EFFICACY SUPPLEMENT REVIEW
BLA 761381/S-005: Opdivo Qvantig (nivolumab-hyaluronidase nvhy)
Disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	761381/005
Priority or Standard	Standard
Submit Date(s)	January 30, 2025
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Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	See stamp date
Established/Proper Name	nivolumab and hyaluronidase-nvhy
(Proposed) Trade Name	Opdivo Qvantig
Applicant	Bristol-Myers Squibb Company
Dosage form	Subcutaneous Use
Applicant proposed Dosing Regimen	Pediatric patients age 12 years and older who weigh ≥40 kg: • 600 mg nivolumab/10,000 units hyaluronidase SC every 2 weeks, or • 1,200 mg nivolumab/20,000 units hyaluronidase SC every 4 weeks Pediatric patients age 12 years and older and weighing 30 kg or greater but less than 40 kg: • 300 mg nivolumab and 5,000 units hyaluronidase every 2 weeks, or • 600 mg nivolumab and 10,000 units hyaluronidase every 4 weeks

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1. Executive Summary

On January 30, 2025, Bristol-Myers Squibb (BMS) submitted this supplemental Biologics License Application (sBLA) to expand the indications of OPDIVO QVANTIG (nivolumab and hyaluronidase-nvhy) for the treatment of pediatric patients (≥ 12 years and older) with unresectable or metastatic melanoma, adjuvant melanoma, and first-line and previously treated microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC). This submission is intended to respond to the postmarketing requirement (PMR) 4762-4, issued at the time of the original BLA approval, as well as PMR 4925-1, issued at the time of approval of sBLA761381/002.

PMR-4925-1: Conduct a modeling and simulation study to support dosing of nivolumab and hyaluronidase-nvhy as first-line treatment in pediatric patients 12 years of age and older with unresectable or metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer (MSI-H/dMMR mCRC)

PMR-4762-4: Conduct a molecularly targeted pediatric cancer investigation using an age appropriate formulation of nivolumab and hyaluronidase-nvhy in pediatric patients 12 years of age and older.

The approval of the current supplement, sBLA761381/005, is supported by the extrapolation of efficacy from adequate and well-controlled studies of intravenous (IV) nivolumab (OPDIVO) for the specified indications in adult patients, combined with pharmacokinetic (PK) modeling and simulation data demonstrating that the proposed subcutaneous (SC) dosing regimens achieve comparable exposures to the approved IV regimens. In addition to the approval recommendation for this supplement, the review teams determined that PMR 4925-1 should be fulfilled and that PMR 4762-4 can be released (because BMS provided the information to support dosing of an age-appropriate formulation of nivolumab and hyaluronidase-nvhy in pediatric patients 12 years of age and older).

2. Clinical Review

The effectiveness of OPDIVO QVANTIG in pediatric patients 12 years and older has been established as:

- Monotherapy or maintenance monotherapy after nivolumab IV in combination with ipilimumab IV for unresectable or metastatic melanoma
- Monotherapy for adjuvant treatment of melanoma
- Maintenance monotherapy after nivolumab IV in combination with ipilimumab IV for MSI-H/dMMR mCRC
- monotherapy or as monotherapy following treatment with intravenous nivolumab and ipilimumab combination therapy for MSI-H/dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

OPDIVO QVANTIG is not indicated in combination with ipilimumab for any of these indications.

Use of OPDIVO QVANTIG for these indications in pediatric patients 12 years and older is supported by evidence from adequate and well-controlled studies conducted with intravenous nivolumab and additional pharmacokinetic and safety data that demonstrated comparable pharmacokinetics and safety profiles between OPDIVO QVANTIG and intravenous nivolumab in CHECKMATE-67T. Modeling and simulation data provided in this submission support the use of nivolumab SC for the proposed indications of unresectable or metastatic melanoma, adjuvant treatment of melanoma, and MSI-H/dMMR mCRC in pediatric patients 12 years and older and weighing ≥ 30 kg and address the pediatric requirements outlined in PMR 4672-4 and PMR 4925-1.

