Office of Clinical Pharmacology Review

NDA	BLA 761097/S-032 (SDN 1501)
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Applicant	Regeneron Pharmaceuticals, Inc
Submission Date	4/30/2025
Submission Type	Efficacy Supplement-Pediatric Exclusivity
Brand Name	LIBTAYO®
Generic Name	Cemiplimab-rwlc
Dosage Form and Strength	Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial
Route of Administration	IV infusion
Approved Indications[1]	• Cutaneous Squamous Cell Carcinoma • Basal Cell Carcinoma (BCC): • Non-Small Cell Lung Cancer (NSCLC)
Approved Dosages	350 mg/Q3W/IV infusion over 30 minutes
OCP Primary Review	Om Anand, Yangbing Li
OCP Secondary Review	Stacy Shord, Da Zhang
OCP Final Signatory	Ruby Leong

1. Executive Summary

LIBTAYO® (cemiplimab-rwlc) is an PD-1 blocking antibody. The Applicant submitted this sBLA to obtain pediatric exclusivity following completion of the pediatric studies described in the Written Request (WR) dated 4/15/2025 and to update the approved labeling with the results of the pediatric studies.

The submission includes the pediatric pharmacokinetic (PK) and safety data from Study R2810-ONC-1690 and an updated population PK (PopPK) analysis. The updated PopPK model includes data from 55 patients aged 0 to 25 years who received cemiplimab at dosages of 3 mg/kg or 4.5 mg/kg Q2W in this trial. The PK data from the 46 pediatric patients aged 1 to < 17 years included in this trial was within range of values previously observed in adults given similar dose based on body weight. The pharmacokinetic (PK) sampling and analysis plan completed as part of this trial are consistent with that described in the WR.

The revised labeling includes a description of the results from this pediatric study in Section 8.4 (Pediatric Use). FDA revised the proposed labeling to align with regulations and current best practices.

[1] For details see the USPI LINK

1.1 Recommendations

The Office of Clinical Pharmacology supports granting pediatric exclusivity and approving the supplement.

2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

2.1 Overview of the Regulatory Background

The Applicant submitted a Proposed Pediatric Study Request (PPSR) for cemiplimab and requested the issuance of a Written Request (WR) for the evaluation of cemiplimab in pediatric patients with relapsed/refractory solid tumors and CNS tumors. The final WR was issued on April 15, 2025 (Reference ID: 5572338) (b) (4)

The final WR included Study R2810-ONC-1690, a multicenter trial designed to determine the safety and recommended phase 2 dose (RP2D) of cemiplimab as monotherapy and in combination with radiation therapy. The study was conducted in two components:

- A Phase 1 dose-escalation to determine the safety, pharmacokinetics, and RP2D of cemiplimab monotherapy, with separate cohorts of patients with solid tumors and patients with CNS tumors
- An activity-estimating phase with a safety run-in to determine the safety and RP2D of cemiplimab in combination with radiation, conducted in patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG), newly diagnosed high-grade glioma (HGG), and recurrent HGG

The Applicant completed Study R2810-ONC-1690 and submitted supplemental BLA 761097/S-032 on April 30, 2025, to fulfill the WR commitments. The study met its futility criteria in the activity-estimating phase and was terminated early. Based on the lack of activity/efficacy observed in the pediatric patient population across the study, the Applicant is not seeking an indication for cemiplimab in pediatric patients; however, the Applicant updated the USPI with pediatric safety, efficacy, and PK information and is requesting Pediatric Exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act.

2.2 General Pharmacological and Pharmacokinetic Characteristics

The clinical pharmacology of cemiplimab was previously described in detail in the clinical pharmacology review of the original BLA 761,097. Refer to the original BLA Clinical Pharmacology Review[2] for a detailed description of the clinical pharmacology data.

Briefly, cemiplimab is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and is administered as an intravenous (IV) infusion over 30 minutes. Cemiplimab exhibits dose-proportional PK over the dose range of 1 mg/kg to 10 mg/kg Q2W. Steady state is achieved within 16 weeks following the approved recommended dosage.

The PK of cemiplimab is best described by a 2-compartment model with linear elimination. The steady-state volume of distribution of 5.2 L (24% CV). The estimated elimination half-life at steady state is approximately 19 days with a total clearance of cemiplimab of approximately 0.33 L/day (40% CV). Individual clearance estimates demonstrated time-varying changes in clearance described by a sigmoid-Emax function, with clearance decreasing by more than 30% over time

[2] DARRT: BLA-761097: REV-CLINPHARM-21 (Primary Review): LINK [MDR Link]

compared to baseline clearance (from 0.33 L/day to 0.21 L/day within 16 weeks of treatment); however, this decrease in clearance with time is not considered clinically important.

As a monoclonal antibody, the metabolism of cemiplimab is limited to proteolytic catabolism into small peptides and individual amino acids, predominantly by the reticuloendothelial system. Traditional distribution, metabolism, and excretion studies were not conducted as cemiplimab is a monoclonal antibody.

3. CLINICAL PHARMACOLOGY QUESTIONS

3.1 How do the exposure and PK parameters of cemiplimab in pediatric patients compare to that of adult patients receiving the approved recommended starting dose of 350 mg Q3W?

The Applicant revised the PopPK analysis to include the data from Study R2810-ONC-1690 to evaluate cemiplimab PK in pediatric and adult patients. The PopPK model included data from 55 patients aged 0 to 25 years who received cemiplimab at dosages of 3 mg/kg or 4.5 mg/kg IV (over 30 min) Q2W. The Applicant used the final model to simulate cemiplimab exposure after administration of age-appropriate dosing regimens and compare to adult reference exposures.

Based on single and multiple dose simulations, cemiplimab exposures (AUC, Cmax, and Ctrough) for the pediatrics who received 3 mg/kg IV Q2W were within range of that of adults who received 350 mg IV Q3W, but higher exposures were observed in pediatrics 0 to <12 years old who received 4.5 mg/kg IV Q2W compared to that of adults who received 350 mg IV Q3W. Overall, the lowest predicted median Ctrough,ss and highest Cmax,ss for all pediatrics were within the observed range for adults who received 350 mg IV Q3W.

The analysis demonstrates that systemic exposures in pediatric patients are within range of that of adult patients observed at a similar dose based on body weight. See the PopPK analysis summary (Section 5.2 Appendix) for detailed exposure metrics across pediatric age groups. These comparisons support the labeling statement that "*cemiplimab exposures in pediatric patients were within range of those observed in adults given a similar dose based on body weight*.

3.2 Do the components in the current submission fulfill the Written Request from a clinical pharmacology perspective?

Yes, the review team agrees that the clinical pharmacology components included in the final study report meet the WR requirements. The Applicant provided PK data across required age groups, conducted appropriate popPK modeling, and demonstrated adequate characterization of cemiplimab PK in the pediatric population. The WR components pertinent to clinical pharmacology are summarized below.

Study Population

Table 1 summarizes the enrollment summary and Written Request requirements versus actual enrollment for Study R2810-ONC-1690, and Table 2 summarizes the age-stratified PK analysis showing patient distribution across pediatric age groups and PK evaluable patients by study component.

