21 May 2026
EMADOC-1700519818-2968830
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMA/VR/0000316576

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

%CV percent coefficient of variation

AUC area under the curve

ADA antidrug antibodies

ADC antibody-drug conjugate

BLA biologics license application

CDE Centre of Drug Evaluation

cHL classical Hodgkin lymphoma

CHMP Committee for Medicinal Products for Human Use

CL clearance

Cmax maximal concentration

Ctrough trough concentration

dMMR deficient mismatch repair

E-R exposure-response

EBV Epstein-Barr virus

EC50 effective concentration

ESR erythrocyte sedimentation rates

EU European Union

F bioavailability

FDA Food and Drug Administration

GM geometric mean

HC Health Canada

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IgG4 immunoglobulin G4

IL-2 Interleukin 2

IV intravenous

Ka absorption rate constant

LLOQ lower limit of quantification

M&S modeling and simulation

mAb monoclonal antibody

MCC merkel cell carcinoma

MSI-H microsatellite instability-high

NSCLC non-small cell lung cancer

ORR objective response rate

OS overall survival

PD-1 programmed cell death 1 protein

PD-L1 programmed cell death ligand 1

PD-L2 programmed cell death ligand 2

PFS progression-free survival

PIP Paediatric Investigation Plan

PK pharmacokinetic

PMBCL primary mediastinal B-cell lymphoma

PMDA Pharmaceuticals and Medical Device Agency

Q2W every 2 weeks

Q3W every 3 weeks

Q6W every 6 weeks

RCC renal cell carcinoma

SC subcutaneous

SmPC summary of product characteristics

TKI tyrosine kinase inhibitor

Vc central compartment volume of distribution

Vp peripheral compartment volume of distribution

VPC visual predictive check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 02 December 2025 an application for a group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

A grouped application consisting of:

C.I.6. Extension of indication for KEYTRUDA for subcutaneous use to include treatment of melanoma for adolescents aged 12 years and older based on an extrapolation approach from adults to adolescents using pharmacokinetics modelling and simulation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 52.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to implement some minor editorial and formatting changes in the PI.

C.I.6. Extension of indication for KEYTRUDA for subcutaneous use to include treatment of classical Hodgkin lymphoma for adolescents aged 12 years and older based on an extrapolation approach from adults to adolescents using pharmacokinetics modelling and simulation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0096/2023 on the granting of a (product-specific) waiver for malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) and Hodgkin Lymphoma.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Paolo Gasparini

Timetable	Actual dates
Submission date	2 December 2025
Start of procedure:	27 December 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 February 2026
PRAC Rapporteur's preliminary assessment report circulated on:	26 February 2026
Joint Rapporteur's updated assessment report circulated on:	19 March 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 March 2026
MAH's responses submitted to the CHMP on:	20 April 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	6 May 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	13 May 2026
CHMP opinion:	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The MAH is proposing an extrapolation approach to support the use of MK-3475A (i.e. Keytruda subcutaneous formulation) in adolescents aged 12 years and older for the indication of melanoma and cHL:

KEYTRUDA as monotherapy is indicated for the treatment of adults **and adolescents aged 12 years and older** with advanced (unresectable or metastatic) melanoma.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults **and adolescents aged 12 years and older** with Stage IIB, IIC or III melanoma and who have undergone complete resection (see section 5.1).

KEYTRUDA as monotherapy is indicated for the treatment of adults **and adolescents aged 12 years and older** with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

The extrapolation of indications from adults to adolescents aged 12 years and older relies on several critical factors including shared biological mechanisms, analogous disease presentations, and comparable clinical progression. Based on these factors, pembrolizumab IV has been approved in the EU for paediatric patients with melanoma and cHL and the same extrapolation approach is now

proposed by the MAH to approve the SC formulation also in the adolescent indications already approved for the IV formulation.

Melanoma

The clinical presentation, biological characteristics, risk factors, and prognostic indicators of melanoma are similar in adults and adolescents[1] [2] [3] (see Keytruda-H-C-003820-II-0111).

From a biological perspective, cutaneous melanoma is consistent across age groups. The clinical manifestation of melanoma in adolescents closely resembles that in adults, with the majority of tumours arising in previously healthy skin. The most prevalent subtype of melanoma in both demographics is superficial spreading melanoma. Melanoma in adults and adolescents share various predisposing factors including exposure to UV sunlight, red hair, blue eyes, poor tanning ability, freckling, dysplastic nevi, and a family history of melanoma. Considering genomic characteristics, melanoma in adolescents exhibits important similarities with adult melanoma including an enrichment of UV-induced mutations, a high prevalence of TERT-promoter mutations, and involvement of common oncogenes such as BRAF, in addition to tumour suppressor genes.

Hodgkin lymphoma

Hodgkin lymphoma (HL) is a malignancy that affects both children and adults, demonstrating remarkable similarities in biology and natural history across these age groups. The disease exhibits a bimodal age distribution, with peak incidences occurring between ages 15 and 35, and again after 50 years. Notably, while children under 14 years often present with nodular lymphocyte predominant Hodgkin lymphoma, classical Hodgkin lymphoma (cHL) remains the most common subtype in both paediatric and adult populations. This continuity in disease profile suggests that treatment efficacy evaluated in adults can be extrapolated to adolescents (see Keytruda-H-C-003820-II-0090).

The underlying mechanisms of cHL pathology and treatment response are fundamentally similar in adults and individuals younger than 18 years. This assertion is supported by the shared prognostic factors influencing therapy success across age groups, including advanced disease stages, presence of B symptoms (such as fever, night sweats, and weight loss), bulky disease, elevated ESR and haematocrit levels, as well as initial chemotherapy response. Moreover, the advancements in understanding the immunological landscape of HL, including the role of EBV in pathogenesis and the response to immune therapies, further reinforce the potential for successful treatment strategies to be applicable across age groups.

2.1.2. About the product

Pembrolizumab (MK-3475) is a potent and highly selective anti-PD1 humanized IgG4/kappa isotype mAb which blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection. The antibody potentiates existing immune responses in the presence of antigen only; it does not non-specifically activate T-cells.

[1] Lu C, Zhang J, Nagahawatte P, Easton J, Lee S, Liu Z, et al. The genomic landscape of childhood and adolescent melanoma. J Invest Dermatol. 2015;135:816-23
[2] Al-Himdani S, Naderi N, Whitaker IS, Jones NW. An 18-year study of malignant melanoma in childhood and adolescence. Plast Reconstr Surg Glob Open. 2019;7:e2338.
[3] Smoller BR. Histologic criteria for diagnosing primary cutaneous malignant melanoma. Mod Pathol. 2006;19:S34-40.

MK-5180 is a novel variant of human hyaluronidase PH20 called berahyaluronidase alfa, which acts as a permeation enhancer.

The addition of berahyaluronidase alfa, a permeation enhancer, is included to enhance dispersion and allows for the administration of pembrolizumab via SC administration in 1 injection for both Q3W and Q6W dosing regimens.

The currently recommended dose of Keytruda in adults is: 1) 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) administered as an IV infusion over 30 minutes and 2) 395 mg Q3W or 790 mg Q6W SC administered in approximately 1 minute and 2 minutes respectively in the abdomen or thigh by a healthcare professional.

The two currently approved paediatric indications are melanoma and Hodgkin lymphoma as IV infusion.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Immunotherapy with anti-PD1/anti-PDL1 drugs has changed the treatment paradigm for a number of cancers. To date, Keytruda (pembrolizumab) is approved in the EU as monotherapy or in combination with chemotherapy or other agents (e.g. ADC, TKI, antiangiogenic, RT) in several tumour types and in both early and metastatic disease settings. The IV formulation is administered as an infusion over 30 minutes, either Q3W or Q6W, until disease progression or unacceptable toxicity, or up to a maximum duration of therapy if specified for an indication (usually 1 or 2 years).