3. Clinical Pharmacology Review

The proposed recommended dosages for nivolumab and hyaluronidase as monotherapy and as combination treatment for the pediatric indications are:

- Pediatric patients ≥ 12 years old who weigh ≥40 kg: 600 mg nivolumab/10,000 units hyaluronidase SC every 2 weeks (Q2W) or 1,200 mg nivolumab/20,000 units hyaluronidase SC every 4 weeks (Q4W)
- Pediatric patients ≥ 12 years old who weigh ≥30 kg but less than <40 kg: 300 mg nivolumab/5,000 units hyluronidase SC Q2W or 600 mg nivolumab/10,000 units hyluronidase SC Q4W.

The Applicant supported these proposed recommended dosages using an extrapolation approach based on the following:

- Previously developed nivolumab IV population PK (popPK) models for pediatric patients (≥12 years old).
- PK data from ongoing Study CA20967T to evaluate the non-inferiority of nivolumab hyaluronidase 1,200 mg/20,000 units SC Q4W versus nivolumab IV 3 mg/kg Q2W as monotherapy in adult patients with previously treated clear cell renal cell carcinoma (ccRCC).

The proposed recommended dosages for the nivolumab and hyaluronidase SC product provide PK exposures (i.e., Cavgd28 and Cminss) that are non-inferior (geometric mean ratio [GMR] >1 for SC/IV) to that observed for the nivoluamb IV product (Table 3 in Appendix 1). Based on the modeling and simulation analyses (refer to Section 7.1 for detailed review), the proposed recommended dosages are acceptable in the proposed pediatric indications.

The clinical pharmacology review team recommends approval of this supplemental BLA.

4. Labeling

- **New Pediatric Indications:**
  - The Highlights of the OPDIVO QVANTIG US Prescribing Information (USPI) and Sections 1.2, 1.3, and 1.9 of the USPI were updated to include new indications for the treatment of unresectable or metastatic melanoma, adjuvant treatment of melanoma, and treatment of MSI-H or dMMR metastatic colorectal cancer for pediatric patients aged 12 years and older who weigh 30 kg or greater. Section 14.2 "Unresectable or Metastatic Melanoma," was updated to expand the indicated patient population to include "adult and pediatric patients 12 years and older who weigh 30 kg or greater." The changes were made to the introductory text for both the "Previously Treated Metastatic Melanoma" and "Previously Untreated Metastatic Melanoma" subsections. The statement, "OPDIVO QVANTIG is not indicated for the treatment of pediatric patients," has been removed from both subsections.
  - Section 14.3 " Adjuvant Treatment of Melanoma" was updated to expand the indicated patient population to include "adult and pediatric patients 12 years and older who weigh 30 kg or greater." The statement, "OPDIVO QVANTIG is not indicated for the treatment of pediatric patients," has been removed.
  - Section 14.9 " Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer," was updated to expand the indicated patient population to include "adult and pediatric patients 12 years and older who weigh 30 kg or greater." The changes were made to the introductory text for both the "Treatment of MSI-H or dMMR mCRC" and "Treatment of MSI-H or dMMR mCRC after Progression Following Treatment with a Fluoropyrimidine, Oxaliplatin, and Irinotecan" subsections. The statement, "OPDIVO QVANTIG is not indicated for the treatment of pediatric patients," has been removed from both subsections.

- **New Dosage Form and Dosing Recommendations:** A new dosage form and strength of 300 mg nivolumab and 5,000 units hyaluronidase per 2.5 mL has been added to Section 3 (Dosage Forms and Strengths), Section 11 (Description), and Section 16 (How Supplied/Storage and Handling). Section 2.3 (Recommended Dosage) and the corresponding tables were updated to include new weight-based dosing recommendations for pediatric patients with melanoma and MSI-H/dMMR mCRC.

- **Updated Preparation Instructions**: Section 2.5 (Preparation and Administration) was revised to include instructions for preparing the new 300 mg/2.5 mL dosage form. The instructions now detail how to prepare doses using the 300 mg vial alone or in combination with the 600 mg vial to achieve the prescribed dose.