Table 1: Study 1 (R2810-ONC-1690) Enrollment Summary

Component	Cemiplimab Dose	WR Requirement	Actual Enrollment
Phase 1 - Solid Tumors	3 mg/kg Q2W	A sufficient number of patients with solid tumors	8 patients
Phase 1 - CNS Tumors	3 mg/kg and 4.5 mg/kg Q2W	A minimum of 9 patients with CNS tumors	17 patients
Phase 1 Age Distribution	3 mg/kg and 4.5 mg/kg Q2W	At least 6 patients between birth to < 12 years and at least 3 patients between 12 to < 18 years	Birth to <12 years: 15 patients 12 to <18 years: 10 patients
Efficacy Phase (Phase 2) Total	RP2D from Phase 1	A minimum of 100 patients	32 patients total (*study terminated for futility*)
ndDIPG Cohort	3 mg/kg and 4.5 mg/kg Q2W	Approximately 40 patients will be randomized 1:1 to either conventionally fractionated radiation or hypofractionated radiation	11 patients
ndHGG Cohort	3 mg/kg and 4.5 mg/kg Q2W	Approximately 40 patients will be randomized 1:1 to either conventionally fractionated or hypofractionated radiation	12 patients
rHGG Cohort	3 mg/kg and 4.5 mg/kg Q2W	Approximately 20 patients will be enrolled	9 patients

Table 2: Study 1 Age Distribution

Age Group	Study Component	WR Requirement	Actual Enrollment	PK Evaluable Patients
Birth to <12 years	Phase 1: 15 patients; Activity Phase: 7 patients	A minimum of 12 patients birth to < 12 years	22 patients	21 patients with PK data
12 to ≤18 years	Phase 1: 10 patients; Activity Phase: 17 patients	A sufficient number of patients 12 to ≤ 18 years	27 patients	26 patients with PK data
>18 to ≤25 years	Activity Phase only: 8 patients	Phase 2 only (not specified for PK)	8 patients	8 patients with PK data[3]
Total PK Analysis Set	Phase 1: 25 patients; Activity Phase: 30 patients	PK samples from adequate patient numbers across age group	57 patients	55 patients with PK data

Review Team Comment:

- *Study terminated early for futility, enrolling only 32 of the minimum 100 patients*

[3]

required.

- *Age range expanded to include patients ≤25 years (8 patients ≥18 years enrolled across activity-estimating phase cohorts).*

PK Parameters (Clearance and Volume of Distribution)

PopPK analysis provided estimates of clearance and volume of distribution parameters across pediatric age groups, enabling comparison with adult PK parameters. Briefly, the PopPK Analysis (R2810-PK-24032-CP-01V2) included the following:

- Model development: Characterized cemiplimab in pediatric and adult patients
- Covariate analysis: Investigated effect of age and body size on CL and Vd
- Individual parameters: PK parameters reported by age groups
- Age-appropriate dosing: 3 mg/kg Q2W for ≥12 years; 4.5 mg/kg Q2W for <12 years achieved exposures comparable to efficacious adult doses
- Steady-State Achievement: Confirmed based on trough concentration comparisons between cycles
- Pediatric-Adult Exposure Comparison: Exposures for pediatric patients within range of that of adults receiving similar dose based on body weight
- Combination therapy PK: No clinically significant differences when administered with radiation therapy

Bioanalytical Method

A previously validated ELISA assay for cemiplimab quantification was used to determine serum levels in pediatric patients, consistent with ICH M10 guidelines. The method demonstrated adequate accuracy (within ±15% of nominal values, average101%), precision (CV% 5-6%), and linearity (78 ng/mL (LLOQ) to 100 ng/mL (ULOQ)) for characterizing cemiplimab concentrations collected from the pediatric patients. Method performance monitoring during study conduct, including run acceptance criteria verification (96% plate passing rate) and incurred sample reanalysis (94.6% passing rate), confirmed method suitability for the samples collected in this pediatric population.

3.3 Are other changes to the labeling warranted based on the pediatric clinical pharmacology data?

No, no other changes to the labeling are warranted beyond the pediatric information proposed for Section 8.4 (Pediatric Use).

4. LABELING CHANGES

The proposed key labeling changes to **Section 8.4: Pediatric Use** and Clinical Pharmacology assessment are summarized in the table below.

Applicant's Proposed Language	(b) (4)

	(b) (4) [redacted]
FDA Revision	Cemiplimab exposure in 46 pediatric patients aged 1 to < 17 years was within the range of values previously observed in adults given a similar dose based on body weight.
Rationale for Revision	• Restricted the summary of the trial to pediatric patients as defined by 21 CFR 201.57(c)(9)(iv)(A), which defines pediatric population(s) and pediatric patient(s) as the pediatric age group, from birth to 16 years. • Removed (b) (4) [redacted]

5. APPENDICES

5.1 Summary of Study R2810-ONC-1690

Study Overview

Study R2810-ONC-1690 was a multicenter trial with two components:

i. Phase 1 safety and PK study of single agent cemiplimab (REGN2810) in pediatric patients with r/r solid or CNS tumors.

ii. Safety and efficacy trial of cemiplimab in combination with radiotherapy in pediatric patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG), newly diagnosed high-grade glioma (HGG), or recurrent HGG.

Study Objectives

- Primary: Confirm safety and RP2D of cemiplimab in pediatric patients
- Primary: Characterize PK of cemiplimab in pediatric populations
- Secondary: Assess anti-tumor activity, immunogenicity, and safety profiles

Study Design: Multicenter trial with two parallel phases conducted simultaneously

- Phase 1: 3+3 dose escalation in participants 0 to <18 years with r/r solid or CNS tumors (n=25)
- Efficacy Phase: Safety and activity-estimating evaluation in participants 3 to <25 years (newly diagnosed DIPG, newly diagnosed HGG, or recurrent HGG) receiving cemiplimab with radiotherapy (n=32)
- Cohort Stratification:
    - *Phase 1*: 4 cohorts by age (0 to <12, 12 to<18 years) × tumor type (solid, CNS) with 3 or 4.5 mg/kg Q2W
    - *Efficacy Phase*: 6 cohorts by age (3 to <12, 12 to 25 years) × tumor type (ndDIPG, ndHGG, rHGG)

Patient Demographics

- Analysis sets: 55 participants in PK analysis set, 47 in immunogenicity analysis
- Age range: 1-24 years with cohort-specific distributions
- Baseline characteristics: Median body weight varies by cohort (range 8.4-101.2 kg)

Dosing Regimen

- Standard dose: 3 mg/kg IV Q2W (30-minute infusion)
- Higher dose: 4.5 mg/kg IV Q2W for participants <12 years
- Rationale: Dosages selected to approximate adult efficacy exposures (350 mg Q3W)
- Administration: Every 14 days

The following clinical pharmacology evaluations were included in the trial:

- PK: Describe concentration-time profiles of cemiplimab in pediatric patients receiving monotherapy (Phase 1) and combination with radiotherapy (Efficacy Phase)
- Immunogenicity Assessment: Characterize ADA and NAb responses and their relationship to systemic exposure.
- Dosage Selection: Evaluate age-appropriate dosing regimens to achieve exposures

comparable to efficacious adult dosages

- PopPK: Incorporate pediatric data into existing PopPK models to refine parameter estimates

Reviewer's note: The efficacy evaluation was terminated early due to futility analysis leading to study closure; confirming that efficacy was not established in the pediatric population.

PK Sampling and Analysis Methodology

- Assay: Validated ELISA (LLOQ: 0.078 mg/L)
- Sampling schedule: Pre-dose, end of infusion, 8h, 24h post-dose through multiple cycles
- Follow-up: Additional samples at EOT and every 12 weeks up to 52 weeks
- Sample analysis: 704 samples collected, 92.2% quantifiable
- Parameters assessed: Ctrough and Cmax at first dose and steady state (Week 16)

Immunogenicity Results[4]

- Overall incidence: 4.3% treatment-emergent ADA (2/47 participants)
- ADA characterized as transient, low titer (<1,000); no neutralizing antibodies detected.
- No effect on cemiplimab concentrations observed in this study population.

Reviewer's note: The ADA incidence in pediatric patients (4.3%) is generally consistent with that observed in adults (2%). The slightly higher incidence in pediatrics may be due to the smaller sample size (47 vs 1029 patients).

