Office of Clinical Pharmacology Review

BLA #	761089/Suppl-31
Associated IND #	106533
Applicant	Teva Pharmaceuticals USA, Inc.
Submission Type	Pediatric Efficacy Supplement (Priority Review)
Submission Date(s)	02/05/2025
Link to EDR	\\CDSESUB1\EVSPROD\BLA761089\0966
Brand Name	AJOVY®
Generic Name	Fremanezumab-vfrm
Formulation and Strength	Solution for injection (single-dose prefilled syringe; and autoinjector); 225 mg/1.5 mL (150 mg/mL)
Route of Administration	Subcutaneous (SC)
Approved Indication	Preventive treatment of migraine in adults
Proposed Indication	Preventive treatment of episodic migraine in pediatric patients aged 6 years and older, weighing at least 45 kg
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
OCP Review Team	Ping Du, Ph.D. Poonam Delvadia, Ph.D. Atul Bhattaram, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

Contents

1. Executive Summary

AJOVY® (fremanezumab-vfrm) is a fully humanized IgG2Δa/kappa monoclonal antibody targeted against the calcitonin gene-related peptide (CGRP) receptor. It was originally approved on September 14, 2018, for the preventive treatment of migraine in adults.

In this pediatric supplemental biologic license application (sBLA), Teva Pharmaceuticals USA, Inc. is seeking approval for AJOVY (fremanezumab-vfrm) for the preventive treatment of episodic migraine (EM) in pediatric patients aged 6 years and older, weighing at least 45 kg. The application is based on one pivotal randomized, double-blind, placebo-controlled, Phase 3 efficacy and safety study (TV48125-CNS-10083) in pediatric patients with EM. The primary efficacy results demonstrated that both 120 mg monthly (for patients <45 kg) and 225 mg monthly (for patients ≥45 kg) dose regimens are safe and effective in reducing the mean change from baseline in the monthly average number of migraine days during the 12-week period. However, despite the pivotal clinical trial demonstrating the efficacy of a 120 mg once monthly dose regimen in pediatric patients weighing less than 45 kg, the Applicant has not proposed indication for pediatric patients weighing less than 45 kg. This is due to the absence of appropriate commercial formulation/device for this patient population.

The primary focus of this clinical pharmacology review is to evaluate the proposed dosing regimen in pediatric patients with EM, assess immunogenicity of AJOVY (fremanezumab-vfrm) in pediatric patients, assess population pharmacokinetic (popPK) and exposure-response data, and review the proposed labeling.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this sBLA 761089 (Supp-31) to support the approval of 225 mg once monthly dosing regimen of AJVOY for preventive treatment of EM in pediatric patients aged 6 years and older, weighing at least 45 kg.

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The evidence of effectiveness is from one placebo controlled, randomized, double-blind, Phase 3 efficacy and safety study in pediatric patients with EM (TV48125-CNS-30083).
General dosing instructions	To be administered subcutaneously using pre-filled syringe (PFS) and/or autoinjector: • 225 mg once monthly in pediatric patients aged 6 years and older, weighing at least 45 kg
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose adjustments are needed by body weight. • 120 mg once monthly in pediatric patients aged 6 years and older, weighing less than 45 kg (applicant is not seeking approval in this patient population in this supplement due to the lack of commercial formulation/device for this body weight group; development (b) (6) is ongoing) • 225 mg once monthly in pediatric patients aged 6 years and older, weighing at least 45 kg
Bridge between the "to-be marketed" and clinical trial formulations	• 120 mg once monthly for pediatric patients aged 6 years and older, weighing less than 45 kg: The clinical trial formulation is vial formulation. Development of the (b) (6) is ongoing for extending dosing in pediatric patients 6 years and older weighing less than 45 kg. • 225 mg once monthly for pediatric patients aged 6 years and older, weighing at least 45 kg: Additional PK bridging study is not needed. The to-be-marketed product (PFS) is same as the clinical trial presentation/formulation (PFS) for 225 mg once monthly dosing regimen. A bioequivalence study has

	been conducted between the PFS and another to-be-marketed product (autoinjector) for 225 mg once monthly dosing regimen.

1.2 Summary of Proposed Labeling

AJOVY® is indicated for:

- the preventive treatment of migraine in adults, and
- the preventive treatment of episodic migraine in pediatric patients 6 to 17 years of age and weighing at least 45 kg or more.

Pediatric Patients 6 to 17 Years of Age and Weighing at least 45 kg or More:

The recommended dosage in pediatric patients 6 to 17 years of age and weighing at least 45 kg or more for the preventive treatment of episodic migraine is 225 mg administered once monthly by subcutaneous injection.

AJOVY® is not approved in pediatric patients weighing less than 45 kg because of the lack of an appropriate commercial formulation/device.

