Office of Clinical Pharmacology Review

NDA or BLA Number	BLA 125377
Link to EDR	\\CDSESUB1\evsprod\BLA125377\0253
Submission Date	January 23, 2017
Submission Type	Priority
Brand Name	YERVOY
Generic Name	Ipilimumab
Dosage Form and Strength	Injection: 50 mg/10 mL; 200 mg/40 mL (5 mg/mL)
Route of Administration	Intravenous infusion
Proposed Indication	Treatment of unresectable or metastatic melanoma in adult and pediatric patients (>=12 years old)
Applicant	BMS
Associated IND	IND 119313
OCP Review Team	Youwei Bi, Ph.D.; Safaa Burns, Ph.D.; Jiang Liu, Ph.D.; Jeanne Fourie Zirkelbach, Ph.D.
OCP Final Signatory	

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1. EXECUTIVE SUMMARY

The applicant submitted a pediatric supplement to support the approval of ipilimumab for the treatment of unresectable or metastatic melanoma in pediatric patients (>=12 and <18 years old). The pediatric dosing regimen proposed by applicant is 3 mg/kg Q3W for a total of 4 doses, which is the same as approved in adult patients with advanced melanoma.

Ipilimumab was studied in two clinical trials with a total of 45 pediatric patients, including 17 adolescent patients 12 years of age and older with advanced melanoma. The overall safety profile of ipilimumab in adolescent patients 12 years of age and older was consistent with the known safety profile in adults. The efficacy for adolescent patients 12 years of age and older is extrapolated from the results in the adult patient population with advanced melanoma.

Based on the population pharmacokinetic analysis, a dosing regimen of 3 mg/kg Q3W provides a similar exposure in adolescent patients (>=12 and <18 years old) compared to adult patients with melanoma.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in this supplement for BLA 125377. This supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/ comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy for adolescent patients (>=12 & <18 years old) is extrapolated from the results in the adult patient population with advanced melanoma.
General dosing instructions	The recommended dose of Ipilimumab for treatmentof adult and pediatric patients (>=12 & <18 years old) with advanced melanoma is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No additional dose individualization based on intrinsic factors is needed for adolescent patients (>=12 & <18 years old) after dosing is adjusted for body weight. As in adults, an appropriate dose has not been established for patients with moderate or severe hepatic impairment.
Labeling	Generally acceptable. The review team has provided recommendations on specific content and formatting changes.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. To-be-marketed formulation was used in clinical trials.
Other (specify)	Not applicable.

1.2 Post-Marketing Requirements and Commitments

Not applicable

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Ipilimumab (YERVOY®) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody currently indicated for the treatment of unresectable or metastatic melanoma in adults. The pharmacokinetics of Ipilimumab has been studied in 6 phase 1 or 2 studies in adult subjects with advanced melanoma who received 3 or 10 mg/kg. The mean terminal half-life (T-HALF) of ipilimumab following IV administration was 15 days based on the non-compartmental analysis across studies. The mean clearance (CL) and volume of distribution at steady-state (VSS) were 15.2 mL/hr (range: 12.8 to 18.3 mL/hr) and 5.98 L (range: 5.5 to 6.7 L), respectively. Upon multiple repeated doses every 3 weeks, the accumulation ratio was less than or equal to 1.5, and steady-state was achieved by the third dose. A dose proportional increase in ipilimumab exposure from 0.3 to 10 mg/kg was also established by PPK analysis.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose of Ipilimumab for treatment of metastatic melanoma in adult and adolescent patients (>=12 & <18 years old) is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses.

2.2.2 Therapeutic individualization

Renal Impairment

No dose adjustment is needed for patients with renal impairment.

Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (total bilirubin [TB] >1.0 to 1.5 times the upper limit of normal [ULN] or AST >ULN). Ipilimumab has not been studied in patients with moderate (TB >1.5 to 3.0 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment.

Drug-Drug Interactions

No formal pharmacokinetic drug interaction studies have been conducted with Ipilimumab.

2.3 Outstanding Issues

Not applicable

2.4 Summary of Labeling Recommendations

The office of Clinical Pharmacology recommends the following labeling language with regard to pediatric indication in section 12.3:

"Based on a population PK analysis using available pooled data from 565 patients from 4 phase 2 adult studies (N=521) and 2 pediatric studies (N=44), body weight normalized clearance of ipilimumab is comparable between adult and pediatric subjects. In pediatric patients with a dosing regimen of 3 mg/kg every 3 weeks, the model simulated geometric mean (CV%) steady-state serum peak and trough concentrations of ipilimumab were 65.8 (17.6%) and 20.7 (33.1%) mcg/mL (for 2 to 6 years old), 70.1 (19.6%) and 19.6 (42.9%) mcg/mL (for 6 to <12 years old), and 73.3 (20.6%) and 17.8 (50.8%) mcg/mL (for 12 years and older), which are comparable to those in adult patients."

