMR being at 0.8 or above. See Section 6 of the Assessment Aid for a discussion of the PK primary endpoints and results. Descriptive analyses of ORR, DOR, PFS, and OS were also comparable between treatment arms in Study MK-3475A-D7, which supports that there is comparable efficacy of MK-3475A SC and pembrolizumab IV.

Substantial evidence of effectiveness for the proposed indications for MK-3475A SC 790 mg Q6W in adult patients was established based on a demonstration of comparable PK exposure of MK-3475A and pembrolizumab IV, and comparable ORR, DOR, PFS, and OS in descriptive efficacy analyses, between MK-3475A SC and pembrolizumab IV in Study MK-3475A-D77. The efficacy of MK-3475A SC at 395 mg Q3W and 790 mg Q6W across solid tumor indications for adult and pediatric (12 to <17 years old) patients is extrapolated from the pembrolizumab IV indications, based on the following:

- Demonstration of comparability of PK exposure of MK-3475A SC to pembrolizumab IV when administered in combination with platinum-based chemotherapy in adult patients with previously untreated metastatic NSCLC.
- The PK are predicted to be comparable between the Q6W dosing regimen at 790 mg SC and the Q3W dosing regimen at 395 mg SC based on modeling and simulation data and supported by available data for the 395 mg Q3W dosing regimen in patients with melanoma in Study MK-3475A-C18.
- The PK of the two proposed SC dosages (i.e., 790 mg Q6W and 395 mg Q3W) is predicted to be comparable between the adult and pediatric (12 to <17 years old) patients, based on modeling and simulation. This prediction is supported by the PK comparability observed between adults and pediatric patients (12 to <17 years old) for the approved IV dosages.
- Extrapolation of the SC dosages to other solid tumor indications is supported by PK comparability of SC and IV dosages based on results from the pivotal trial MK-3475A-D77, combined with the demonstrated PK comparability across all approved solid tumor indications for pembrolizumab IV.

8.2 Review of Safety

The Applicant's Position:

The results from MK-3475A-D77 demonstrated that the safety profile of MK-3475A in combination with chemotherapy is consistent with the safety data of pembrolizumab monotherapy and chemotherapy. The safety data is also similar to prior data of pembrolizumab in combination with chemotherapy from other trials conducted in NSCLC

Moreover, MK-3475A in combination with chemotherapy was compared to the pooled pembrolizumab IV and chemotherapy dataset and the pembrolizumab monotherapy RSD, both of

which evaluated pembrolizumab in various settings, including early-stage and metastatic diseases, as monotherapy and in combinations, and in women's cancers. These comparisons demonstrated that the safety profile of MK-3475A in combination with chemotherapy is consistent with the safety profiles of the pooled pembrolizumab IV and chemotherapy dataset and the pembrolizumab monotherapy RSD. Therefore, MK-3475A can be administered safely to patients across multiple tumor types, combinations, and treatment settings.

Results of supporting studies (MK-3475A-C18, MK-3475A-F11) substantiate that the safety profile of MK-3475A is generally consistent with the established safety profile of pembrolizumab IV, with the exception of local injection-site reactions with SC administration. No new safety concerns for MK-3475A were identified.
The frequency and severity of AEOSI among participants who received MK-3475A in the pivotal MK-3475A-D77 and supporting studies were consistent with the established safety profile of pembrolizumab. No new immune-mediated AE safety findings that were unique to MK-3475A were identified.
Safety findings across special groups were generally consistent with the established safety profile of pembrolizumab.

The FDA's Assessment:

FDA agrees with the Applicant's description of the primary and pooled safety populations evaluated during the review of this application except that the data from the final analysis for the supporting Study MK-3475A-F11 will be submitted after the review cycle for this application. As further reviewed in this section of the Assessment Aid, FDA agrees with the Applicant that the safety profile of MK-3475A SC is generally consistent with the safety profile of pembrolizumab IV, with the exception of local injection-site reactions with SC administration.

FDA notes that the Applicant originally submitted a 351(a) BLA for pembrolizumab and berahyaluronidase alfa for subcutaneous injection on January 23, 2025, with safety data based on a data cutoff date of July 12, 2024.The Applicant submitted a 120-day safety update on March 20, 2025, based on a DCO date of November 6, 2024. In this Assessment Aid, the Applicant primarily presents data based on the July 12, 2024, DCO date. FDA also reviewed safety data from the November 6, 2024, DCO date, which were largely similar to the safety data provided in the original BLA submission.

Throughout the review of safety data, FDA sent multiple requests for additional clinical information including about fatal adverse events, and hypersensitivity and injection site reactions, which are further detailed in the relevant sections of the Assessment Aid.

8.2.1. Safety Review Approach

The Applicant's Position:

Safety results are presented for the following datasets.

- **D77 MK-3475A + Chemotherapy** (N=251): Safety data from participants with NSCLC treated with MK-3475A plus chemotherapy in MK-3475A-D77. Hereafter referred to as "MK-3475A + chemo" or "D77 MK-3475A + chemo dataset."
- **D77 Pembrolizumab IV + Chemotherapy** (N=126): Safety data from participants with NSCLC treated with pembrolizumab IV plus chemotherapy in MK-3475A-D77. Hereafter referred to as "pembro IV + chemo" or "D77 pembro IV + chemo dataset."
- **Pooled Pembrolizumab + Chemotherapy SD** (N=5711): Pooled safety data from participants with NSCLC, HNSCC, TNBC, Gastric, Esophageal, or Gastroesophageal Carcinoma, Cervical Cancer, or BTC treated with pembrolizumab IV plus chemotherapy. Hereafter referred to as the "pooled pembro IV + chemo dataset."
- **Pembrolizumab Monotherapy RSD** (N=7631): Pooled safety data from participants with melanoma, NSCLC, HNSCC, cHL, Bladder Cancer, MSI-H, Colorectal Carcinoma, and RCC treated with pembrolizumab IV monotherapy. Hereafter referred to as the "pembro RSD."

Pooled datasets include data from participants with various tumor types and stages of disease, and if applicable, different chemotherapeutic agents.

The results from the pivotal MK-3475A-D77 study are supported by safety data from MK-3475A-C18, ALT-BB4-01, and MK-3475A-F11 (see Section 7.1).

The FDA's Assessment: FDA agrees with the Applicant's position. The primary safety review was based on the pivotal trial MK-3475A-D77 with safety data from patients with NSCLC treated with MK-3475A SC plus chemotherapy (n=251) and patients treated with pembrolizumab IV plus chemotherapy (n=126).

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 29: Applicant – Summary of Drug Exposure (APaT Population)

	MK-3475A + chemo (N=251)	pembro IV + chemo (N=126)
Number of Days on Therapy		
n	251	126
Mean (SD)	194.1 (101.4)	188.8 (103.2)
Median	209	189
Range	1 to 401	1 to 483
Number of Days on MK-3475A/pembrolizumab		
n	251	126
Mean (SD)	185.7 (104.5)	179.6 (104.8)
Median	199	180.5
Range	1 to 381	1 to 462

	MK-3475A + chemo (N=251)	pembro IV + chemo (N=126)
Number of Cycles		
n	251	126
Mean (SD)	5.2 (2.4)	5.1 (2.4)
Median	5	5
Range	1 to 10	1 to 12
Database Cutoff Date: 12JUL2024		

Source: [PD77V01MK3475A: adam-adsl; adexsum]

The Applicant's Position:

The median durations of therapy in the D77 MK-3475A + chemo dataset and the D77 pembro IV + chemo dataset were 209 days and 189 days, respectively. The median number of cycles (Q6W dosing) was 5 in both datasets in MK-3475A-D77 [].
The median duration of therapy in the pooled pembro IV + chemo dataset was 246 days. The median duration of therapy in the pembro RSD was 176 days.

The FDA's Assessment: FDA agrees with the Applicant's position.

Relevant characteristics of the safety population:

The Applicant's Position:

Baseline demographic and disease characteristics of participants in the APaT population were identical to those of the ITT population (all randomized participants were treated) and generally representative of a patient population with treatment-naïve metastatic NSCLC [].

The FDA's Assessment: FDA agrees with the Applicant's position. The majority of patients were male, and White or Asian. On the pembrolizumab SC plus chemotherapy arm, 29% of the patients were Hispanic or Latino while 33% of patients were Hispanic or Latino on the pembrolizumab IV plus chemotherapy arm. The median age of patients was 65 years old on the pembrolizumab SC plus chemotherapy arm versus 66 years old on the pembrolizumab IV plus chemotherapy arm. Overall, the treatment arms were well balanced.

Adequacy of the safety database:

The Applicant's Position:

The clinical safety data are derived from MK-3475A-D77. The number of participants with treatment-naïve metastatic NSCLC included in the safety datasets represents an adequate size considering exposure to appropriate dose, duration of treatment, participant demographics, and disease characteristics for this study population.

The FDA's Assessment: FDA agrees with the Applicant's position that the primary safety data is derived from Study MK-3475A-D77. FDA also agrees with the Applicant that the safety data from Study MK-3475A-D77 are adequate to support a benefit risk assessment of pembrolizumab SC in comparison with pembrolizumab IV. FDA issued several information requests (IRs) to the

Applicant during the review cycle to obtain clarification and additional information regarding safety data included in the BLA; all requests were addressed appropriately.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

There were no issues with data integrity or analysis that precluded the inclusion of data in the safety analysis.

The FDA's Assessment: FDA agrees with the Applicant's position.

Categorization of Adverse Event

The Applicant's Position:

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints, including, but not limited to, the incidence, severity, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values.
All AEs from the time of treatment randomization through 30 days following cessation of study treatment were reported by the investigator. All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiated new anticancer therapy, whichever was earlier, were reported by the investigator. AEs and SAEs whether or not assessed as related to the Sponsor's product were recorded. AEs were graded by the investigator using NCI CTCAE version 5.0.
MedDRA version 27.0 was used at the time of table generation. The following MedDRA PTs were excluded from the statistical safety tables if the AEs were reported as not related to study intervention: neoplasm progression, malignant neoplasm progression, and disease progression.
AEOSI are immune-mediated events and infusion-related reactions associated with pembrolizumab. The frequency and maximum severity of AEOSI analyses are based on a predefined list of preferred AE terms deemed clinically consistent with the identified risks of pembrolizumab and potentially associated with an immune etiology. This list was developed by the Applicant and includes AEOSI terms identified to allow consistent assessment of AEOSI across pembrolizumab studies.
Participants randomized to receive MK-3475A received directed physical examination of the injection site at time points specified in the protocol and reported any injection-site AE that occurred at any time during the study. Any injection-site AE was reported using standard AE/SAE reporting methods and retrieved using the MedDRA High Level Term "Injection site reactions."

The FDA's Assessment: FDA generally agrees with the Applicant's description of the categorization of adverse events (AEs). MedDRA version 27.0 was used for Study MK-3475A-D77 for categorizing AEs and CTCAE v 5.0 was used for grading AEs. During the review cycle,

FDA sent several IRs to clarify preferred terms used for a given group term.

Routine Clinical Tests

The Applicant's Position:

The schedule of activities from MK-3475A-D77 is provided in Section 1.3 of the study protocol, including key laboratory assessments such as the frequency of laboratory testing, vital signs, physical examination, and AE monitoring.

The FDA's Assessment: FDA agrees with the Applicant's position.

8.2.4. Safety Results

Deaths

Data:

Table 30: Applicant – Participants With Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
with one or more adverse events	26	(10.4)	12	(9.5)
with no adverse events	225	(89.6)	114	(90.5)
Pneumonia	7	(2.8)	4	(3.2)
Death	4	(1.6)	1	(0.8)
Febrile neutropenia	3	(1.2)	0	(0.0)
Respiratory failure	3	(1.2)	1	(0.8)
COVID-19 pneumonia	1	(0.4)	0	(0.0)
Epilepsy	1	(0.4)	0	(0.0)
Neutropenic colitis	1	(0.4)	0	(0.0)
Neutropenic sepsis	1	(0.4)	0	(0.0)
Parotitis	1	(0.4)	0	(0.0)
Pneumonitis	1	(0.4)	0	(0.0)
Pneumothorax	1	(0.4)	0	(0.0)
Pulmonary embolism	1	(0.4)	2	(1.6)
Septic shock	1	(0.4)	2	(1.6)
Femoral neck fracture	0	(0.0)	1	(0.8)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.8)

Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adae]

The Applicant's Position:

The AEs that led to death in participants in the D77 MK-3475A + chemo dataset were generally consistent in nature with the known safety profiles of pembrolizumab monotherapy and chemotherapy [Table 30]. AEs leading to death in ≥2 participants in the D77 MK-3475A + chemo dataset were pneumonia, death, febrile neutropenia, and respiratory failure. All other AEs leading to death occurred in 1 participant each. The PT "Death" was reported in situations where limited information on the cause of death was available, or where the investigator could not assign a specific AE term. Pneumonia is a known infectious complication in patients with underlying metastatic NSCLC. Deaths due to febrile neutropenia and associated infections (neutropenic colitis, neutropenic sepsis, parotitis, septic shock), which are known complications of chemotherapy, occurred during the first cycles in the D77 MK-3475A + chemo dataset when platinum doublets were administered with pembrolizumab.

AEs leading to death in the D77 MK-3475A + chemo dataset that were considered by the investigator to be related to study drug included febrile neutropenia (n=3) and neutropenic colitis, neutropenic sepsis, parotitis, pneumonia, septic shock, and pneumonitis (n=1 each). Pneumonitis was related to MK-3475A and is a known immune mediated AE of pembrolizumab monotherapy. The remaining 8 AEs leading to death, which were due to febrile neutropenia and associated infections, were related to chemotherapy.

In the D77 pembro IV + chemo dataset, AEs leading to death that were considered by the investigator to be related to study drug included septic shock (n=2) and multiple organ dysfunction syndrome (n=1). Multiple organ dysfunction was related to both pembrolizumab and carboplatin; the septic shock AEs were related to chemotherapy. These AEs have been reported in the safety profiles of pembrolizumab and chemotherapy, respectively.

The FDA's Assessment: FDA reviewed all fatal adverse events that occurred in patients from the primary safety population in Study MK-3475A-D77. A total of 10% of patients (n=26) had an event of death due to AEs that were not clearly related to disease progression in the pembrolizumab SC arm compared to 9.5% (n=12) of patients in the pembrolizumab IV arm. The 26 fatal AEs in the pembrolizumab SC arm were due to pneumonia (3.2%); neutropenic sepsis (2.0%); death not otherwise specified (1.6%); respiratory failure (1.2%); and neutropenic colitis, parotitis, pneumonitis, pneumothorax, pulmonary embolism, and seizure (0.4% each). Brief summaries of the fatal AEs are provided in the table below.

Table 31: FDA – Assessment of Causality of Fatal Adverse Events Not Clearly Attributable to Disease Progression in the Primary Safety Population of Study MK-3475A-D77

Patient ID	Brief Narrative	FDA Assessment of Causality	Included in USPI
(b) (6)	76-year-old male hospitalized with respiratory failure on day 60. Chest CT showed extensive alveolar infiltrate in the right lower lobe and right middle lobe. Patient was	**Pneumonia** FDA agrees with the investigator's assessment of the cause of death as due to	Yes

	intubated and treated with inotropics (details not available). On day 71, patient required mechanical respiratory assistance. The investigator reported that the patient died on day 73 due to a fatal adverse event of pneumonia. Last dose of MK-3475A, carboplatin, and nab-paclitaxel were given on day 1, 28 and 47 (Cycle 1, Day 1, 22 and 36), respectively.	pneumonia, although pneumonitis/interstitial lung disease may also have been possible. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	
(b) (6)	69-year-old male experienced chest tightness, dyspnea, fatigue, and weakness on days 25 and 28. On day 29, the patient was admitted to the hospital. Patient was diagnosed with Grade 3 pneumonia, and treated with piperacillin/tazobactam, ipratropium, terbutaline, beclomethasone, and ambroxol. Day 30 vitals were BP 85/52, HR 121, and oxygen saturation 85. Blood cultures were positive for an unspecified microorganism, and 3 sputum cultures were positive for Pseudomonas aeruginosa and Streptococcus pneumoniae (methicillin-resistant). Imipenem and vancomycin were added as additional antibiotics. However, the patient died on the same day due to a Grade 5 event reported as pneumonia. The last dose of MK-3475A was given on day 1 (Cycle 1), and carboplatin and nab-paclitaxel were given on day 23 (Cycle 1, Day 22).	**Pneumonia** FDA agrees with the investigator's assessment of the cause of death as due to pneumonia. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes
(b) (6)	64-year-old male presented to emergency department on day 149 with HR 108, RR 18, BP 82/63, and oxygen saturation 88. A chest X-ray showed bilateral interstitial infiltrates. No additional laboratory tests were reported. Patient was diagnosed with Grade 3 pneumonia and treated with piperacillin/tazobactam and high flow	**Pneumonia** The narrative supports the diagnosis of pneumonia. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes

	oxygen. Patient died on day 163 due to a Grade 5 event reported as pneumonia. Last dose of MK-3475A was given on day 126 (Cycle 4, day 1) and last dose of pemetrexed was given on 147 (Cycle 4, day 22).		
(b) (6)	64-year-old female hospitalized on day 29 due to severe dyspnea. Laboratory test results showed increased CRP. Chest x-ray showed lung infiltration consistent with Grade 3 pneumonia. The patient was treated with ceftriaxone. On day 34, repeat chest X-ray showed ongoing pneumonia. Patient continued to deteriorate and died on day 40 due to Grade 5 pneumonia. The last dose of MK-3475A was given on day 1 (Cycle 1), and the last doses of carboplatin and paclitaxel were given on day 21 (Cycle 1, Day 22).	**Pneumonia** The narrative supports the diagnosis of pneumonia. Although pneumonia was unlikely related to treatment with pembrolizumab SC, this cannot be completely ruled out.	Yes
(b) (6)	77-year-old male was hospitalized with Grade 1 pyrexia (temperature not reported). Blood culture was negative. On day 5, oxygen saturation was 87. Patient was initiated on oxygen therapy. Based on CT scan, diagnosis of pneumonia was made; patient was treated with ceftriaxone and levofloxacin. On day 7 WBC are reported as abnormal low (count is not reported). Patient died on day 8 due to Grade 5 pneumonia. The last dose of MK-3475A, carboplatin and paclitaxel were given on day 1 (Cycle 1).	**Pneumonia** The narrative supports the diagnosis of pneumonia. Pembrolizumab SC cannot be ruled out as contributing to death.	Yes
(b) (6)	65-year-old female discontinued treatment with MK-3475A and pemetrexed on day 198 due to progressive disease. Prior to that patient received treatment on day 190 (Cycle 5, day 22) with pemetrexed and last dose of MK-3475A was on day 169 (Cycle 5, day 1). On day 222	**Pneumonia** FDA considers this event unlikely due to pembrolizumab SC given the determination of disease progression. However, death occurred within the 90-day	Yes

	patient was hospitalized with cough and dyspnea and diagnosed with COVID-19 pneumonia. No supporting laboratory test results, procedures, or treatment were reported. Patient died on day 227.	follow up period from the last study dose of pembrolizumab SC and the Applicant reported this as a fatal event due to COVID-19 pneumonia. Based on the information provided, FDA agrees with Applicant's diagnosis of COVID-19 pneumonia. Although COVID-19 pneumonia was unlikely related to treatment with pembrolizumab SC, this cannot be completely ruled out.	
(b) (6)	62-year-old male experienced dyspnea and weakness on day 111. He was treated with moxifloxacin. On day 121 he presented with worsening dyspnea and weakness, and he was hospitalized with Grade 3 pneumonia diagnosed per CT scan. Treatment included methylprednisolone, piperacillin/tazobactam and ciprofloxacin. His condition continued to worsen, and he was transferred to the ICU on day 134. He developed respiratory failure due to pneumonia and died the same day. The last doses of MK-3475A, paclitaxel, and carboplatin were given on Day 49 (Cycle 2, Day 1).	**Pneumonia** FDA agrees that the narrative supports the diagnosis of pneumonia. The contribution of pembrolizumab SC to the fatal adverse event cannot be completely ruled out.	Yes
(b) (6)	67-year-old male was diagnosed with pleural effusion on day 81 based on a thoracic CT scan. On day 83 he had confusion and Grade 4 seizure after amputation (due to arterial thrombosis). On day 84, a chest x-ray showed hydropneumothorax. He was treated with broad spectrum antibiotics (meropenem). On day 86 he was diagnosed with Grade 4 pneumonia; teicoplanin was added to meropenem. On day 87 patient had a	**Pneumonia** FDA considers this event unlikely due to pembrolizumab SC. However, death occurred within 90-days of treatment and the contribution of pembrolizumab SC cannot be completely ruled out.	