A new formulation for the SC route of administration, which contains a higher concentration of pembrolizumab in comparison with the IV formulation, i.e. 395 mg Q3W and 790 mg Q6W, has been recently authorised covering all adults' therapeutic indications (EMA/X/0000248795). Timing of administration is approximately 1 minute and 2 minutes, respectively, as compared to 30 minutes of the IV infusion. The SC injection should be administered in the abdomen or thigh. The SC injection should be administered by a healthcare professional only.

In the SC formulation (MK-3475A or Keytruda SC), pembrolizumab (MK-3475) is co-formulated with berahyaluronidase alfa (MK-5180), a novel variant of human hyaluronidase PH20 which acts as a permeation enhancer, allowing for the administration of pembrolizumab via SC administration in 1 injection for both Q3W and Q6W dosing regimens.

No Scientific Advice was sought regarding the development of SC formulation in adolescents.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Pembrolizumab and berahyaluronidase alfa are proteins composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk for the environment. As a protein, pembrolizumab is exempt from submitting environmental risk assessment studies in line with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00 Rev. 1- Corr.). Keytruda SC and the product excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The Applicant is proposing to apply an extrapolation approach to support the use of MK-3475A in adolescents aged 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 adolescents with melanoma and cHL. In turn, melanoma and cHL indications in paediatrics have been previously approved for pembrolizumab IV based on an extrapolation approach from adult data.

The extrapolation is based on the totality of PK, safety, and efficacy results from the final analysis of the pivotal study MK-3475A-D77, supporting studies of MK-3475A, and from model-based simulation using a paediatric population PK model for pembrolizumab previously developed using data from paediatric and adult patients.

In paediatric patients, the approved dosing regimen for pembrolizumab IV was also supported by a model-based bridging analysis. The paediatric population PK model (04LL90) for pembrolizumab was previously developed using data from paediatric patients in KEYNOTE-051 and adult patients and served as the basis for approval of a paediatric pembrolizumab IV indication in melanoma and cHL. This popPK analysis showed lower clearance and volume of distribution with decreasing body weight and age in the paediatric population but demonstrated that a dose of 2 mg/kg (up to 200 mg) Q3W in paediatric participants provided PK exposures similar to those achieved at 2 mg/kg (or 200 mg) Q3W in adults, suggesting similar PK between adults and paediatrics.

2.3.2. Pharmacokinetics

To support the development of MK-3475A (pembrolizumab with MK-5180) in adults, the reference population PK analysis of pembrolizumab IV (report 04M52F) was expanded using SC pooled data from study MK-3475A-C18 (Arm 1, 2 and 3) and from pivotal study MK-3475A-D77, to finally characterize pembrolizumab PK after SC administration of MK-3475A (report 08QL4V).

Report 08QL4V was the final popPK model describing pembrolizumab PK after either IV and SC administration.

During model development, the absorption phase PK parameters (i.e. first-order absorption rate constant (Ka) and bioavailability (F)) for SC administration were estimated from the SC data collected, while all model parameters describing systemic PK (including fixed effects, random effects, and covariate effects) were fixed from the reference IV PK model based on historical IV data.

Finally, for the combined IV and SC model, the absorption phase for SC administration was characterized by first order absorption rate constant (Ka) and bioavailability (F) parameters. Distribution and elimination phases were described by a two-compartment model with time-dependent clearance and a fixed effect of body weight, as established historically in the reference pembrolizumab PK model.

Absorption

The PK profile of MK-5180 (berahyaluronidase alfa) was previously evaluated in study ALT-BB4-01, study C18 and in Study D77.

Overall results from these studies showed that although few subjects had pre-dose concentration, no subjects with only post-dose samples containing MK-5180 concentrations above the LLOQ were observed, suggesting a negligible absorption of MK-5180 in humans.

There were no adult participants in the lowest body weight quartile (37-59 kg) with post-dose samples containing measurable MK-5180 concentrations (ie, above the detection level of the assay) in absence of positive pre-dose samples, following SC administration of MK-3475A.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state 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.

Elimination

Pembrolizumab CL is approximately 23% lower (geometric mean, 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 value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

Dose proportionality and time dependencies

Exposure to intravenous pembrolizumab as expressed by peak concentration (Cmax) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3 week regimen and the systemic accumulation was 2.1-fold.

Model-predicted PK exposures at 395 mg Q3W SC were consistent with 790 mg Q6W SC with both regimens given as MK-3475A and no meaningful difference in bioavailability or absorption rate was found between the 130 mg/mL and 165 mg/mL MK-3475A SC formulation strengths.

Special populations

The MK-3475A development program leverages extensive data from the pembrolizumab IV development program and studied only fixed doses and in this context, the reference adult PK IV model for pembrolizumab was expanded to characterize the PK profile after SC administration of MK-3475A (based on a pooled phase 1 study MK-3475A-C18 (Arms 1, 2, and 3) and Phase 3 study MK-3475A-D77 dataset).

This adult combined SC and IV PK model for pembrolizumab based on pooled data from Phase 1 study MK-3475A-C18 and Phase 3 study MK-3475A-D77 (popPK report 08QL4V) with allometric exponents for body weight and with an additional age effect on clearance and volume of distribution for paediatric population estimated using a combined dataset of adult and paediatric patients (IV data, popPK report 04LL90) was used to predict pembrolizumab concentrations following a single dose and at steady state with the proposed dosing regimens pembrolizumab 790 mg Q6W SC and 395 mg Q3W SC as MK-3475A in adult and in adolescents aged 12 years and older who weight greater than 40 kg (also the higher clinically evaluated 10 mg/kg Q3W IV regimen with established safety was simulated in adults).

Table 1. Datasets Used to Obtain Demographic Parameter Values for Adult and Adolescent Population

Source	Total number of subjects	Selected Population	Subjects belonging to selected population
Pembrolizumab NONMEM dataset	3346	Adolescents (12- <18 years) with body weight > 40 kg	80
Pediatric oncology dataset from internal another program previously used for pembrolizumab simulations	171	Adolescents (12- <18 years) with body weight > 40 kg	29
A pooled dataset from MK-3475A-C18 (Arms 1 to 3) and MK-3475A-D77 used for adult PopPK model development	473	Adults (≥ 18 years)	473

The objectives of this updated population PK analysis (**report 08ZJ7F**) were to:

1) Compare pembrolizumab PK exposures after SC administration in adolescent (12 years and older who weigh greater than 40 kg) and adult patient populations to support dose selection in adolescent patients.

For simulations in both adolescents and adults, the adult SC and IV combined popPK model with the previously estimated body weight and age effects from the paediatric IV popPK model was used to capture the impact of body size and maturation on PK.

Model parameter estimates of the combined SC and IV population PK model including the effect of body weight and additional effect of age from the paediatric IV popPK model, as used for adolescent and adult population simulations are presented in the following table:

Table 2: Parameter estimates of the combined SC and IV population PK model used for simulations

Parameter	Typical Parameter	%CV
Ka (day^{-1})	0.322	46.9%
F	0.599	14.2%
CL (L/day)	0.28	30.6%
Q (L/day)	0.89	
Vc (L)	3.53	19.1%
Vp (L)	2.75	
Maximum effect of time on CL	-0.218	79.4%
TI50 (days)	65.5	-
Hill coefficient	2.99	
α for CL and Q (allometric scaling factor)	0.573	-
α for Vc and Vp (allometric scaling factor)	0.54	-
Age effect on CL[a]	0.602	
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	-
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	-
Sex effect on Ka	-0.192	
Age effect on Vc[a]	0.34	

Source: Model.jl [Appendix 2]
[a] = Age effect only for adolescent population
Abbreviations: CV=coefficient of variation of between-subject distributions of parameters; eGFR=estimated glomerular filtration rate; NSCLC=non-small cell lung cancer; 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.