- **Updated Pediatric Use Information:** Section 8.4 (Pediatric Use) was updated to reflect that the safety and effectiveness of OPDIVO QVANTIG have been established for specific indications in pediatric patients 12 years and older who weigh 30 kg or greater.

- **Revised Medication Guide:** The Medication Guide was updated to inform patients and caregivers about the new pediatric indications for melanoma and MSI-H/dMMR colorectal cancer. The guide now specifies the approved use in "adults and children 12 years of age and older" for these cancers.

5. Recommended Regulatory Action

The clinical and clinical pharmacology review teams recommend approval of this supplemental BLA (supplement 005). The data submitted to this supplement fulfills the postmarketing requirement 4925-1. The FDA will release BMS from the requirements under the FDARA amendments to conduct a molecularly targeted pediatric cancer investigation (PMR 4762-4) as it is no longer needed because the Applicant has provided the necessary information to support dosing of an age-appropriate formulation of nivolumab and hyaluronidase-nvhy in pediatric patients 12 years of age and older.

Appendix 1

1.1. OCP Appendices (Technical documents supporting OCP recommendations)

1.1.1. Assessment of MIDD evidence

The pharmacometrics analyses were focused on assessing the appropriateness of proposed recommended dosage of nivolumab-hyaluronidase SC in pediatric patients 12 years and older for the same approved indications as those listed for nivolumab IV without conducting a new clinical study (Table 1).

The overall model risk is considered medium. In line with the determined model risk and specific objectives, the model evaluation/additional analysis was conducted for the respective methodologies as outlined in Table 2.

The pharmacometrics analyses support the following:

- Uncertainty in SC absorption (lower and upper bound of 95% CI of bioavailability and absorption rate constant) showed limited impact on GMR of primary PK endpoints.
- Based on population PK modeling and simulation, the following weight-based dosages for pediatric patients 12 years and older will provide exposure within range of that in adults who receive the recommended nivolumab IV dosage.
  - ≥40 kg: 600 mg/10,000 units SC Q2W or 1200 mg/20,000 units SC Q4W (same as the adult dosage)

- <40 kg: 300 mg/5,000 units SC Q2W or 600 mg/ 10,000 units SC Q4W (half of the adult dosage)

Table 1. FDA - Assessment of Model Risk

Question of interest	Will the proposed recommended dosage for nivolumab-hyaluronidase SC provide exposure within range of that of nivolumab IV for indications inclusive of pediatric patients 12 years and older (i.e., unresectable or metastatic melanoma, adjuvant treatment of melanoma, and MSI-H or dMMR mCRC)?
Context of use	PopPK was used to predict PK exposure based on patient factors and uncertainty in SC absorption (rate and extent). Evaluated SC dosages in pediatric patients 12 years and older.
Decision consequence	Low Uncertainty in SC absorption is not likely to result in an elevated risk for efficacy reduction, toxicity, or immunogenicity in pediatric patients 12 years and older, given the following reasons • The safety margin has been established for nivolumab IV, which is higher than exposure following nivolumab-hyaluronidase SC. • Flat E-R relationship for efficacy and safety across wide dose/exposure range
Model influence	Medium The current approved recommended dosage for nivolumab-hyaluronidase SC is determined by modeling and simulation without clinical data. The SC absorption of the model for pediatric patients 12 years and older was extrapolated from adults, where other PK parameters (e.g., clearance, volume) were adequately characterized with data of pediatric patients 12 years and older with nivolumab IV dosage.
Model risk	Medium

Table 2. FDA - Model Evaluation

Methodology	Objective	Model evaluation	Section
PopPK	Predict PK profile of nivolumab- hyaluronidase in pediatric patients 12 years and older by patient factors for respective indications inclusive of pediatric patients.	In pediatric patients 12 years and older, predicted PK for the proposed nivolumab-hyaluronidase SC dosages were compared to that for approved nivolumab IV dosages as well as nivolumab-hyaluronidase SC dosage in adults.	7.1.2

Methodology	Objective	Model evaluation	Section
		Uncertainty in SC absorption (rate and extent) was assessed via sensitivity analysis.	