Pharmacokinetic Results

The Applicant summarized the PK data as follows:

Phase 1 (Monotherapy)

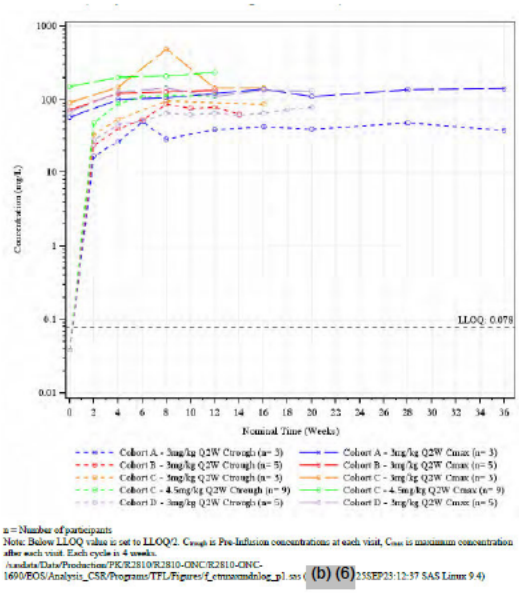
- 3 mg/kg Q2W (total n=16, steady-state n=3): At steady state (Week 16), median (Q1:Q3) Ctrough is 66.1 (39.4:78.6) mg/L and Cmax is 129 (117:140) mg/L
- 4.5 mg/kg Q2W (total n=9, steady-state data n=1): At steady state (Week 16), Ctrough is 113 mg/L and Cmax is 236 mg/L.

Efficacy Phase (Combination with Radiotherapy)

- 3 mg/kg Q2W (total n=23, steady-state n=16): At steady state (Week 16), median (Q1:Q3) Ctrough is 90.2 (77.3:104) mg/L and Cmax is 177 (149:200) mg/L.
- 4.5 mg/kg Q2W (total n=7, steady-state n=6): At steady state (Week 16), median (Q1:Q3) Ctrough is 106 (70.0:137) mg/L and Cmax is 217 (198:260) mg/L.

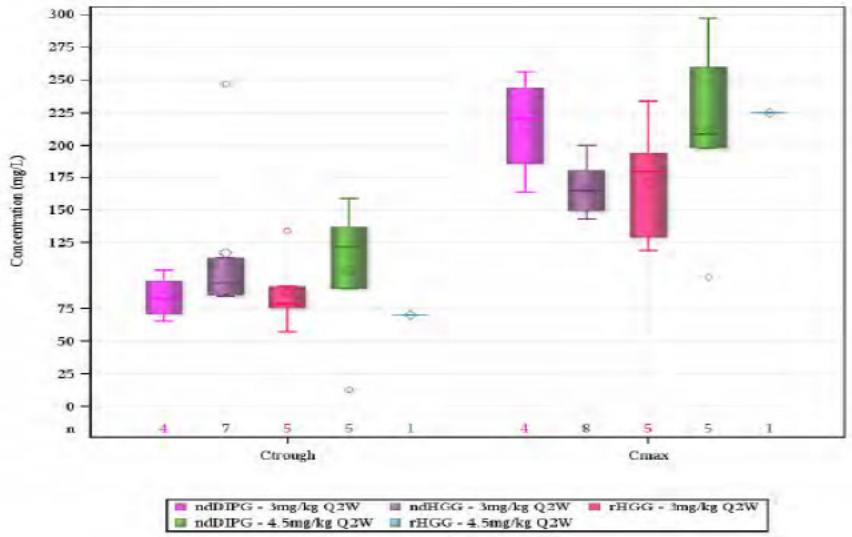
[4] Clinical Pharmacology Report R2810-ONC-1690-CP-01V1, Pages 46-49, Table 6, Figures 13-14

Figure 1: Median Concentration-Time Profiles by Dose Level[5]



n = Number of participants
Note: Below LLOQ value is set to LLOQ/2. Ctrough is Pre-Infusion concentrations at each visit, Cmax is maximum concentration after each visit. Each cycle is 4 weeks.
/sasdata/Data/Production/PK/R2810/R2810-ONC/R2810-ONC-1690/EOS/Analysis_CSR/Programs/TFL/Figures/f_ctrmaxmdnlog_p1.sas ((b) (6) 25SEP23:12:37 SAS Linux 9.4)

Figure 2: Steady-State Exposure Comparison[6]

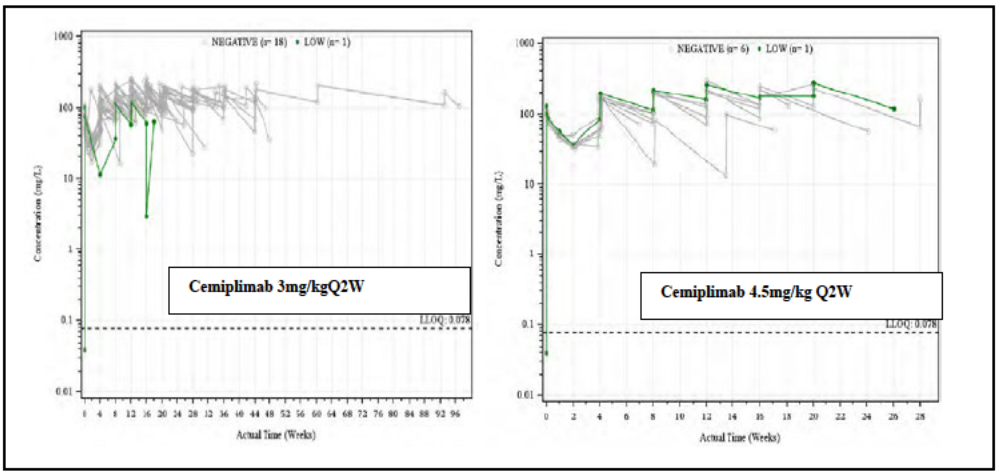


n = Number of participants; ndDIPG = Newly diagnosed diffuse intrinsic pontine glioma; ndHGG = Newly diagnosed high-grade glioma; rHGG = Recurrent high-grade glioma
Note: Steady State: Ctrough at Cycle 4 Day 1 Pre-Dose; Cmax at Cycle 4 Day 1 End of Infusion. Below LLOQ value is set to 0. Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1. Each cycle is 4 weeks.
/sasdata/Data/Production/PK/R2810/R2810-ONC/R2810-ONC-1690/EOS/Analysis_CSR/Programs/TFL/Figures/f_ctrmaxbox_ss_eff.sas ((b) (6) 25SEP23:12:37 SAS Linux 9.4)

[5] Source: Figure 2: Median Ctrough and Cmax of Functional Cemiplimab in Serum from Pediatric Participants by Nominal Time, Cohort, and Dose Level in Phase 1 (Study R2810-ONC-1690, Log-Scaled, PKAS)

[6] Source: Figure 8: Box Plot of Steady State (Week 16) Ctrough and Cmax of Functional Cemiplimab in Serum from Pediatric Participants by Tumor Type and Dose Level in Efficacy Phase (Study R2810-ONC-1690, PKAS)

Figure 3: Individual Cemiplimab Concentrations Over Time by ADA Status[7]



[7] Source: Figure 13 and Figure 14: Individual Concentrations of Functional Cemiplimab in Serum from Pediatric Participants by Maximum Titer Category in Efficacy Phase (Study R2810-ONC-1690)

5.2 Population PK Analysis

5.2.1 Executive Summary

The FDA's Assessment: The pharmacometrics analyses were focused on population PK analysis of cemiplimab in serum using combined data from pediatric and adult patients to estimate model-based PK parameters; and compare the exposures of cemiplimab between pediatric and adult patients.

The overall model risk is considered low. In line with the determined model risk and specific objectives, following model evaluation/additional analysis was conducted for the respective methodologies as outlined in **Error! Reference source not found.**4.