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Clinical Pharmacology Review Questions

3.1.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Two pediatric studies including advanced metastatic melanoma have been completed: CA184070 and CA184178. Study CA184070 was a Phase 1, dose-escalation trial in which 33 pediatric patients with untreatable, relapsed or refractory solid malignant tumors were enrolled. 5 adolescents patients 12 years of age and older with metastatic melanoma were treated with either ipilimumab 5 mg/kg (N=3) or 10 mg/kg (N=2) Q3W for 4 doses and then every 12 weeks thereafter. None of these 5 patients responded to the treatment. Study CA184178 was a single-arm open-label Phase 2 study in which 12 adolescents (ages 12 to 16 years) were treated with either 3mg/kg Q3W (N=4) or 10mg/kg Q3W (N=8). None of the participants treated with ipilimumab 3 mg/kg experienced a partial response (PR). Two participants treated with ipilimumab 10 mg/kg experienced a partial response (PR), and the PR for one participant was durable (ongoing for more than 1 year) (Table 1). Because of the limited experience with ipilimumab in pediatric patients, the efficacy of ipilimumab in pediatric patients between 12 and 18 years old is mainly extrapolated from the results in the adult advanced melanoma population. The efficacy in children younger than 12 years old has not been established.

Table 1: Summary of Efficacy Results from CA184070 and CA184178

NCI7458/CA184070	
5 mg/kg (n=3)	**10 mg/kg (n=2)**
Participants with Stable Disease, RECIST Criteria	
2/3[a]	0/2
Participants with Objective Response (PR or CR), RECIST Criteria	
0/3	0/2
CA184178	
3 mg/kg (n=4)	**10 mg/kg (n=8)**
1-year Survival Rate, mWHO Criteria	
75.0% (95% CI: 12.8, 96.1)	62.5% (95% CI: 22.9, 86.1)
Participants with Stable Disease, mWHO Criteria[b]	
1/4	1/8
Participants with Objective Response (PR or CR), mWHO Criteria	
0/4	2/8[c]
BORR, mWHO Criteria	
0% (95% CI: 0, 60.2)	25% (95% CI: 3.2, 65.1)
DCR, mWHO Criteria	
25% (95% CI: 0.6, 80.6)	37.5% (95% CI: 8.5, 75.5)
Median PFS, mWHO Criteria	
2.6 months (95% CI: 2.3, 8.5)	2.9 months (95% CI: 0.7, -)
Median OS	
18.2 months (95% CI: 8.9, 18.2)	not reached (95% CI: 5.2, -)

Source: Table 4 in Clinical Overview [Section 4.4], Page 18

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

The overall safety profile of ipilimumab in adolescent patients 12 years of age and older was consistent with the known safety profile in adults. The efficacy in adolescent patients 12 years of age and older is extrapolated from the results in the adult population with advanced melanoma. Based on the population pharmacokinetic analysis, a dosing regimen of 3 mg/kg Q3W produces a similar exposure to ipilimumab in adolescent patients (>=12 and <18 years old) as that in adult patients with melanoma. A positive exposure-response relationship was identified in adult patients with melanoma, where an increase in exposure is associated with an increase in overall survival and immune-related adverse events. Because of limited efficacy and safety data in adolescent patients 12 years of age and older, no exposure-response analysis was conducted in this population.

The efficacy and safety of ipilimumab in pediatric patients younger than 12 years of age have not been established.

3.2.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No dose adjustment is needed for patients with renal impairment. No dose adjustment is needed for patients with mild hepatic impairment (total bilirubin [TB] >1.0 to 1.5 times the upper limit of normal [ULN] or AST >ULN). Ipilimumab has not been studied in patients with moderate (TB >1.5 to 3.0 times ULN and any AST) or severe (TB >3 times ULN and any AST) hepatic impairment.

4. APPENDICES

4.1 Population PK Analyses

4.1.1 Introduction

In this submission, PPK analysis was intended to extend the characterization of ipilimumab PK from adult melanoma patients to children and adolescent patients with solid tumors. The PPK model has been used to compare the pediatric exposure with the approved dosing regimen (3 mg/kg Q3W) to exposure achieved in adult patients.