1.1.2. Population PK analysis

1.1.2.1. Executive Summary

Due to the lack of PK data in pediatric patients with nivolumab-hyaluronidase, population PK models for pediatrics with nivolumab-hyaluronidase were constructed by combining:

- distribution and elimination components from the population PK models previously developed for pediatrics of relevant indications receiving nivolumab IV,
- absorption component from the population PK model previously developed for adult renal cell carcinoma receiving nivolumab-hyaluronidase SC or nivolumab IV.

The final population PK models for pediatric patients with nivolumab-hyaluronidase were subsequently used to simulate PK profiles in virtual pediatric patients to justify the proposed nivolumab-hyaluronidase SC dosages for relevant indications whose exposure in general aligns with that observed in adult patients.

1.1.2.2. PPK Assessment Summary

PPK model construction	Final model constructed by incorporating the absorption (Ka, F1) component in the model for adults with RCC who received nivolumab-hyaluronidase SC into the model for pediatric patients who received nivolumab IV for relevant indications.
Key assumptions	• Absorption (Ka, F1) is the same across tumor types and does not require additional covariates (previously evaluated and supported by data) • Absorption (Ka, F1) is the same in pediatric patients and adults and does not require additional covariates • PK difference between pediatric patients and adults is driven by covariates in the popPK model
Virtual patients	(nominally) Statistically significant covariates, i.e., weight, lean body mass, sex, race, and eGFR (by Schwartz) were sampled from NHANES data, and disease related covariate was sampled from adult patients (i.e., performance status) or determined according to the indication and subject type (i.e., adult melanoma, adult adjuvant treatment of melanoma, adult CRC, adolescent solid tumor).
Simulation based analysis	With weight-based dosages, nivolumab exposures for nivolumab-hyaluronidase SC in pediatric patients are expected to be non-inferior to nivolumab IV with sensitivity analysis of varying Ka and F1 (

	), and are predicted to be within the range of those observed in adults receiving nivolumab IV at corresponding dosing intervals (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**).

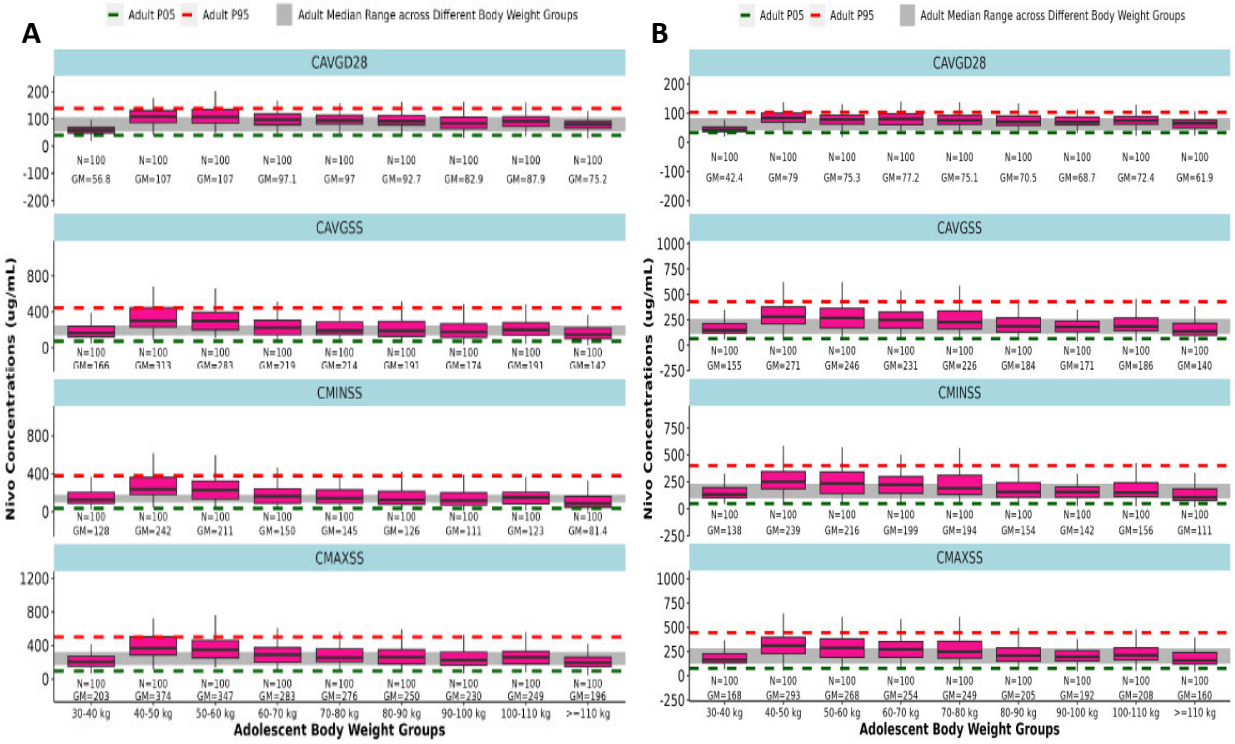
Table 3. Predicted GMR for primary PK endpoints (Cavgd28 and Cminss) based on varying Ka and F1