	cardiac arrest due to sepsis caused by pneumonia. The investigator reported pneumonia as the cause of death. The last dose of MK-3475A was Cycle 1, day1.		
(b) (6)	75-year-old male presented on day 8 with nausea, asthenia, and urinary difficulty. He was stated on methylprednisone 8 mg daily x3 days. On day 10, he presented to the hospital with difficulty breathing. At presentation he was confused, poorly perfused, with peripheral cyanosis, bilateral rales, and oxygen saturation of 60. No CT scan was performed. Patient died the same day due to Grade 5 respiratory failure.	**Respiratory Failure** FDA agrees with the investigator's assessment of the cause of death as due to respiratory failure. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes
(b) (6)	77-year-old male presented with dyspnea, cough, and nasal congestion without fever on day 104. He was treated with azithromycin, fluticasone salmeterol, and desloratadine. On Day 108, he was taken to the ED with worsening symptoms; upon arrival to the ED, he had no pulse. Despite resuscitation efforts, the patient died. The primary reported cause of death was respiratory failure. The last doses of MK-3475A and pemetrexed were given on Day 84 (Cycle 3) and Day 106 (Cycle 3, Day 22).	**Respiratory Failure** The narrative supports a diagnosis of respiratory failure. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes
(b) (6)	65-year-male died at home on day 184 with reported cause of death as respiratory failure. Last treatment with MK-3475A was administered on day 127 (Cycle 4) and last pemetrexed was given on day 149 (cycle 4, day 22). On day 160 patient was discontinued on MK-3475A and pemetrexed due to disease progression.	**Respiratory Failure** Based on the information provided and the Applicant's assessment, FDA agrees with the diagnosis of respiratory failure and that pembrolizumab SC's contribution to the patient's death cannot be ruled out. However, FDA notes that the respiratory failure may	Yes

		have alternatively been due to disease progression.	
(b) (6)	79-year-old female was hospitalized on day 55 with general poor health, asthenia, and vomiting. An abdominal ultrasound showed distended intestinal loops. Labs showed decreased WBC and neutrophils. CT imaging revealed a severely distended abdomen and diverticular formations in the sigmoid colon. Patient was diagnosed with Grade 3 neutropenic colitis and kidney failure. The last doses of MK-3475A SC in combination with pemetrexed, and cisplatin were given on Day 50 (Cycle 2, Day 1).	**Neutropenic Colitis** FDA agrees with the investigator's assessment of the cause of death as due to neutropenic colitis. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes
(b) (6)	59-year-old female on day 77 presented with diarrhea, vomiting and fever (not reported). On day 80, patient presented to the ER with dyspnea and fever (38.3), BP 60/40 and oxygen saturation at 66. Labs showed ANC of 300. Patient was diagnosed with Grade 3 febrile neutropenia (onset Day 77), treated with vancomycin, cefepime, and volume expansion with crystalloids (0.9%). No cultures were done. Approximately 4 hours later, patient developed respiratory failure and worsening hypotension (BP 70/40) despite volume expansion requiring intubation. However, prior to intubation patient had cardiorespiratory arrest with asystole. CPR was performed for 20 minutes without success and the patient died, reported as a Grade 5 event of febrile neutropenia. The last dose of MK-3475A was given on Day 51 (Cycle	**Neutropenic sepsis** Based on the provided narrative, FDA assessed the cause of death as due to neutropenic sepsis, including febrile neutropenia. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes

	2), and the last doses of carboplatin and paclitaxel were given on Day 72 (Cycle 2, Day 22).		
(b) (6)	73-year-old male presented with fever (38.6) on Day 7, ANC of 120; he was diagnosed with Grade 4 febrile neutropenia and Grade 4 leukopenia. On day 9 he was hospitalized, and no additional information was available. Patient died on day 12 with cause of death reported as febrile neutropenia.	**Neutropenic sepsis** Although the narrative is lacking complete details, FDA assessed this fatal adverse event as neutropenic sepsis, including febrile neutropenia. Pembrolizumab SC cannot be ruled out as contributing to the patient's death.	Yes
(b) (6)	64-year-old female was hospitalized on day 6 with severe deterioration of health including dehydration, fatigue, dyspnea, impaired consciousness, and fever (38.5). Laboratory test showed ANC of 110, platelets 82, AST 284 and elevated bilirubin at107. Patient was diagnosed with Grade 4 febrile neutropenia and Grade 3 hepatic failure. On day 7 chest X-ray showed pleural effusion and congestion, diagnosed as Grade 3 pneumonia. Patient was treated with cefuroxime, ceftriaxone, filgrastim, enoxaparin, fluconazole, dexamethasone, morphine, oxygen therapy, and sodium chloride. On day 7, the patient's condition worsened and she died; resuscitation was not attempted .	**Neutropenic sepsis** FDA assessed this fatal adverse event as neutropenic sepsis, including febrile neutropenia. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes
(b) (6)	83-year-old female presented with Grade 3 fatigue, anemia, Grade 3 thrombocytopenia (platelet of 30) on day 10; she was treated with dexamethasone 4 mg IV once and sodium chloride. Vitals included temperature 36.2, HR 128, RR 20, and BP 89/44. On day 14 a soft tissue US showed right Grade 3 parotitis (onset day 10). On day 16 patient was	**Parotitis** Based on the available information, FDA agrees with the investigator's assessment of the cause of death as parotitis and that pembrolizumab SC cannot be ruled out as possibly	Yes

	lethargic, requiring higher FiO2. Patient's family requested to limit interventions; patient died the same day. Investigator assessed this to be due to grade 5 parotitis.	contributing to the patient's death.	
(b) (6)	79-year-old male with a past medical history of epilepsy presented on day 173 with reported worsening of epilepsy. He had seizures followed by cardiorespiratory arrest and died despite resuscitation attempts. The last doses of MK-3475A and pemetrexed were administered on Day 168 (Cycle 4, Day 1).	**Seizure** FDA agrees with the investigator's assessment of the cause of death as due to seizures. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes
(b) (6)	81-year-old male presented on day 211 with Grade 1 pyrexia and oxygen desaturation to 80%. A chest CT on Day 217 showed a pleural effusion. The patient was diagnosed with Grade 3 pneumonitis. and the patient was also treated with antibiotics. Viral panel and cultures were negative and on day 232 an infectious cause was thought to be ruled out; antibiotics were discontinued and prednisone was initiated. On day 239 patient was discharged with oral steroids. On day 255, the patient decompensated with loss of consciousness, tachycardia, and oxygen desaturation (values not reported). Pneumonitis was reported as Grade 4. On day 256 he had progressive deterioration and died the same day which was assessed as a Grade 5 event of pneumonitis. The last doses of MK-3475A and pemetrexed were given on Day 183 (Cycle 5, Day 1).	**Pneumonitis** FDA agrees with the investigator's assessment of the cause of death as pneumonitis and was likely due to pembrolizumab SC.	Yes
(b) (6)	83-year-old male presented to the ED on day 7 with diarrhea, nausea, abdominal discomfort, vomiting, and extreme weakness (ongoing from day	**Neutropenic sepsis** The narrative supports the diagnosis of neutropenia	Yes

	4). Per laboratory tests, neutrophils were 0.31 (Grade 4 neutropenia) and serum creatinine was 2.6. SARS-CoV-2 RNA, Streptococcus pneumoniae antigen, and influenza A and B antigen tests were negative. Patient was admitted with Grade 4 septic shock and was treated with piperacillin/ tazobactam and meropenem. On day 8, the patient deteriorated rapidly with oliguria, altered consciousness, and ultimately cardiopulmonary arrest. The patient died from septic shock with renal failure as a contributing fatal consequence.	sepsis and septic shock. The contribution of pembrolizumab SC to the patient's death cannot be ruled out.	
(b) (6)	63-year-old male was hospitalized with Grade 4 neutropenia (ANC 800), and Grade 3 febrile neutropenia (fever with temperature 38 C) on Day 145. He had a fall on Day 148 resulting in a left nasal bone fracture. On Day 149 he developed pneumonia and was treated with meropenem. During an ear, nose, and throat examination, the patient experienced respiratory arrest followed by Grade 4 cardiac arrest with successful cardiopulmonary resuscitation. On day 156 teicoplanin and metronidazole, polymyxin b, and methylprednisolone were added for treatment of pneumonia. Patient's course remained complicated with pneumonia, nasal passage obstruction, and suspected hemorrhage in the oropharynx and nasopharynx areas. The patient died on Day 164 due to neutropenic sepsis. The last doses of MK-3475A and pemetrexed were given on Day 137 (Cycle 4, Day 1).	**Neutropenic Sepsis** FDA agrees with the investigator's assessment of the cause of death as due to neutropenic sepsis. Pembrolizumab SC cannot be ruled out as possibly contributing to death.	Yes

(b) (6)	67-year-old male presented to emergency department on Day 4 with dyspnea, cough, and chest pain. The patient was reported to be hypotensive, tachycardic, and with oxygen saturation of 80%. An angiogram showed bilateral Grade 4 pulmonary emboli. The patient had a history of two deep vein thromboses (DVTs), occurring 2 months and 1 month prior to initiating study drugs. He was treated with acenocoumarol. The patient died on day 5 due to Grade 5 pulmonary embolism.	**Pulmonary Embolism** FDA considers this event unlikely due to pembrolizumab SC given the patient's recent DVT history prior to starting study therapy. However, pembrolizumab SC cannot be completely ruled out as contributing to death. FDA agrees with the Applicant's diagnosis of pulmonary embolism as the cause of death.	Yes
(b) (6)	62-year-old male was hospitalized with oxygen saturation at 66% (on room air) on Day 157. Laboratory test showed increased CRP, LDH, WBC, and neutrophils. Patient was diagnosed with Grade 3 pneumothorax due to progression of COPD, and was treated with piperacillin-tazobactam, morphine, and methylprednisolone. On Day 175, the patient died due to a reported Grade 5 event of pneumothorax.	**Pneumothorax** FDA considers this event unlikely due to pembrolizumab SC given the patient's underlying COPD. However, pembrolizumab SC cannot be completely ruled out as contributing to death.	Yes
(b) (6)	72-year-old male was diagnosed with Grade 3 pneumonitis on day 65. MK-3475A was discontinued due to pneumonitis, with the last dose on day 52 (Cycle 2). Carboplatin and pemetrexed were interrupted due to pneumonitis. On day 75, chest CT showed pleural effusion. On day 81 carboplatin and pemetrexed resumed (Cycle 2, day 22, last dose). On day 84, repeat CT showed decrease pleural fluid. However, on day 95 the patient's family reported decline of the patient's general health including inability to walk and confinement to bed more than 50% of waking hours (ECOG 3). Patient experienced chest	**Death not otherwise specified** Based on the narrative provided FDA cannot rule out pembrolizumab SC as contributing to the patient's death.	Yes

	tightness, wheezing, productive cough, loss of appetite and fatigue. On day 98 he died at home due to an unknown cause.		
(b) (6)	62-year-old male died on day 354 reported by the investigator as due to an unknown cause. Per the narrative, the patient had unresolved cellulitis (i.e., he had underlying diabetes and developed intermittent and recurrent cellulitis initially on day 175 despite treatment). The last doses of pemetrexed and MK-3475A were given on day 338 (Cycle 9, day 1).	**Death not otherwise specified** Due to the lack of narrative details, pembrolizumab SC cannot be ruled out as contributing to death.	Yes
(b) (6)	72-year-old male was hospitalized on day 144 with dyspnea and was diagnosed with pneumonia. Mycoplasma pneumoniae IgG antibody was 300.542 AU/ml (NR: 0-36), troponin I was 3.59 µg/L, and procalcitonin was 1.6 µg/L, and platelets were 56. Pneumonia worsened to Grade 4 and he was treated with methylprednisolone, levofloxacin, cefoperazone-sulbactam, aminophylline, cilastatin-imipenem, ambroxol, fluconazole, and piperacillin. On day 153, pneumonia was reported as improving to Grade 3. On day 159, the patient was discharged home. Patient died on the same day due to unknown cause. At the time of death, anemia, thrombocytopenia and pneumonia were not resolved. The last dose of MK-3475A and pemetrexed was given on day 126 (Cycle 3, day 22).	**Death not otherwise specified** FDA agrees with the investigator's assessment that the cause of death is unknown. Based on the provided narrative, FDA cannot completely rule out pembrolizumab SC as contributing to the patient's death.	Yes
(b) (6)	66-year-old female died on day 172 due to an unknown cause. Patient had the last doses of carboplatin, MK-3475A, and pemetrexed administered on day 51 (Cycle 2, Day 1), day 135	**Death not otherwise specified** Due to the lack of narrative details surrounding the cause of death,	Yes

	(Cycle 4), and day 156 (Cycle 4, Day 22), respectively.	pembrolizumab SC cannot be ruled out as contributing to death.	

Source: Module 5.3.5.3 (adverse event data: patient narratives)

Serious Adverse Events

Data:

Table 32: Applicant – Participants With Serious Adverse Events (Sorted by Decreasing Incidence) (Incidence ≥2% in One or More Treatment Groups) (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
with one or more adverse events	98	(39.0)	51	(40.5)
with no adverse events	153	(61.0)	75	(59.5)
Pneumonia	25	(10.0)	13	(10.3)
Febrile neutropenia	10	(4.0)	2	(1.6)
Thrombocytopenia	10	(4.0)	3	(2.4)
Neutropenia	7	(2.8)	2	(1.6)
Anaemia	3	(1.2)	6	(4.8)
Pulmonary embolism	2	(0.8)	3	(2.4)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adae]

The Applicant's Position:

The overall frequency of SAEs was similar between the D77 MK-3475A + chemo dataset (39%) and the D77 pembro IV + chemo dataset (40.5%) [Table 32].
The only SAE reported in ≥10% participants in the D77 MK-3475A + chemo dataset and the D77 pembro IV + chemo dataset was pneumonia, a commonly observed infectious complication in patients with NSCLC. Other common SAEs (≥2% incidence) were thrombocytopenia, febrile neutropenia, and neutropenia [Table 32]. These SAEs were frequently considered drug-related, and frequencies were generally consistent between the MK-3475A-D77 study arms.
Of note, the incidence of the SAE of febrile neutropenia in the D77 MK-3475A + chemo dataset (4.0%) was consistent with the pooled pembro IV + chemo dataset (4.1%) and is reflective of the addition of chemotherapy to pembrolizumab.

The FDA's Assessment: FDA agrees with the Applicant's position that the frequency of SAEs was generally similar between the pembrolizumab SC + chemo arm compared to the

pembrolizumab IV + chemo arm in Study MK-3475A-D77. However, as there may be heterogeneity between investigators and difficulty in accurately assigning attribution of adverse events to study therapy, FDA reports all treatment-emergent adverse events and generally does not report drug-related adverse events.

SAEs occurred in 39% of patients who received pembrolizumab SC. The incidence of serious adverse reactions occurring in ≥1% of patients on the pembrolizumab SC arm in Study MK-3475A-D77 is shown in the table below:

Table 33: FDA – Serious Adverse Events Occurring in ≥1% of Patients Receiving MK-3475A SC in Study MK-3475A-D77

Serious Adverse Event	MK-3475A SC + chemo N = 251 N (%)	Pembro IV + chemo N = 126 N (%)
All	98 (39)	51 (41)
Pneumonia[1]	25 (10)	13 (10)
Thrombocytopenia	10 (4)	3 (2.4)
Febrile neutropenia	10 (4)	2 (1.6)
Neutropenia	7 (2.8)	2 (1.6)
Musculoskeletal Pain[2]	5 (2)	1 (0.8)
Pneumonitis[3]	5 (2)	0
Diarrhea[4]	4 (1.6)	2 (1.6)
Rash[5]	3 (1.2)	0
Respiratory Failure	3 (1.2)	1 (0.8)
Anemia	3 (1.2)	6 (4.8)

Source: BLA761467/0001/m5/datasets/pd77v01mk3475a/analysis/adam/datasets/adae.xpt
Data cutoff date: Jul 12, 2024
Pneumonia[1] (GT) includes COVID-19 pneumonia, lower respiratory tract infection, lung abscess, pneumocystis jirovecii pneumonia, pneumonia bacterial, and pneumonia mycoplasmal.
Musculoskeletal pain[2] (GT) includes back pain, bone pain, myalgia, and pain in extremity.
Pneumonitis[3](GT) includes immune-mediated lung disease, interstitial lung disease, and pneumonitis.
Diarrhea[4] (GT) includes colitis, diarrhea, and enterocolitis.
Rash[5] (GT) includes dermatitis exfoliative, erythema multiforme, and rash.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 34: Applicant – Participants With Adverse Events Resulting in Any Treatment Discontinuation (Incidence >0% in One or More Treatment Groups) (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
with one or more adverse events	62	(24.7)	30	(23.8)
with no adverse events	189	(75.3)	96	(76.2)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Blood and lymphatic system disorders	**17**	**(6.8)**	**6**	**(4.8)**
Anaemia	5	(2.0)	4	(3.2)
Febrile neutropenia	4	(1.6)	0	(0.0)
Neutropenia	4	(1.6)	0	(0.0)
Thrombocytopenia	5	(2.0)	2	(1.6)
Cardiac disorders	**1**	**(0.4)**	**0**	**(0.0)**
Cardiac failure	1	(0.4)	0	(0.0)
Ear and labyrinth disorders	**1**	**(0.4)**	**0**	**(0.0)**
Deafness	1	(0.4)	0	(0.0)
Endocrine disorders	**1**	**(0.4)**	**1**	**(0.8)**
Hyperthyroidism	1	(0.4)	0	(0.0)
Immune-mediated hypophysitis	0	(0.0)	1	(0.8)
Gastrointestinal disorders	**5**	**(2.0)**	**4**	**(3.2)**
Colitis	0	(0.0)	1	(0.8)
Diarrhoea	0	(0.0)	1	(0.8)
Enterocolitis	1	(0.4)	0	(0.0)
Immune-mediated enterocolitis	0	(0.0)	1	(0.8)
Intestinal obstruction	1	(0.4)	0	(0.0)
Intestinal perforation	0	(0.0)	1	(0.8)
Nausea	1	(0.4)	0	(0.0)
Neutropenic colitis	1	(0.4)	0	(0.0)
Stomatitis	1	(0.4)	0	(0.0)
General disorders and administration site conditions	**5**	**(2.0)**	**3**	**(2.4)**
Death	4	(1.6)	1	(0.8)
Fatigue	0	(0.0)	1	(0.8)
Multiple organ dysfunction syndrome	0	(0.0)	1	(0.8)
Oedema peripheral	1	(0.4)	0	(0.0)
Infections and infestations	**16**	**(6.4)**	**6**	**(4.8)**
Abdominal infection	1	(0.4)	0	(0.0)
COVID-19	1	(0.4)	0	(0.0)
Lung abscess	1	(0.4)	0	(0.0)
Neutropenic sepsis	1	(0.4)	0	(0.0)
Parotitis	1	(0.4)	0	(0.0)
Pneumonia	8	(3.2)	4	(3.2)
Pneumonia bacterial	1	(0.4)	0	(0.0)
Septic shock	1	(0.4)	2	(1.6)
Viral infection	1	(0.4)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(0.4)**	**1**	**(0.8)**
Femoral neck fracture	0	(0.0)	1	(0.8)
Infusion related reaction	1	(0.4)	0	(0.0)
Investigations	**6**	**(2.4)**	**4**	**(3.2)**
Alanine aminotransferase increased	4	(1.6)	0	(0.0)
Aspartate aminotransferase increased	1	(0.4)	2	(1.6)
Blood creatinine increased	1	(0.4)	0	(0.0)
Creatinine renal clearance decreased	0	(0.0)	1	(0.8)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Gamma-glutamyltransferase increased	1	(0.4)	0	(0.0)
Myocardial necrosis marker increased	0	(0.0)	1	(0.8)
Nervous system disorders	**1**	**(0.4)**	**1**	**(0.8)**
Cerebrovascular accident	0	(0.0)	1	(0.8)
Epilepsy	1	(0.4)	0	(0.0)
Renal and urinary disorders	**1**	**(0.4)**	**2**	**(1.6)**
Acute kidney injury	0	(0.0)	1	(0.8)
Nephritis	0	(0.0)	1	(0.8)
Renal impairment	1	(0.4)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**10**	**(4.0)**	**3**	**(2.4)**
Immune-mediated lung disease	1	(0.4)	0	(0.0)
Interstitial lung disease	1	(0.4)	0	(0.0)
Pneumonitis	4	(1.6)	0	(0.0)
Pneumothorax	1	(0.4)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**10**	**(4.0)**	**3**	**(2.4)**
Pulmonary embolism	1	(0.4)	2	(1.6)
Respiratory failure	2	(0.8)	1	(0.8)
Skin and subcutaneous tissue disorders	**2**	**(0.8)**	**0**	**(0.0)**
Dermatitis exfoliative	1	(0.4)	0	(0.0)
Rash	1	(0.4)	0	(0.0)
Vascular disorders	**1**	**(0.4)**	**0**	**(0.0)**
Arterial thrombosis	1	(0.4)	0	(0.0)

Every participant is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adae]

The Applicant's Position:

The type and incidence of AEs leading to discontinuation of study drug in the D77 MK-3475A + chemo dataset were generally consistent with the known safety profiles of pembrolizumab monotherapy and chemotherapy.
Anemia, frequently considered to be drug-related by the investigator, was the most common AE (2% incidence) leading to discontinuation of any study drug, MK-3475A or chemotherapy, in the D77 MK-3475A + chemo dataset [Table 34].
The incidence of all-cause and drug-related AEs leading to discontinuation of MK-3475A and pembrolizumab IV were similar in the D77 MK-3475A + chemo dataset and the D77 pembro IV + chemo dataset.