A dataset of individual patient covariate information was constructed from simulation datasets which were obtained through resampling. The resampling dataset consisted of the adult patients from the Phase 1 study MK-3475A-C18 (Arm 1, Arm 2 and Arm 3) and the Phase 3 study MK-3475A-D77 and adolescent patients from KEYNOTE-051 and studies in other internal oncology development programs.

The simulation dataset consisted of a total of 1000 adolescent and 2000 adult patients sampled with replacement from the covariate dataset. The same set of sampled subjects was used to simulate different dosing regimens.

A summary of subjects included in the resampling dataset is shown in the following table:

Table 3. Summary of subjects in the resampling dataset

Study	Population	Indication(s)[a]	Number of subjects	% of Subjects	Age Median (Min, Max)		Body Weight Median (Min, Max)		Sex Number of subject (%)	
MK-3475A-C18	Adult	NSCLS	33	5.7	66 (37, 84)	65 (37, 87)	78 (42, 144)	69 (37, 144)	Male: 65 (68%) Female: 31 (32%)	Male: 333 (70%) Female: 140 (30%)
		Melanoma	32	5.5						
		RCC	31	5.3						
MK-3475A-D77	Adult	NSCLC	377	64.8	65 (37, 87)		68 (37, 129)		Male: 268 (71%) Female: 109 (29%)	
KN-051	Adolescent	Adrenocortical carcinoma	2	0.3	15 (12, 17)	15 (12, 17.5)	56 (41, 120)	57 (41, 120)	Male: 45 (57%) Female: 34 (43%)	Male: 66 (61%) Female: 43 (39%)
		Brain/CNS	14	2.4						
		DLBCL	1	0.2						
		Hepatoblastoma	5	0.9						
		HL	14	2.4						
		Melanoma	4	0.7						
		Osteosarcoma	7	1.2						
		Soft tissue neoplasm	10	1.7						
		Others	22	3.8						
KN-02	Adolescent	Melanoma	1	0.2	15 (15, 15)		45 (45, 45)		Male: 1 (100%)	
Internal oncology program	Adolescent	Acute Promyelocytic Leukemia	1	0.2	14.7 (12.3, 17.5)		58 (44, 99)		Male: 20 (69%) Female 9 (31%)	
		CNS	3	0.5						
		Head and Neck	1	0.2						
		Lymphoproliferative	1	0.2						
		Myeloproliferative	1	0.2						
		Osteosarcoma	1	0.2						
		Rhadomyosarcoma	1	0.2						
		Sarcoma	19	3.3						
		Urogenital	1	0.2						

Source: resampling-data.R [Appendix 1]
Abbreviations: Min= minimum; Max = maximum;
[a]: all other indications except NSCLC are grouped as "Others" for tumor type effects on Vc for modeling purposes.
KN = KEYNOTE; NSCLC= non-small cell lung cancer; RCC= renal cell carcinoma; CNS= central nervous system tumor; DLBCL= diffuse large B-cell lymphoma; HL= Hodgkin lymphoma

Model predictions were simulated at daily time points.

Individual PK exposure metrics (Cycle 1 and steady-state AUC, Cmax, and Ctrough) were derived from the simulated concentration-time profiles by means of noncompartmental PK analysis. Comparison of

individual exposure metrics between adolescent and adult populations were made by means of boxplots and tabular summaries of descriptive statistics

The software Pumas (version 2.6.0; Pumas-AI, Inc., DE, USA) was used for the analysis. PK simulations were performed within the Pumas software. R (version 4.2.3) was used for data preparation, graphical analysis, model diagnostics, and statistical summaries.

Results:

A visual comparison of concentration-time profiles between adolescents and the full adult population is shown in the following figure:

Figure 1. Pembrolizumab PK Profile (median and 90% prediction interval) for 395 mg Q3W SC and 790 mg Q6W SC as MK-3475A in Adults and Adolescents and Pembrolizumab 10 mg/kg Q3W IV in Adults in Cycle 1 and at Steady-state