Table 3. FDA - Assessment of Model Risk

Question of interest	Could the population PK model describe the PK of cemiplimab in pediatric patients?
Context of use	Population PK analysis was used to describe the PK and compare the exposures of cemiplimab in pediatric and adult patients.
Decision consequence	Low
Model influence	Low No dosages for pediatric patients are proposed in the labeling. Comparison of cemiplimab exposures between pediatric and adult patients were added in section 8.4 of labeling.
Model risk	Low

Table 4. FDA - Model Evaluation

Methodology	Objective	Model evaluation	Section
PopPK	Assess the PK of cemiplimab in pediatric and adult patients	The population PK model was evaluated by goodness-of-fit plots and pcVPC analysis.	5.2.2

5.2.2 PPK Assessment Summary

The Applicant's Position:

General Information	
Objectives of PPK Analysis	Develop a popPK model of cemiplimab in serum using combined data from pediatric and adult participants to estimate model-based PK parameters. • Obtain PK parameter estimates of clearance and volumes of distribution for pediatric participants. • Characterize relationships between dose, exposure, and covariates. • Determine model predicted exposure metrics (e.g., Cmax, Ctrough, AUC) after first dose and at steady-state, etc.) in a simulated pediatric population receiving 3 and 4.5 mg/kg IV Q2W compared to an adult population receiving 350 mg IV Q3W
Study Included (Table **5**)	Adults: R2810-ONC-1423, R2810-ONC-1540, R2810-ONC-1620, R2810-ONC-1624 Pediatrics: R2810-ONC-1690
Dose(s) Included (	Adults:1, 3, 10 mg/kg Q2W, 3 mg/kg Q3W, 200 mg Q2W, 350 mg Q3W Pediatrics: 3, 4.5 mg/kg Q2W

Table **5**)			
Population Included		Adult patients with advanced malignancies, CSCC, BCC, NSCLC Pediatric patients with solid or CNS tumors, DIPG, HGG	
Population Characteristics (Table and Table)	General	Age median: 66 (range: 1 - 96) years old Weight median: 72.7 (range: 8.4 - 172) kg Gender: 914 (70.8%) male Race: 1140 (88.3%) White 26 (2.0%) Black/African American 49 (3.8%) Asian 76 (5.9%) Other or missing	
	Organ Impairment	NA	
	Pediatrics	46 Pediatrics: Age median: 12 (range: 1-16) years old Weight median: 41.6 (range: 8.4 – 87.5) kg	
No. of Patients, PK Samples, and BLQ		996 PK samples from 197 patients. 67 (6.77%) BLQ samples.	
Sampling Schedule	Rich Sampling	NA	
	In ITT Population	Sparse sampling.	
Covariates Evaluated	Static	NA	
	Time-varying	NA	
Final Model		**Summary**	**Acceptability [FDA's comments]**
Software and Version		Nonlinear mixed effects modeling methodology was performed by NONMEM (version 7.5.0) with FOCEI method.	Acceptable
Model Structure		Two-compartment model with linear elimination and a sigmoid elimination function for the time-varying change in clearance.	Acceptable
Model Parameter Estimates			
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)			Acceptable
BLQ for Parameter Accuracy		BLQ samples were excluded from the analysis	Acceptable
GOF, VPC		Figure 1 and Figure 2	Acceptable
Significant Covariates and Clinical Relevance		Figure 3	Acceptable
Analysis Based on Simulation		Figure **4** and **Figure 5** The exposure in pediatric patients was comparable to that in adults receiving cemiplimab intravenously 350 mg every 3 weeks, with slightly higher exposure seen for pediatric patients 0 to less than 12 years old receiving 4.5 mg/kg every 2 weeks.	Acceptable. Additional simulation was performed by reviewer, and results are shown in section **Error! Reference source not found.**
Labeling Language		**Description**	**Acceptability [FDA's comments]**
12.3 PK		NA	Exposures comparison between

		pediatric and adult patients were described in section 8.4 of labeling

Table 5. Summary of Studies in Population PK Analysis

Study Number	N	Phase	Cancer Type	Population Type	Dosing Regimens	Sampling Schedule
R2810-ONC-1423	398	1	Advanced Malignancies	Adult	1, 3, or 10 mg/kg Q2W, 200 mg Q2W, or 3 mg/kg Q3W	Dense (cycle 1), Sparse (other cycles)
R2810-ONC-1540	361	2	CSCC	Adult	3 mg/kg IV Q2W, 350 mg IV Q3W	Sparse (all cycles)
R2810-ONC-1620	132	2	BCC	Adult	350 mg IV Q3W	Sparse (all cycles)
R2810-ONC-1624	345	3	NSCLC	Adult	350 mg IV Q3W	Sparse (all cycles)
R2810-ONC-1690	55	1	Solid or CNS tumors, DIPG, HGG	Pediatric	3 mg/kg or 4.5 mg/kg IV Q2W	Sparse (all cycles)

BCC = Basal Cell Carcinoma; CNS = Central Nervous System; CSCC = Cutaneous Squamous Cell Carcinoma; DIPG = Diffuse Intrinsic Pontine Glioma; HGG = High Grade Glioma; IV = Intravenous; NSCLC = Non-Small Cell Lung Cancer; Q2W = Every 2 Weeks; Q3W = Every 3 Weeks

Source: R2810-PK-24032-CP-01V2, Page 17, Table 2.

Table 6. Summary of Patient Characteristics (Continuous) Stratified by Study and Overall

Covariate	1423 (N=398)	1540 (N=361)	1620 (N=132)	1624 (N=345)	1690 (N=55)	Overall (N=1291)
Age (years)						
Mean (SD)	61.1 (12.1)	72.6 (11.5)	67.1 (12.6)	62.9 (8.16)	12.0 (5.21)	63.3 (16.0)
Median [Min, Max]	62.0 [27.0, 88.0]	74.0 [38.0, 96.0]	68.0 [38.0, 90.0]	63.0 [31.0, 79.0]	12.0 [1.00, 24.0]	66.0 [1.00, 96.0]
Baseline Weight (kg)						
Mean (SD)	77.0 (18.8)	79.1 (18.7)	77.0 (19.2)	70.9 (15.2)	47.5 (21.2)	74.7 (19.2)
Median [Min, Max]	75.3 [30.9, 156]	77.0 [31.0, 172]	73.2 [44.6, 135]	69.6 [37.6, 138]	46.8 [8.40, 101]	72.7 [8.40, 172]
Baseline Height (cm)						
Mean (SD)	168 (10.1)	171 (9.89)	171 (9.20)	169 (8.40)	147 (23.6)	169 (11.5)
Median [Min, Max]	167 [142, 199]	173 [140, 198]	171 [147, 194]	170 [143, 194]	151 [77.0, 183]	170 [77.0, 199]
Baseline Body Mass Index (kg/m2)						
Mean (SD)	27.0 (5.76)	26.9 (5.54)	26.2 (5.60)	24.7 (4.58)	20.8 (5.37)	26.0 (5.56)
Median [Min, Max]	26.3 [14.8, 56.3]	26.1 [13.8, 55.5]	24.8 [16.8, 42.9]	24.3 [15.5, 43.1]	19.8 [10.1, 35.9]	25.4 [10.1, 56.3]
Baseline Body Surface Area (m2)						
Mean (SD)	1.86 (0.242)	1.91 (0.237)	1.88 (0.244)	1.80 (0.203)	1.37 (0.408)	1.84 (0.263)
Median [Min, Max]	1.85 [1.12, 2.67]	1.90 [1.17, 2.72]	1.85 [1.38, 2.53]	1.81 [1.27, 2.54]	1.40 [0.414, 2.23]	1.84 [0.414, 2.72]
Baseline Albumin (g/L)						
Mean (SD)	36.7 (4.46)	38.5 (5.17)	41.6 (6.60)	38.4 (5.41)	41.5 (5.79)	38.4 (5.43)
Median [Min, Max]	37.0 [22.0, 48.0]	40.0 [19.5, 50.0]	41.0 [28.0, 93.0]	38.9 [20.0, 53.5]	42.0 [25.0, 53.0]	39.0 [19.5, 93.0]
Baseline Creatinine (micromol/L)						
Mean (SD)	78.0 (23.8)	1390 (10100)	79.5 (23.6)	75.7 (20.2)	48.4 (17.5)	443 (5390)
Median [Min, Max]	73.4 [33.6, 186]	79.6 [41.0, 95000]	75.1 [37.1, 156]	73.2 [35.4, 168]	43.3 [17.7, 93.7]	74.3 [17.7, 95000]
Baseline ALP (IU/L)						
Mean (SD)	116 (82.9)	92.1 (45.0)	94.2 (44.9)	118 (74.1)	161 (267)	110 (87.0)
Median [Min, Max]	90.8 [32.0, 673]	83.0 [41.0, 501]	86.0 [34.0, 385]	97.0 [25.0, 583]	106 [37.0, 2050]	89.0 [25.0, 2050]
Baseline Creatinine Clearance (mL/min)						
Mean (SD)	95.9 (40.1)	80.2 (35.7)	88.2 (34.1)	92.1 (30.3)	117 (66.9)	90.6 (38.3)
Median [Min, Max]	91.3 [24.9, 419]	73.8 [0.0476, 218]	84.3 [28.6, 208]	88.3 [35.9, 253]	114 [1.19, 290]	85.4 [0.0476, 419]