1.3 Post Marketing Requirement

None

2. Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical pharmacokinetics

Reference is made to the approved labeling for AJVOY (fremanezumab-vfrm) injection for subcutaneous use.[1] Refer to the label for details on clinical pharmacology and pharmacokinetics (PK) characteristics of fremanezumab-vfrm. As per the approved

[1] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761089s000lbl.pdf

label, no dose adjustment is recommended for AJOVY in adults for intrinsic factors such as age, race, sex, and body weight.

Pediatrics:

- Body weight has a significant effect on fremanezumab-vfrm PK.
- The PK exposures of 120 mg once monthly in pediatric patients weighing less than 45 kg is comparable to PK exposures of 225 mg once monthly in adults.
- The PK exposures of 225 mg once monthly in pediatric patients weighing at least 45 kg or more is comparable to PK exposures of 225 mg once monthly in adults.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosing regimen is 225 mg once monthly, administered subcutaneously using pre-filled syringe (PFS) and/or autoinjector, for preventive treatment of EM in pediatric patients aged 6 years and older, weighing at least 45 kg.

This recommendation is supported by the pivotal Phase 3 efficacy and safety study in pediatric patients with EM (TV48125-CNS-30083), and comparable PK exposures of 225 mg once monthly dosing regimen between pediatric patients (≥45 kg) and adults.

2.2.2 Therapeutic individualization

A body weight-based dosing was evaluated in the pivotal Phase 3 efficacy and safety clinical study in pediatric patients with EM (TV48125-CNS-30083). Specifically, 225 mg once monthly was evaluated in patients weighing ≥ 45 kg, and 120 mg monthly was evaluated in patients < 45 kg. As mentioned above, in this supplement the Applicant is seeking approval only for 225 mg once monthly dosing regimen for EM pediatric patients weighing ≥ 45 kg.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Fremanezumab pediatric clinical program consisted of 5 studies in patients with EM and CM: (1) one Phase 1 study charactering the pharmacokinetics, safety and tolerability of subcutaneous administration of fremanezumab-vfrm in pediatric migraine patients, (2) one bioequivalence study comparing pharmacokinetics of fremanezumab administered subcutaneously using an autoinjector and a prefilled syringe configuration, (3) one Phase 3 double-blind, placebo-controlled safety and efficacy study in pediatric patients with EM, (4) one Phase 3 double-blind, placebo-controlled safety and efficacy study in pediatric patients with CM (ongoing), and (5) one Phase 3 long-term safety study in pediatric patients with EM and CM (ongoing). The key aspects of these five studies are summarized in **Table 1** below.

Table1 Summary of safety and efficacy studies in the pediatric clinical development program of Fremanezumab

Trial number	Phase	Trial title	N[a]
Healthy participants			
TV48125-BE-10145	1	Open-label, Single Dose, Randomized, Parallel, Bioequivalence Study to Compare the Pharmacokinetics of Fremanezumab Administered Subcutaneously Using an Autoinjector Referenced to a Prefilled Syringe Configuration	218[b]
Total		Total Healthy Participants	218
Participants with Migraine			
TV48125-CNS-10141	1	A Single-Dose, Open-Label Study to Characterize the Pharmacokinetics, Safety and Tolerability of Subcutaneous Administration of Fremanezumab in Pediatric Migraine Patients (6 to 11 Years of Age Inclusive)	15[c]

Trial number	Phase	Trial title	N[a]
TV48125-CNS-30082	3	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Chronic Migraine in Pediatric Patients 6 to 17 Years of Age	Ongoing[d]
TV48125-CNS-30083	3	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age	235[e]
TV48125-CNS-30084	3	A Multicenter, Open-Label Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Monthly Subcutaneous Administration of Fremanezumab for the Preventive Treatment of Episodic and Chronic Migraine in Pediatric Patients 6 to 17 Years of Age	Ongoing[f]

3.2 Clinical Pharmacology Review Questions

3.2.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness in pediatric patients aged 6 years and older?

The evidence of effectiveness of fremanezumab in the prevention of EM in pediatric patients is based on one placebo-controlled, randomized, double-blind, efficacy and safety study (TV48125-CNS-30083; **Table 1**). The dose of fremanezumab administered was determined by the patient's body weight at randomization (visit 2):