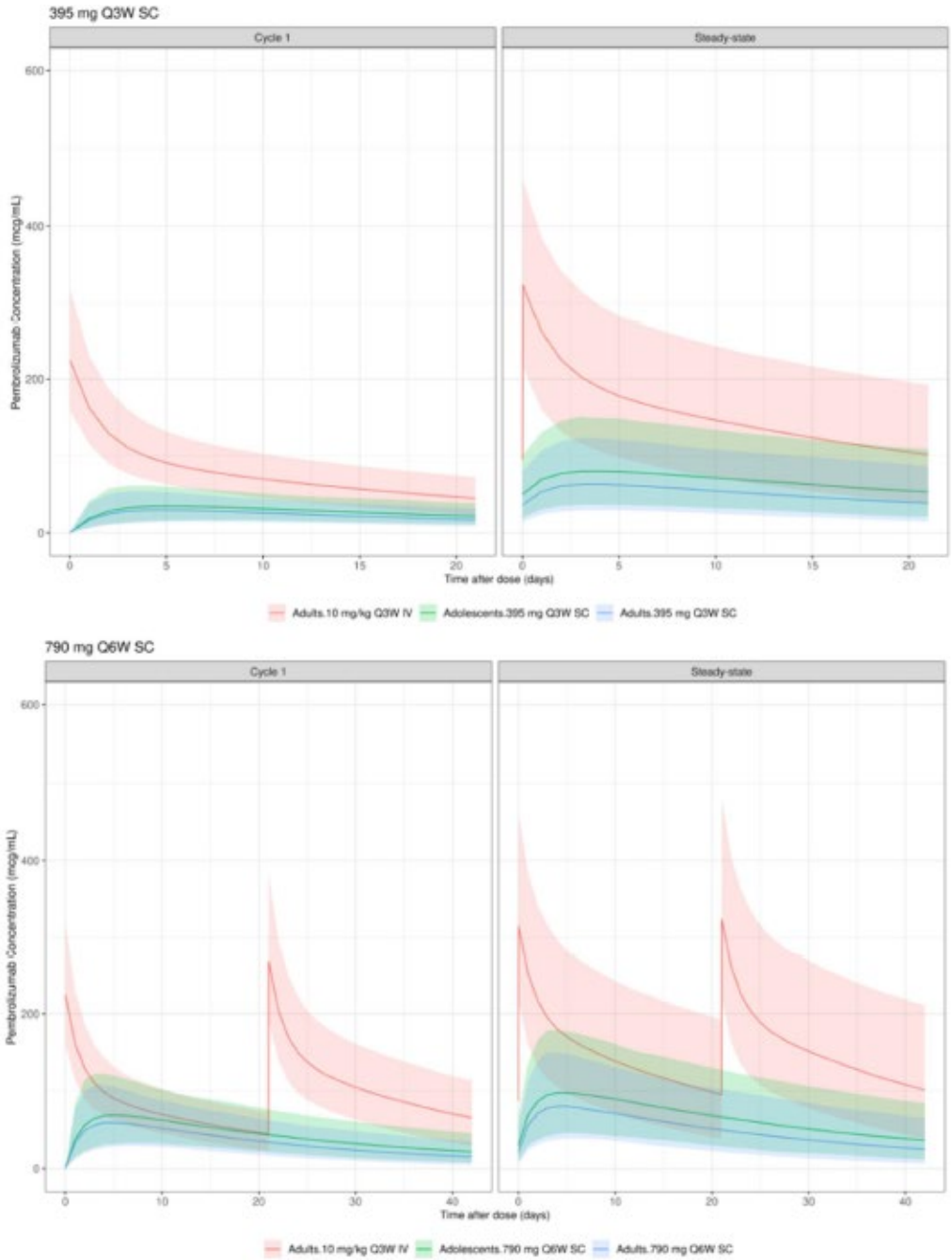
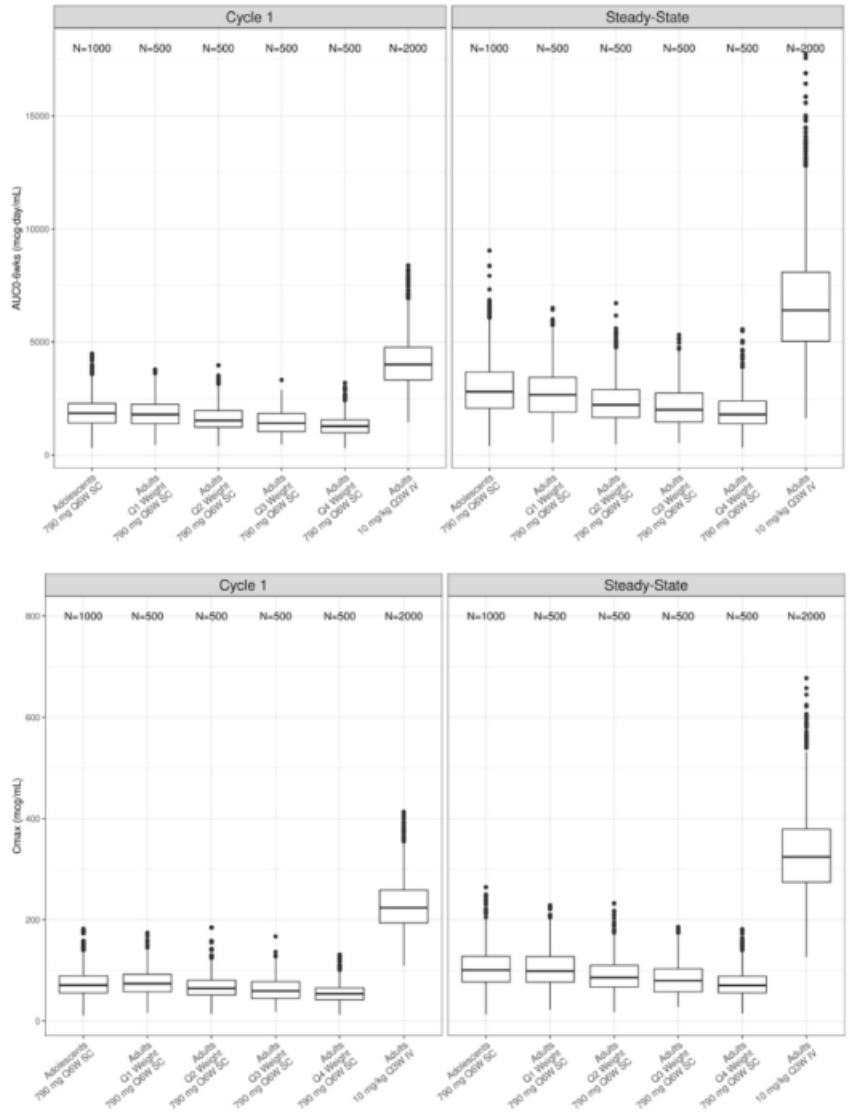
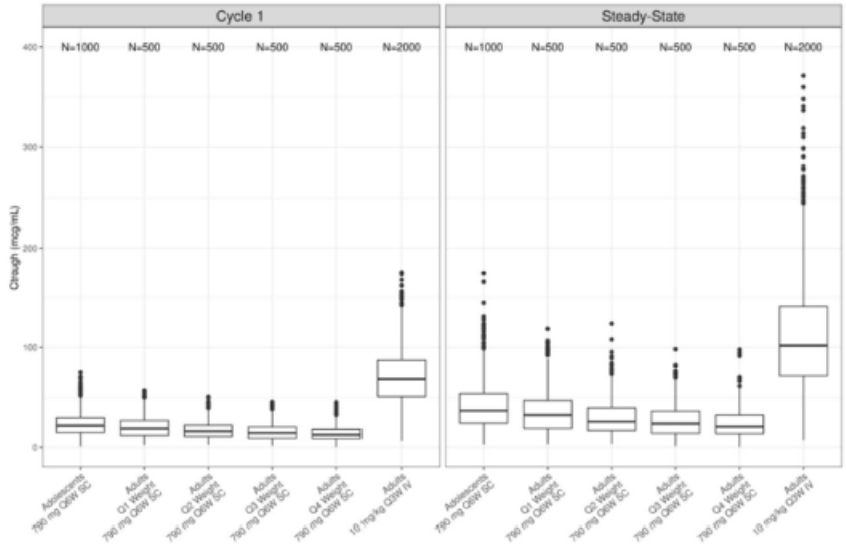


Figure 2and Table 4 and Table 5 show the predicted exposures for pembrolizumab 790 mg Q6W administered SC as MK-3475A in adolescents and adults compared to pembrolizumab 10 mg/kg Q3W IV in adults.

Figure 3 and Table 6 and Table 7 show the predicted exposures for 395 mg Q3W administered SC as MK-3475A in adolescents and adults compared to pembrolizumab 10 mg/kg Q3W IV in adults.

Figure 2. Comparison of Cycle 1 and Steady-state PK Exposure Estimates (AUC0-6wks, Cmax, Ctrough) for 790 mg Q6W SC as MK-3475A in Adolescents and Adults and Pembrolizumab 10 mg/kg Q3W IV in Adults





Source: sim-comparison-q6w-v6.Rmd [Appendix 6]
Abbreviations: $AUC_{0\text{-}6wks}$ =area under the concentration-time curve for 0-6 weeks; C_{max}=peak concentration; C_{trough}= trough concentration; N = number of subjects; Q3W = every 3 weeks; Q6W = every 6 weeks
Note: For adults at 790 mg Q6W 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
For 10 mg/kg Q3W IV, Cycle 1 $AUC_{0\text{-}6wks}$ is calculated as the sum of Cycle 1 and 2, and steady-state $AUC_{0\text{-}6wks}$ is calculated as the sum of Cycle 5, and 6; Cycle 1 C_{max} is used for comparison with Cycle 1 C_{max} and Cycle 6 C_{max} is used for comparison with steady-state C_{max} of the Q6W regimen; Cycle 2 C_{trough} is used for comparison with Cycle 1 C_{trough} of the Q6W regimen and Cycle 6 C_{trough} is used for comparison with steady-state C_{trough} of the Q6W regimen.
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.