The FDA's Assessment: The FDA agrees with the Applicant's position that the type of AEs leading to permanent discontinuation of pembrolizumab SC is consistent with the known safety profile of pembrolizumab IV. The table below shows the adverse events leading to permanent discontinuation of pembrolizumab SC or pembrolizumab IV in Study MK-3475A-D77.

Table 35: FDA – Adverse Events Leading to Permanent Discontinuation in ≥1% of Patients Receiving Pembrolizumab SC in Study MK-3475A-D77

AE leading to Discontinuation	MK-3475A SC + chemo N = 251 N (%)		Pembro IV + chemo N = 126 N (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
All	68 (26)	30 (12)	33 (26)	12 (10)
Pneumonia[1]	10 (4)	3 (1.2)	4 (3.2)	0
Pneumonitis [2]	6 (2.4)	5 (2)	0	0
Thrombocytopenia	5 (2)	3 (1.2)	2 (1.6)	1 (0.8)
Anemia	5 (2)	4 (1.6)	4 (3.2)	4 (3.2)
Neutropenia	4 (1.6)	2 (0.8)	0	0
Febrile neutropenia	4 (1.6)	1 (0.4)	0	0

Source: BLA761467/0001/m5/datasets/pd77v01mk3475a/analysis/adam/datasets/adae.xpt
Data cutoff date: Jul 12, 2024
Pneumonia[1] (GT): lung abscess, pneumonia, and pneumonia bacterial.
Pneumonitis[2] (GT): immune-mediated lung disease, interstitial lung disease, and pneumonitis.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

The Applicant's Position:

The type and incidence of AEs leading to interruption of study drug in the D77 MK-3475A + chemo dataset were generally consistent with the known safety profiles of pembrolizumab monotherapy and chemotherapy.

Neutropenia, anemia, and thrombocytopenia leading to interruption of any study drug (≥10% incidence) were frequently considered related to study drug.

The most common all-cause AEs leading to interruption of MK-3475A (≥5% incidence) in the D77 MK-3475A + chemo dataset were neutropenia, anemia, and thrombocytopenia. Neutropenia was the most common all-cause and drug-related AE leading to interruption of MK-3475A. Neutropenia and anemia were the most common AEs leading to interruption of chemotherapy (≥10% incidence) in both the MK-3475A-D77 datasets.

The overall incidence of AEs leading to interruption of any study drug and interruption of MK-3475A were lower in the D77 MK-3475A + chemo dataset compared with the pooled pembro IV + chemo dataset. The incidences of most common AEs were generally consistent between the 2 datasets.

The FDA's Assessment: FDA generally agrees with the Applicant's position. Based on the FDA's review of the safety dataset, dosage interruptions due to an AE occurred in 45% of the patients in pembrolizumab SC arm compared to 44% in pembrolizumab IV arm. Adverse reactions which required dosage interruption in ≥2% of patients in the pembrolizumab SC arm

are shown in the table below:

Table 36: FDA – Adverse Events Leading to Treatment Interruption in ≥2% of Patients Receiving Pembrolizumab SC in Study MK-3475A-D77

Adverse Event leading to dose interruption in ≥2%)	MK-3475A + chemo N = 251 n (%)		pembro IV + chemo N = 126 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Any TEAE	113 (45)	71 (28)	55 (44)	37 (29)
Neutropenia	39 (16)	25 (10)	14 (11)	8 (6)
Anemia	20 (8)	13 (5)	18 (14)	15 (12)
Thrombocytopenia	19 (8)	10 (4)	8 (6)	2 (1.6)
Pneumonia[1]	12 (4.8)	9 (3.6)	4 (3.2)	3 (2.4)
Rash[2]	7 (2.8)	2 (0.8)	1 (0.8)	0
Increased alanine aminotransferase	5 (2)	1 (0.4)	0	0

Source: BLA761467/0001/m5/datasets/pd77v01mk3475a/analysis/adam/datasets/adae.xpt
Data cutoff date: Jul 12, 2024
Pneumonia[1] (GT) includes lung abscess, pneumonia, and pneumonia bacterial.
Rash[2] (GT) dermatitis, dermatitis acneiform, erythema multiforme, immune-mediated dermatitis, rash, rash maculo-papular, rash pruritic, and skin exfoliation.

Significant Adverse Events

Data:

Table 37: Applicant – Adverse Event Summary – AEOSI (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	78	(31.1)	33	(26.2)	1,900	(33.3)	2,095	(27.5)
with no adverse event	173	(68.9)	93	(73.8)	3,811	(66.7)	5,536	(72.5)
with drug-related[a] adverse events	66	(26.3)	31	(24.6)	1,676	(29.3)	1,815	(23.8)
with toxicity grade 3-5 adverse events	16	(6.4)	7	(5.6)	543	(9.5)	543	(7.1)
with toxicity grade 3-5 drug-related adverse events	15	(6.0)	7	(5.6)	491	(8.6)	475	(6.2)
with serious adverse events	14	(5.6)	6	(4.8)	433	(7.6)	527	(6.9)
with serious drug-related adverse events	13	(5.2)	6	(4.8)	391	(6.8)	462	(6.1)
who died	1	(0.4)	0	(0.0)	17	(0.3)	13	(0.2)
who died due to a drug-related adverse event	1	(0.4)	0	(0.0)	15	(0.3)	13	(0.2)
discontinued any drug due to an adverse event	11	(4.4)	4	(3.2)	363	(6.4)	363	(4.8)
discontinued MK-3475A/pembrolizumab	9	(3.6)	4	(3.2)	284	(5.0)	363	(4.8)
discontinued any chemotherapy	6	(2.4)	2	(1.6)	190	(3.3)	0	(0.0)
discontinued any drug due to a drug-related adverse event	11	(4.4)	4	(3.2)	354	(6.2)	356	(4.7)
discontinued MK-3475A/pembrolizumab	9	(3.6)	4	(3.2)	277	(4.9)	356	(4.7)
discontinued any chemotherapy	6	(2.4)	2	(1.6)	184	(3.2)	0	(0.0)
discontinued any drug due to a serious adverse event	7	(2.8)	3	(2.4)	234	(4.1)	231	(3.0)
discontinued MK-3475A/pembrolizumab	7	(2.8)	3	(2.4)	213	(3.7)	231	(3.0)
discontinued any chemotherapy	3	(1.2)	2	(1.6)	114	(2.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	7	(2.8)	3	(2.4)	226	(4.0)	229	(3.0)
discontinued MK-3475A/pembrolizumab	7	(2.8)	3	(2.4)	207	(3.6)	229	(3.0)
discontinued any chemotherapy	3	(1.2)	2	(1.6)	109	(1.9)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
For KN-D77, grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database cutoff date for KN-D77: 12JUL2024.
The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.

Source: [ISS: adam-adsl; adae]

Table 38: Applicant – Participants With Adverse Events of Special Interest (AEOSI) (Incidence > 0% in One or More Treatment Groups) (APaT Population)

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	251		126		5,711		7,631	
with one or more adverse events	78	(31.1)	33	(26.2)	1,900	(33.3)	2,095	(27.5)
with no adverse events	173	(68.9)	93	(73.8)	3,811	(66.7)	5,536	(72.5)
Adrenal Insufficiency	**5**	**(2.0)**	**3**	**(2.4)**	**62**	**(1.1)**	**74**	**(1.0)**
Arthritis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**5**	**(0.1)**
Cholangitis Sclerosing	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**0**	**(0.0)**
Colitis	**3**	**(1.2)**	**3**	**(2.4)**	**155**	**(2.7)**	**159**	**(2.1)**
Encephalitis	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**5**	**(0.1)**
Exocrine Pancreatic Insufficiency	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**5**	**(0.1)**
Gastritis	**7**	**(2.8)**	**1**	**(0.8)**	**125**	**(2.2)**	**57**	**(0.7)**
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.1)**	**6**	**(0.1)**
Haemolytic Anaemia	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**2**	**(0.0)**
Hepatitis	**1**	**(0.4)**	**0**	**(0.0)**	**65**	**(1.1)**	**80**	**(1.0)**
Hyperthyroidism	**20**	**(8.0)**	**6**	**(4.8)**	**330**	**(5.8)**	**398**	**(5.2)**
Hypoparathyroidism	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**1**	**(0.0)**
Hypophysitis	**0**	**(0.0)**	**1**	**(0.8)**	**40**	**(0.7)**	**52**	**(0.7)**
Hypothyroidism	**35**	**(13.9)**	**15**	**(11.9)**	**787**	**(13.8)**	**939**	**(12.3)**
Infusion Reactions	**8**	**(3.2)**	**3**	**(2.4)**	**368**	**(6.4)**	**165**	**(2.2)**
Myasthenic Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**	**8**	**(0.1)**
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(0.0)**
Myocarditis	**0**	**(0.0)**	**0**	**(0.0)**	**10**	**(0.2)**	**9**	**(0.1)**
Myositis	**1**	**(0.4)**	**0**	**(0.0)**	**18**	**(0.3)**	**34**	**(0.4)**
Nephritis	**0**	**(0.0)**	**2**	**(1.6)**	**38**	**(0.7)**	**37**	**(0.5)**
Optic Neuritis	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**	**2**	**(0.0)**
Pancreatitis	**0**	**(0.0)**	**0**	**(0.0)**	**24**	**(0.4)**	**28**	**(0.4)**
Pericarditis	**0**	**(0.0)**	**0**	**(0.0)**	**8**	**(0.1)**	**11**	**(0.1)**
Pneumonitis	**13**	**(5.2)**	**1**	**(0.8)**	**228**	**(4.0)**	**324**	**(4.2)**
Sarcoidosis	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**	**20**	**(0.3)**
Severe Skin Reactions	**4**	**(1.6)**	**3**	**(2.4)**	**140**	**(2.5)**	**130**	**(1.7)**
Thyroiditis	**1**	**(0.4)**	**1**	**(0.8)**	**72**	**(1.3)**	**74**	**(1.0)**
Type 1 Diabetes Mellitus	**1**	**(0.4)**	**0**	**(0.0)**	**18**	**(0.3)**	**34**	**(0.4)**
Uveitis	**0**	**(0.0)**	**0**	**(0.0)**	**7**	**(0.1)**	**25**	**(0.3)**
Vasculitis	**0**	**(0.0)**	**0**	**(0.0)**	**32**	**(0.6)**	**5**	**(0.1)**

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the

	D77 MK-3475A + Chemotherapy		D77 Pembrolizumab IV + Chemotherapy Control		Pooled Pembrolizumab + Chemotherapy SD		Pembrolizumab Monotherapy RSD	
	n	(%)	n	(%)	n	(%)	n	(%)
incidence criterion in the report title, after rounding. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. Database cutoff date for KN-D77: 12JUL2024. The list of studies and database cutoff dates for the aggregate safety datasets within this table are provided in the appendix of Module 2.7.4.								

Source: [ISS: adam-adsl; adae]

The Applicant's Position:

The frequency, severity, and types of AEOSI observed in the D77 MK-3475A + chemo dataset were consistent with the established safety profile of pembrolizumab (pembro RSD). No immune-mediated AEs unique to MK-3475A were identified in the D77 MK-3475A + chemo dataset. Most AEOSI were nonserious, Grade 1 to 2, and manageable with standard clinical practice.

- The overall incidence of AEOSI was similar in the D77 MK-3475A + chemo dataset compared with the pooled pembro IV + chemo dataset and the pembro RSD []. The exposure-adjusted event rates of AE categories also remained similar.

- Hypothyroidism was the most commonly reported AEOSI in the D77 MK-3475A + chemo dataset. The incidence of hypothyroidism was similar in the D77 MK-3475A + chemo dataset (13.9%) compared with the D77 pembro IV + chemo dataset (11.9%), pooled pembro IV + chemo dataset (13.8%), and the pembro RSD (12.3%) [] and the exposure-adjusted event rates of hypothyroidism in all datasets remained similar.

- The majority of AEOSI reported in the D77 MK-3475A + chemo dataset were mild to moderate (Grade 1 or 2) in severity. There was 1 fatal (Grade 5) AEOSI of pneumonitis in the D77 MK-3475A + chemo dataset.

- The majority of AEOSI were reported as resolved (33.3%) or resolving (21.8%) in participants in the D77 MK-3475A + chemo dataset at the time of data cutoff. These incidences were comparable to those observed in the pooled pembro IV + chemo dataset and the pembro RSD. As of the data cutoff, 42.3% of the AEOSI in the D77 MK-3475A + chemo dataset were not resolved. These were mainly due to hypothyroidism (54.3% not resolved) and hyperthyroidism (20% not resolved). Events of hypothyroidism are often well managed with continued hormone therapy.

The FDA's Assessment: FDA agrees with the Applicant's position that the safety analysis for adverse events of special interest (AEOSI) from Study MK-3475A-D77 were consistent with the known safety profile of pembrolizumab IV.

The Applicant defined an immune related AE as a suspected event which based on medical

review is consistent with an immune mediated mechanism of action, with no alternative etiologies. A prespecified list of PTs was developed by the Applicant to consistently characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators.

Per the Applicant, AEOSIs included, but were not limited to, cases of pneumonitis, colitis, diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, hypothyroidism, hypophysitis, hepatitis, nephritis, thyroiditis, type 1 diabetes mellitus, severe skin reactions including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) or any severe skin reaction ≥ Grade 3, uveitis, pancreatitis, myositis, Guillain-Barré syndrome, myocarditis, encephalitis, sarcoidosis, infusion reactions, myasthenic syndrome, myelitis, vasculitis, cholangitis sclerosing, hypoparathyroidism, arthritis, hemophagocytic lymphohistiocytosis (HLH), optic neuritis, gastritis, hemolytic amenia, exocrine pancreatic insufficiency and pericarditis.

AEOSI reported in MK-3475A-D77 are shown in the table below. The majority of AEOSI were Grade 1 to 2 in severity.

Table below summarizes the AEOSIs observed in the pembrolizumab SC arm compared to the pembrolizumab IV arm in Study MK-3475A-D77.

Table 39: FDA – Adverse Events of Special Interest in Study MK-3475A-D77

Adverse Event of Special Interest (AEOSI)	MK-3475A + Chemo N = 251 N (%)		Pembro IV + Chemo N = 126 N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Immune-Mediated Pneumonitis	13 (5)	3 (2)	0	0
Immune-Mediated Colitis	3 (1.2)	2 (0.8)	1 (0.8)	1 (0.8)
Immune-Mediated Hepatitis	1 (0.4)	0	0	0
Immune-Mediated Adrenal Insufficiency	5 (2)	1 (0.4)	0	0
Immune-Mediated Thyroiditis	1 (0.4)	0	0	0
Immune-Mediated Diabetes Mellitus	1 (0.4)	0	0	0
Immune-Mediated Rash/Dermatitis	4 (1.6)	4 (1.6)	0	0

Data cutoff date: Jul 12, 2024
Source: PD77V01MK3475A: adam-adsl, adae

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 40: Applicant – Adverse Event Summary (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)

Participants in population	251		126	
with one or more adverse events	249	(99.2)	123	(97.6)
with no adverse event	2	(0.8)	3	(2.4)
with drug-related[a] adverse events	226	(90.0)	121	(96.0)
with toxicity grade 3-5 adverse events	151	(60.2)	82	(65.1)
with toxicity grade 3-5 drug-related adverse events	118	(47.0)	60	(47.6)
with serious adverse events	98	(39.0)	51	(40.5)
with serious drug-related adverse events	53	(21.1)	25	(19.8)
who died	26	(10.4)	12	(9.5)
who died due to a drug-related adverse event	9	(3.6)	3	(2.4)
discontinued any drug due to an adverse event	62	(24.7)	30	(23.8)
discontinued MK-3475A/pembrolizumab	39	(15.5)	21	(16.7)
discontinued any chemotherapy	57	(22.7)	24	(19.0)
discontinued any drug due to a drug-related adverse event	44	(17.5)	19	(15.1)
discontinued MK-3475A/pembrolizumab	21	(8.4)	11	(8.7)
discontinued any chemotherapy	38	(15.1)	15	(11.9)
discontinued any drug due to a serious adverse event	41	(16.3)	21	(16.7)
discontinued MK-3475A/pembrolizumab	33	(13.1)	19	(15.1)
discontinued any chemotherapy	35	(13.9)	16	(12.7)
discontinued any drug due to a serious drug-related adverse event	23	(9.2)	10	(7.9)
discontinued MK-3475A/pembrolizumab	16	(6.4)	9	(7.1)
discontinued any chemotherapy	17	(6.8)	7	(5.6)

[a] Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 5.0.

Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adae]

Table 41: Applicant – Participants With Adverse Events (Sorted by Decreasing Incidence) (Incidence ≥10% in One or More Treatment Groups) (APaT Population)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Participants in population	251		126	
with one or more adverse events	249	(99.2)	123	(97.6)
with no adverse events	2	(0.8)	3	(2.4)
Anaemia	147	(58.6)	89	(70.6)
Neutropenia	109	(43.4)	41	(32.5)
Leukopenia	75	(29.9)	33	(26.2)
Thrombocytopenia	74	(29.5)	35	(27.8)
Nausea	63	(25.1)	31	(24.6)
Aspartate aminotransferase increased	47	(18.7)	18	(14.3)
Alanine aminotransferase increased	44	(17.5)	18	(14.3)
Fatigue	41	(16.3)	18	(14.3)
Diarrhoea	37	(14.7)	17	(13.5)
Pneumonia	36	(14.3)	17	(13.5)

	MK-3475A + chemo		pembro IV + chemo	
	n	(%)	n	(%)
Constipation	35	(13.9)	23	(18.3)
Hypothyroidism	35	(13.9)	15	(11.9)
Hypoalbuminaemia	30	(12.0)	17	(13.5)
Pruritus	29	(11.6)	16	(12.7)
Decreased appetite	28	(11.2)	27	(21.4)
Hyperglycaemia	28	(11.2)	14	(11.1)
Lymphocyte count decreased	25	(10.0)	9	(7.1)
Rash	25	(10.0)	12	(9.5)
Asthenia	24	(9.6)	16	(12.7)
Alopecia	22	(8.8)	13	(10.3)
Pyrexia	20	(8.0)	14	(11.1)
Arthralgia	19	(7.6)	15	(11.9)
Blood alkaline phosphatase increased	18	(7.2)	13	(10.3)
Hyponatraemia	17	(6.8)	13	(10.3)

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adae]

The Applicant's Position:

The incidence, type, and severity of all AEs in participants in the D77 MK-3475A + chemo dataset were generally consistent with the D77 pembro IV + chemo dataset and the known safety profiles of pembrolizumab as monotherapy and chemotherapy.

The overall incidence and type of most frequently reported AEs in participants in the D77 MK-3475A + chemo dataset were generally consistent with the D77 pembro IV + chemo dataset [].

The most frequently reported AEs (≥20% incidence) in the D77 MK-3475A + chemo dataset and in the D77 pembro IV + chemo dataset were anemia, neutropenia, leukopenia, thrombocytopenia, and nausea []. These AEs were frequently considered drug-related by the investigator and are consistent with the known safety profile of chemotherapy.

The incidences of leukopenia, thrombocytopenia, and nausea were similar between the 2 datasets. While the incidence of anemia was lower, neutropenia was higher in the D77 MK-3475A + chemo dataset compared with the D77 pembro IV + chemo dataset []. The exposure-adjusted event rates for neutropenia were similar between both datasets (13.49 vs 10.67, respectively).