4.1.2 Population PK analysis

The PPK analysis dataset included 521 adult patients (2250 PK samples) from 4 phase 2 studies and 44 pediatric patients (289 PK samples) from a phase 1 study CA184070 and a phase 2 study CA184178. A summary table was provided to describe the age distribution among these patients (Table 2).

Ipilimumab pharmacokinetic profiles in adult and pediatric patients were adequately described using a two-compartment model with zero-order IV infusion and first-order elimination. The covariate effects retained in the base model include covariate effects of baseline weight and baseline LDH on clearance (CL), and baseline weight on central volume of distribution (VC). The age effect was incorporated into the full model regardless of statistical significance. The model estimates of the full model are shown in Table 3.

Based on the PPK analysis results, the applicant concludes that age does not appear to have an additional clinically relevant effect on CL, and a dose regimen of 3mg/kg Q3W ipilimumab was predicted to achieve similar exposures in adolescent and adult patients with metastatic melanoma.

Table 2: Summary of Age Distribution in 565 Patients included in PPK Analysis

Age group	Total	1mg/kg	3mg/kg	5mg/kg	10mg/kg
>=2 & <6	**N = 4**	1	1	2	
>=6 & <12	**N = 5**			2	3
>=12 & <18	**N = 26**		5	5	16
>=18 & <22	**N = 9**	2		4	2
>= 22	**N = 521**		104		360

Table 3: Parameter Estimates of the Full PPK Model

Name (Units)[a,b]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL (L/h)	θ_1	0.0141	2.45E-04 (1.74)	0.0136 - 0.0146
VC (L)	θ_2	4.12	0.0417 (1.01)	4.03 - 4.19
Q (L/h)	θ_3	0.0234	0.00257 (11.0)	0.0196 - 0.0292
VP (L)	θ_4	2.10	0.152 (7.24)	1.86 - 2.44
CL~WT	θ_7	0.954	0.0756 (7.92)	0.787 - 1.09
CL~LDH	θ_8	1.08	0.173 (16.0)	0.747 - 1.44
VC~WT	θ_{12}	0.891	0.0305 (3.42)	0.830 - 0.946
CL~AGE	θ_{14}	0.0529	0.0416 (78.6)	-0.0286 - 0.136
Random Effects[f]				
IIV CL[g]	$\omega_{1,1}$	0.131 (0.362)	0.0120 (9.16)	0.107 - 0.154
COV CL~VC	$\omega_{2,2}$	0.0248 (0.157)	0.00354 (14.3)	0.0208 - 0.0415
IIV CL:COV CL~VC	$\omega_{1,2}$	0.0309 (0.542)	0.00494 (16.0)	0.0178 - 0.0318
Residual Error				
Proportional Error	θ_5	0.175	0.00688 (3.93)	0.159 - 0.187
Additive Error (μg/mL)	θ_6	0.211	0.130 (61.6)	4.48E-05 - 0.763

Source: Table 5.1.1.2-1 in Population PK report section 5.1.1.2, Page 37

Reviewer's comments:

1. Goodness-of-fit plots (Figure 1 and Figure 2) and simulation-based diagnostics (prediction-corrected visual predictive check) (Figure 3) stratified by age groups showed that the final model adequately described the observed PK profile in adult (>18 years old) and adolescent patients (>=12 & <18 years old). All PK parameters were estimated with acceptable precision. The reviewer agrees with the applicant that the PK profile of ipilimumab in adolescent and adult patients can be adequately described by the proposed PPK model.