Table 4. Summary Statistics of Predicted Individual Exposure Estimates (AUC0-6wks, Cmax, Ctrough) between Adolescents and Adults for 790 mg Q6W SC as MK-3475A and Adults for Pembrolizumab 10 mg/kg IV Q3W in Cycle 1

		790 mg Q6W SC					10 mg/kg Q3W IV
		Adolescents 12- <18 years	Adults ≥18 years Q1 Weight	Adults ≥18 years Q2 Weight	Adults ≥18 years Q3 Weight	Adults ≥18 years Q4 Weight	Adults ≥18 years (all)
Cycle 1	N	1000	500	500	500	500	2000
	$AUC_{0\text{-}6wks}$ (µg·day/mL)[a]						
	Mean (SD)	1898.9 (678.8)	1845.9 (653.0)	1617.5 (555.4)	1466.5 (519.1)	1307.4 (453.2)	4094.3 (1056.8)
	GM (CV%)	1776.8 (38.9)	1726.9 (39.1)	1523.1 (36.7)	1375.2 (37.7)	1229.8 (37.1)	3960.1 (26.5)
	Median (range)	1843.4 (310.3-4472)	1788.3 (441.9-3778.4)	1525.9 (392.3-3962)	1403.1 (467-3318.2)	1271.4 (299.3-3188.1)	3998.1 (1453.5-8389.9)
	Median adolescents vs. median adults (% difference)	-	3.1	20.8	31.4	45.0	-53.9
	C_{max} (µg/mL)[b]						
	Mean (SD)	74.2 (27.6)	76.2 (27.2)	67.9 (24.6)	62.3 (23.4)	55.1 (19.7)	228.8 (48.7)
	GM (CV%)	69.1 (40.7)	71.3 (39.5)	63.5 (39.1)	58.0 (39.8)	51.7 (38.1)	223.8 (21.3)
	Median (range)	71 (10.4-181.9)	73.7 (16.5-174.1)	64.7 (14.5-184.4)	59.3 (18-167.1)	53.5 (11.9-130.6)	223.7 (109.3-413.5)
	Median adolescents vs. median adults (% difference)	-	-3.6	9.8	19.7	32.8	-68.3
	C_{trough} (µg/mL)[c]						
	Mean (SD)	23.2 (11.6)	20.3 (11.0)	17.4 (9.2)	15.5 (8.2)	14.0 (7.5)	70.4 (26.2)
	GM (CV%)	20.3 (58.4)	17.1 (70.1)	14.9 (64.1)	13.3 (62.6)	12.0 (66.1)	65.3 (41.8)
	Median (range)	21.8 (1-75)	18.8 (2.2-56.6)	16.1 (2.4-50.4)	14.3 (1.6-45.1)	12.5 (0.3-45)	68.2 (6.4-174.5)
	Median adolescents vs. median adults (% difference)	-	15.6	35.5	52.0	74.1	-68.1

Source: sim-comparison-q6w-v6.Rmd [Appendix 6]
Abbreviations: $AUC_{0\text{-}6wks}$ =area under the concentration-time curve for 0-6 weeks; C_{max}=peak concentration; C_{trough}= trough concentration; N = number of subjects; Q3W = every 3 weeks; Q6W = every 6 weeks
Note: For adults at 790 mg Q6W 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
[a]: For 10 mg/kg Q3W IV, Cycle 1 $AUC_{0\text{-}6wks}$ represents Cycle 1 and 2.
[b]: For 10 mg/kg Q3W IV, Cycle 1 C_{max} is reported.
[c]: For 10 mg/kg Q3W IV, Cycle 2 C_{trough} is used for comparison with Cycle 1 of the Q6W regimen

Table 5. Summary Statistics of Predicted Individual Exposure Estimates (AUC0-6wks, Cmax, Ctrough) between Adolescents and Adults for 790 mg Q6W SC as MK-3475A and Adults for Pembrolizumab 10 mg/kg IV Q3W at Steady state

		790 mg Q6W SC					10 mg/kg Q3W IV
		Adolescents 12- <18 years	Adults ≥18 years Q1 Weight	Adults ≥18 years Q2 Weight	Adults ≥18 years Q3 Weight	Adults ≥18 years Q4 Weight	Adults ≥18 years (all)
Steady-State	N	1000	500	500	500	500	2000
	$AUC_{0\text{-}6wks}$ (µg·day/mL)[a]						
	Mean (SD)	2968.8 (1249.1)	2764.5 (1148.6)	2388.6 (985.9)	2171.8 (918.1)	1939.6 (819.8)	6741.1 (2371.0)
	GM (CV%)	2714.0 (45.6)	2523.5 (46.4)	2199.0 (43.1)	1984.4 (45.4)	1776.5 (44.9)	6339.0 (36.7)
	Median (range)	2794.3 (393.2-9045.1)	2664.1 (546.3-6494.4)	2220.5 (480.4-6706.6)	1999.8 (531.3-5315.3)	1788.6 (325.2-5553.3)	6397.3 (1630-17734.7)
	Median adolescents vs. median adults (% difference)	-	4.9	25.8	39.7	56.2	-56.3
	C_{max} (µg/mL)[b]						
	Mean (SD)	105.4 (40.8)	103.1 (37.8)	90.6 (34.0)	83.0 (32.1)	73.8 (27.8)	331.9 (79.3)
	GM (CV%)	97.5 (42.3)	95.9 (40.9)	84.4 (40.0)	76.9 (41.4)	68.8 (39.8)	322.7 (24.0)
	Median (range)	100.3 (13-264.2)	98.4 (22.3-228.4)	86 (17.6-232.2)	79.6 (27.7-185.7)	70.6 (15-181.2)	324.1 (126.7-677.3)
	Median adolescents vs. median adults (% difference)	-	2.0	16.6	26.1	42.2	-69.0
	C_{trough} (µg/mL)[c]						
	Mean (SD)	41.3 (23.6)	35.3 (21.5)	29.8 (18.4)	27.0 (16.5)	24.4 (15.4)	110.6 (53.3)
	GM (CV%)	34.7 (68.9)	28.6 (79.1)	24.6 (73.0)	22.1 (76.2)	19.8 (79.1)	98.0 (54.8)
	Median (range)	36.6 (2.6-173.8)	32.3 (3-118.3)	25.6 (3.2-123.6)	23.7 (1.2-98.2)	20.7 (0.4-97.8)	101.7 (7-371.3)
	Median adolescents vs. median adults (% difference)	-	13.2	42.5	54.4	76.7	-64.1

Source: sim-comparison-q6w-v6.Rmd [Appendix 6]

Abbreviations: $AUC_{0\text{-}6wks}$ =area under the concentration-time curve for 0-6 weeks; C_{max}=peak concentration; C_{trough}= trough concentration; N = number of subjects; Q3W = every 3 weeks; Q6W = every 6 weeks

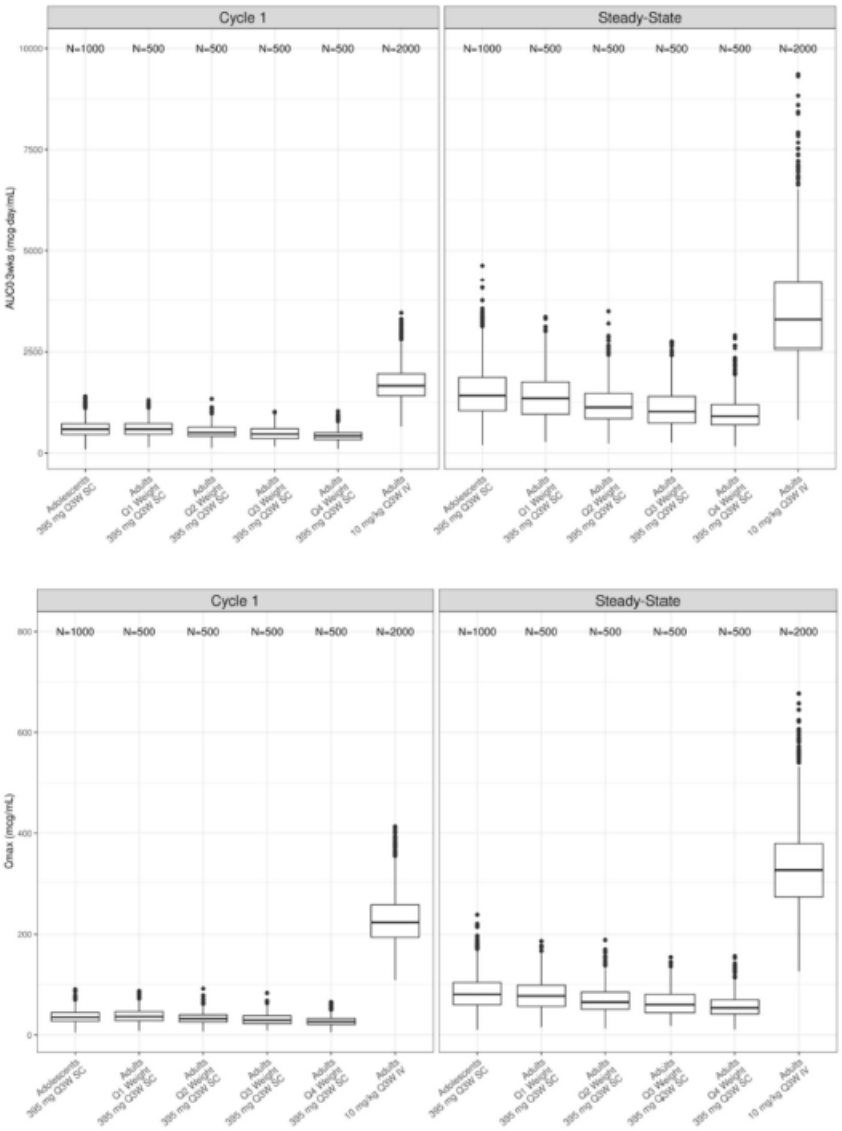
Note: For adults at 790 mg Q6W SC, results are presented by body weight quartile: Q1= 37-59 kg; Q2 = 59-69 kg; Q3 = 69-79.4 kg; Q4 = 79.4-143.9 kg