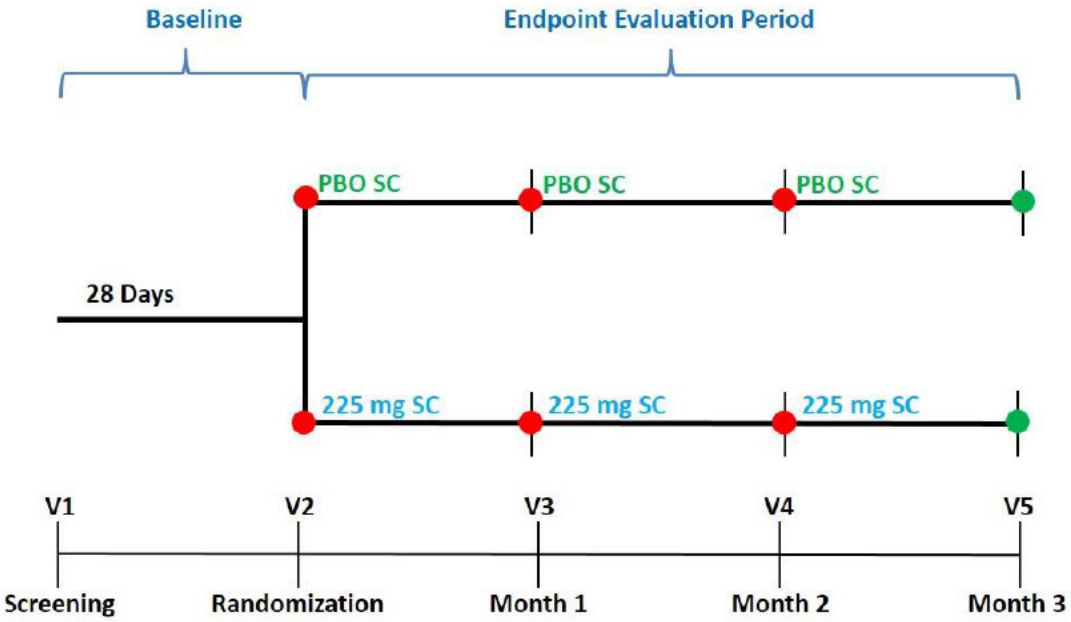
- Patients weighing ≥45 kg received monthly administration of fremanezumab at 225 mg (supplied as 1 pre-filled syringe) (**Figure 1**)
- Patients weighing <45 kg received monthly administration of fremanezumab at 120 mg (supplied as 2 vials) (**Figure 2**)

Dose Selection for Pediatric Patients Weighing <45 kg (TV48125-CNS-30083):

Dosing regimen was selected based on comparable exposures between 120 mg sc administered once monthly in pediatric patients weighing <45 kg and 225 mg sc administered once monthly in adult patients.

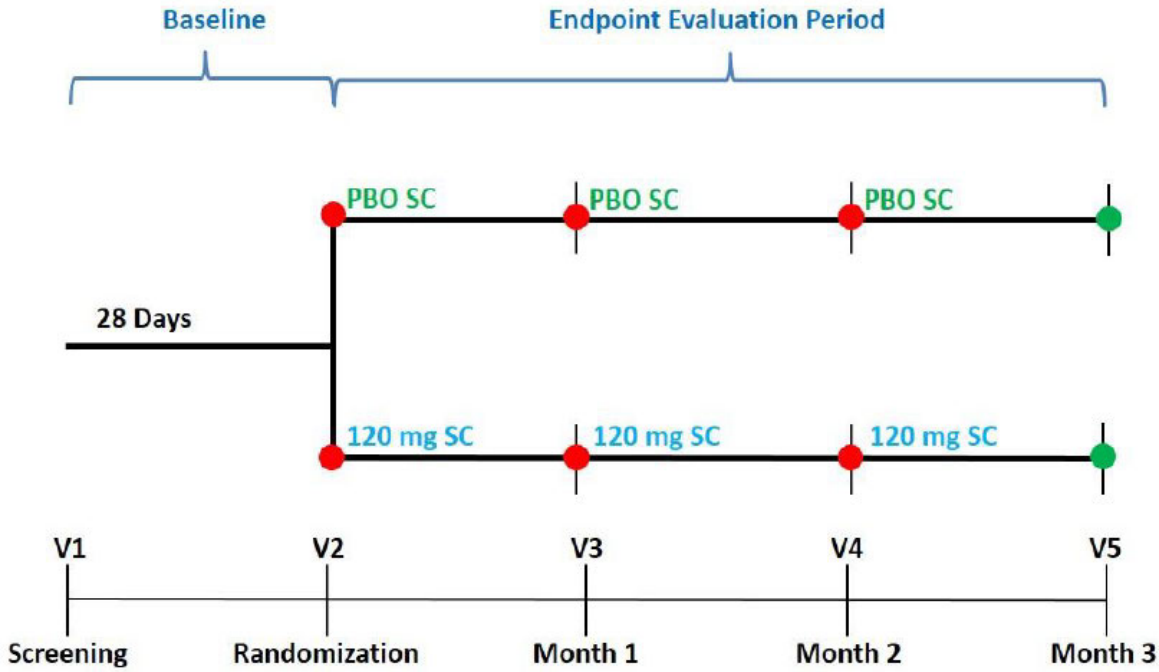
For the per protocol (PP) and intent to treat (ITT) analysis sets, the primary efficacy variable also showed nominally statistically significant differences ($p<0.05$) between placebo and fremanezumab, whereby patients in the fremanezumab group had a larger reduction in number of migraine days during the 12-week period after the first dose of fremanezumab (**Figure 3**).