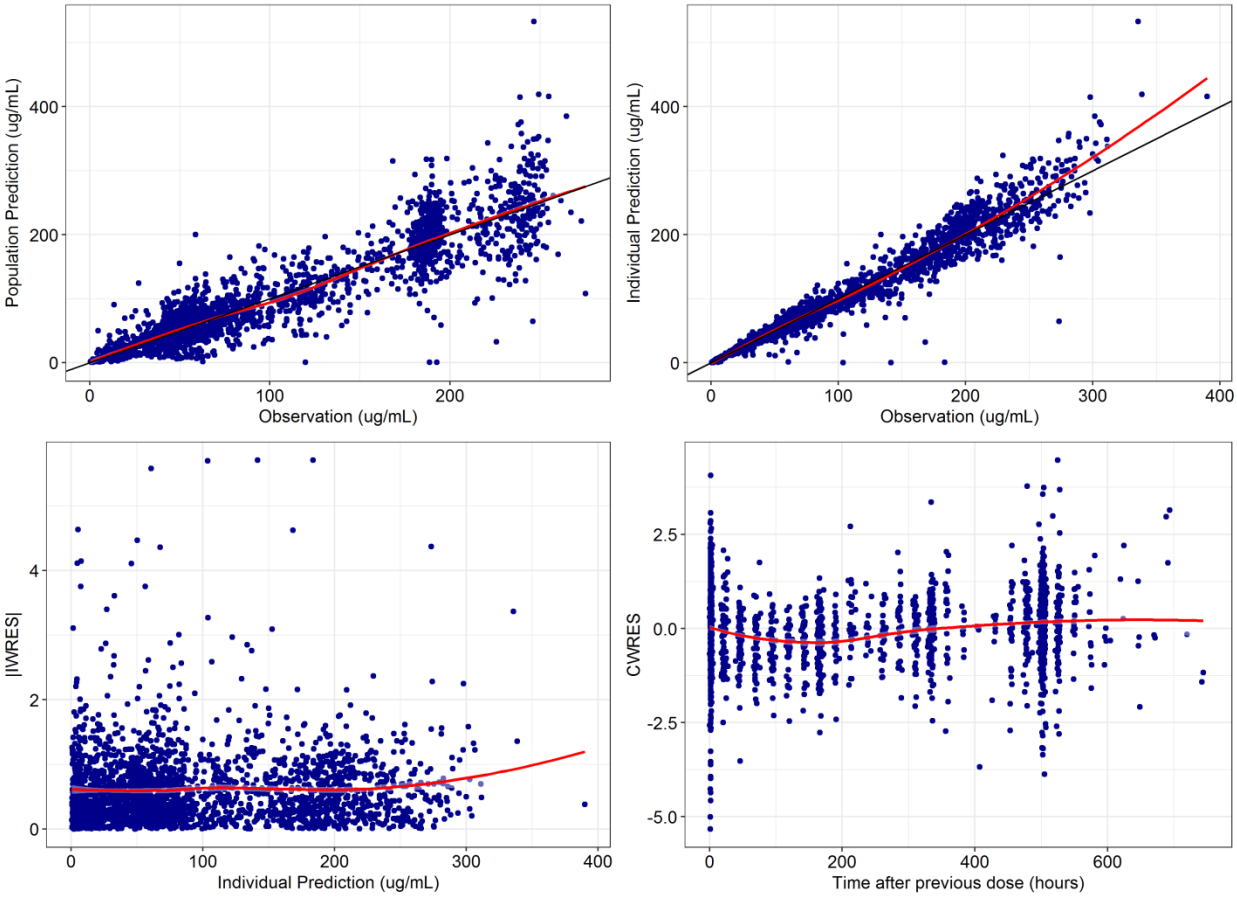
2. The estimated covariates effects (and 95% CIs) were shown in Figure 4. Weight has a clinically relevant effect on CL and V. Clearance increases only slightly less than proportional to body weight (allometric exponent of body weight on CL estimated to be ~0.95), which suggests a body weight-based dosing regimen will achieve similar exposure in patients across different weight groups. Age, however, was not found to be clinically relevant. The ratio of CL comparing a 15-year-old pediatric patient to a 57-year-old adult patient was estimated to be 0.93 with 95% CI including 1.

3. Simulations were conducted to compare exposures between adult and adolescent patients. The simulated Cmin, Cmax and Cavg after the fourth dose of ipilimumab for each age group ([2, 6), [6, 12), [12, 18) and older than 18) were presented in Figure 5. The geometric mean of Cmin after the fourth dose was 16.88% greater, the Cmax after the fourth dose was 0.83% greater, and the Cavg after the fourth dose was 5.10% greater in the pediatric group (12 to 18 years of age) compared with the adult group (18 to 80 years of age), respectively. Based on the simulation results, 3 mg/kg Q3W was deemed

to achieve similar exposure in adolescent (12 to 18 years of age) and adult patients (differences in GM exposures <20%).