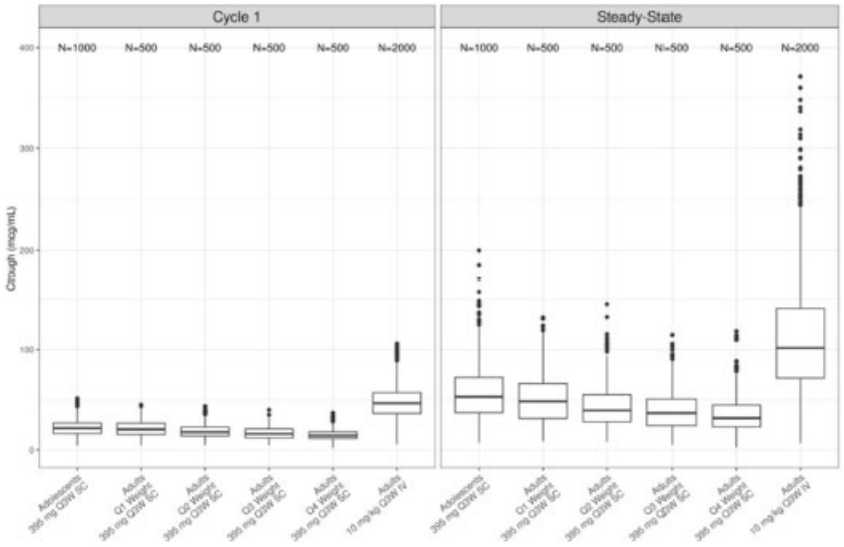
[a]: For 10 mg/kg Q3W IV, Steady-state $AUC_{0\text{-}6wks}$ represents Cycle 5 and 6.

[b]: For 10 mg/kg Q3W IV, Cycle 6 C_{max} is used for comparison with Steady-state C_{max} of the Q6W regimen.

[c]: For 10 mg/kg Q3W IV, Cycle 6 C_{trough} is used for comparison with Steady-state C_{trough} of the Q6W regimen.

Figure 3. Comparison of Cycle 1 and Steady-state PK Exposure Estimates (AUC0 3wks, Cmax, Ctrough) for 395 mg Q3W SC as MK-3475A in Adolescents and Adults and Pembrolizumab 10 mg/kg Q3W IV in Adults





Source: sim-comparison-q3w-v6.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 (50th) and box (25th-75th). 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.

Table 6. Summary Statistics of Predicted Individual Exposure Estimates (AUC0-3wks, Cmax, Ctrough) between Adolescents and Adults for 395 mg Q3W SC as MK-3475A and Adults for Pembrolizumab 10 mg/kg Q3W IV in Cycle 1

		395 mg Q3W SC					10 mg/kg Q3W IV
		Adolescents 12- <18 years	Adults ≥18 years Q1 Weight	Adults ≥18 years Q2 Weight	Adults ≥18 years Q3 Weight	Adults ≥18 years Q4 Weight	Adults ≥18 years (all)
Cycle 1	N	1000	500	500	500	500	2000
	$AUC_{0\text{-}3wks}$ (µg·day/mL)						
	Mean (SD)	604.6 (209.4)	606.0 (202.3)	535.4 (175.3)	488.4 (166.9)	433.7 (142.1)	1709.3 (406.0)
	GM (CV%)	567.5 (38.0)	570.8 (37.0)	506.4 (35.4)	459.9 (36.4)	410.5 (35.1)	1662.1 (24.1)
	Median (range)	587.8 (91.5-1397)	588.1 (144.1-1310.8)	505.4 (127.5-1339.5)	469.5 (162.1-1022.4)	422.1 (105.5-1036.3)	1666 (658.1-3428.6)
	Median adolescents vs. median adults (% difference)	-	-0.1	16.3	25.2	39.2	-64.7
	Cmax (µg/mL)						
	Mean (SD)	37.1 (13.8)	38.1 (13.6)	33.9 (12.3)	31.2 (11.7)	27.6 (9.9)	228.8 (48.7)
	GM (CV%)	34.5 (40.7)	35.6 (39.5)	31.7 (39.1)	29.0 (39.8)	25.8 (38.1)	223.8 (21.3)
	Median (range)	35.5 (5.2-91)	36.8 (8.2-87.1)	32.3 (7.3-92.2)	29.7 (9-83.6)	26.7 (6-65.3)	223.7 (109.3-413.5)
	Median adolescents vs. median adults (% difference)	-	-3.6	9.8	19.7	32.8	-84.1
	Ctrough (µg/mL)						
	Mean (SD)	22.6 (8.2)	21.6 (8.1)	18.8 (6.7)	16.9 (6.1)	15.1 (5.4)	47.6 (15.2)
	GM (CV%)	21.1 (39.4)	20.0 (42.1)	17.6 (38.2)	15.8 (39)	14.1 (39.4)	45.1 (35.1)
	Median (range)	21.8 (4.4-51.5)	20.7 (4.8-45.2)	18 (5.1-43.5)	16.3 (4.7-40.1)	14.4 (2.2-37)	46.6 (5.9-105.8)
	Median adolescents vs. median adults (% difference)	-	5.6	21.0	33.8	51.5	-53.2

Source: sim-comparison-q3w-v6.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

Table 7. Summary Statistics of Predicted Individual Exposure Estimates (AUC0-3wks, Cmax, Ctrough) between Adolescents and Adults for 395 mg Q3W SC as MK-3475A and Adults for Pembrolizumab 10 mg/kg Q3W IV at Steady state