Figure 1: Overall Trial Schema for Patients Weighing ≥ 45.0 kg at Randomization



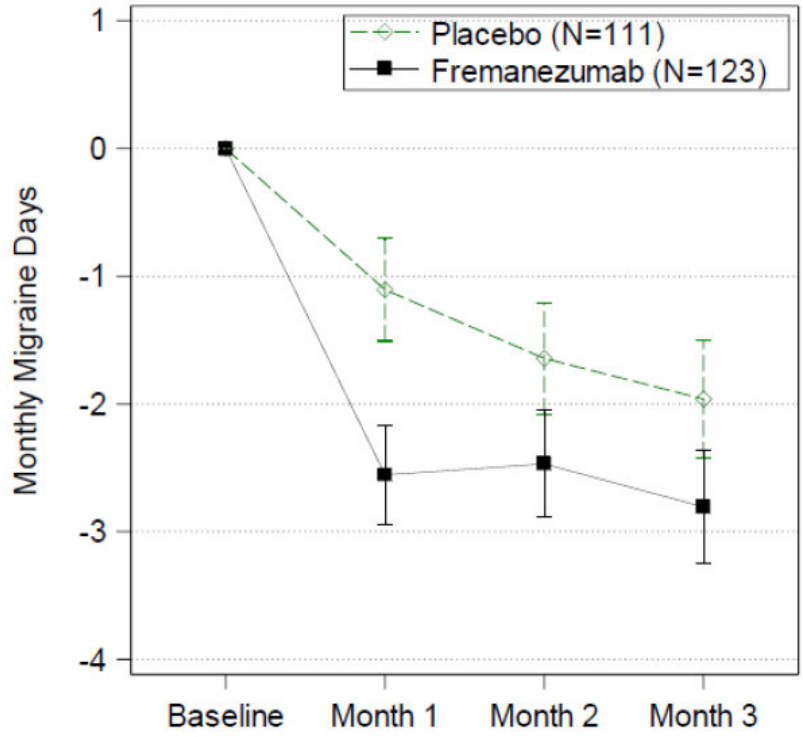
Source: Clinical study report of Trial TV48125-CNS-30083, Figure 1 on page 23

Figure 2: Overall Trial Schema for Patients Weighing < 45.0 kg at Randomization



Source: Clinical study report of Trial TV48125-CNS-30083, Figure 1 on page 24

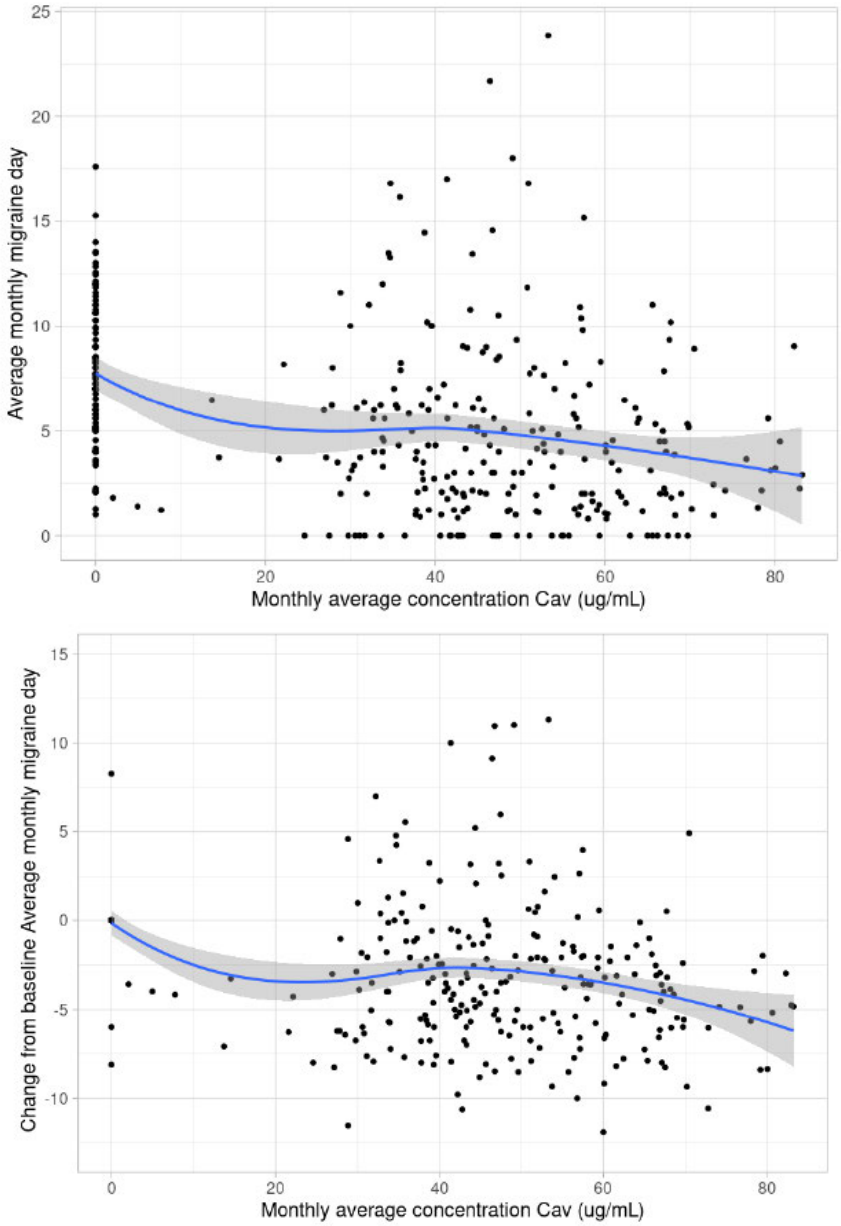
Figure 3: Line Plot of LS Mean (± SE) Change from Baseline in Monthly Average Number of Migraine Days During 12-Week Period by Treatment Group Using MMRM (Full Analysis Set)