Indication	Monotherapy or Monotherapy Maintenance	Body-weight tier	Regimen	Exposure Measure	Geometric Mean Ratio		
					Lower bound of 95% CI	Point Estimates	Upper bound of 95% CI
					Ka (0.0118) F (0.761)	Ka (0.0123) F (0.788)	Ka (0.0129) F (0.815)
Unresectable or metastatic melanoma	Monotherapy	< 40 kg	Q4W (600 mg SC vs 6 mg/kg IV)	Cavgd28	1.792	1.872	1.954
				Cminss	2.188	2.266	2.344
		≥ 40 kg	Q4W (1200 mg SC vs 480 mg IV)	Cavgd28	1.642	1.715	1.790
				Cminss	2.016	2.086	2.155
		< 40 kg	Q2W (300 mg SC vs 3 mg/kg IV)	Cavgd28	1.700	1.781	1.866
				Cminss	2.192	2.274	2.357
		≥ 40 kg	Q2W (600 mg SC vs 240 mg IV)	Cavgd28	1.548	1.621	1.697
				Cminss	2.008	2.081	2.153
	Monotherapy Maintenance	< 40 kg	Q4W (600 mg SC vs 6 mg/kg IV)	Cavgss	2.014	2.093	2.173
				Cminss	2.245	2.323	2.400
		≥ 40 kg	Q4W (1200 mg SC vs 480 mg IV)	Cavgss	1.800	1.871	1.943
				Cminss	2.089	2.158	2.226
		< 40 kg	Q2W (300 mg SC vs 3 mg/kg IV)	Cavgss	2.018	2.099	2.182
				Cminss	2.248	2.33	2.413
		≥ 40 kg	Q2W (600 mg SC vs 240 mg IV)	Cavgss	1.803	1.875	1.948
				Cminss	2.077	2.15	2.222
Adjuvant treatment of melanoma		< 40 kg	Q4W (600 mg SC vs 6 mg/kg IV)	Cavgd28	1.773	1.852	1.934
				Cminss	2.123	2.2	2.278
		≥ 40 kg	Q4W (1200 mg SC vs 480 mg IV)	Cavgd28	1.618	1.69	1.766
				Cminss	1.972	2.042	2.113
		< 40 kg	Q2W (300 mg SC vs 3 mg/kg IV)	Cavgd28	1.679	1.759	1.843
				Cminss	2.107	2.187	2.268
		≥ 40 kg	Q2W (600 mg SC vs 240 mg IV)	Cavgss	1.529	1.601	1.676
				Cminss	1.955	2.027	2.1
MSI-H or dMMR mCRC	Monotherapy	< 40 kg	Q4W (600 mg SC vs 6 mg/kg IV)	Cavgd28	1.791	1.87	1.952
				Cminss	2.202	2.28	2.358
		≥ 40 kg	Q4W (1200 mg SC vs 480 mg IV)	Cavgd28	1.646	1.719	1.794
				Cminss	2.021	2.091	2.16
		< 40 kg	Q2W (300 mg SC vs 3 mg/kg IV)	Cavgd28	1.693	1.773	1.858
				Cminss	2.16	2.241	2.323