		395 mg Q3W SC					10 mg/kg Q3W IV
		Adolescents 12- <18 years	Adults ≥18 years Q1 Weight	Adults ≥18 years Q2 Weight	Adults ≥18 years Q3 Weight	Adults ≥18 years Q4 Weight	Adults ≥18 years (all)
Steady-state	N	1000	500	500	500	500	2000
	$AUC_{0\text{-}3wks}$ (µg·day/mL)						
	Mean (SD)	1512.6 (639.2)	1409.5 (588.8)	1217.0 (506.8)	1108.1 (473.0)	988.7 (421.4)	3463.5 (1249.9)
	GM (CV%)	1381.4 (46.0)	1285.2 (46.8)	1119.0 (43.4)	1010.6 (45.9)	904.1 (45.4)	3247.2 (37.6)
	Median (range)	1421.6 (197.1-4623)	1355.9 (276.7-3322.6)	1129.9 (241.2-3466.8)	1025.8 (261.7-2717.9)	910.4 (164-2867.9)	3264.7 (820.3-9363.1)
	Median adolescents vs. median adults (% difference)	-	4.8	25.8	38.6	56.2	-56.5
	Cmax (µg/mL)						
	Mean (SD)	85.2 (34.5)	81.1 (31.6)	70.7 (28.0)	64.6 (26.3)	57.6 (23.1)	331.9 (79.3)
	GM (CV%)	78.3 (44.1)	74.8 (43.5)	65.4 (41.6)	59.4 (43.7)	53.2 (42.4)	322.7 (24)
	Median (range)	80.9 (10.4-238.7)	77.8 (16.3-186.2)	65.3 (13.4-188.6)	60.7 (18.4-154.3)	54 (11.1-156.6)	324.1 (126.7-677.3)
	Median adolescents vs. median adults (% difference)	-	4.0	24.0	33.4	49.8	-75.0
	Ctrough (µg/mL)						
	Mean (SD)	57.1 (27.4)	51.4 (25.4)	43.9 (21.6)	39.8 (19.8)	35.6 (18.0)	110.6 (53.3)
	GM (CV%)	50.8 (53.5)	45.1 (57.7)	39.0 (52.7)	35.1 (55.8)	31.4 (56.5)	98.0 (54.8)
	Median (range)	53.1 (7.5-199.9)	48.6 (8.8-131.8)	39.6 (8.4-145.1)	36.8 (5.4-114.5)	31.8 (2.8-118.2)	101.7 (7-371.3)
	Median adolescents vs. median adults (% difference)	-	9.4	34.0	44.2	66.9	-47.8

Source: sim-comparison-q3w-v6.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

2.3.3. PK/PD modelling

No new data have been submitted.

2.3.4. Discussion on clinical pharmacology

The Applicant is proposing to apply an extrapolation approach, relying on the reference guideline (ICH E11) to support the use of MK-3475A in adolescents aged 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 adolescents with melanoma and cHL, applying then to the indications that have been previously approved for pembrolizumab IV in paediatric patients (adolescents and older) in Melanoma and cHL.

For this purpose, model 08ZJ7F was developed. This model combined the previously developed SC/IV PK model (popPK report 08QL4V in adults) for pembrolizumab based on pooled data from Phase 1 study MK-3475A-C18 and Phase 3 study MK-3475A-D77 with allometric exponents for body weight and an additional age effect on clearance and volume of distribution for paediatric population estimated using a combined dataset of adult and paediatric patients (IV data, popPK report 04LL90).The adequacy of the structural model was assessed by different model diagnostics and overall, the updated/expanded model seemed to adequately describe the shape of observed IV and SC serum concentration, indeed, the model well centered the absorption phase of the SC route.

Model 08ZJ7F was used to predict pembrolizumab concentrations following a single dose and at steady state with the proposed dosing regimens pembrolizumab 790 mg Q6W SC and 395 mg Q3W SC as MK-3475A in adult and in adolescents aged 12 years and older who weight greater than 40 kg. In addition, the higher clinically evaluated dosing regimen of 10 mg/kg Q3W IV with established safety was also

simulated in adults. This combined popPK model (08ZJ7F) has not been validated with experimental evidence.

The exposure simulated in adults (overall weight range) using the adult model (08QL4V) appeared to be slightly higher than that simulated using the current paediatric model (08ZJ7F), where exposures in adults were presented split by quartiles weight, due to use of different simulation methods given no observed data available for pembrolizumab SC in adolescents. Simulations obtained with PopPK 08ZJ7F showed that the predicted exposures for pembrolizumab 790 mg Q6W and 395 mg Q3W administered SC as MK-3475A in adolescents weighing greater than 40 kg were comparable with those in adults in the lowest body weight quartile (Q1: 37-59 kg) for both 790 mg Q6W SC and 395 mg Q3W SC as MK-3475A, while higher than in adults in the other quartiles of body weight (Q2 = 59-69 kg; Q3 = 69-79.4 kg; Q4 = 79.4-143.9 kg).

The age effect function on CL and Vc was included in the adolescent population only in the new combined popPK model (08ZJ7F). In addition, body weight had been already included in the adult PopPK model with estimated values of 0.534 and 0.514 for CL/Q and Vc/Vp respectively. This effect was re-estimated previously in the paediatric PopPK IV model based on adult and pediatric data, yielding similar values (0.573 and 0.540 for CL/Q and Vc/Vp), and used in the new combined popPK model (08ZJ7F). The MAH explained the differences derived from use of different simulation methods between adult exposures simulated using the previous model (08QL4V) and those simulated in the overall adult population (without quartiles weight splits) using the new model 08ZJ7F. The data provided are considered sufficient to demonstrate a largely overlapping range of simulated exposures between adolescents and adults, as well as consistency in simulated adult exposures across the two models (08QL4V and 08ZJ7F).

Additional simulations by weight quartiles, in both adolescents and adults, showed comparable exposure within corresponding quartiles (adult Q1= 37-59 kg vs adolescents Q1= 40.5-48.3 kg; etc.). Furthermore, simulations of the overall populations (pooling all weight quartiles) indicated comparable exposure levels, although slightly higher (approximately 30%) in adolescents. Importantly, adolescent exposure remains within the safety margin established at the highest tested adult dose (10 mg/kg).

Overall, these findings further support the similarity in PK exposures between adolescents and adults.

Model performance for both 08QL4V and 04LL90 model have been adequately provided and assessed in the context of previously submitted variations (EMA/X/0000248795 and EMEA/H/C/003820/II/0090, respectively).

The MAH also provided model performance evaluation of the combined model (08ZJ7F) used to simulate exposures in adolescents.

The VPC in adolescents treated with SC formulation could not be provided since no observed data is available. The MAH has therefore presented the VPC of adolescents treated with IV formulation using model 08ZJ7F, containing IV and SC data from adults with the addition of allometric exponents for body weight and an additional age effect on clearance and volume of distribution for paediatric population estimated from IV paediatric model 04LL90. Looking at the submitted VPC in adolescent IV, the model 08ZJ7F seems to adequately predict exposure in adolescents administered with IV formulation. The only uncertainty is regarding the difference, if any, in the absorption phase after the SC administration compared to the IV in adolescents. Considering that the SC PK profile has been extensively evaluated in adults and the factors impacting exposure in adolescent were included in the model (weight and age), differences in the absorption phase are not expected in the adolescents. Overall, the model is considered reliable to also predict SC exposure in adolescents.

To support the extrapolation approach for the use of SC formulation, the MAH also provided literature evidence relying on physiology and historical data and highlighting the similarity between adults and adolescents of the absorption process for monoclonal antibodies[4] [5] [6] [7] [8].

Regarding the new excipient, berahyaluronidae (MK-5180) it has been demonstrated that it is absorbed in a negligible amount in adults as observed in Phase 1 study MK-3475A-C18 and Phase 3 study MK-3475A-D77. Indeed, no subjects with only post-dose samples containing MK-5180 concentrations above the LLOQ were observed; whereas, 2 out of 140 subjects in study C18 and 3 out of 226 subjects in study D77 showed concentration of berahyaluronidase above the LLOQ pre- and post-dose.

Overall, based on these data, the absorption of berahyaluronidase is considered negligible also due to the fast degradation, limiting the persistence in systemic circulation. These data together with historical data demonstrating safety and efficacy of recombinant hyaluronidase as permeation enhancer in paediatric patients facilitating the subcutaneous infusion of immunoglobulins[9] support the expectation of a similar negligible systemic absorption of MK-5180 in adolescents.