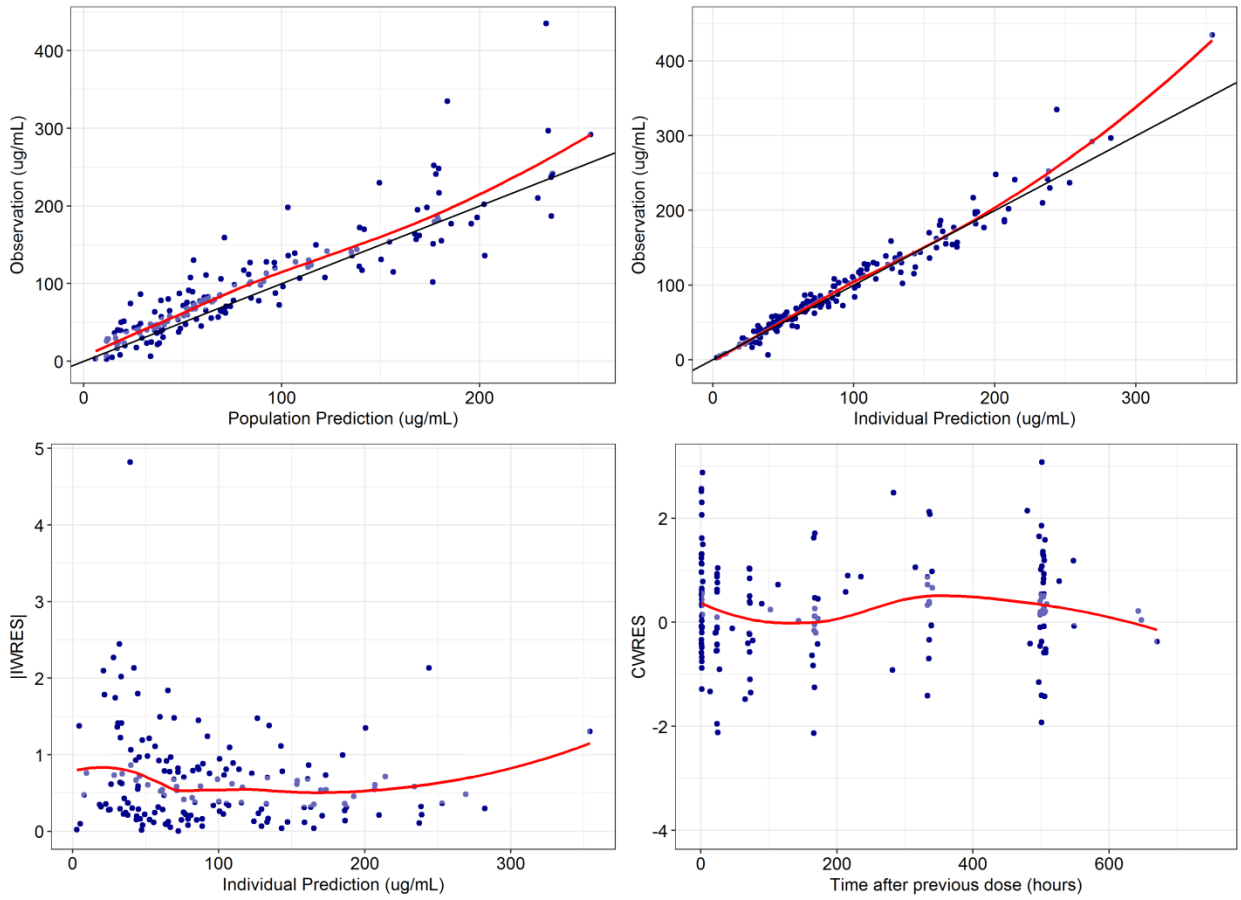
4. Simulations were also conducted to compare exposures among patients across different weight groups (Figure 6). The geometric mean of Cmin after the fourth dose was 17.1% greater, the Cmax after the fourth dose was 12.2% lower, and the Cavg after the fourth dose was 17.6% lower in the low weight group (10 to 20kg) compared with the high weight group (>57 kg), respectively. The exposure achieved by 3 mg/kg Q3W was predicted to be similar among patients with different body weights.

Figure 1: Goodness-of-fit Plots of Ipilimumab in Adult Patients (>= 18 Years Old) from Pop-PK Model.