Source: Clinical study report of Trial TV48125-CNS-30083, Figure 3 on page 68

Exposure-response (E-R) analyses were conducted using individual Bayesian estimates of fremanezumab exposure (Cav) in pediatric patients with EM. The E-R analysis included placebo and 225 mg dose groups for pediatric patients weighing ≥ 45 kg in Study TV48125-CNS-30083. These analyses examined the relationship between fremanezumab concentrations and two efficacy endpoints: a) Monthly migraine days; and b) Change from baseline in the number of migraine days. Per applicant, the E-R analyses generally revealed a shallow relationship between fremanezumab concentrations and efficacy measures (**Figure 4**).

Figure 4: Scatterplots of Observed Monthly Migraine Days and Change from Baseline in Number of Migraine Days Versus Individual Bayesian Fremanezumab Exposure (Cav) in Pediatric EM Patients from Placebo and 225 mg Dose Groups



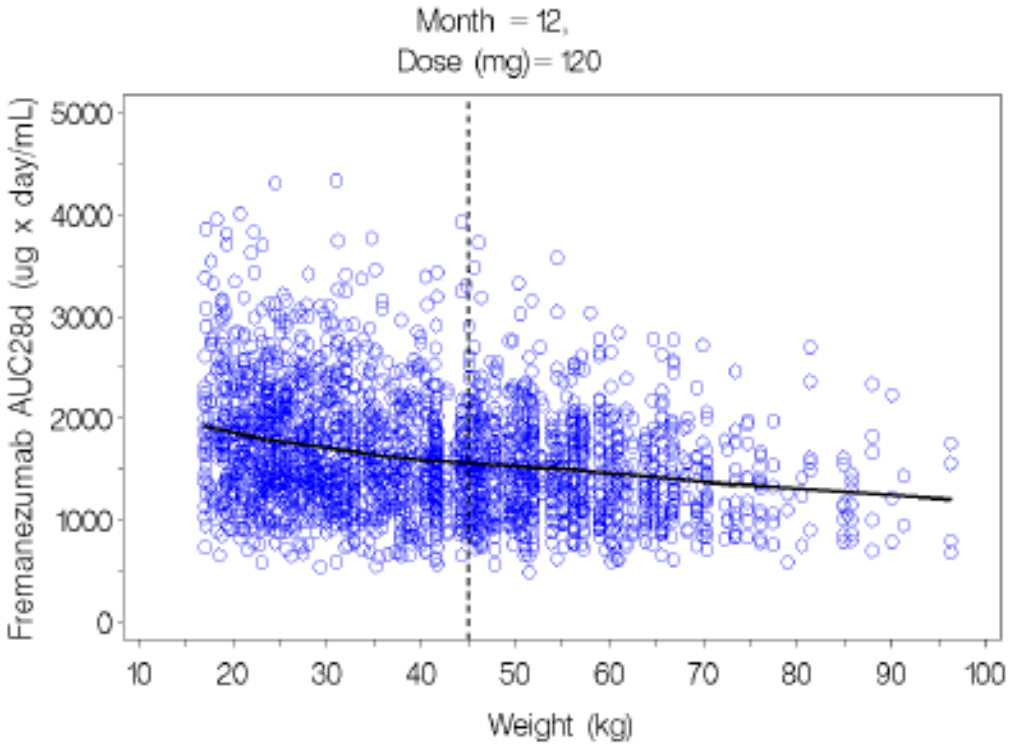
Source: Pediatric Population Pharmacokinetics and Exposure Response Report (Fremanezumab TV-48125, PMXR-2024-22), Figure 8 on page 58