Covariate	1423	1540	1620	1624	1690	Overall
	(N=398)	(N=361)	(N=132)	(N=345)	(N=55)	(N=1291)
Baseline AST (IU/L)						
Mean (SD)	32.0 (25.4)	22.3 (10.7)	22.3 (9.76)	21.3 (11.9)	27.9 (13.8)	25.3 (17.6)
Median [Min, Max]	24.0 [6.00, 179]	20.0 [7.00, 99.0]	20.0 [9.00, 92.0]	18.0 [6.97, 133]	26.0 [8.00, 70.0]	21.0 [6.00, 179]
Baseline ALT (IU/L)						
Mean (SD)	27.9 (24.5)	20.9 (19.8)	19.9 (11.8)	22.1 (17.1)	30.4 (21.6)	23.7 (20.4)
Median [Min, Max]	22.0 [5.00, 196]	17.0 [5.00, 234]	16.0 [5.00, 69.0]	17.0 [4.00, 133]	24.0 [5.00, 101]	19.0 [4.00, 234]
Baseline Bilirubin (micromol/L)						
Mean (SD)	9.04 (5.04)	161 (2340)	8.08 (4.58)	9.34 (4.75)	7.61 (5.37)	51.5 (1240)
Median [Min, Max]	8.21 [0.350, 44.5]	8.55 [1.71, 43700]	6.84 [1.71, 31.1]	8.55 [1.80, 49.1]	6.84 [1.71, 34.2]	8.00 [0.350, 43700]
Baseline LDH (IU/L)						
Mean (SD)	379 (344)	213 (89.6)	NA (NA)	311 (259)	NA (NA)	304 (266)
Median [Min, Max]	282 [80.0, 3120]	190 [88.0, 664]	NA [NA, NA]	247 [69.0, 2650]	NA [NA, NA]	222 [69.0, 3120]
Missing	0 (0%)	0 (0%)	132 (100%)	0 (0%)	55 (100%)	187 (14.5%)
Baseline IgG (g/L)						
Mean (SD)	10.2 (3.97)	10.3 (3.26)	NA (NA)	NA (NA)	NA (NA)	10.2 (3.74)
Median [Min, Max]	9.55 [1.29, 27.9]	10.2 [1.24, 21.6]	NA [NA, NA]	NA [NA, NA]	NA [NA, NA]	9.67 [1.24, 27.9]
Missing	0 (0%)	164 (45.4%)	132 (100%)	345 (100%)	55 (100%)	696 (53.9%)
Baseline PD-L1 (%)						
Mean (SD)	9.94 (23.1)	25.8 (33.3)	0.960 (2.19)	69.3 (24.0)	NA (NA)	40.8 (37.6)
Median [Min, Max]	0 [0, 95.0]	5.00 [0, 100]	0 [0, 10.0]	70.0 [0, 100]	NA [NA, NA]	50.0 [0, 100]
Missing	260 (65.3%)	206 (57.1%)	82 (62.1%)	44 (12.8%)	55 (100%)	647 (50.1%)

ALP = Alkaline Phosphatase; ALT = Alanine Transaminase; AST = Asparate Transferase; IgG = Immunoglobulin G; IU = International Units; LDH = Lactate Dehydrogenase; Min = Minimum; Max = Maximum; PD-L1 = Programmed Cell Death

Source: R2810-PK-24032-CP-01V2, Page 29-30, Table 3.

Table 7 Summary of Participant Characteristics (Categorical)
Stratified by Study and Overall

Covariate	1423 (N=398)	1540 (N=361)	1620 (N=132)	1624 (N=345)	1690 (N=55)	Overall (N=1291)
Sex						
Male	204 (51.3%)	288 (79.8%)	89 (67.4%)	302 (87.5%)	31 (56.4%)	914 (70.8%)
Female	194 (48.7%)	73 (20.2%)	43 (32.6%)	43 (12.5%)	24 (43.6%)	377 (29.2%)
Race						
White	352 (88.4%)	351 (97.2%)	98 (74.2%)	300 (87.0%)	39 (70.9%)	1140 (88.3%)
Black/African American	19 (4.8%)	1 (0.3%)	0 (0%)	1 (0.3%)	5 (9.1%)	26 (2.0%)
Asian	7 (1.8%)	5 (1.4%)	0 (0%)	36 (10.4%)	1 (1.8%)	49 (3.8%)
American Indian/Alaska Native	1 (0.3%)	0 (0%)	0 (0%)	6 (1.7%)	2 (3.6%)	9 (0.7%)
Native Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.8%)	1 (0.1%)
Other	1 (0.3%)	0 (0%)	0 (0%)	2 (0.6%)	1 (1.8%)	4 (0.3%)
Unknown	12 (3.0%)	1 (0.3%)	0 (0%)	0 (0%)	4 (7.3%)	17 (1.3%)
Not reported	6 (1.5%)	3 (0.8%)	1 (0.8%)	0 (0%)	2 (3.6%)	12 (0.9%)
Missing	0 (0%)	0 (0%)	33 (25.0%)	0 (0%)	0 (0%)	33 (2.6%)
Ethnicity						
Not Hispanic/Latino	348 (87.4%)	335 (92.8%)	97 (73.5%)	311 (90.1%)	31 (56.4%)	1122 (86.9%)
Hispanic/Latino	35 (8.8%)	8 (2.2%)	2 (1.5%)	34 (9.9%)	21 (38.2%)	100 (7.7%)
Not reported	15 (3.8%)	18 (5.0%)	0 (0%)	0 (0%)	3 (5.5%)	36 (2.8%)
Missing	0 (0%)	0 (0%)	33 (25.0%)	0 (0%)	0 (0%)	33 (2.6%)
Tumor Type						
CSCC	26 (6.5%)	361 (100%)	0 (0%)	0 (0%)	0 (0%)	387 (30.0%)
BCC	4 (1.0%)	0 (0%)	132 (100%)	0 (0%)	0 (0%)	136 (10.5%)
NSCLC	71 (17.8%)	0 (0%)	0 (0%)	345 (100%)	0 (0%)	416 (32.2%)
CC	20 (5.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (1.5%)
Others	277 (69.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	277 (21.5%)
CNS tumor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	17 (30.9%)	17 (1.3%)
ndDIPG (Newly Diagnosed DIPG)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (18.2%)	10 (0.8%)
ndHGG (Newly Diagnosed HGG)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (21.8%)	12 (0.9%)
rHGG (Recurrent HGG)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (14.5%)	8 (0.6%)
Solid tumor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (14.5%)	8 (0.6%)
Monotherapy						
R2810+radiation	268 (67.3%)	173 (47.9%)	0 (0%)	0 (0%)	30 (54.5%)	471 (36.5%)
R2810 only	130 (32.7%)	188 (52.1%)	132 (100%)	345 (100%)	25 (45.5%)	820 (63.5%)