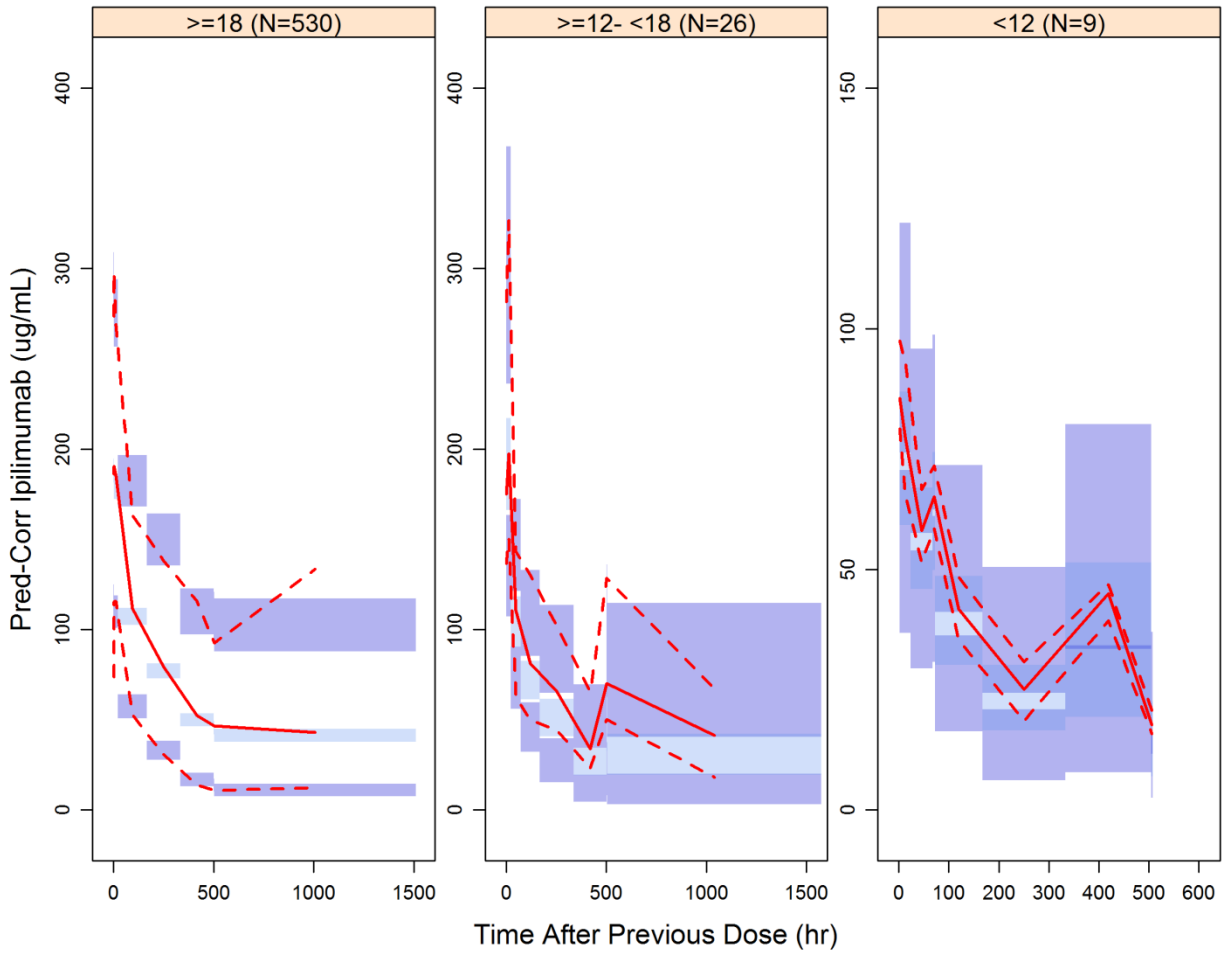
DV: Observations; PRED: Population Predictions; IPRED: Individual Predictions; CWRES: Conditional Weighted Residuals. Blue dots: steady-state concentrations. Red dots: non steady-state concentrations. Red solid line: Loess smooth through data.

Figure 2: Goodness-of-fit Plots of Ipilimumab in Adolescent Patients (>= 12 & <18 years old) from Pop-PK Model.