3.2.2 Is the proposed dosing regimen appropriate for pediatric patients aged 6 years and older weighting at least 45 kg?

Body weight significantly influences fremanezumab pharmacokinetics in pediatric patients, as demonstrated by the Applicant's analysis below. The relationship between body weight and fremanezumab PK is visually represented in **Figure 5**. Consequently, dose adjustments based on body weight are necessary for this population. The proposed weight-based dosing adjustments are depicted in **Figures 6** and **7**. Per Applicant's analysis in **Figure 6** and **7**, 120 mg sc administered once monthly in pediatric patients weighing <45 kg achieves exposures (AUCt, and Cmax) comparable to 225 mg sc administered once monthly in adult patients. The analysis is limited to data from a single Phase 1 study (TV48125-CNS-10141) in pediatric patients 6-11 years of age. Despite the limitation of data, the Applicant proposed to study 120 mg sc once monthly in pediatric patients weighing <45 kg, and 225 mg sc once monthly in pediatric patients weighing ≥45 kg in the Phase 3 double-blind, placebo-controlled safety and efficacy study in pediatric patients with EM and CM. The Phase 3 double-blind, placebo-controlled safety and efficacy study in pediatric patients with EM showed positive efficacy outcome (**Figure 3**) and achieved statistical significance in pediatric patients more than 6 years old, weighing <45 kg and weighing ≥45 kg. The Phase 3 double-blind, placebo-controlled safety and efficacy study in pediatric patients with CM is still ongoing.

Applicant's analysis

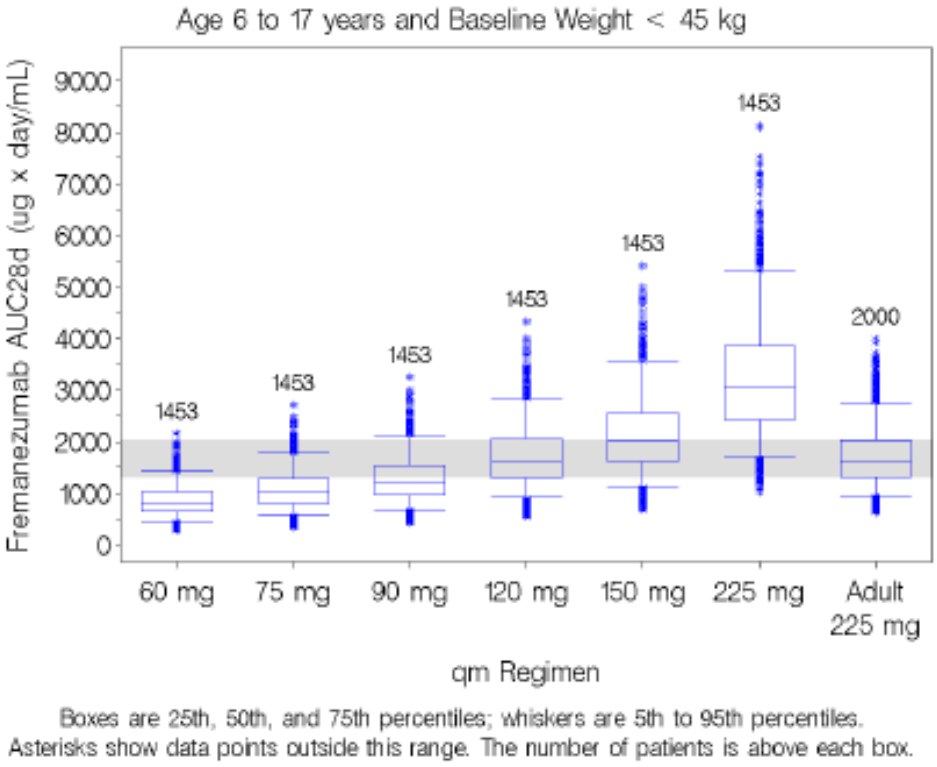
Figure 5: Simulated Steady-State Fremanezumab AUC_{28d} Versus Body Weight



The solid black line represents a smoothing spline fit to the data. The vertical dashed black line represents the 45 kg cutoff.