		≥ 40 kg	Q2W (600 mg SC vs 240 mg IV)	Cavgss	1.551	1.624	1.699
				Cminss	2.006	2.079	2.152
	Monotherapy Maintenance	< 40 kg	Q4W (600 mg SC vs 6 mg/kg IV)	Cavgd28	2.016	2.095	2.174
				Cminss	2.2	2.279	2.357
		≥ 40 kg	Q4W (1200 mg SC vs 480 mg IV)	Cavgd28	2.124	2.208	2.293
				Cminss	2.374	2.456	2.538
		< 40 kg	Q2W (300 mg SC vs 3 mg/kg IV)	Cavgd28	1.988	2.068	2.15
				Cminss	2.157	2.238	2.319
		≥ 40 kg	Q2W (600 mg SC vs 240 mg IV)	Cavgss	2.126	2.21	2.296
				Cminss	2.361	2.447	2.533

Source: Pediatric simulation report Tables 6.6.1.1-1, 6.1.1.2-1, 6.1.1.3-1.

Figure 1. Unresectable or metastatic melanoma: predicted nivolumab exposures in pediatric subjects with 2-weight band SC dosages (Q2W or Q4W) for monotherapy or monotherapy maintenance.



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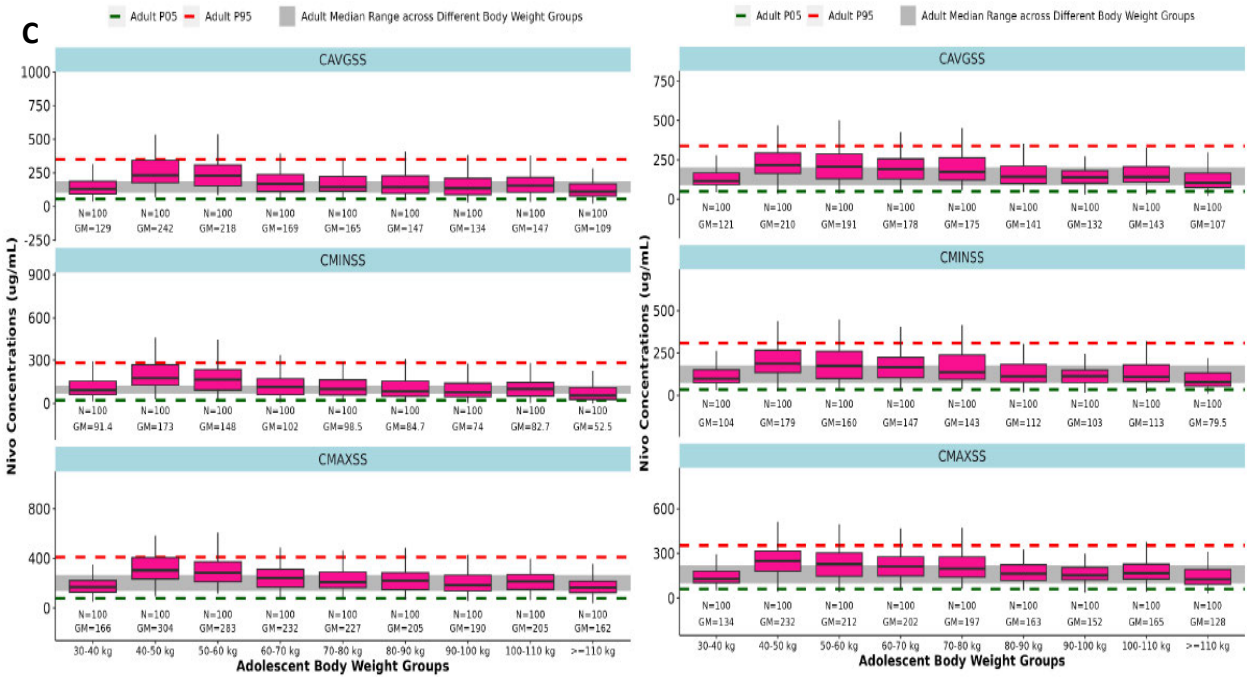
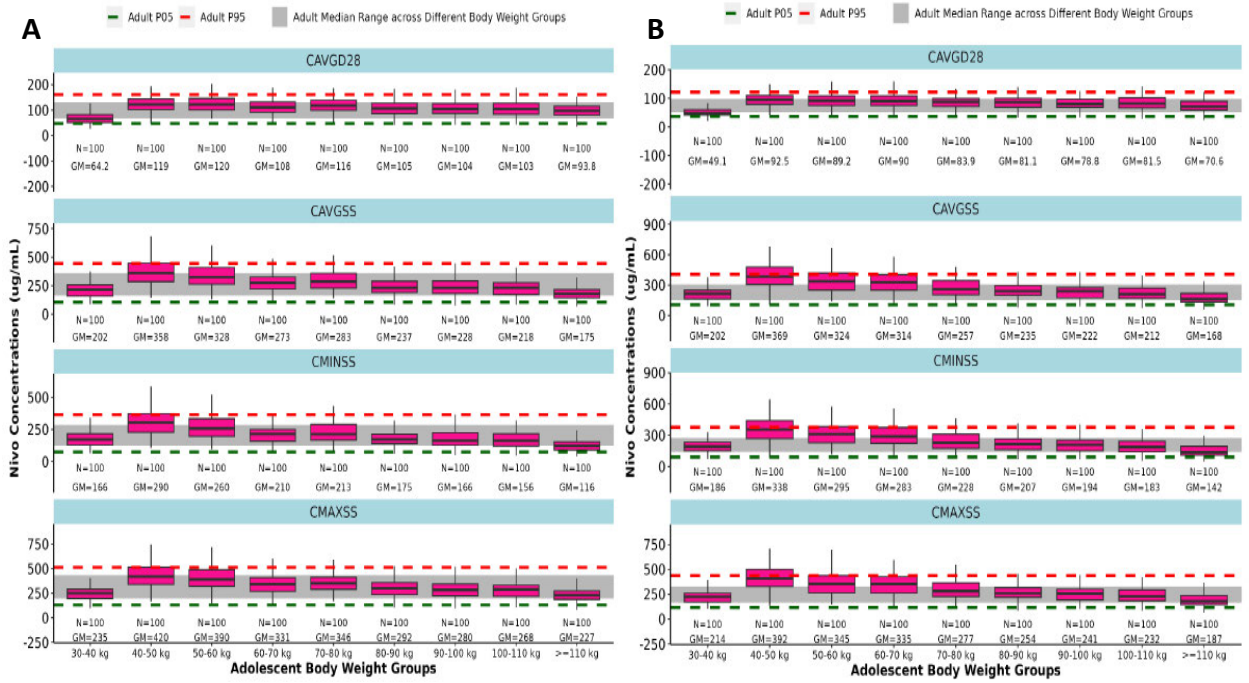