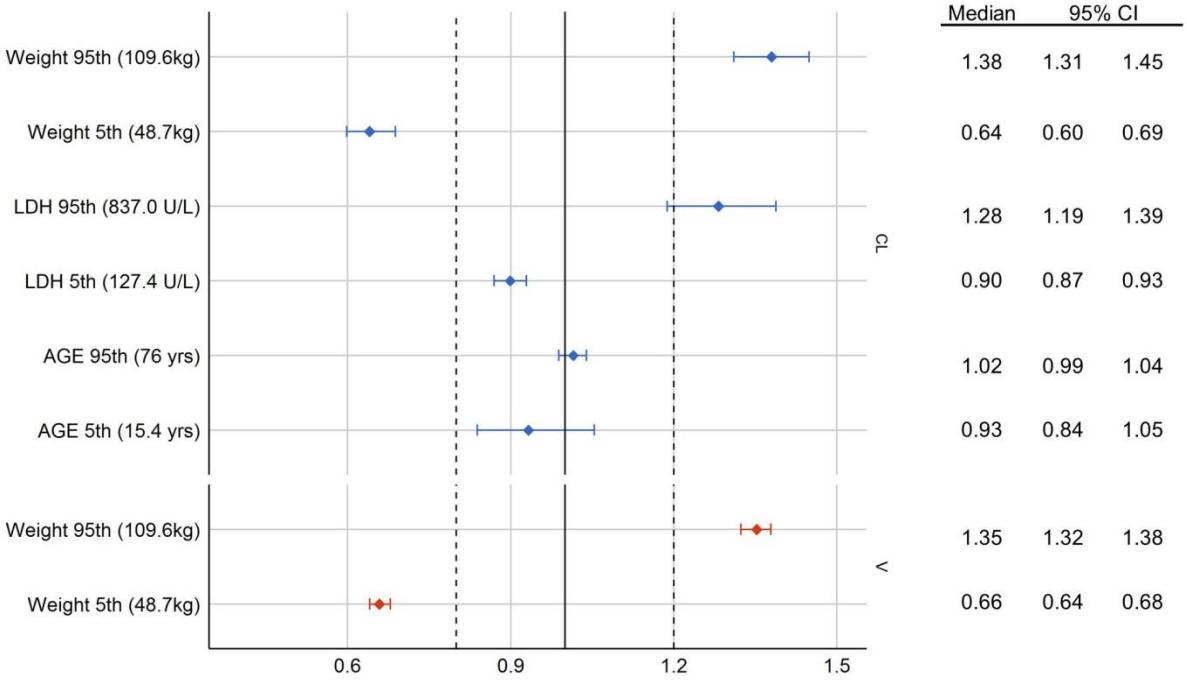
DV: Observations; PRED: Population Predictions; IPRED: Individual Predictions; CWRES: Conditional Weighted Residuals. Blue dots: steady-state concentrations. Red dots: non steady-state concentrations. Red solid line: Loess smooth through data.

Figure 3: Prediction-Corrected Visual Predictive Check for Ipilimumab Stratified by Age Groups



Red solid lines are median percentiles for observed data. Red dashed lines are 5th and 95th percentiles for observed data. Light blue area is the 95% confidence interval (CI) around the simulated median. Dark blue area is the 95% confidence interval (CI) around the simulated 5th and 95th percentiles.

Figure 4: Covariate Effects on PPK Model Parameters



Reference: Age (57 yrs), Weight (78 kg), LDH (210 U/L)

Figure 5: Simulated Cmin, Cmax and Cavg after the Fourth Dose of 3 mg/kg Q3W Ipilimumab Stratified by Age Groups ([2, 6), [6, 12), [12, 18) and larger than 18)