When the Applicant performed additional analyses by combining PTs "neutropenia" and "neutrophil count decreased," to account for reporting and coding differences of these terms between the MK-3457A-D77 study and pooled dataset, the incidence of neutropenia was lower

in the D77 MK-3475A + chemo dataset (43.4%) and the D77 pembro IV + chemo dataset (32.5%) compared with the pooled pembro IV + chemo dataset (51.5%).

Drug-related AEs were generally consistent between the D77 MK-3475A + chemo dataset and the D77 pembro IV + chemo dataset and were consistent with the established safety profiles of pembrolizumab IV or chemotherapy. Anemia, neutropenia, thrombocytopenia, leukopenia, and nausea were the most frequently reported (≥20%) drug-related AEs.

The FDA's Assessment: FDA generally agrees with the Applicant. However, FDA identified slight differences in the frequency of some adverse events based on differences in grouping of preferred terms. The table below summarizes FDA's analysis of the most frequent adverse events occurring in ≥10% of patients on the pembrolizumab SC arm.

Table 42: FDA – Adverse Reactions Occurring in ≥10% of Patients With Metastatic NSCLC Receiving Pembrolizumab SC in Study MK-3475A-D77

Adverse Reaction	MK-3475A + chemo N=251		Pembro IV + chemo N=126	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	25	1.2	25	0.8
Diarrhea[†]	16	2	14	0.8
Constipation	14	0	18	1.6
General				
Fatigue[‡]	25	3.6	26	3.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[§]	21	2.4	30	2.4
Skin and Subcutaneous Tissue				
Rash[¶]	18	2	19	0.8
Pruritis	12	0	13	0.8
Endocrine				
Hypothyroidism	14	0	12	0
Infections				
Pneumonia[#]	17	10	16	7
Nervous System				
Peripheral neuropathy[Þ]	11	0.4	14	0
Metabolism and Nutrition				
Decreased appetite	11	0.8	21	2.4
Hyperglycemia	11	0.8	11	0.8
Respiratory, Thoracic and Mediastinal				
Cough[β]	10	0	11	0.8

Source: BLA761467/0001/m5/datasets/pd77v01mk3475a/analysis/adam/datasets/adae.xpt
Data Cutoff Date: July 12, 2024
Graded per NCI CTCAE v 5.0

† Includes diarrhea, colitis, and enterocolitis.
‡ Includes fatigue, asthenia.
§ Includes musculoskeletal pain, arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, non-cardiac chest pain, and pain in extremity.
¶ Includes rash, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, eczema, erythema multiforme, immune-mediated dermatitis, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and skin exfoliation.
# Includes pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung abscess, pneumocystis jirovecii pneumonia, pneumonia bacterial, and pneumonia mycoplasmal.
Þ Includes neuropathy peripheral, hypoaesthesia, neuralgia, paraesthesia, and peripheral sensory neuropathy.
β Includes cough, productive cough, and upper-airway cough syndrome.

Laboratory Findings

The Applicant's Position:

The most frequently reported laboratory abnormalities (including Grade 3 or 4 events) in the D77 MK-3475A + chemo dataset were generally consistent with the known safety profiles of pembrolizumab monotherapy and chemotherapy. No new safety concerns were identified based on laboratory abnormalities reported in the D77 MK-3475A + chemo dataset.

The frequency, severity, and types of laboratory abnormalities reported in the D77 MK-3475A + chemo dataset were generally consistent with the D77 pembro IV + chemo dataset, pooled pembro IV + chemo dataset, and the pembro RSD. The majority were CTCAE Grade 1 to 2 toxicity.

A clinically relevant laboratory finding (defined as Grade 3 to 4 events) of neutrophil count decreased was higher in the D77 MK-3475A + chemo dataset (27.8%) compared with the D77 pembro IV + chemo dataset (19.2%). In the MK-3475A-D77 study, the laboratory data on "neutrophil count decreased" was consistent with the reported AE results of neutropenia.

Shifts in events of leukocytes decreased and neutrophils count decreased were consistent between the D77 MK-3475A + chemo dataset and the D77 pembro IV + chemo dataset.

Neutrophil count decreased was lower in the D77 MK-3475A + chemo dataset compared with the pooled pembro IV + chemo dataset (58.4% vs 71.2%), including Grade 3 to 4 events (27.8% vs 39.4%).

No participants met the predetermined laboratory criteria for potential DILI (ALT or AST ≥3 × ULN, bilirubin ≥2 × ULN, and alkaline phosphatase <2 × ULN).

The FDA's Assessment: FDA agrees with the data and position presented by the Applicant. Several IRs were sent to clarify the variables used to define laboratory abnormalities.

Table 43: FDA – Laboratory Abnormalities Worsened From Baseline Occurring in ≥20% of Patients With Metastatic NSCLC Receiving Pembrolizumab SC in Study MK-3475A-D77

Laboratory Test*	MK-3475A + Chemo		Pembrolizumab IV + Chemo	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Hematology				
Anemia	80	22	86	26
Leukopenia	61	13	52	10
Neutropenia	58	28	49	19
Lymphopenia	55	22	54	18
Thrombocytopenia	43	11	41	6
Chemistry				
Increased AST	43	2.5	38	3.2
Hypoalbuminemia	38	0.4	39	0
Increased ALT	37	2.1	36	0.8
Hyponatremia	35	4.1	42	7
Increased creatinine	33	4.5	38	6
Hypocalcemia	31	2.1	31	2.4
Increased alkaline phosphatase	29	0.4	34	0
Hypokalemia	21	5	24	6

Source: ADLB dataset, data cutoff date: July 12, 2024
Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: pembrolizumab SC plus platinum doublet chemotherapy (range: 240 to 246 patients) and intravenous pembrolizumab plus platinum doublet chemotherapy (range: 124 to 125 patients). Graded per NCI CTCAE V5.0.

Vital Signs

The Applicant's Position:

Clinically meaningful abnormalities in vital signs and physical examinations were reported as AEs. There were no safety concerns identified from the review of vital sign AEs.

The FDA's Assessment: FDA agrees with the Applicant's position.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG was performed at baseline and thereafter as clinically indicated. There were no safety concerns identified from review of ECGs.

The FDA's Assessment: FDA agrees with the Applicant's position.

QT

The Applicant's Position:

No clinically meaningful effects on QTc were identified in the analyses included in previous submissions (KEYTRUDA BLA 125514).

The FDA's Assessment: FDA agrees with the Applicant's position regarding the original submission under BLA 125514. No QT Studies were performed with pembrolizumab SC.

Immunogenicity

The Applicant's Position:

Clinical immunogenicity results for pembrolizumab and MK-5180 from MK-3475A-D77, MK-3475-C18, and ALT-BB4-01 are presented in Section 6.2.1. There were no clinically meaningful safety findings attributable to ADA and no SAEs attributable to immunogenicity in participants who were ADA positive for either pembrolizumab or MK-5180.

The FDA's Assessment:

FDA agrees with the Applicant that based on the evaluation of immunogenicity for pembrolizumab, overall, ADA incidence was low and there were no major safety findings in patients who were ADA positive for pembrolizumab in both the SC and IV arms of the pivotal study. Additionally for the SC arm, ADA incidence was low for berahyaluronidase and there were no safety concerns in ADA positive patients. See Section 6.2.1 of the Assessment Aid for additional details.

Additional Analyses

Safety data from participants in MK-3475A-F11 (Section 7.1) support the safety of switching from one route of administration to another. See Section 8.2.11 for a summary of these data.

The FDA's Assessment: FDA did not review data from Study MK-3475A-F11 during this review cycle as data from the final analysis were not available.

Additional Analyses

8.2.5. Analysis of Submission-Specific Safety Issues

Injection-site Reactions

Data:

Table 44: Applicant – Participants With Injection-Site Reactions Adverse Events by Maximum Toxicity Grade (Incidence > 0%) (APaT Population)

	MK-3475A + chemo	
	n	(%)
Participants in population	251	
with one or more adverse events	6	(2.4)
Grade 1	6	(2.4)
with no adverse events	245	(97.6)
Injection site erythema	1	(0.4)
Grade 1	1	(0.4)
Injection site haemorrhage	1	(0.4)
Grade 1	1	(0.4)
Injection site induration	1	(0.4)
Grade 1	1	(0.4)
Injection site pain	1	(0.4)
Grade 1	1	(0.4)
Injection site reaction	2	(0.8)
Grade 1	2	(0.8)

Every participant is counted a single time for each applicable specific adverse event.
Only the highest reported grade of a given adverse event is counted for the individual participant.
Grades are based on NCI CTCAE version 5.0.
Non-serious adverse events up to 30 days of last treatment and serious adverse events up to 90 days of last treatment are included.
Database Cutoff Date: 12JUL2024.

Source: [PD77V01MK3475A: adam-adsl; adae]

The Applicant's Position:

Injection site reactions in the D77 MK-3475A + chemo dataset were low in frequency (2.4%) and mild (Grade 1) in severity []. None of the injection-site reactions resulted in discontinuation of study intervention. In participants with injection-site reactions, the median time to onset of the first injection-site reaction from initial dose administration was 2.0 days (range: 1 to 126 days).

The FDA's Assessment: FDA agrees with the Applicant's position. Given the different route of administration of pembrolizumab SC and infusion-related reactions included in the Warnings and Precautions section of the USPI for pembrolizumab IV, FDA evaluated events of injection site reactions, hypersensitivity reactions and incidence of anaphylaxis.

FDA review of injection related reactions

To evaluate injection related reactions, FDA requested narratives from the Applicant on May 23, 2025, for 10 patients (4%) treated with pembrolizumab SC in Study MK-3475A-D77 who experienced the following events that may have been consistent with local injection site reactions: infusion related reaction, infusion site reaction, infusion site pain, injection site erythema, injection site hemorrhage, injection site pain, and injection site induration. Based on the narratives provided by the Applicant, FDA determined that 6 of these patients (2.4%) treated

in the pembrolizumab SC plus chemotherapy arm in MK-3475A-D77 experienced local injection site reactions from pembrolizumab SC. Brief narratives of these adverse events are reported in the table below.

Table 45: FDA – Potential Adverse Events of Injection Site Reactions for Patients Who Received Pembrolizumab SC in MK-3475A-D77

Patient ID	Narrative	Adverse Event	FDA Assessment
(b) (6)	Patient received Cycle 4 of MK-3475A and pemetrexed on day 125. On day 126 patient developed Grade 1 injection site erythema. No treatment was given. On day 130 it was resolved.	Injection site erythema	Given the temporal relationship between the event of injection site erythema and receipt of pembrolizumab SC, FDA determined that this event is likely related to pembrolizumab SC and consistent with a local injection site reaction.
(b) (6)	Patient received Cycle 1, day 1 of MK-3475A, pemetrexed and carboplatin. On day 2 he experienced Grade 1 injection site hemorrhage (bleeding at the injection site); treated with tranexamic acid. On day 21 injection site hemorrhage was considered resolved.	Injection site hemorrhage	Given the temporal relationship between the event of injection site hemorrhage and receipt of pembrolizumab SC, FDA determined that this event is likely related to pembrolizumab SC and consistent with a local injection site reaction.
(b) (6)	Patient received treatment with MK-3475A on day 85 (Cycle 3). From days 86 to 103, the patient experienced hardness/induration at the injection site. No additional symptoms or treatment were reported.	Injection site induration	Given the temporal relationship between the event of injection site induration and receipt of pembrolizumab SC, FDA determined that this event is likely related to pembrolizumab SC.
(b) (6)	Patient experienced injection site pain from days 2 to 7 and a second occurrence on days	Injection site pain	Given the temporal relationship between the event of injection site

	21 to 47, both reported as Grade 1 events. No additional symptoms or treatment were reported.		pain and receipt of pembrolizumab SC, FDA determined that this event is likely related to pembrolizumab SC
(b) (6)	Patient received Cycle 1, day 1 treatment with MK-3475A, pemetrexed, and carboplatin. On day 2 patient experienced Grade 1 injection site reaction. No treatment was reported, and it was considered resolved on day 4.	Injection site reaction	Given the temporal relationship between the injection site reaction and receipt of pembrolizumab SC, FDA determined that this event is likely related to pembrolizumab SC.
(b) (6)	Patient received Cycle 1, day 1 treatment with MK-3475A, pemetrexed, and carboplatin. Post administration of MK-3475A the patient experienced Grade 1 injection site erythema on the abdomen. No treatment was reported, and the event was considered resolved on day 2.	Injection site reaction	Given the temporal relationship between the injection site reaction and receipt of pembrolizumab SC, FDA determined that this event is likely related to pembrolizumab SC.

Source: Response document to FDA's IR dated May 23, 2025.

For FDA's review of potential events of hypersensitivity, FDA sent an information request on May 23, 2025, to the Applicant to obtain narratives for the following adverse events reported for patients who received pembrolizumab SC in Study MK-3475A-D77: hypersensitivity, drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, serum sickness, serum sickness-like reaction, infusion related reaction and infusion related hypersensitivity reaction. Based on review of the narratives and given the temporality of the adverse events in relationship to receiving pembrolizumab SC, hypersensitivity and administration-related systemic reactions occurred in 3.2% (8/251) of patients receiving pembrolizumab SC in combination with chemotherapy, of which 2.8% were Grade 2. Therefore, Section 5.2 of the USPI was updated to include newly identified signal of "hypersensitivity and administration-related reactions".

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Results from PRO analyses are in Section 8.1.2.

The FDA's Assessment: Refer to Section 8.1.2 of the Assessment Aid.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

No clinically meaningful differences in AE profiles were observed within and across intervention groups when analyzed by age, BMI, ECOG, race, region, sex, or weight.

The FDA's Assessment: FDA generally agrees with the Applicant's assessment that no overall differences in safety were observed between patients aged 65 years or older and younger adult patients. FDA did not independently review AEs by other factors such as race, BMI, region etc.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable; no studies were conducted to evaluate a specific safety concern.

The FDA's Assessment: FDA agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No information concerning human carcinogenicity or tumor development is provided in this submission.

The FDA's Assessment: FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

There were no reports of pregnancy in MK-3475A-D77 or in the supporting studies.

The FDA's Assessment: FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:
MK-3475A has not been assessed in pediatric patients. A rationale for a model-based PK analysis to support pembrolizumab SC as MK-3475A in pediatric patients 12 years and older is provided in Section 10.

The FDA's Assessment: FDA agrees with the Applicant's position. Refer to Section 10 Pediatrics in the Assessment Aid for additional discussion.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There were no reports of overdose in MK-3475A-D77 or in the supporting studies. There were no reports of drug abuse with MK-3475A. Potential for drug abuse or dependence is not expected for an anti-PD-1 mAb. No reports of drug abuse with pembrolizumab administered IV or SC as MK-3475A have occurred. There were no reports of withdrawal and rebound with MK-3475A. No withdrawal or rebound effects are expected with an anti-PD-1 mAb; none have been observed in pembrolizumab clinical studies to date.

The FDA's Assessment: The FDA agrees with Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

This section is not applicable for MK-3475A.

The FDA's Assessment: FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Postmarketing data from the safety reporting database will be routinely reviewed for MK-3475A. The Applicant's AE reporting system will contain all data from postmarket sources, including health care providers, consumers, and scientific literature. The Applicant will monitor postmarketing data associated with MK-3475A.

The FDA's Assessment: FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The pivotal Phase 3 MK-3475A-D77 study was conducted in participants in need of first-line therapy for metastatic NSCLC. The safety profile of MK-3475A in combination with chemotherapy observed is as expected for pembrolizumab in combination with chemotherapy in participants with NSCLC and more generally, consistent with the safety profiles of pembrolizumab monotherapy and chemotherapy. Injection-site reactions, which are expected for SC administration, were of low frequency, nonserious, and mild (Grade 1) in severity.

MK-3475A-C18 Safety Summary
The overall safety profiles during study treatment with MK-3475A and pembrolizumab IV, both as monotherapy (melanoma) and with standard of care therapy (NSCLC and RCC), were consistent with the known safety profiles of pembrolizumab monotherapy or the applicable standard of care therapies administered. Immune-mediated events (AEOSI) were consistent in nature and severity with that of the established pembrolizumab IV safety profile.
Local injection reactions were reported for 7 (15.2%) participants in Arm 1, 5 (11.4%) in Arm 2, 1 (16.7%) in Arm 3, and 9 (20.5%) in Arm 4. These events were nonserious, mostly mild (Grade 1), and effectively managed; no injection-site reactions resulted in discontinuation of study drug.
MK-3475A-F11 Safety Summary
The reported AEs observed with MK-3475A monotherapy in MK-3475A-F11 were generally consistent with the established safety profile of pembrolizumab IV based on Crossover Period 1 data (comparison between MK-3475A SC and pembrolizumab IV). For participants who received MK-3475A then pembrolizumab IV, AE rates (all grades) were reported pre- and post-switching for 79.4% and 52.9% of participants, respectively. For those who received pembrolizumab IV then MK-3475A SC, AE rates (all grades) were reported pre- and post-switching for 71.0% and 62.3% of participants, respectively. AE rates were similar between study arms in both pre- and post-switching time periods. No new safety issues were identified when participants switched from SC to IV and vice versa.
In the overall safety reporting period (Treatment Crossover Period + Treatment Continuation Period), AEOSI were reported in 27.0% of participants in Arm A and 20.3% participants in Arm B with similar AEOSI safety profiles regardless of the order of route of administration. The most common AEOSI in both arms were hypothyroidism and hyperthyroidism. AEOSI considered related to study drug were reported in 20.6% of participants in Arm A and 17.4% of participants in Arm B.
Local injection reactions were observed in 7 (11.1%) participants who received MK-3475A during Crossover Period 1 and in 4 (7.5%) participants who received MK-3475A during Crossover Period 2. These events were nonserious, ≤Grade 2 in severity, and effectively managed.
ALT-BB4-01 Safety Summary
No systemic safety concerns were identified, and no SAEs were reported when ALT-BB4 (containing MK-5180) was administered SC in healthy volunteers. Local injection-site reactions were reported in 26.09% of participants receiving ALT-BB4 in Part II-A and in 16.90% of participants receiving ALT-BB4 in Part II-B; no injection-site reactions were reported in the Part II-B control group. All injection-site reactions were nonserious and clinically managed.

The FDA's Assessment: FDA agrees that the observed safety profile of pembrolizumab SC is acceptable when considered in the context of a life-threatening disease and comparable to the safety profile for the pembrolizumab IV formulation. FDA reviewed safety data from Study MK-3475A-D77, based on a DCO date of July 12, 2024. FDA also reviewed data from the 120-day safety update for Study MK-3475A-D77 (DCO date of November 6, 2024) which revealed similar results compared to safety data submitted at the time of the original BLA submission.

Based on a DCO date of July 12, 2024, the most common adverse reactions (≥20% and not including laboratory abnormalities) in patients treated with pembrolizumab SC in combination

with chemotherapy were nausea (25%), fatigue (25%), and musculoskeletal pain (21%). Dosage interruptions due to an adverse reaction occurred in 45% of patients on the pembrolizumab SC arm. Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia (14%), anemia (8%), thrombocytopenia (7%), pneumonia (4.4%), leukopenia (3.6%), rash (2.8%), and increased aspartate aminotransferase (2%). Serious adverse reactions occurred in 39% of patients who received pembrolizumab SC in combination with chemotherapy. Serious adverse reactions in ≥1% of patients who received pembrolizumab SC were pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%) musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%) and anemia (1.2%). Fatal adverse reactions occurred in 10% of patients who received pembrolizumab SC in combination with chemotherapy including pneumonia (3.2%), neutropenic sepsis (2%), death not otherwise specified (1.6%), respiratory failure (1.2%), parotitis (0.4%), pneumonitis (0.4%), pneumothorax (0.4%), pulmonary embolism (0.4%), neutropenic colitis (0.4%), and seizure (0.4%).

Permanent discontinuation of pembrolizumab SC due to an adverse reaction occurred in 16% of patients. Adverse reactions which resulted in permanent discontinuation of pembrolizumab SC in ≥2% of patients included pneumonia (3.2%) and pneumonitis (2.4%). Dosage interruptions of pembrolizumab SC due to an adverse reaction occurred in 45% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia (16%), anemia (8%), thrombocytopenia (8%), pneumonia (4.8%), rash (2.8%), and increased aspartate aminotransferase (2%).

No additional safety signals for pembrolizumab SC were identified, compared with the known safety profile of pembrolizumab IV, other than hypersensitivity and administration-related systemic reactions which occurred in 3.2% (8/251) of patients receiving pembrolizumab SC, including Grade 2 (2.8%). Hypersensitivity and administration-related systemic reactions have been included in the USPI for KEYTRUDA QLEX (pembrolizumab SC), Section 5, Warnings and Precautions.