Covariate	1423	1540	1620	1624	1690	Overall
	(N=398)	(N=361)	(N=132)	(N=345)	(N=55)	(N=1291)
Anti-Drug Antibody Status						
No	328 (82.4%)	274 (75.9%)	121 (91.7%)	216 (62.6%)	45 (81.8%)	984 (76.2%)
Yes	9 (2.3%)	5 (1.4%)	4 (3.0%)	5 (1.4%)	2 (3.6%)	25 (1.9%)
Missing	61 (15.3%)	82 (22.7%)	7 (5.3%)	124 (35.9%)	8 (14.5%)	282 (21.8%)
Neutralizing Antibody Status						
No	337 (84.7%)	279 (77.3%)	125 (94.7%)	221 (64.1%)	47 (85.5%)	1009 (78.2%)
Missing	61 (15.3%)	82 (22.7%)	7 (5.3%)	124 (35.9%)	8 (14.5%)	282 (21.8%)
PD-L1 Categories						
<1%	88 (22.1%)	18 (5.0%)	35 (26.5%)	3 (0.9%)	0 (0%)	144 (11.2%)
1-49%	36 (9.0%)	58 (16.1%)	15 (11.4%)	26 (7.5%)	0 (0%)	135 (10.5%)
<1% & ≥50%	14 (3.5%)	50 (13.9%)	0 (0%)	272 (78.8%)	0 (0%)	336 (26.0%)
≥50%	0 (0%)	29 (8.0%)	0 (0%)	0 (0%)	0 (0%)	29 (2.2%)
Missing	260 (65.3%)	206 (57.1%)	82 (62.1%)	44 (12.8%)	55 (100%)	647 (50.1%)

BCC = Basal Cell Carcinoma; CC = Cervical Cancer; CNS = Central Nervous System; CSCC = Cutaneous Squamous Cell Carcinoma; DIPG = Diffuse Intrinsic Pontine Glioma; HGG = High Grade Glioma; NSCLC = Non-Small Cell Lung Cancer; PD-L1 = Programmed Cell Death Protein Ligand 1

Source: R2810-PK-24032-CP-01V2, Page 31-32, Table 4.

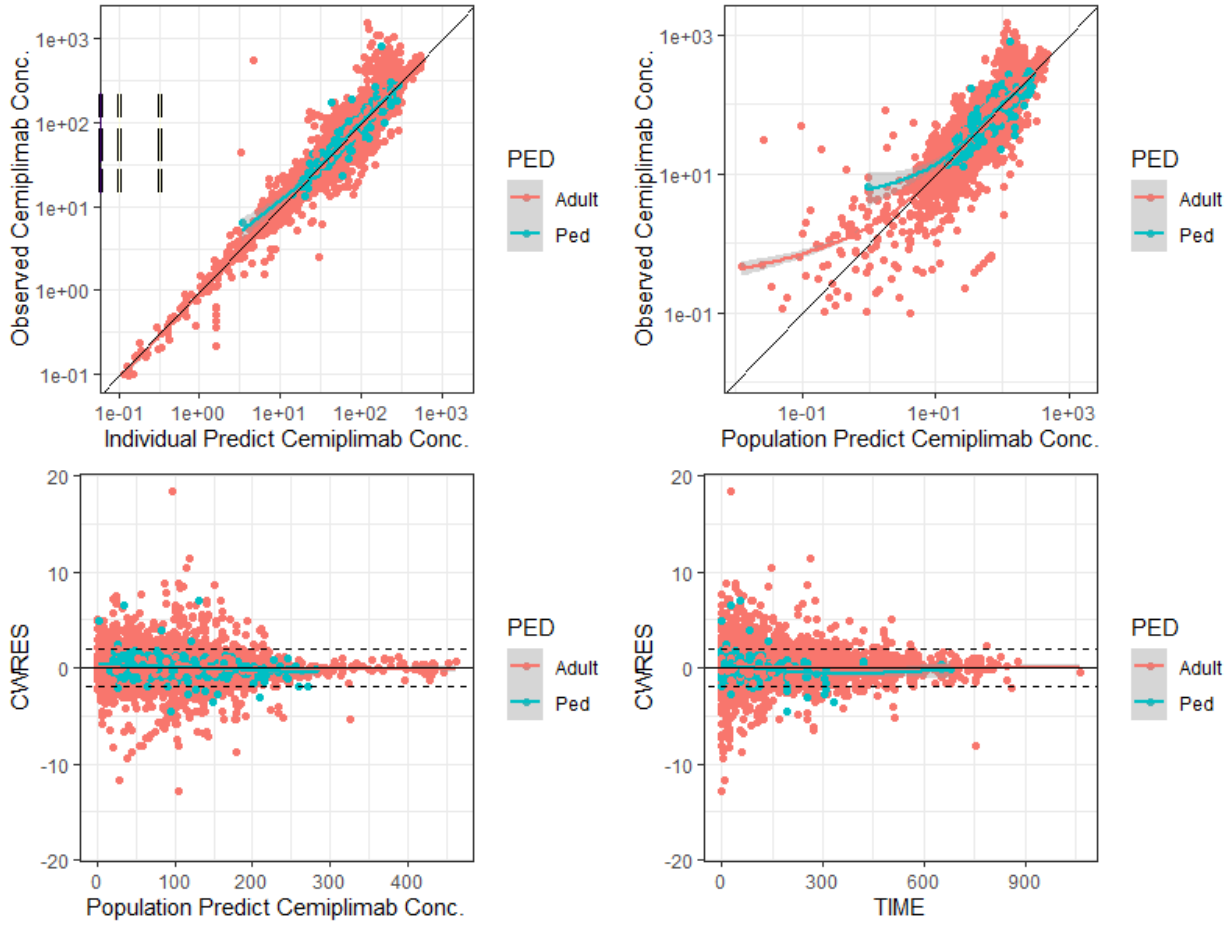
Table 8. Parameter Estimates for the Final Population PK Model

Parameter	Description	Estimate	RSE %
theta_{1}	Typical value CL (L/day)	0.259	2.09
theta_{2}	Typical value Q (L/day)	0.625	2.9
theta_{3}	Typical value V1 (L)	3.33	1.19
theta_{4}	Typical value V2 (L)	2.41	3.21
theta_{6}	Residual variance (log additive)	0.224	0.171
theta_{7}	Typical value E_{MAX} (maximum change in CL with time)	-0.148	8.47
theta_{8}	Typical value T50 (time to reach 50% maximum change in CL)	38.9	8.21
theta_{9}	Typical value Hill coefficient (gamma in sigmoid E_{MAX} model)	2.5	—
theta_{10}	Covariate effect of baseline weight on CL and Q	0.75	—
theta_{11}	Covariate effect of baseline weight on V1 and V2	1	—
theta_{12}	Covariate effect of time-varying albumin on CL	-1.08	2.64
theta_{15}	Covariate effect of sex on CL	-0.107	16.8
theta_{17}	Covariate effect of baseline albumin on V1	-0.295	26.4
theta_{18}	Covariate effect of baseline albumin on CL	-1.29	5.47
theta_{19}	Covariate effect of time-varying weight on CL	-0.345	16.5
theta_{20}	Covariate effect of baseline ALT on CL	-0.0706	23.6
theta_{21}	Covariate effect of tumor type (CSCC) on CL	-0.172	11.2
theta_{22}	Covariate effect of tumor type (BCC) on CL	-0.16	18.3
theta_{23}	Covariate effect of tumor type (OTHERS) on CL	-0.116	18.7
theta_{24}	Covariate effect of tumor type (PTUMOR) on CL	-0.394	9.12
Omega_{1,1}	Inter-individual variance CL	0.0819	3.85
Omega_{3,3}	Inter-individual variance V1	0.0957	2.27
Omega_{4,4}	Inter-individual variance V2	0.337	5.48