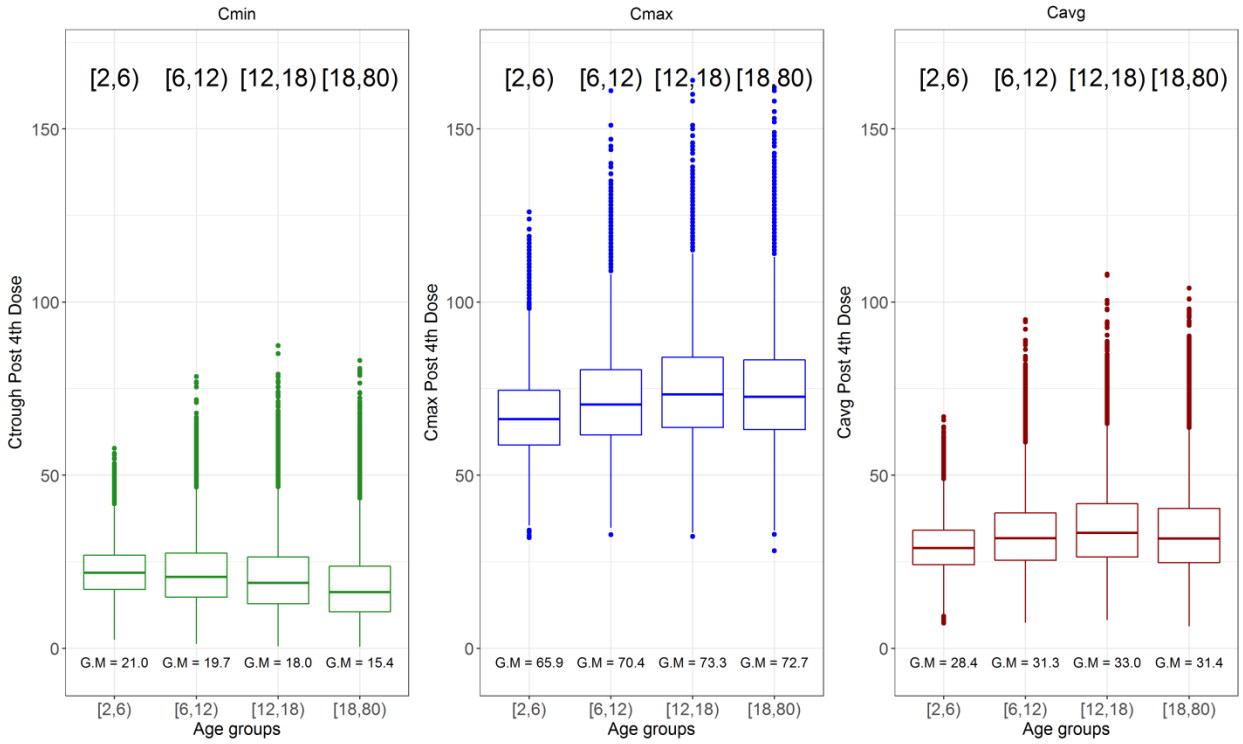
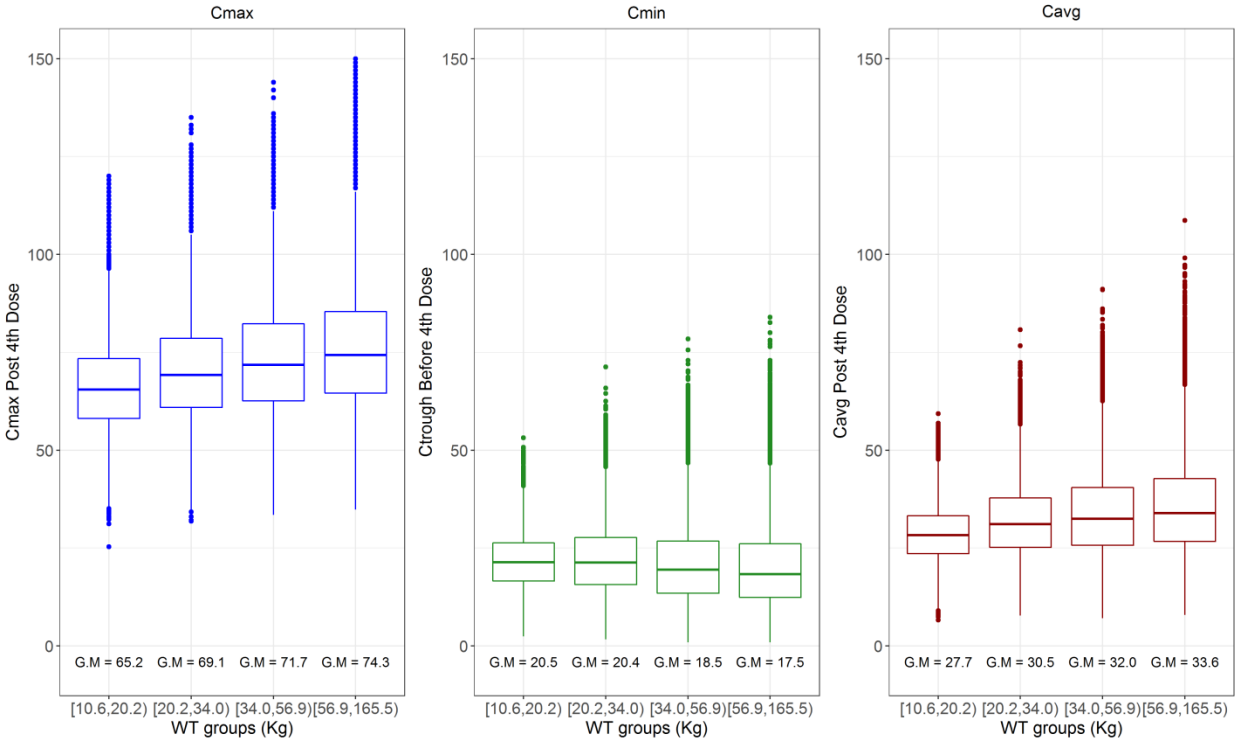


Figure 6: Simulated Cmin, Cmax and Cavg after the Fourth Dose of 3 mg/kg Q3W Ipilimumab Stratified by 4 Quartiles of Body Weight



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