In conclusion, the safety profile of pembrolizumab SC is comparable to the safety profile of pembrolizumab IV and offers a new route of administration for patients. The safety profile is acceptable in the intended patient populations.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

Study MK-3475A-D77 was a randomized, open-label clinical study designed to evaluate the PK, efficacy, and safety of MK-3475A administered subcutaneously in combination with histology-based platinum doublet chemotherapy versus pembrolizumab IV in combination with histology-based platinum doublet chemotherapy, in patients in need of treatment for first-line metastatic NSCLC.

Eligible patients were randomly assigned in a 2:1 ratio to Arm 1 (MK-3475A [790 mg SC Q6W] + chemotherapy) or Arm 2 (pembrolizumab IV [400 mg IV Q6W] + chemotherapy). The trial had dual primary objectives comparing pembrolizumab PK exposure between formulations, while secondary efficacy endpoints (ORR, PFS, OS, DOR) were included for descriptive analysis without alpha allocation to demonstrate comparable clinical performance and enable bridging to pembrolizumab IV indications.

The ORR was 45% (95% CI: 39, 52) for MK-3475A + chemotherapy versus 42% (95% CI: 33, 51) for pembrolizumab IV + chemotherapy per RECIST 1.1 by BICR, indicating comparable response rates between treatment groups. The median duration of response for MK-3475A + chemotherapy was 9.1 months (95% CI: 6.9, NR) compared to 8.0 months (95% CI: 7.4, NR) for pembrolizumab IV + chemotherapy.

The median PFS was 8.1 months (95% CI: 6.3, 8.3) for MK-3475A + chemotherapy versus 7.8 months (95% CI: 6.2, 9.7) for pembrolizumab IV + chemotherapy, with a hazard ratio of 1.05 (95% CI: 0.78, 1.43), indicating comparable treatment effects.

Due to the short follow-up duration compared to historic NSCLC studies limiting interpretation of the OS endpoint, FDA requested additional OS data from the Applicant during the review. At an updated analysis with a DCO date of June 03, 2025, 49% of patients had experienced OS events; the median OS was 19.4 months (95% CI: 17.2, NR) for MK-3475A + chemotherapy versus 17.7 months (95% CI: 13.9, NR) for pembrolizumab IV + chemotherapy, with a hazard ratio of 0.92 (95% CI: 0.68, 1.25). These results suggest that there is no notable difference in OS for MK-3475A SC compared to pembrolizumab IV.

There were no major statistical issues identified in the review of this application. In summary, the efficacy data from Study MK-3475A-D77 demonstrate that the clinical activity of MK-3475A, with respect to ORR, DOR, PFS, and OS, was generally consistent with pembrolizumab administered by IV infusion in combination with chemotherapy for the first-line treatment of patients with metastatic NSCLC, supporting MK-3475A as a viable subcutaneous alternative.

8.4 **Conclusions and Recommendations**

The FDA's Assessment:

Study MK-3475A-D77 was a randomized (2:1), open-label, multiregional clinical trial comparing the pharmacokinetics, efficacy and safety of pembrolizumab SC to pembrolizumab IV in patients with treatment-naïve metastatic NSCLC in whom there were no EGFR, ALK, or ROS1 genomic tumor aberrations. The trial met the dual primary PK endpoints of Cycle 1 $AUC_{0\text{-}6\ weeks}$ and Cycle 3 (i.e., Steady State) C_{trough} to demonstrate comparable clinical performance and enable bridging of pembrolizumab SC to pembrolizumab IV. The geometric mean ratio (GMR) for Cycle 1 $AUC_{0\text{-}6weeks}$ was 1.14 (96% CI: 1.06, 1.22) and GMR for Cycle 3 C_{trough}, was 1.67 (94% CI: 1.52, 1.84).

Analyses of the secondary efficacy endpoints of ORR and PFS per RECIST v1.1, and OS were all descriptive. Based on descriptive analyses, no differences in ORR, PFS, or OS were observed between patients who received pembrolizumab SC with chemotherapy and pembrolizumab IV with chemotherapy. Safety was an additional secondary endpoint. Local injection site reactions was the only newly identified safety signal for pembrolizumab SC compared to the known safety profile of pembrolizumab IV.

The development approach of pembrolizumab SC is consistent with the FDA Guidance on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", which states the following: "In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form." When being applied to different doses, regimens, or dosage forms, the above FDA Guidance states that "it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of PK data without an additional clinical efficacy trial".

In the current application, PK data, together with descriptive analyses of efficacy endpoints (i.e., ORR, PFS, and OS) from Study MK-3475A-D77 can bridge to establish efficacy results between pembrolizumab SC and pembrolizumab IV for approved adult solid tumor indications for pembrolizumab IV. Modeling and simulation data in pediatric patients (12 years and older and who weigh at least 40 kg) with melanoma, Merkel cell carcinoma, microsatellite instability high, and tumor mutation burden high tumors, support approval of MK-3475A in these indications for pediatric patients 12 years to <17 years old. Modeling and simulation data to predict whether PK data are comparable between pembrolizumab SC 790 mg Q6W and pembrolizumab SC 395 mg Q3W, and observed data for the 395 mg SC Q3W dosing regimen in patients with melanoma in Study MK-3475A-C18, were used to support approval of pembrolizumab SC 395 Q3W. The well-established efficacy and safety profile of pembrolizumab IV also supports approval of pembrolizumab SC for the indications not studied in Study MK-3475A-D77.

The submitted evidence for pembrolizumab SC (pembrolizumab 395 mg/ berahyaluronidase alfa-pmph 4,800 units Q3W and pembrolizumab 790 mg/ berahyaluronidase alfa-pmph 9600

units Q6W injection) provides substantial evidence of effectiveness and meets the statutory evidentiary standard for approval. Based on a favorable risk-benefit assessment, the review team recommends traditional approval of pembrolizumab SC for the proposed indications in adult and pediatric (12 years and older) patients, except for tumor mutational burden-high cancers; pembrolizumab IV is approved for tumor mutational burden-high cancers under accelerated approval and pembrolizumab SC should also be approved under accelerated approval for this indication.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication *(enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response)*:

   Pembrolizumab SC is indicated for adult and pediatric (12 years and older) solid tumor indications for pembrolizumab IV approved at the time of the BLA submission.

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment: FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indications.

10 Pediatrics

The Applicant's Position:

In line with the framework proposed by the FDA and EMA Reflection Paper [17], the Sponsor is proposing to apply an extrapolation approach to support the use of MK-3475A in pediatric patients 12 years and older based on: 1) similarity of disease, 2) expected similarity of PK to adults, 3) expected similarity for efficacy and safety between adult and pediatric patients with melanoma, MCC, and MSI-H and TMB-H tumors. This extrapolation approach has been accepted by the FDA in support of the approval of the use of pembrolizumab IV in pediatrics across several indications including melanoma, MCC, and MSI-H and TMB-H tumors.

A model-based PK analysis supports SC dosing regimens of pembrolizumab as MK-3475A in pediatric patients 12 years and older who weigh greater than 40 kg, while targeting comparable PK exposures to adults. For this purpose, simulations of PK profiles were performed at both 790 mg SC Q6W and 395 mg SC Q3W in pediatric patients 12 years and older who weigh greater than 40 kg, which showed exposures to be comparable to those for the lowest body weight quartile in adults.

The active ingredient in MK-3475A is identical to the approved pembrolizumab IV product; as such, based on MK-3475A-D77 demonstration of noninferiority of the systemic drug exposure after Q6W SC administration as characterized by Cycle 1 AUC and steady state (Cycle 3) C_{trough} would provide evidence of systemic exposures necessary to provide efficacy similar to pembrolizumab IV. A lower C_{max} throughout treatment duration was shown after SC administration compared with IV administration and is expected to produce a similar systemic safety profile to that for the currently approved pediatric solid tumor indications for pembrolizumab IV.

In summary, the dosing regimens of 790 mg SC Q6W and 395 mg SC Q3W as MK-3475A are expected to provide comparable pembrolizumab exposures between pediatric patients 12 years and older who weigh greater than 40 kg and adult patients and thereby similar efficacy and safety in pediatric patients 12 years and older to pembrolizumab IV for adjuvant melanoma, recurrent locally advanced or metastatic MCC, and unresectable or metastatic MSI-H and TMB-H tumors.

The FDA's Assessment: Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the Pediatric Research Equity Act (PREA) to create section 505B(a)(1)(B), which requires that original marketing applications 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. 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 which are subject to the requirements of section 505B(a)(1)(B) are required to include reports of

molecularly targeted pediatric investigations, unless such investigations are waived or deferred.

The agreed iPSP for this product, which aligned with prior discussions between FDA and the Applicant during a Type D meeting on March 15, 2024 under IND 161465, included a plan to seek a partial waiver of the requirement for a molecularly targeted pediatric cancer investigation in patients less than 12 years of age due to rarity of patients in this age group, rendering an investigation infeasible in this age group. The agreed iPSP also included a plan to request a deferral of reports of a molecularly targeted pediatric cancer investigation in patients 12 years of age and older.

In this BLA, the Applicant requested a partial waiver of the requirements to conduct a molecularly targeted pediatric cancer investigation in pediatric patients less than 12 years of age in alignment with the agreed iPSP and submitted the information needed to support dosing in patients 12 years of age and older with melanoma, Merkel cell carcinoma, and microsatellite instability high and tumor mutation burden high solid tumors. At the July 30, 2025 meeting of the OCE subcommittee of the Pediatric Review Committee, the Committee determined that a partial waiver in patients less than 12 years of age was warranted and deferral of the molecularly targeted pediatric cancer investigation in patients 12 years of age and older was not needed.

The review division agrees with granting a partial waiver of the requirement for a molecularly targeted pediatric cancer investigation in pediatric patients less than 12 years of age, as outlined in the agreed iPSP for MK-3475A.

11 Labeling Recommendations

The Applicant's Position: This is an original application for a fixed-dose combination of pembrolizumab and berahyaluronidase alfa. The Indications and Usage and Contraindications sections of the proposed label are similar to the current KEYTRUDA USPI. All other sections contain partially/completely new information. Proposed labeling is provided separately in Module 1.14.1.

The FDA's Assessment: The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

Table 46: FDA – Labeling Key Changes

Section	FDA's Proposed Labeling
1 INDICATIONS AND USAGE	FDA agrees with the Applicant's proposal. The text is largely consistent with the approved intravenous pembrolizumab labeling. One indication for pembrolizumab IV for patients with resectable head and neck squamous cell carcinoma (HNSCC) was approved after the current original BLA was submitted. This indication is not included in the current label for KEYTRUDA QLEX (b) (4)
2 DOSAGE AND ADMINISTRATION	FDA moved important administration instructions to the beginning of this section and added the duration of injection administration time for each strength of KEYTRUDA QLEX.
5 WARNINGS AND PRECAUTIONS	5.2 FDA revised (b) (4) to "hypersensitivity and administration-related reactions" to better characterize the adverse reactions related to this subcutaneous product.
6 ADVERSE REACTIONS	FDA added the most common adverse reactions for intravenous pembrolizumab given as a single agent or in combination with other antitumor medicines to provide a complete presentation of the known safety of pembrolizumab. FDA revised the description of Study MK-3475A-D77 to present the most important adverse reaction data completely and succinctly.
8 USE IN SPECIFIC POPULATIONS	8.1: FDA provided details from the rabbit pregnancy study of berahyaluronidase alfa. 8.4: FDA specified the indications that are supported by

	safety and efficacy data for the use of KEYTRUDA QLEX in pediatric patients. 8.5: FDA provided the exposure of patients 65 years and older and 75 years and older to KEYTRUDA QLEX.
12 CLINICAL PHARMACOLOGY	12.3: FDA stated that steady state is similar between intravenous pembrolizumab and subcutaneous KEYTRUDA QLEX. 12.6 Text was revised for consistency with the *Guidance for Industry: Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling – Content and Format.*
13 NONCLINICAL TOXICOLOGY	FDA provided details from the rat fertility and early embryonic development study.
14 CLINICAL STUDIES	FDA revised the efficacy description of NSCLC (Study MK-3475A-D77) for clarity and brevity. FDA added clarifying text to explain the inclusion of the efficacy studies of intravenous pembrolizumab in this labeling.
Medication Guide	The Medication Guide was reviewed and revised by the Patient Labeling Team, Office of Prescription Drug Promotion and the Division of Medication Error Prevention and Analysis.

The FDA's Assessment: The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table above summarizes key changes.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment: The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of pembrolizumab and berahyaluronidase alfa-pmph for the indicated populations. Recommendations for the safe and effective use of pembrolizumab SC are made in labeling and FDA-approved patient labeling (Medication Guide). There are no additional risk management strategies required beyond the recommended labeling. Although pembrolizumab SC can cause severe/serious toxicity, it will be prescribed by oncologists who, by training and experience, understand how to monitor and manage such toxicities.

13 Postmarketing Requirements and Commitment

The FDA's Assessment: Pembrolizumab SC will be subject to the accelerated approval postmarketing requirement (PMR) that was issued for pembrolizumab IV under BLA 125514 for the indication for tumor mutational burden-high (TMB-H) cancers, as this PMR has not been fulfilled and the indication currently remains under accelerated approval. The PMR uses verbatim language from the existing PMR for pembrolizumab IV. The final study reports referenced in this PMR will be used to support the conversion of accelerated approval to traditional approval for pembrolizumab SC for this indication.

The following Accelerated Approval PMR will be issued for this application upon approval:

PMR – Accelerated Approval:

Submit the final report and datasets from clinical trials evaluating overall response rate and duration of response, to verify and describe the clinical benefit of pembrolizumab in adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors (as determined by an FDA-approved test) that have progressed following prior treatment and who have no satisfactory alternative treatment options. A sufficient number of patients and representation of tumor types (other than lung cancers, MSI-H or dMMR cancers, or melanoma; and including CNS tumors that were determined to be TMB-H based on testing of tissue obtained prior to initiation of temozolomide chemotherapy), and with cancers having a TMB of 10 to <13 mut/Mb, will be evaluated to characterize response and duration of response. A minimum of 20 pediatric patients will be studied. Overall response rate and duration of response will be assessed by independent central review for patients with cancers having a TMB of ≥10 mut/Mb, ≥10 mut/Mb to <13 mut/Mb, and ≥13 mut/Mb. All responding patients will be followed for at least 12 months from the onset of response.

Final Report Submission: 12/2025

Table 47: FDA – PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes X No. Black and African American patients were underrepresented in Study MK-3475A-D77. However, there is extensive experience with pembrolizumab IV in U.S. patients and in diverse patient populations. No clinically significant differences in the pharmacokinetics of pembrolizumab

		have been observed based on race or age. Therefore, FDA is not requesting a Diversity PMC. See Section 8.1.2 of the Assessment Aid.
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes X No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes X No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X _____

16 Division Director (OB)

X

17 Division Director (Clinical)

X _____

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1 References

The Applicant's References:

[1]	Kang SP, Gergich K, Lubiniecki GM, de Alwis DP, Chen C, Tice MAB, et al. Pembrolizumab KEYNOTE-001: an adaptive study leading to accelerated approval for two indications and a companion diagnostic. Ann Oncol. 2017;28(6):1388-98.	[08NDMN]
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[3]	Novello S, Kowalski DM, Luft A, Gumus M, Vicente D, Mazieres J, et al. Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 study. J Clin Oncol. In press 2023.	[087NW3]
[4]	Long GV, Carlino MS, McNeil C, Ribas A, Gaudy-Marqueste C, Schachter J, et al. Pembrolizumab versus ipilimumab for advanced melanoma: 10-year follow-up of the phase III KEYNOTE-006 study. Ann Oncol. 2024;35(12):1191-9.	[08R2XL]
[5]	Pivot X, Gligorov J, Muller V, Barrett-Lee P, Verma S, Knoop A, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol. 2013 Sep;14:962-70.	[05D4TZ]
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[7]	O'Shaughnessy J, Sousa S, Cruz J, Fallowfield L, Auvinen P, Pulido C, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): a randomised, open-label phase II study. Eur J Cancer. 2021;152:223-32.	[085PXP]

[8]	Aguiar-Ibanez R, Fotheringham I, Mittal L, Sillah A, Pathak S. Differences between intravenous and subcutaneous modes of administration in oncology from the patient, healthcare provider, and healthcare system perspectives: a systematic review. Adv Ther. 2024;41:4396-417.	[08R2PF]
[9]	Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229-63.	[08LCQN]
[10]	Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. In press 2024.	[08KHPG]
[11]	Surveillance, Epidemiology, and End Results Program [Internet]. Bethesda (MD): National Cancer Institute (NCI). Cancer stat facts: lung and bronchus cancer; [cited 2024 Apr 24]; [about 26 screens]. Available from: https://seer.cancer.gov/statfacts/html/lungb.html.	[08KPSP]
[12]	Elassaiss-Schaap J, Rossenu S, Lindauer A, Kang SP, de Greef R, Sachs JR, et al. Using model-based "learn and confirm" to Reveal the pharmacokinetics-pharmacodynamics relationship of pembrolizumab in the KEYNOTE-001 trial. CPT Pharmacometrics Syst Pharmacol. 2017;6:21-8.	[0534YZ]
[13]	Miettinen O and Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00VMQY]
[14]	Maurer W, Glimm E, Bretz F. Multiple and repeated testing of primary, coprimary, and secondary hypotheses. Stat Biopharm Res. 2011;3(2):336-52.	[045MYM]
[15]	Gadgeel S, Rodriguez-Abreu D, Speranza G, Esteban E, Felip E, Domine M, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol. In press 2020.	[05GQFS]
[16]	Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazieres J, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. J Thorac Oncol. 2020 Oct;15(10):1657-69.	[05MTS0]
[17]	European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics. London (England): European Medicines Agency (EMA); 2018. 20 p. EMA/189724/2018.	[06DZ0B]

The FDA's References:

Creasy D, Bube A, de Rijk E, Kandori H, Kuwahara M, Masson R, Nolte T, Reams R, Regan K, Rehm S, Rogerson P, Whitney K. Proliferative and nonproliferative lesions of the rat and mouse male reproductive system. Toxicol Pathol. 2012; 40(6 Suppl):40S-121S.

(b) (4)

19.2 Financial Disclosure

The Applicant's Position:

Disclosure of financial interests and/or arrangements, including statements of due diligence for the investigators who conducted the MK-3475A-D77 study, are described in FDA forms 3454, 3455, and Module 1.3.4.

Covered Clinical Study (Name and/or Number):* MK-3475A-D77

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2441		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 1 Sponsor of covered study: MSD		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒ X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒ X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ X (Since all investigators have provided a financial disclosure form, no Note to Files have been generated for Unable to Obtain Investigators)

*The table above should be filled by the applicant and confirmed/edited by the FDA.

The FDA's Assessment: FDA agrees.

19.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position: All nonclinical pharmacology/toxicology information is included in Section 5 above.

The FDA's Assessment:

FDA agrees that there is no additional information to add here. See Section 5 for the FDA nonclinical review.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical analysis

The Office of Clinical Pharmacology review team has assessed the adequacy and acceptability of the following bioanalytical methods used in clinical studies.

Pembrolizumab
For studies MK-3475A-C18 and MK-3475A-D77, serum/plasma Pembrolizumab concentrations were determined with following method.

Table 48: FDA – Summary of Bioanalytical Method Validation and Performance for Pembrolizumab PK Characterization

Bioanalytical method summary	All serum pembrolizumab samples from studies KEYNOTE-555, KEYNOTE-A86, MK-3475A-C18, and MK-3475A-D77 were analyzed using a 3rd generation assay (b) (4) with MK-3475A-D77 China samples processed (b) (4) This assay, in use since August 2014, has supported multiple pembrolizumab IV program submissions and the current submission's clinical studies.