ALT = Alanine Transaminase; BCC = Basal Cell Carcinoma; CL = Clearance; CSCC = Cutaneous Squamous Cell Cancer; E_{MAX} = Maximum Change in Clearance With Time; IIV = Inter-Individual Variability; PK = Pharmacokinetics; PTUMOR = Pediatric Tumor Types; Q = Intercompartmental Clearance; RSE = Relative Standard Error; V1 = Central Volume; V2 = Peripheral Volume

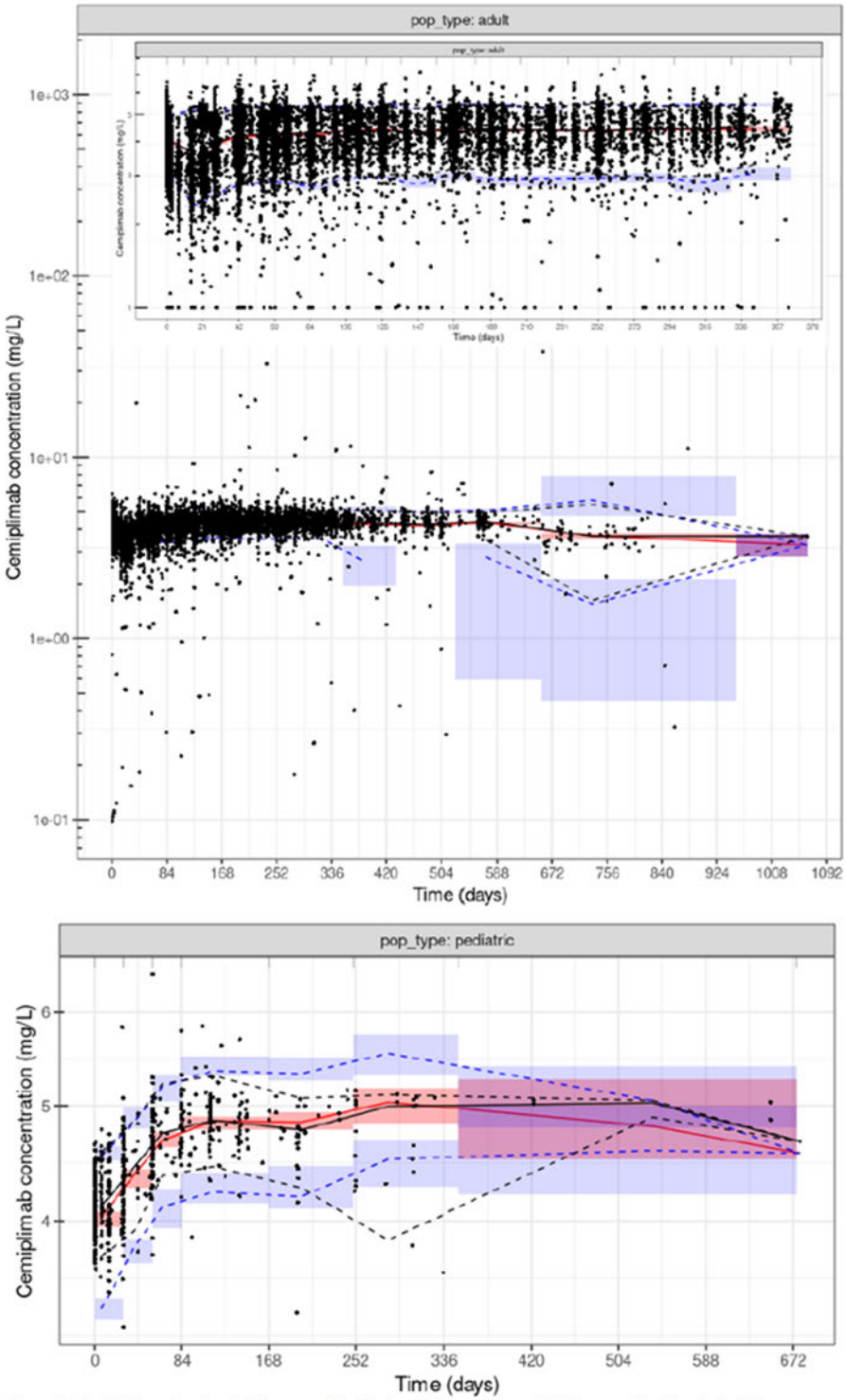
Source: R2810-PK-24032-CP-01V2, Page 34, Table 5.

Figure 1. Goodness of Fit Plots for the Final Population PK Model



Source: Reviewer's analysis.,

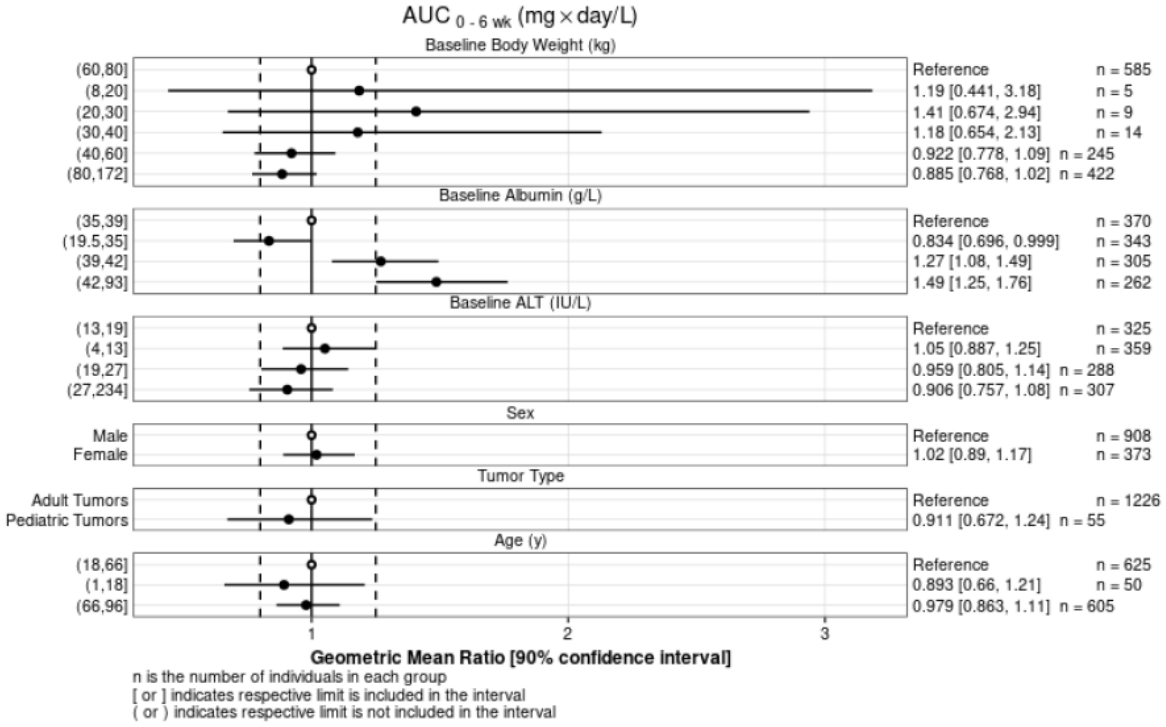
Figure 2. Visual Predictive Check for the Final Population PK Model



Notes: Red solid line: simulated 50th percentile, black solid line: observed 50th percentile, blue dashed lines: simulated 5th and 95th percentiles; black dashed lines: observed 5th and 95th percentiles; symbols: observed data; shaded area, 90% simulation-based confidence interval around median (pink) and upper/lower percentiles (blue).