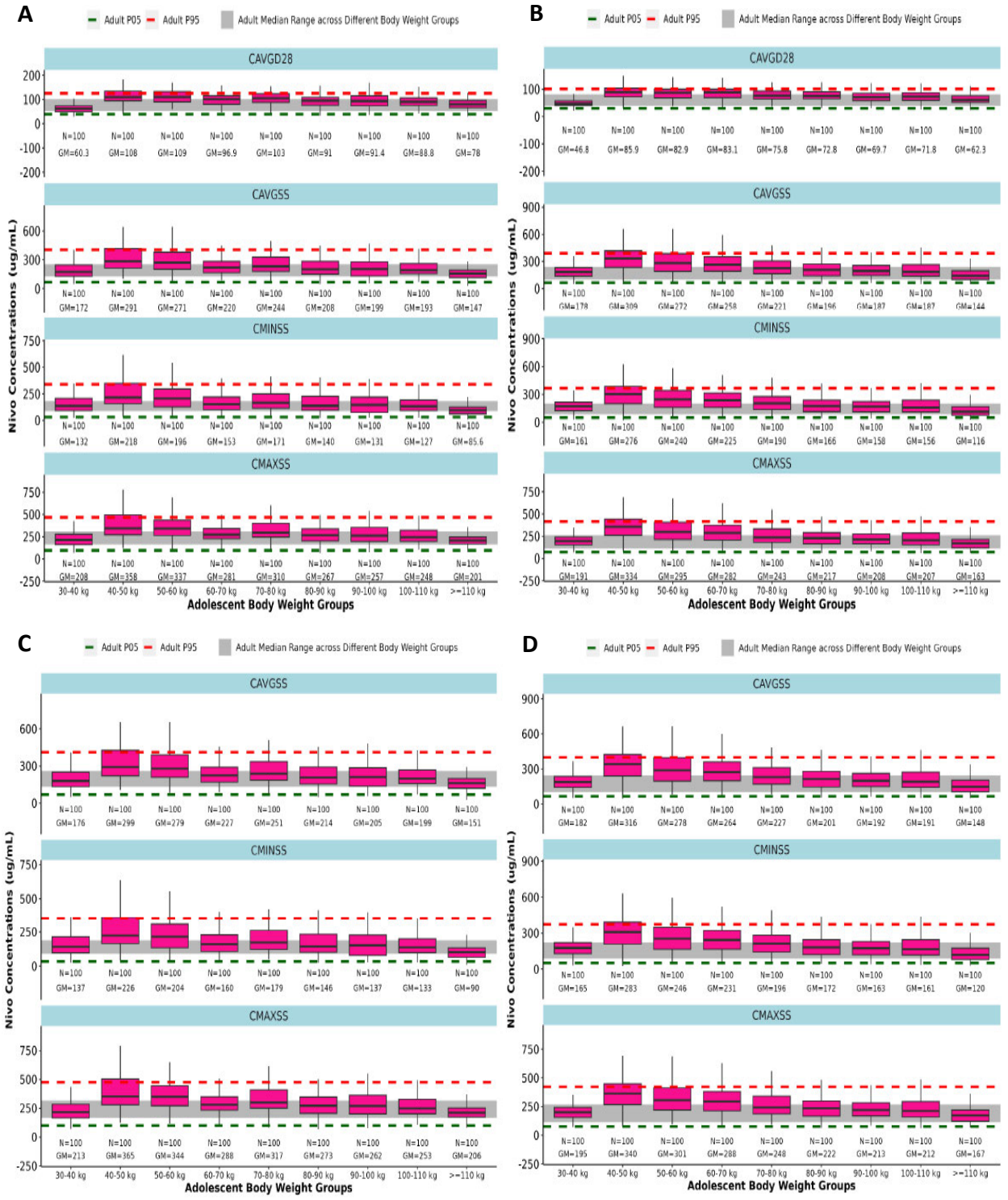
Source: Pediatric simulation report Figures 6.1.1.4-1, 6.1.1.4-2, 6.1.1.4-3, 6.1.1.4-4. Monotherapy with Q4W (A) or (B) Q2W. Monotherapy maintenance with Q4W (C) or Q2W (D).

Figure 2. Adjuvant treatment of melanoma: predicted nivolumab exposures in pediatric subjects with 2-weight band SC dosages of Q4W (A) or Q2W (B).



Source: Pediatric simulation report Figures 6.1.1.4-5, 6.1.1.4-6.

Figure 3. MSI-H or dMMR mCRC: predicted nivolumab exposures in pediatric subjects with 2-weight band SC dosages (Q2W or Q4W) for monotherapy or monotherapy maintenance.



Source: Pediatric simulation report Figures 6.1.1.4-7, 6.1.1.4-8, 6.1.1.4-9, 6.1.1.4-10. Monotherapy with Q4W (A) or (B) Q2W. Monotherapy maintenance with Q4W (C) or Q2W (D).

1.1.2.3. The FDA's assessment

The population PK analysis is considered adequate to predict exposure of pediatric patients 12 years and older to:

- verify that SC/IV GMR point estimate for PK endpoints is above 1 with uncertainties in SC absorptions for pediatric patients factored in,
- confirm alignment in exposure distribution with adults.

Based on the results from modeling and simulation, the proposed weight-based nivolumab-hyaluronidase SC dosages in pediatric patients 12 years and older for the indications evaluated are reasonable.

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