2.3.5. Conclusions on clinical pharmacology

Overall, considering that the PK profile of pembrolizumab co-formulated with berayaluronidase (MK-3475A) as well as the PK profile of berahyaluronidase itself (MK-5180) have been sufficiently characterized in adults, and also considering the similarity of disease, the expected similarity of PK to adults and the expected similarity for efficacy and safety between adult and adolescents with melanoma and cHL, the extrapolation approach to support the use of pembrolizumab SC formulation in adolescents aged 12 years and older based on the above mentioned conditions is acceptable.

2.4. Clinical efficacy/safety

No new clinical data have been provided which is agreed.

For the efficacy and safety of intravenously administered pembrolizumab in paediatric patients, please refer to Keytruda II/71 relating to the paediatric study KEYNOTE-051. Efficacy and safety details on the classical Hodgkin Lymphoma indication for paediatric patients of 3 years and on the melanoma indication for adolescents aged 12 years and older have been previously assessed by CHMP (Keytruda II/90 and Keytruda II/111, respectively).

For efficacy and safety of subcutaneously administered pembrolizumab in adult patients, please refer to the pembrolizumab solution for injection (MK-3475A) line extension (Keytruda X-0000248795).

2.4.1. PSUR cycle

[4] Yan L, Wang B, Chia YL, Roskos LK. Population pharmacokinetic modeling of benralizumab in adult and adolescent patients with asthma. Clin Pharmacokinet. 2019;58:943-58.
[5] Baverel PG, Jain M, Stelmach I, She D, Agoram B, Sandbach S, et al. Pharmacokinetics of tralokinumab in adolescents with asthma: implications for future dosing. Br J Clin Pharmacol. 2015;80(6):1337-49.
[6] Sharma S, Eckert D, Hyams JS, Mensing S, Thakkar RB, Robinson AM, et al. Pharmacokinetics and exposureefficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. Inflamm Bowel Dis. 2015 Apr;21(4):783-92.
[7] Valentin J. Basic anatomical and physiological data for use in radiological protection: reference values - ICRP publication 89
[8] Temrikar ZH, Suryawanshi S, Meibohm B. Pharmacokinetics and clinical pharmacology of monoclonal antibodies in pediatric patients. Paediatr Drugs. 2020;22:199-216.
[9] Wasserman RL, Melamed I, Kobrynski L, Puck J, Gupta S, Doralt J, et al. Recombinant human hyaluronidase facilitated subcutaneous immunoglobulin treatment in pediatric patients with primary immunodeficiencies: long-term efficacy, safety and tolerability. Immunotherapy. 2016;8(10):1175-86.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 48.0 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

The MAH should bring the key elements in annex 6 of the RMP in line with the approved key elements presented in annex IID of the SmPC.

Safety concerns

Table 8. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-mediated adverse reactions
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

No new safety concerns were identified as a result of the review of the data from this extension of indication.

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table 9. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	**Risk minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks: Immune-Mediated Adverse Reactions		

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Immune-mediated adverse reactions	Routine risk minimisation measures: The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities
	Additional risk minimisation measures: Patient card	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: Safety monitoring in the ongoing HL trial (KN204).
	Routine risk minimisation measures:	Routine pharmacovigilance activities

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

The risk minimisation activities remain unchanged.

2.6. Update of the Product information

As a result of this variation, section(s) 4.1, 4.2, 4.8, 5.1 of the SmPC of the SC formulation are being updated. The Package Leaflet (PL) is updated accordingly.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No changes on the key messages for the safe use of the medicinal product are proposed, and the design, layout and format of the package leaflet is not affected by the agreed revisions.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is an extension of indication for KEYTRUDA SC to include treatment of melanoma and classical Hodgkin lymphoma for adolescents aged 12 years and older (already approved for IV) based on an extrapolation approach from adults to adolescents using PK modelling and simulation.

Of note, the current KEYTRUDA IV indication in Hodgkin lymphoma is for patients aged 3 years and older (Keytruda II/90); the Applicant is thus requesting to extend the use of the SC formulation only in adolescent.

3.1.2. Main clinical studies

For the purpose of the present extrapolation approach, model 08ZJ7F was developed. This model combined the previously developed SC/IV PK model (popPK report 08QL4V in adults) for pembrolizumab based on pooled data from Phase 1 study MK-3475A-C18 and Phase 3 study MK-3475A-D77 with allometric exponents for body weight and an additional age effect on clearance and volume of distribution for paediatric population estimated using a combined dataset of adult and paediatric patients (IV data, popPK report 04LL90).

3.2. Favourable effects

The efficacy of pembrolizumab SC formulation for the treatment of melanoma and cHL in adolescents aged 12 years and older who weigh greater than 40 kg is extrapolated from studies of intravenous pembrolizumab in adults based on PK model 08ZJ7F. Pharmacokinetic modelling and simulation analyses showed similar pembrolizumab exposures with subcutaneous doses of 395 mg every 3 weeks or 790 mg every 6 weeks in adolescents aged 12 years and older who weigh greater than 40 kg compared to adults suggesting similar efficacy to adult patients.

3.3. Uncertainties and limitations about favourable effects

Not applicable.

3.4. Unfavourable effects

A similar profile of unfavourable effects to the IV formulation in adolescents aged 12 years and older in melanoma and cHL is expected for the SC formulation.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Benefit-risk assessment and discussion

3.6.1. Balance of benefits and risks

An extrapolation approach, relying on the reference guideline (ICH E11) to support the use of MK-3475A in adolescents aged 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 adolescents with melanoma and cHL, applying then to the indications that have been previously approved for pembrolizumab IV in paediatric patients (adolescents and older) in Melanoma and cHL. Model 08ZJ7F combined the previously developed SC/IV PK model (popPK report 08QL4V in adults) for pembrolizumab based on pooled data from Phase 1 study MK-3475A-C18 and Phase 3 study MK-3475A-D77 with allometric exponents for body weight and an additional age effect on clearance and volume of distribution for paediatric population estimated using a combined dataset of adult and paediatric patients (IV data, popPK report 04LL90). Considering that the PK profile of pembrolizumab co-formulated with berayaluronidase (MK-3475A) as well as the PK profile of berahyaluronidase itself (MK-5180) have been sufficiently characterized in adults, and also considering the similarity of disease, the expected similarity of PK to adults and the expected similarity for efficacy and safety between adult and adolescents with melanoma and cHL, the extrapolation approach to support the use of the SC formulation in adolescents aged 12 years and older is acceptable. The benefit/risk balance of the SC in adolescents aged 12 years and older is considered positive in melanoma and cHL.

3.7. Conclusions

The overall B/R of Keytruda SC formulation in adolescents aged 12 years and older in melanoma and cHL is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

A grouped application consisting of:

-C.I.6. Extension of indication for KEYTRUDA for subcutaneous use to include treatment of melanoma for adolescents aged 12 years and older based on an extrapolation approach from adults to adolescents using pharmacokinetics modelling and simulation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 48.0 of the RMP is agreed. In addition, the Marketing authorisation holder took the opportunity to implement some minor editorial and formatting changes in the PI.

-C.I.6. Extension of indication for KEYTRUDA for subcutaneous use to include treatment of classical Hodgkin lymphoma for adolescents aged 12 years and older based on an extrapolation approach from adults to adolescents using pharmacokinetics modelling and simulation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The group of variations leads to amendments to annexes I and IIIB and to the Risk Management Plan (RMP).

The MAH should bring the key elements in annex 6 of the RMP in line with the approved key elements presented in annex IID of the SmPC.