Source: Population Pharmacokinetic Report (Teva Report No. CP-18-05), on page 11

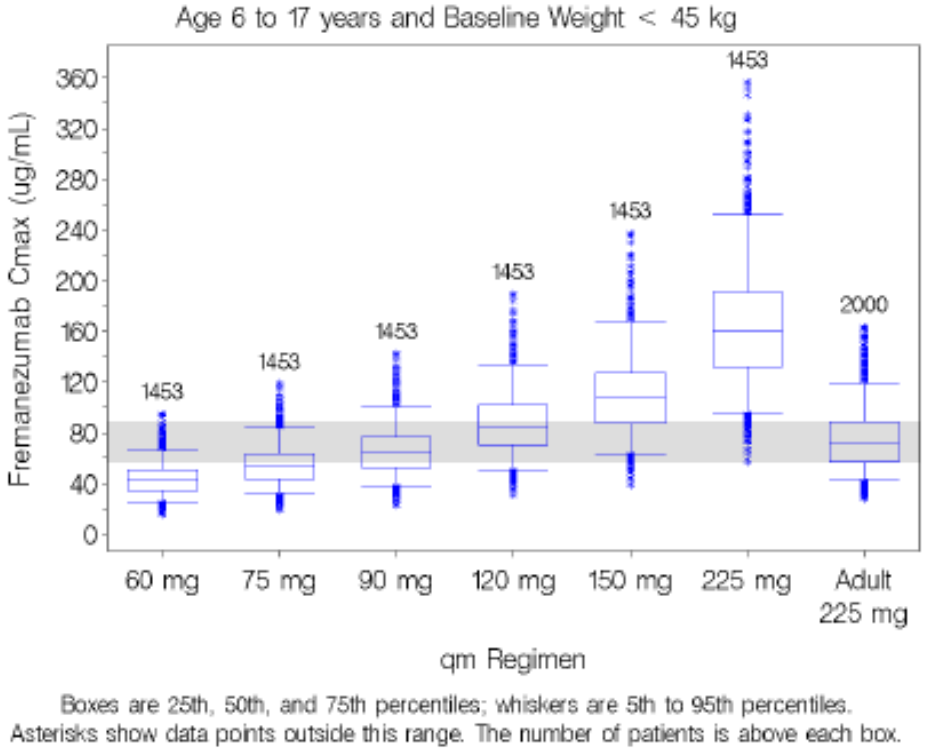
Figure 6: Simulated Steady-State Fremanezumab AUC_{28d} for Pediatric Patients 6 to 17 Years of Age with Baseline Body Weight <45 kg Compared to the Adult Distribution Following Fremanezumab 225 mg Subcutaneous Monthly Administration



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of patients is above each box.

Source: Population Pharmacokinetic Report (Teva Report No. CP-18-05), on page 9

Figure 7: Simulated Steady-State Fremanezumab Cmax for Pediatric Patients 6 to 17 Years of Age with Baseline Body Weight <45 kg Compared to the Adult Distribution Following Fremanezumab 225 mg Subcutaneous Monthly Administration



Source: Population Pharmacokinetic Report (Teva Report No. CP-18-05), on page 9

Reviewer's Analysis and Assessment:

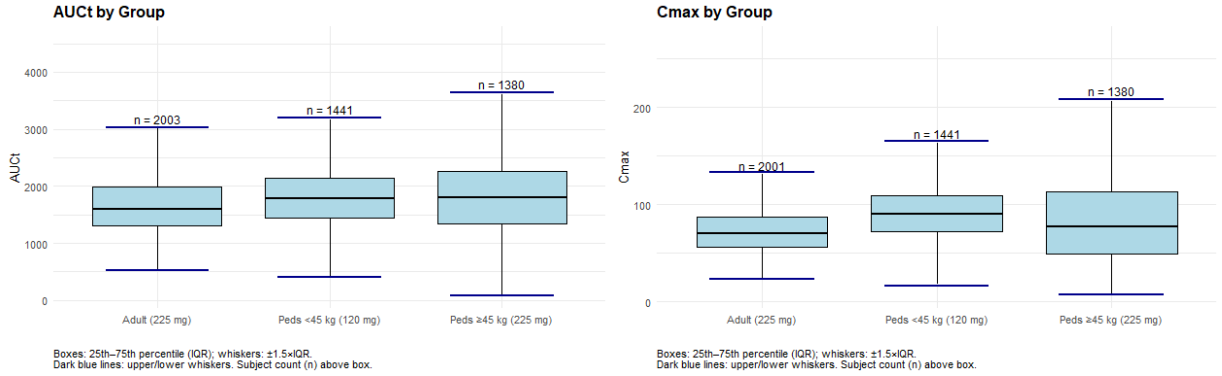
The reviewer evaluated the updated population pharmacokinetic (popPK) model, which incorporates pediatric datasets from three studies (TV48125-CNS-10141, TV48125-CNS-30083, and TV48125-CNS-30084) (For more details about the popPK model, refer to section 3.3.1)

The reviewer's analysis of simulated AUCtau and Cmax across adult and pediatric patients confirm the acceptability of the applicant's proposed weight-based dosing adjustments. **Figure 8** demonstrates PK exposures of 120 mg once monthly in pediatric patients weighing <45 kg are comparable to PK exposures of 225 mg once monthly in adult patients, and PK exposures of 225 mg once monthly in pediatric patients weighing ≥45 kg are comparable to PK exposures of 225 mg once monthly in adult patients.