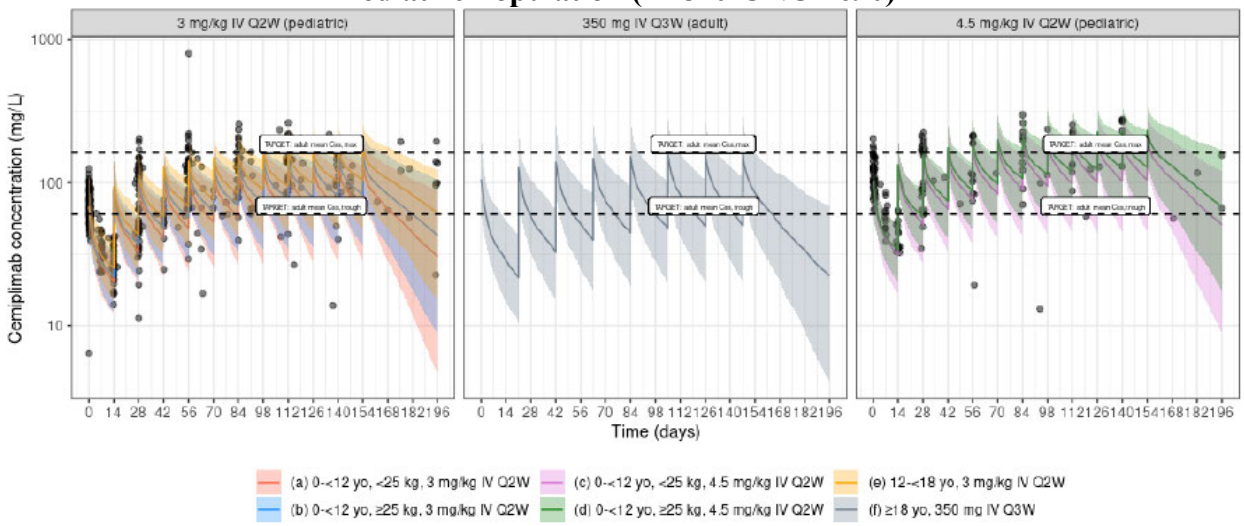
Source: R2810-PK-24032-CP-01V2, Page 36-37, Figure 6 -7.

Figure 3. Forest Plot of Geometric Mean Ratios [90% Confidence Interval] of Post-Hoc Model-Based Predictions of Exposure Metric (AUC0-6wk) of Cemiplimab



Source: R2810-PK-24032-CP-01V2, Page 69, Figure 29.

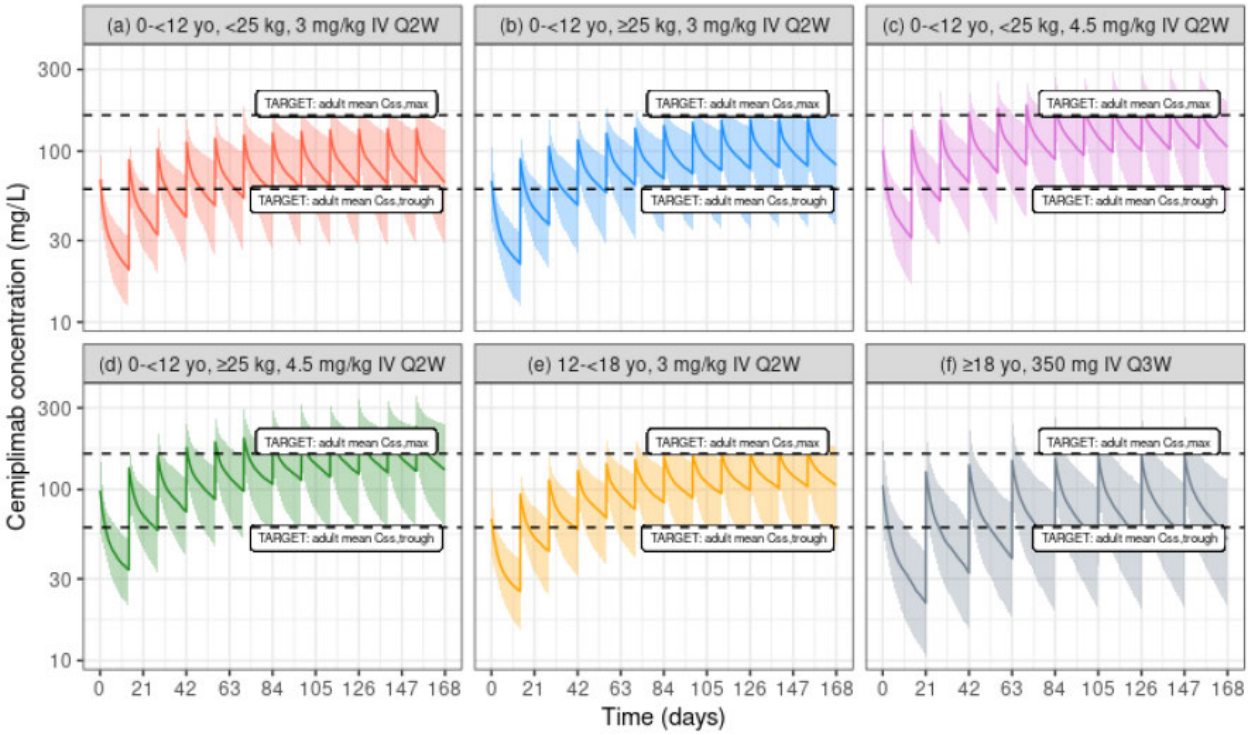
Figure 4. Simulated Longitudinal Concentration-Time Profiles of Cemiplimab for Each Dosing Regimen per Weight Bracket Overlayed With Observed Concentrations From the Pediatric Population (R2810-ONC-1690)



IV = Intravenous; Q2W = Every 2 Weeks; Q3W = Every 3 Weeks; yo = Years Old

Source: R2810-PK-24032-CP-01V2, Page 38, Figure 8.

Figure 5. Simulated Longitudinal Concentration-Time Profiles of Cemiplimab for Each Dosing Regimen per Weight Bracket Stratified by Weight Bracket



IV = Intravenous; Q2W = Every 2 Weeks; Q3W = Every 3 Weeks; yo = Years Old
Source: R2810-PK-24032-CP-01V2, Page 39, Figure 9.

5.2.3 The FDA's Assessment:

FDA reviewed the Applicant's population PK analysis. In general, the population PK model for adult and pediatric patients was reasonable due to the acceptable agreement between the model prediction and observation. Based on the population PK model, simulations were performed to compare the PK exposures of cemiplimab between pediatrics receiving 3 and 4.5 mg/kg IV Q2W and adults receiving 350 mg IV Q3W after a single dose and at steady state following multiple dosing. Higher exposures were predicted for pediatrics 0 to <12 years old receiving 4.5 mg/kg IV Q2W compared to adult patients. Overall, the PK exposures for pediatrics are withing range of that observed in adults receiving a similar dose based on body weight.

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