	The assay was cross validated between (b) (4) laboratories, with an LLOQ of 25 ng/mL at both sites.	
Method description	An ECL immunoassay was developed and validated per regulatory guidance to measure pembrolizumab serum concentrations in clinical studies. The assay used: • **Design**: Direct binding format with biotinylated recombinant human PD-1-Fc as capture reagent and SULFO-TAG™-labeled mouse anti-human IgG4 mAb for detection • **Process**: Samples undergo 1:10 minimum required dilution, followed by incubation, washing, and ECL measurement on MSD platform using a weighted 5-parameter logistic model for concentration determination • **Evolution**: Third-generation method implemented (b) (4) (b) (4) improved automation and throughput while increasing the lower limit of quantification (LLOQ) from 10 to 25 ng/mL to accommodate diverse tumor types. Matrix: Human serum Platform: MSD ECL	
Materials used for calibration curve & concentration	Human serum using biotinylated pembrolizumab as a capture reagent and SULFO-TAG™ labeled pembrolizumab as a detection reagent. Standard: 10.0 (anchor), 25.0, 50.0, 100, 200, 400, 800, 1250 (anchor) ng/mL	
Validated assay range	**25-800 ng/mL** in 100% serum.	
Material used for QCs & concentration	Human serum using biotinylated pembrolizumab as a capture reagent and SULFO-TAG™ labeled pembrolizumab as a detection reagent. Original QCs: 10.0 ng/mL (LLOQ), 30.0 ng/mL (LQC), 100 ng/mL, (MQC) 600 ng/mL, (HQC) 800 ng/mL (ULOQ) Updated QCs when changed LLOQ to 25 ng/mL, amendment 1: 25.0 (LLOQ), 70.0 (LQC), 150 (MQC), 600 (HQC), and 800 ng/mL (ULOQ)	
Minimum required dilutions (MRDs)	1:10	
Regression model & weighting	The pembrolizumab concentration in test samples is determined by interpolation, using a weighted 5-parameter logistic model algorithm to fit a standard curve.	
Validation parameters	**Method validation summary**	
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	6
	Cumulative accuracy (%bias) from LLOQ to ULOQ	(b) (4) % Bias: 1.31 to 1.95 (b) (4) % Bias: -5.7 to 14

	Cumulative precision (%CV) from LLOQ to ULOQ	(b) (4) % CV ≤ 3.58 (b) (4) %CV ≤ 4.6
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	(b) (4) Intra Assay % Bias: -14.4% to 4.07 Inter Assay % Bias: -9.19% to 2.50
Inter-batch %CV		(b) (4) Inter Assay %CV ≤ 8.76 Intra Assay %CV ≤ 4.48
Selectivity & matrix effect	(b) (4) Selectivity demonstrated for unspiked and spiked serum samples for the following matrix types: 10 ng/mL in normal healthy and non-small cell lung cancer 25 ng/mL in melanoma, gastric cancer, small cell lung cancer 10 ng/mL in hemolytic and lipemic samples	
Interference & specificity	100 ng/mL of PD-L1 and PD-L2, and 500 µg/mL of human IgG4 had no effect on ULOQ and LLOQ quantitation. 20 ng/mL of MK-5180 had no effect on the quantitation of pembrolizumab.	
Dilution linearity & hook effect	No apparent "hook effect" was observed at concentrations up to 1,000,000 ng/mL	
Bench-top/process stability	(b) (4) Freeze/Thaw Stability: up to 8 freeze/thaw cycles QC Sample Stability at Room Temperature: up to 26 hours QC Sample Stability at Refrigerated Condition (2-8 °C): up to 26 hours	
Freeze-Thaw stability	Up to 8 freeze/thaw cycles	
Long-term storage	QC Sample Stability at -20 °C: up to 6 months QC Sample Stability at -70 °C: up to 5 years	
Method performance in study MK-3475A-D77		
Run Acceptance Rate % (pass/total)	(b) (4) 92.2 (165/179) (b) (4) 100% (31/31)	
Std Curve Performance	(b) (4) Bias (%): -0.709 to 0.830 CV (%):1.88 to 2.59 (b) (4) Bias (%): -2.8 to 2.0 CV (%): 0.9 to 1.3	
QC Performance	(b) (4) Bias (%): 0.599 to 2.17 CV (%): 6.77 to 7.52 (b) (4) Bias (%): -5.8 to -1.3 CV(%): 3.1 to 3.3	

ISR Passing Rate	(b) (4) 98.4% (b) (4) 100%

Source: Summary of Biopharmaceutics, Table 2.7.1, page 17

Table 49: FDA – Cross-Validation Summary Per the Summary of Biopharmaceutics

Cross validation	Details
Cross-Lab (b) (4) Validation Test on Spiked QCs	(b) (4) demonstrated cross-lab reproducibility with a set of high, med and low spiked QC samples prepared (b) (4) (All QCs were within 20% from nominal concentration)
Cross-Lab (b) (4) Validation Test on Pooled Study Samples	Demonstrated cross-lab reproducibility on the same set of 30 pooled study samples (29 out of 30, 97% of tested samples were within 30% relative bias)
Inter Laboratory Method Performance Evaluation (b) (4)	Demonstrated cross-lab reproducibility on 30 spiked QC samples

Source: Summary of Biopharmaceutics, Table 2.7.1, page 17

MK-5180/Berahyaluronidase

For studies MK-3475A-C18, and MK-3475A-D77, serum/plasma berayaluronidase alfa concentrations were determined with following method:

Table 50: FDA – Summary of Bioanalytical Method Validation and Performance for Berayaluronidase PK Characterization

Bioanalytical method summary	An ECL immunoassay was developed and validated per regulatory guidance to measure MK-5180 concentrations in human plasma for clinical studies.
Method description	**Assay Design:** - Direct binding format using recombinant anti-MK-5180 mAb as capture reagent and biotinylated rabbit anti-MK-5180 pAb as detection reagent. - Streptavidin SULFO-TAG™ serves as secondary detection reagent. **Methodology:** - Samples analyzed at 1:4 minimum required dilution on High Bind MSD plates. - ECL response measured via MSD platform.
Materials used for calibration curve & concentration	- Anti-MK-5180 mAb as capture reagent and a biotinylated rabbit anti-MK- 5180 pAb as detection reagent with streptavidin labeled with SULFO-TAG™ as the secondary detection reagent. Standards: 0.078125 (anchor), 0.15625 (anchor), 0.3125, 0.625, 1.25, 2.50, 5.00, 10.0, 20.0, 40.0, 80.0, and 160 ng/mL
Validated assay range	0.3125 to 160 ng/mL in human plasma

Material used for QCs & concentration	Anti-MK-5180 mAb as capture reagent and a biotinylated rabbit anti-MK- 5180 pAb as detection reagent with streptavidin labeled with SULFO-TAG™ as the secondary detection reagent. QCs: 0.3125 (LLOQ), 0.625 (backup LLOQ), 0.925 (LQC), 15.0 (MQC), 120 (HQC), and 160 ng/mL (ULOQ)	
Minimum required dilutions (MRDs)	1:4	
Source & lot of reagents (LBA)	Not available	
Regression model & weighting	Concentrations determined by interpolating against a standard curve using weighted 4-parameter logistic model.	
Validation parameters	**Method validation summary**	
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	10
	Cumulative accuracy (%bias) from LLOQ to ULOQ	% Bias: -1.49 to 4.93
	Cumulative precision (%CV) from LLOQ to ULOQ	%CV ≤ 8.91
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	Intra Assay % Bias: between -13.9 to 12.2 Inter Assay % Bias: between -7.83 to 8.06
	Inter-batch %CV	Intra Assay %CV ≤ 20.5 Inter Assay %CV ≤ 9.75
Selectivity & matrix effect	Demonstrated unspiked, the LLOQ (0.3125 ng/mL) and high (120 ng/mL) QC levels in human plasma for healthy subjects and advanced solid tumor individual donors Demonstrated unspiked, the LLOQ (0.3125 ng/mL) and high (120 ng/mL) QC levels in human plasma for hemolysis and lipemia	
Interference & specificity	No interference was detected in presence of (up to) 300 µg/mL of pembrolizumab 50 µg/mL of human hyaluronidase (HYAL1)	
Dilution linearity & hook effect	No apparent hook effect was observed at concentrations up to 100,000 ng/mL.	
Bench-top/process stability	Up to 24 hours	
Freeze-Thaw stability	Up to 5 freeze/thaw cycles	
Long-term storage	QC Sample Stability at -25 °C Up to 194 days QC Sample Stability at -80 °C Up to 194 days	
Validation Parameters	**MK-5180 Assay Validation Performance with MK-3475A**	
Standard Curve Accuracy	% Bias -3.19 to 3.49	
Standard Curve Precision	%CV ≤ 6.09	

QC Accuracy	Intra Assay % Bias -9.35 to 2.89
	Inter Assay % Bias -12.1 to 3.01
QC Precision	Intra Assay %CV ≤ 7.93
	Inter Assay %CV ≤ 11.8
Freeze/Thaw Stability	Up to 5 freeze/thaw cycles
QC Sample Stability at Room Temperature	Up to 25 hours
QC Sample Stability at -25 °C	Up to 35 days
QC Sample Stability at -80 °C	Up to 35 days

Source: Applicant's Summary of Biopharmaceutics, Table 2.7.1, page 19

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment:

Pembrolizumab marketed as KEYTRUDA®, is an intravenous (IV) immunotherapy globally approved across a number of cancer indications at doses of 200 mg Q3W and 400 mg Q6W. The key pharmacometrics findings are summarized below:

- The absorption PK of pembrolizumab following Subcutaneous (SC) administration of MK-3475A was well characterized by a first-order process.
- The final combined SC and IV PK model confirmed that the dose of pembrolizumab 790 mgQ6W SC administered as MK-3475A leads to generally consistent exposures as the approved dose of pembrolizumab 400 mg Q6W IV.
- PK exposures for 395 mg Q3W SC as MK-3475A were also consistent with those at the approved 200 mg Q3W IV dosing regimen.
- The dosing regimens of 790 mg SC Q6W and 395 mg SC Q3W as MK-3475A are expected to provide comparable pembrolizumab exposures between pediatric patients (12 years and older who weigh greater than 40 kg) and adult patients.

The model risk for the population PK analysis is as follows:

Table 51: FDA – Anticipated Model Risk for Population PK Analysis

Elements	Details
Question of Interest	• The proposed SC administration for adult and pediatric patients (12 years and older who weigh greater than 40 kg) across solid tumor indications
Context of Use	• Rationale: Exposure-matching between approved IV administration and SC administration by key PK endpoints (AUC at the first dose and Ctrough at steady state) and absorption agnostic to solid tumor types • Population PK modeling and simulation to derive exposures
Model Influence	• Adult: Low: • Pediatrics (12 to <17 years old): medium Although there is no SC data in pediatrics (12 to <17 years old) , the assumption that the bioavailability of pediatrics (12 to <17 years old) is similar to that of adults is reasonable.
Decision Consequence	• Adult: low • Pediatrics (12 to <17 years old): low In adults, the efficacy and safety of the SC dosages are supported by clinical data that were similar to the approved recommended IV dosages. In pediatrics 12 years and older, uncertainty in SC absorption (without clinical data) is not likely to result in an elevated risk for efficacy reduction, toxicity, or immunogenicity, given the following reasons: The safety margin has been established by IV administration, which is much higher than exposures of administrated SC dosages. Flat E-R relationship for efficacy and safety across wide dose/exposure range.
Model Risk	• Adults: low • Pediatrics (12 to <17 years old): medium

Source: Reviewer's analysis

19.4.2.2. PPK Assessment Summary

The Applicant's Position: Key information is summarized in the following table.

General Information	
Objectives of PPK Analysis	• Characterize PK and estimate PK parameters of the absorption phase for pembrolizumab following SC administration of MK-3475A • Evaluate baseline patient characteristics and injection site potentially influencing the SC absorption of pembrolizumab • Derive model-based individual exposure estimates of $AUC_{0\text{-}6wks}$ (first dose) and steady-state (Cycle 3) C_{trough} for participants in MK-3475A-D77, which are the dual primary endpoints in the Phase 3 study.

		• Derive model-based individual exposure estimates of Cycle 1 C_{trough}, Cycle 1 C_{max}, steady-state (Cycle 3) $AUC_{0\text{-}6wks}$ and steady-state (Cycle 3) C_{max} for participants in MK-3475A-D77, which are secondary endpoints in the Phase 3 study • Derive model-based individual exposure estimates of Cycle 1 and steady state (Cycle 6) C_{trough} for participants in the IV arm in MK-3475A-D77 at dose of 200 mg Q3W IV, for descriptive comparison with Cycle 1 and steady state (Cycle 3) C_{trough} in the SC arm at dose of 790 mg Q6W, which are additional secondary endpoints in the Phase 3 study. • Derive model-based individual exposure estimates for participants in MK-3475A-C18 and in the SC arm in MK-3475A-D77 at dose of 395 mg Q3W SC to support confirmation of the Q3W SC doing regimen of pembrolizumab administered as MK-3475A
Study Included		Pivotal Phase 3 Study MK-3475A-D77 Supportive Phase 1 Study MK-3475A-C18 (Arms 1, 2, and 3)
Dose(s) Included		• MK-3475A 790 mg Q6W SC • MK-3475A 395 mg Q3W SC • Pembrolizumab 400 mg Q6W IV • Pembrolizumab 200 mg Q3W IV
Population Included		Per Protocol Population
Population Characteristics	General	Age (years): 65.0 (37.0-87.0, 52.9% subj ≥65 yr) Weight (kg): 69.3 (37.0-144) 330 (70.4%) male;139 (29.6%) female 295 (62.9%) in White; 14 (3.0%) in Black or African American; 129 (27.5%) in Asian; 7 (1.5%) in American Indian or Alaska Native; 17 (3.6%) in Multiple; 7 (1.5%) in Missing
	Organ Impairment	Not applicable for SC absorption. Systemic PK has been thoroughly investigated in pembrolizumab IV program.
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ		Number of participants: 473 Number of PK samples: 6686 Pre-dose BLQ: 442 (6.61%)/Post-dose BLQ: 3 (0.04%)
Sampling Schedule	Rich Sampling	Post-dose timepoints per the planned PK sample collections over a 42-day dosing cycle for Cycle 1 (Weeks 1 to 6) and Cycle 3 (Weeks 13 to 18) • MK-3475A-D77 study: - SC arm: Days 1 (predose), 2, 3, 4, 5, 6, 7, 10, 15, 29, and 42 - IV arm: Days 1(predose and end-of-infusion), 15, 29, and 42 • MK-3475A-C18 study:

		- SC arm: Days 1 (predose), 2, 3, 4, 5, 6, 8, 10, 15, 22, 29, 36, and 42 - IV arm (Arms 1 and 2): Day 1(predose and end-of-infusion), Days 3, 5, 15, 29, and 42 - IV arm (Arm 3): Day 1(predose and end-of-infusion), Days 3 and 42
	In ITT Population	Not applicable
Covariates Evaluated	Static	Age, baseline body weight, sex, tumor type, race, and injection site
	Time-varying	Not applicable

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	Pumas (version 2.5.1; Pumas-AI, Inc., DE, USA)	Acceptable
Model Structure	Combined SC and IV PK model based on a two-compartment structure with a linear and time-dependent clearance, zero-order infusion into the central compartment after IV administration and first-order absorption from the extravascular compartment after SC administration	Acceptable
Model Parameter Estimates	Table	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Absorption parameters bioavailability (F) and absorption rate constant (Ka) were estimated with high precision (relative standard error <4%). Typical value for bioavailability was estimated to be 60% with an inter-individual variability (IIV) of 14%. Individual estimates of bioavailability ranged from 17% to 80%. Typical value for absorption rate constant was estimated to be 0.32/day with an IIV of 47%. Individual estimates of absorption rate constant ranged from 0.30/day to 0.34/day. The model was stable enough to obtain the covariance step. The η-shrinkage was acceptable for both bioavailability and absorption rate constant (32.9% and 23.3%, respectively). The ε-shrinkage was also acceptable (10.6%).	Acceptable

	Non-parametric bootstrap analysis of the final model was performed and . only successfully converged runs from the 1000 bootstrap dataset were used to obtain the medians and 95% CI of the fixed-effects and random-effect parameters (100% of bootstrap runs were successful). The median values for all PK parameters were within 15% of those obtained by the final model, indicating good reliability. The 95% CIs were narrow, indicating that the performance and stability of the final model were acceptable.	
BLQ for Parameter Accuracy	Serum concentrations below the limit of quantitation (BLQ) were excluded from the analysis as described in MAP, which is deemed acceptable given the number of BLQ samples post-dose was small (0.04% of total observations).	Acceptable
GOF, VPC	(GOF) and (VPC)	Time dependent CL appeared to differ in this patient population, but is unlikely to impact conclusions. Refer to 19.4.1.3 for details.
Significant Covariates and Clinical Relevance	Not applicable	
Analysis Based on Simulation (optional)	(Adult SC vs IV, AUC0-6wks), (Adult SC vs IV, Ctrough), (Adult SC vs IV Cmax), (Adult SC vs IV Ctrough), (Pediatrics vs Adults)	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	Proposed labeling is provided separately in Module 1.14.1.	Acceptable

Table 52: Applicant – Final Parameter Estimates of the Combined SC and IV Population PK Model and Bootstrap Results

Parameter	Estimate	%RSE[a]	%CV[b]	%Shrinkage	Bootstrap	Bootstrap 95% CI	
Estimated parameters using MK-3475A-D77 and MK-3475A-C18 data							
Ka (day-1)	0.322	3.25	46.9%	23.3%	0.322	0.302	0.343
F	0.599	1.65	14.2%	32.9%	0.599	0.580	0.619
Corr (ω2Ka, ω2F)	0.089 (R = 33.7)	28.49	-	-	0.089	0.041	0.135
Sex effect on Ka	-0.192	25.87	-	-	-0.192	-0.280	-0.089
Residual error							
IV	0.174	4.21	-	10.6%	0.174	0.160	0.188
SC	0.192	3.09	-		0.191	0.180	0.203
Fixed parameters from reference IV model							
CL (L/day)	0.28	-	30.6%	21.3%	-	-	
Q (L/day)	0.89	-			-	-	
Vc (L)	3.53	-	19.1%	38.5%	-	-	
Vp (L)	2.75	-			-	-	
Maximum effect of time on CL	-0.218	-	79.4%	24.4%	-	-	
TI50 (days)	65.5	-	-	-	-	-	
Hill coefficient	2.99	-	-	-	-	-	
a for CL and Q (allometric scaling factor)	0.534	-	-	-	-	-	
a for Vc and Vp (allometric scaling factor)	0.514	-	-	-	-	-	
Albumin effect on CL	-0.849	-	-	-	-	-	
eGFR effect on CL	0.123	-	-	-	-	-	
Sex effect on CL	-0.162	-	-	-	-	-	

Baseline ECOG effect on CL	-0.0697	-	-	-	-	-
Baseline tumor size effect on CL	0.0933	-	-	-	-	-
Parameter	**Estimate**	**%RSEa**	**%CVb**	**%Shrinkage**	**Bootstrap**	**Bootstrap 95% CI**
Bilirubin effect on CL	**-0.0488**	-	-	-	-	-
Albumin effect on Vc	**-0.233**	-	-	-	-	-
Sex effect on Vc	**-0.131**	-	-	-	-	-
Tumor type effect (NSCLC vs other) on Vc	**-0.059**	-	-	-	-	-

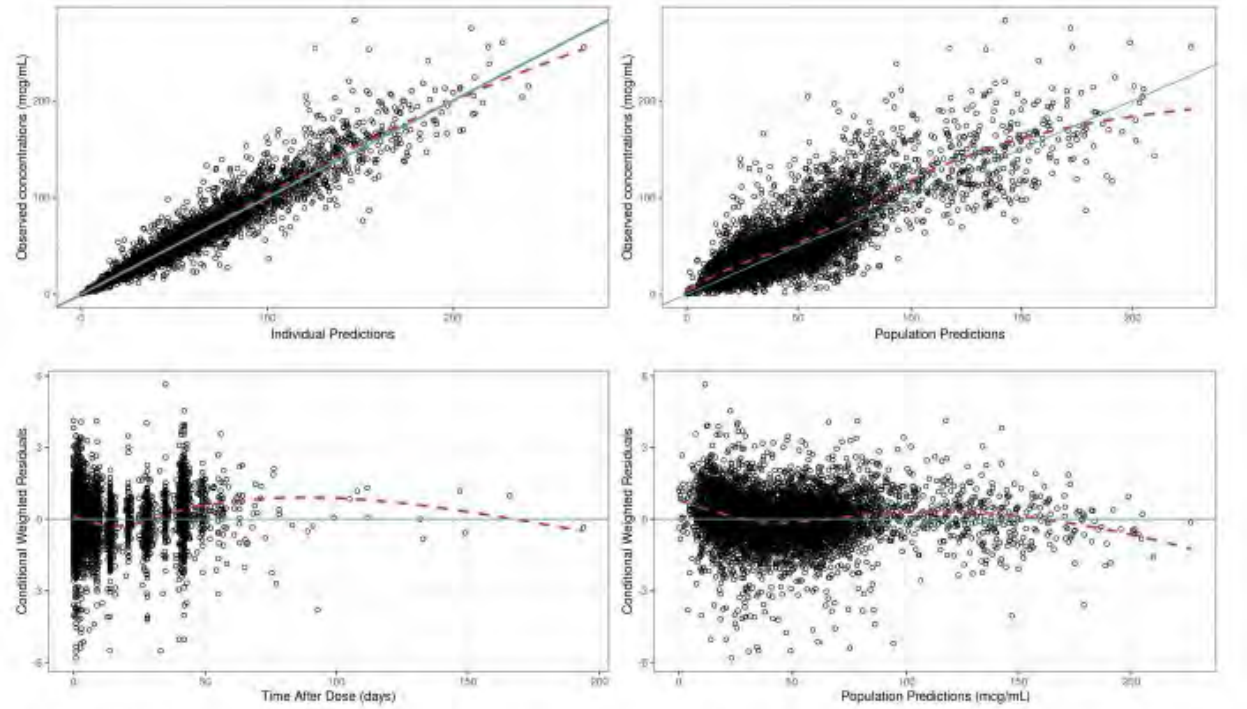
[a]: The RSE of parameter estimate is calculated as 100 ×(SE / typical value); the RSE of correlation between random effects is calculated as 100 ×(SE / variance estimate).

[b]: Estimates for exponential random effects are presented in % CV and, based on the estimated variances, are calculated as √(exp [variance] - 1) ×100, if variance ≥0.15; otherwise, √(variance) ×100. Estimates for additive random effects (Imax) are calculated as √(variance) /|typical value of fixed effect| ×100. The % CV for bioavailability was calculated as √(variance) ×F1 ×(1-F1) ×100 since the random effect was additive in the logit scale.

Abbreviation: CV, coefficient of variation of between-subject distributions of parameters; eGFR, estimated glomerular filtration rate; NSCLC, non-small cell lung cancer; RSE, relative standard error; Ka: absorption rate constant; F: bioavailability; CL: clearance; Vc: volume of distribution in the central compartment; Q: intercompartmental clearance; Vp: volume of distribution of the peripheral compartment; TI50, time at which 50% of the maximum effect on clearance has been achieved

*Source: **Table 6** in report 08QL4V page 26 (link).*

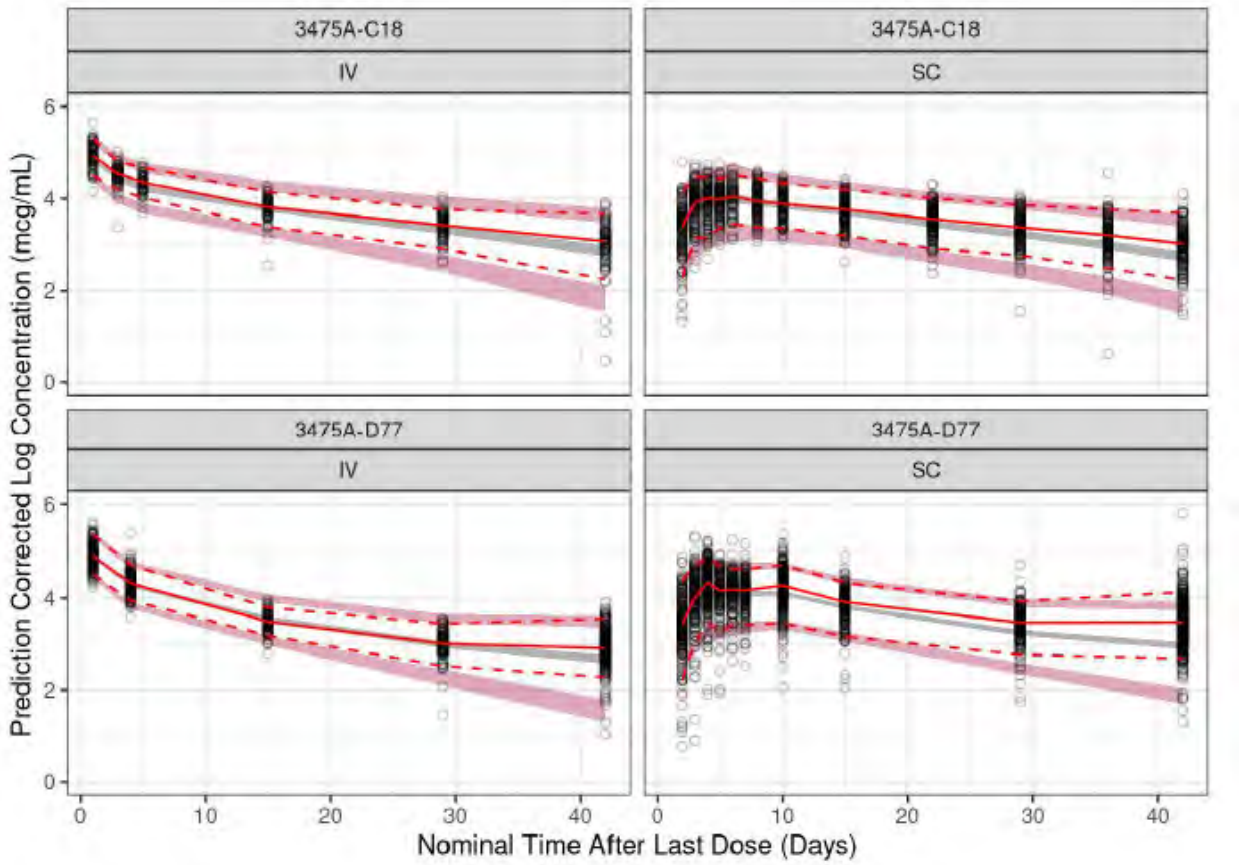
Figure 21: Applicant – Goodness-of-Fit Diagnostic Plots for the Final Combined SC and IV Population PK Model



Open circles represent pembrolizumab observed and predicted concentrations; green line represents the identity line; dashed red line represents the loess regression line.

*Source: **Figure 2** in report 08QL4V page 28 (link).*

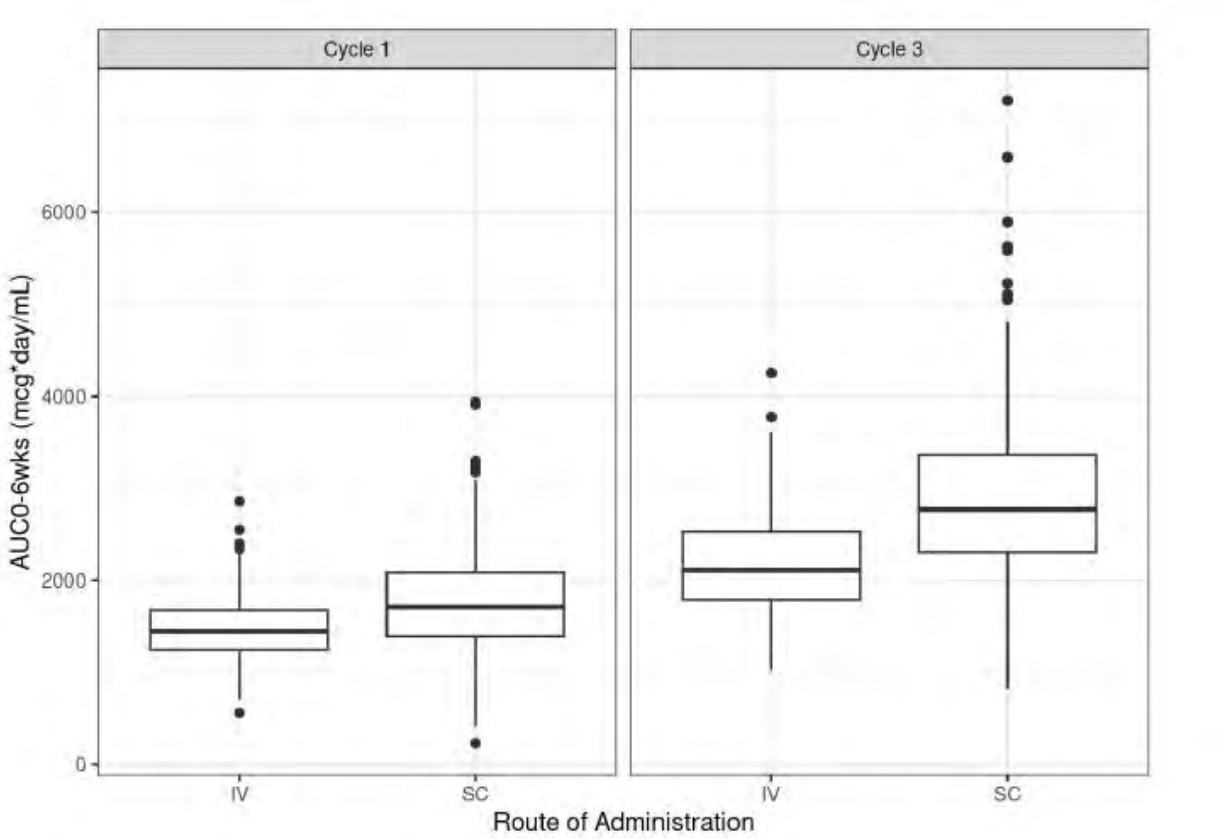
Figure 22: Applicant – Prediction-Corrected VPC by Study and Route



Note: The black circles are the prediction-corrected observed concentrations. The red lines are the 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations. The colored bands are the 90% confidence intervals for the simulated 50th (gray), 5th, and 95th (pink).

*Source: **Figure 3** in report 08QL4V page 29 (link).*

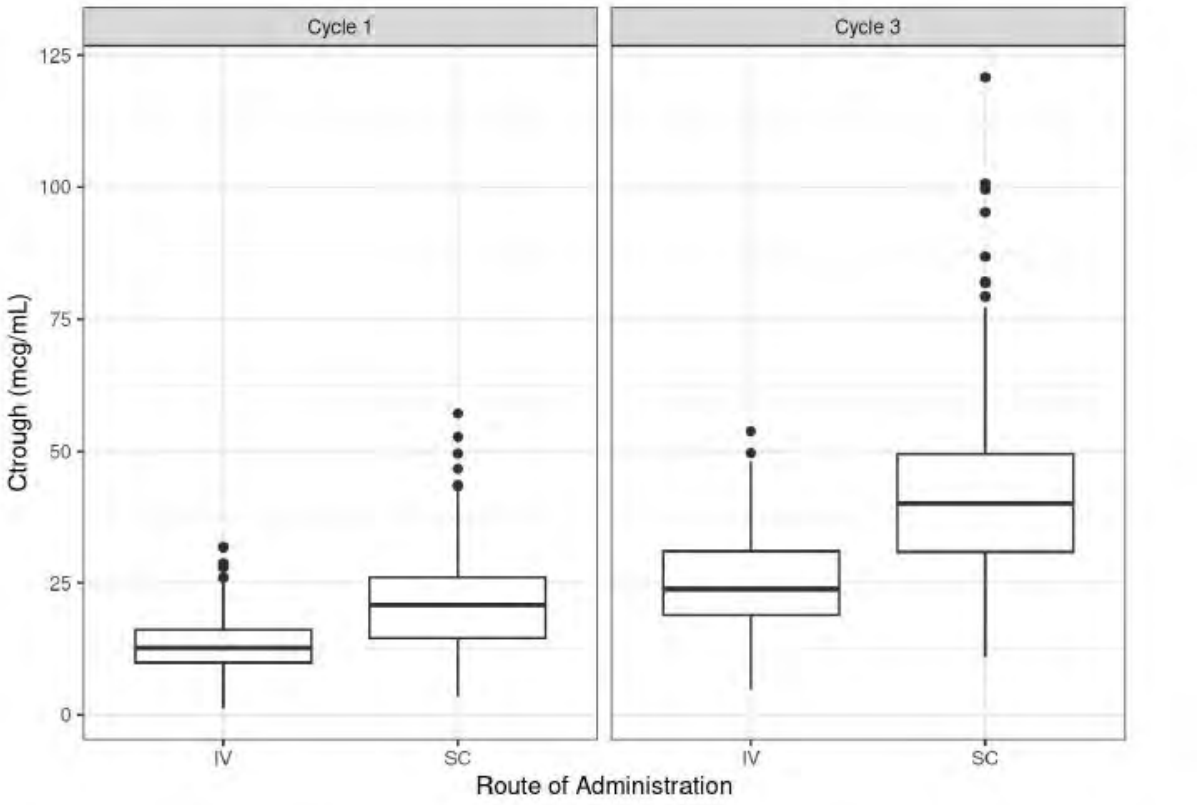
Figure 23: Applicant – Comparison of Model-Based Pembrolizumab Cycle 1 and Steady-State (Cycle 3) $AUC_{0\text{-}6wks}$ After the Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in Study MK-3475A-D77



Note: Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 400 mg Q6W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

*Source: **Figure 4** in report 08QL4V page 32 (link).*

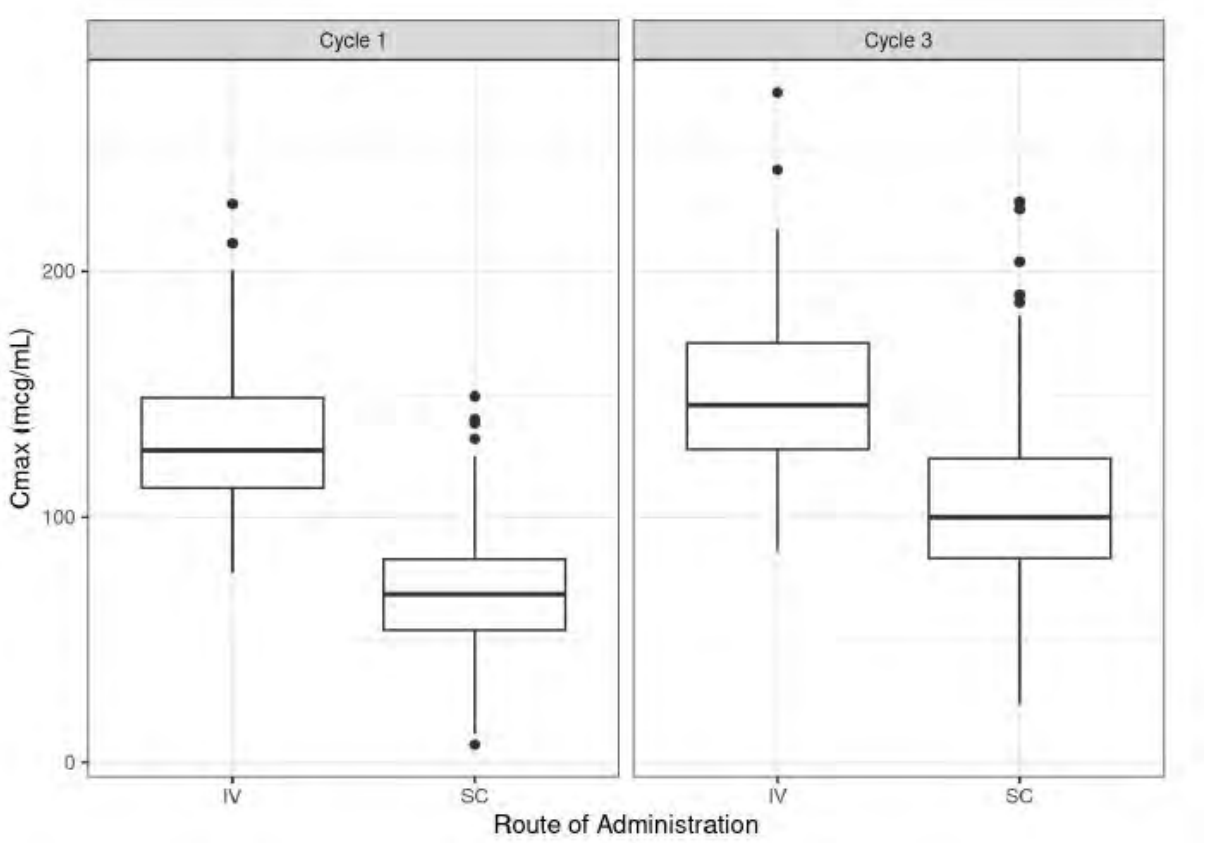
Figure 24: Applicant – Comparison of Model-Based Pembrolizumab Cycle 1 and Steady-State (Cycle 3) C_{trouge} After the Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in Study MK-3475A-D77



Note: Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 400 mg Q6W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

*Source: **Figure 5** in report 08QL4V page 33 (link).*

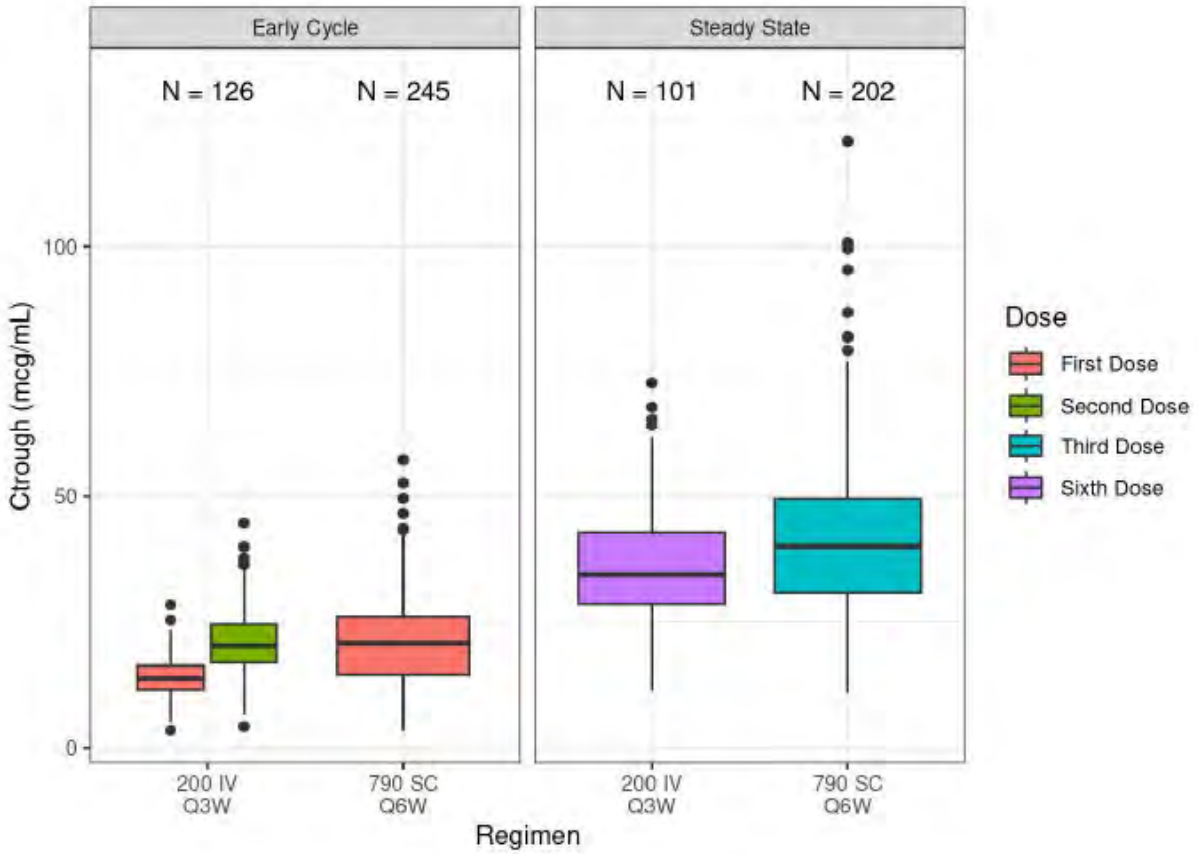
Figure 25: Applicant – Comparison of Model-Based Pembrolizumab Cycle 1 and Steady-State (Cycle 3) C_{max} After the Administration of Pembrolizumab 790 mg Q6W SC as MK-3475A and Pembrolizumab 400 mg Q6W IV in Study MK-3475A-D77



Note: Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 400 mg Q6W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

*Source: **Figure 6** in report 08QL4V page 34 (link).*

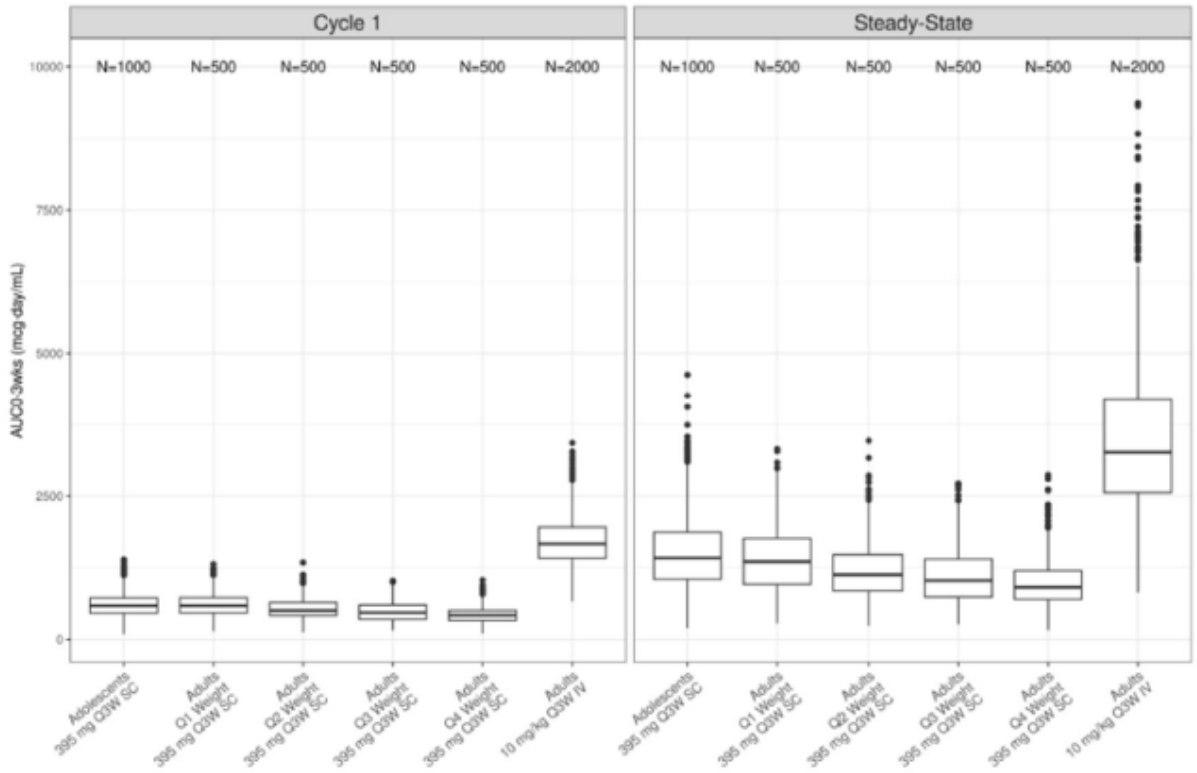
Figure 26: Applicant – Comparison of Model-Based Cycle 1 and Steady-State C_{trough} at Pembrolizumab 790 mg Q6W SC as MK-3475A With Pembrolizumab 200 mg Q3W IV

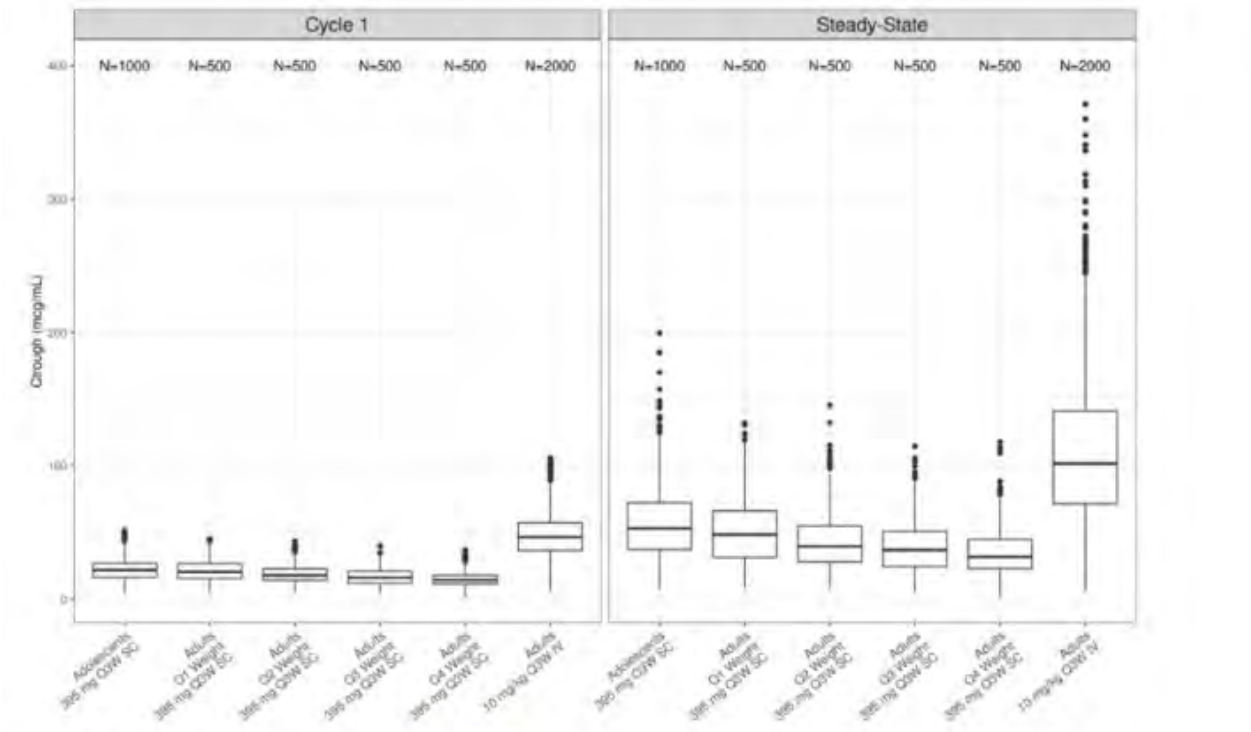


Note: Early Cycle is at Cycle 1 for 790 mg Q6W SC and at Cycle 1 and 2 for 200 mg Q3W IV. Steady-state is at Cycle 3 for 790 mg Q6W SC and at Cycle 6 for 200 mg Q3W IV
Percentiles of model-based PK exposure distribution among 245 subjects in Cycle 1 and 202 subjects at steady-state at 790 mg Q6W SC given as MK-3475A and among 126 subjects in Cycle 1 and 101 subjects at steady-state at 200 mg Q3W IV are represented by the middle line (50^{th}) and box (25^{th}–75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

*Source: **Figure 9** in report 08QL4V page 38 (link).*

Figure 27: Applicant – Comparison of Cycle 1 and Steady-State PK Exposure Estimates ($AUC_{0\text{-}3wks}$, C_{trough}) for 395 mg Q3W SC as MK-3475A in Pediatrics (12 to <17 Years Old) and Adults and Pembrolizumab 10 mg/kg Q3W IV in Adults





Source: sim-comparison-q3w-v3.Rmd [Appendix 7]
Abbreviations: $AUC_{0\text{-}3wks}$ =area under the concentration-time curve for 0-3 weeks; C_{max}=peak concentration; C_{trough}= trough concentration; N = number of subjects; Q3W = every 3 weeks
Note: For adults at 395 mg Q3W SC, results are presented by body weight quartile: Q1= 37-59 kg; Q2 = 59-69 kg; Q3 = 69-79.4 kg; Q4 = 79.4-143.9 kg
Percentiles of the model-predicted PK exposure distribution are represented by the horizontal line (50^{th}) and box (25^{th}-75^{th}). The upper/lower whisker extends from the hinge to the largest/smallest values no further than 1.5*Interquartile range (IQR) from the hinge. Data points beyond the end of the whiskers are plotted individually.

Source: ***Figure 3*** *in report 08QRGC page 22 (link).*

The FDA's Assessment:

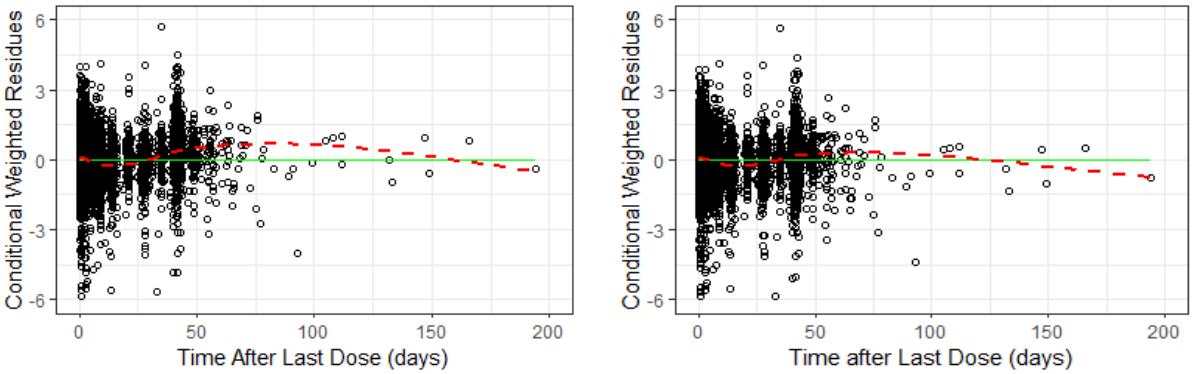
The reviewer agrees with Applicant's conclusions.

19.4.2.3. PPK Review Issues

There were notable discrepancies in VPC diagnostic plot between median observation concentration and predicted concentration at about 41 days after last dose, which is consistent with underprediction observed in the population prediction vs observed concentration plot as well as conditional weighted residues - time after last dose plot (Figure **)**. The discrepancies are primarily contributed by the fixed maximum inhibition (Imax), the value of which is a larger when estimated by the PK data. This parameter describes the magnitude of CL reduction over time, and when fixed, it resulted in an overestimation of the time-varying clearance and an underestimation the pembrolizumab PK population concentration on a population level. When the clearance and Imax estimations in the final population PK model were estimated, the

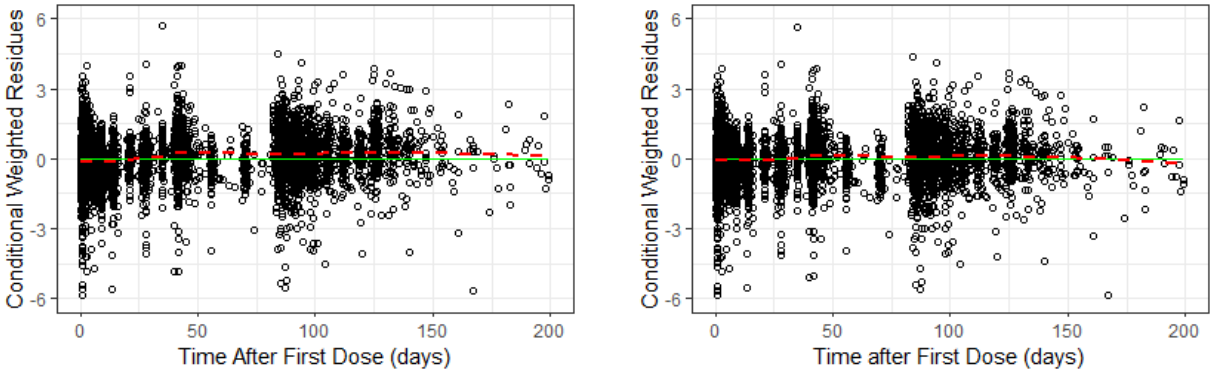
conditional weighted residues are much improved than those of sponsor, shown in Figure and Figure, which was confirmed by the pcVPC plot (Figure 30).
The individual prediction vs observed concentration plot (Figure **)** showed points clustering closely around the line of identity, indicating good agreement between individually predicted and observed concentrations. This is because Imax, despite being fixed, has associated interindividual variability that enables flexibility to fit observations and generate posthoc PK parameters for individuals. Therefore, model-based exposure prediction for individuals (e.g., AUC, Ctrough) remains accurate, and discrepancies in population prediction have minimal impact on individual predicted exposures used in statistical comparison between SC and IV arms for primary/secondary PK endpoints.
In pediatric simulation where the exposure distribution is determined by population prediction, the impact of fixing Imax on exposure is the same for pediatrics and adults, thereby not affecting the relative difference between pediatrics and adults.

Figure 28: FDA – Time After Last Dose vs. CWRES of Final Model (Left) and Revised Model (Right)



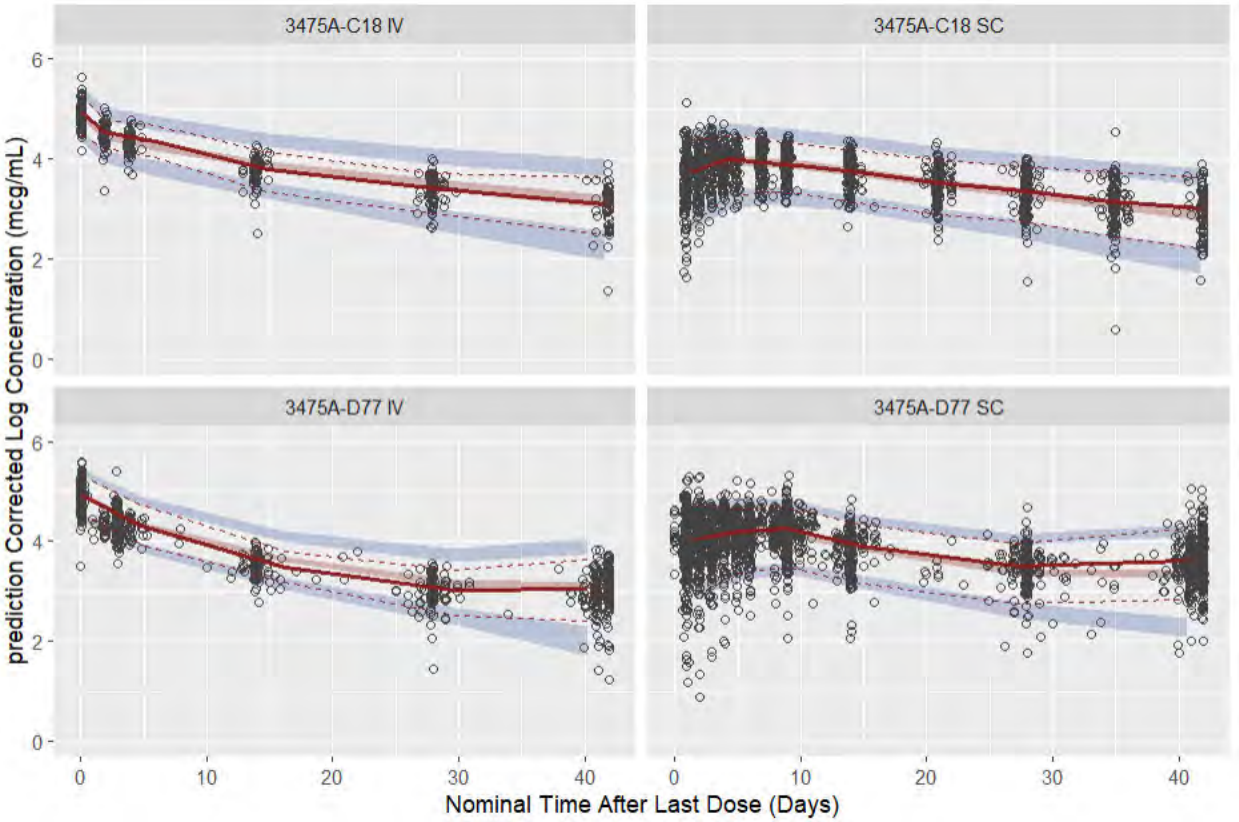
Source: Reviewer independent assessment

Figure 29: FDA – Time After First Dose vs. CWRES of Final Model (Left) and Revised Model (Right)



Source: Reviewer independent assessment

Figure 30: FDA – Prediction-Corrected VPC by Study and Route of Revised Model



Source: reviewer independent analysis

19.4.2.4. Reviewer's Independent Analysis

None.

19.4.3. Exposure-Response Analysis

19.4.3.1. ER (efficacy) Executive Summary

The FDA's Assessment:

E-R analysis was not considered necessary for this application. Refer to Section 8 regarding efficacy and safety evaluation between SC and IV arms.

19.4.3.2. ER (efficacy) Assessment Summary

The Applicant's Position:

This is not applicable for MK-3475A program. Exposure-response relationship for efficacy has been thoroughly investigated in pembrolizumab IV program.

19.4.3.3. ER (safety) Executive Summary

The FDA's Assessment:

E-R analysis was not considered necessary for this application. Refer to Section 8 regarding efficacy and safety evaluation between SC and IV arms.

19.4.3.4. ER (safety) Assessment Summary

The Applicant's Position:

This is not applicable for the MK-3475A program. Exposure-response relationship for safety has been thoroughly investigated in pembrolizumab IV program.

The FDA's Assessment: None.

19.4.3.5. ER Review Issues

19.4.3.6. Reviewer's Independent Analysis

19.4.3.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

This is not applicable for the MK-3475A program. Exposure-response relationship for safety has been thoroughly investigated in pembrolizumab IV program.

The FDA's Assessment: FDA agrees with the Applicant's position.

19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment: None.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Ritu Chadda, PhD	CDER/OTS/OCP/DCPI	Sections: 6, 19.4	**Select one:** _X_Authored ___Approved
	Signature: Ritu Chadda -S Digitally signed by Ritu Chadda -S Date: 2025.09.16 12:36:15 -04'00'			
Clinical Pharmacology Scientific Lead (Acting)	Yixuan Dong, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** __Authored _X_Approved
	Signature: YIXUAN DONG -S Digitally signed by YIXUAN DONG -S Date: 2025.09.16 11:54:08 -04'00'			
Clinical Pharmacology/ Pharmacometrics Reviewer	Hezhen Wang, PhD	CDER/OTS/OCP/DPM	Sections: 19.4	**Select one:** _X_Authored ___Approved
	Signature: Hezhen Wang -S Digitally signed by Hezhen Wang -S Date: 2025.09.17 09:09:13 -04'00'			
Clinical Pharmacology/ Pharmacometrics Team Leader (Acting)	Ye Xiong, PhD	CDER/OTS/OCP/DPM	Sections: 19.4	**Select one:** ___Authored _X_Approved
	Signature: YE XIONG -S Digitally signed by YE XIONG -S Date: 2025.09.16 11:49:46 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** ___Authored _X_Approved
	Signature: NAM A. RAHMAN -S Digitally signed by NAM A. RAHMAN -S Date: 2025.09.16 11:58:24 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Satinder Choudhary, PharmD, BCOP	CDER/ OND/OOD/DOII	Sections: 1-4, 7-13, 19.1, 19.2	**Select one:** _X_ Authored ___Approved
	Signature: Satinder K. Choudhary -S Digitally signed by Satinder K. Choudhary -S **Date:** 2025.09.16 09:18:02 -04'00'			
Supervisory Associate Director (Acting)	Paz Vellanki, MD, PhD	CDER/OND/OOD/DOII	Sections: All	**Select one:** _X_ Approved
	Signature: See signature in DARRTS.			
Biostatistical Reviewer	Shabnam Ford, PhD	CDER/OTS/OB/DBV	Sections: 1, 8.1, 8.3	**Select one:** _X_ Authored ___Approved
	Signature: SHABNAM A. FORD -S Digitally signed by SHABNAM A. FORD -S Date: 2025.09.16 12:41:11 -04'00'			
Biostatistical Team Leader	Flora Mulkey, MS	CDER/OTS/OB/DBV	Sections: 1, 8.1, 8.3	**Select one:** ___Authored _X_ Approved
	Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S Date: 2025.09.15 19:10:17 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ryan Hitzman, PhD	CDER/OND/OOD/DHOT	Sections: 5, 19.1, 19.3	**Select one:** _X_ Authored _X_ Approved
	Signature: Ryan T. Hitzman -S Digitally signed by Ryan T. Hitzman -S **Date: 2025.09.16 09:01:47 -04'00'**			
Nonclinical Team Leader	Emily Wearne, PhD	CDER/OND/OOD/DHOT	Sections: 5, 19.1, 19.3	**Select one:** _X_ Authored _X_ Approved
	Signature: Emily F. Wearne -S Digitally signed by Emily F. Wearne -S Date: 2025.09.16 08:04:49 -04'00'			
Nonclinical Division Director	Haleh Saber, PhD	CDER/OND/OOD/DHOT	Sections: 5, 19.1, 19.3	**Select one:** _X_ Approved
	Signature: HALEH SABER -S Digitally signed by HALEH SABER -S Date: 2025.09.16 15:39:54 -04'00'			
Biostatistical Director	Shenghui Tang, PhD	CDER/OTS/OB/DBV	Sections: 1, 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2025.09.16 12:48:15 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OND/OOD/DOII	Sections: 11	**Select one:** _X_ Authored __ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2025.09.16 10:33:45 -04'00'			
Associate Director for Patient Outcomes	Vishal Bhatnagar, MD	OCE	Sections: 8.1, 8.3	**Select one:** __ Authored _X_ Approved
	Signature: VISHAL BHATNAGAR -S Digitally signed by VISHAL BHATNAGAR -S **Date: 2025.09.15 18:52:53 -04'00'**			

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/

PAZ J VELLANKI
09/19/2025 11:02:35 AM

ROMEO A DE CLARO
09/19/2025 11:30:20 AM