These clinical pharmacology findings support the proposed dosing regimen, for pediatric patients with EM weighing ≥45 kg, of 225 mg once monthly. The 120 mg once monthly dose regimen for pediatric patients with EM <45 kg is also supported. However, the 120 mg monthly dosage could not be approved in this review cycle due to the lack of an appropriate commercial formulation/device.

Figure 8: Simulated Steady-State Fremanezumab AUCt and Cmax for Pediatric Patients 6 to 17 Years of Age Following Fremanezumab 225 mg or 120 mg Subcutaneous Monthly Administration Based on Body Weight Cut Off (45 kg) Compared to the Adults Following Fremanezumab 225 mg Subcutaneous Monthly Administration

Reviewer's independent analysis



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

Per the clinical pharmacology review for original approval of AJOVY (fremanezumab-vfrm), no clinically significant differences in fremanezumab-vfrm pharmacokinetics were predicted based on race (Caucasian, Black, Asian, and other races), sex, mild hepatic impairment (Child-Pugh Class A), and moderate hepatic impairment (Child-Pugh Class B). The effect of severe hepatic impairment (Child-Pugh Class C) on fremanezumab-vfrm pharmacokinetics is unknown.

Refer the section above for impact of weight on fremanezumab-vfrm pharmacokinetics.

Per the original clinical pharmacology review, no clinically relevant food-drug or drug-drug interactions are expected for fremanezumab-vfrm.

3.2.4. Is the to-be-marketed formulation/device the same as the clinical trial formulation/device, and if not, are there bioequivalence data to support the to-be marketed formulation?

The current to-be-marketed (TBM) formulation/device include 225 mg autoinjector and 225 mg pre-filled syringe (PFS). For pediatric patients weighing ≥45.0 kg, the clinical trial formulation/device (225 mg PFS) is identical to one of the TBM pre-filled syringe formulation/device. The pivotal bioequivalence study (TV48125-BE-10145) has been reviewed previously and demonstrated bioequivalence between the 225 mg autoinjector and 225 mg prefilled syringe (PFS).[2,3] The geometric least squares ratios and 90% confidence intervals for the primary pharmacokinetic parameters were as follows: Cmax: 1.03 (90% CI: 0.96-1.09), AUC0-t: 1.04 (90% CI: 0.98-1.10) and AUC0-inf: 1.05 (90% CI: 0.99-1.11). Bioequivalence data support the use of both TBM formulation/device (225 mg PFS and 225 mg autoinjector). Please refer to the clinical pharmacology review (DARTTS: 09/16/2019) for more details about the bioequivalence study.

For pediatric patients weighing <45.0 kg, the clinical trial formulation differs from the Applicant planned TBM formulations/devices. Development of (b) (6) TBM formulations/devices (120 mg dose) is ongoing (b) (6)

3.2.5. Is there any impact of antidrug antibody (ADA)/neutralizing antibody (Nab) on the efficacy, safety and exposure of AJOVY (fremanezumab-vfrm) in pediatric trials?

In 3-month placebo-controlled studies in pediatric patients with episodic migraine (TV48125-CNS-30083), treatment-emergent ADA responses were observed in 2 out of 123 (1.6%) AJOVY-treated patients. One of the 2 patients developed anti-AJOVY

[2] \\CDSESUB1\evsprod\BLA761089\0153

[3] REV-CLINPHARM-21 (Primary Review), date 09/16/2019

neutralizing antibodies at Day 84 (**Table 2**). Because of the low occurrence of patients with ADAs, available data are too limited to make definitive conclusions about the impact of anti-fremanezumab-vfrm antibody on PK, efficacy or safety of AJOVY.

Table 2: Immunogenicity Assessment

		Clinical study information	**Clinical study information**
Study #		30083 in EM	30084 in EM and CM
Status		Completed	Ongoing
Treatment duration		3 Month	
Recommended dosing regimen		225 mg Q1M (include all pediatrics)	225 mg Q1M (include all pediatrics)
# of subjects who received the recommended dosing regimen		125	369
ADA incidence	By applicant	2/123 (1.6%)	16/392 (4.1%) total treated participants had a positive ADA response at one or more time points.
	By reviewer	2/123 (1.6 %)	
NAb incidence	By applicant	1/123 (0.8%)	
	By reviewer	1/2 (50%)	

3.3 Pharmacometrics Assessment: Population PK Analysis

3.3.1 Applicant's Population PK analysis:

Data from 3 clinical studies, which included one Phase 1 study (TV48125-CNS-10141), two Phase 3 studies (TV48125-CNS-30083, and TV48125-CNS-30084) were used in the fremanezumab pediatric population PK analyses. A brief description of these studies, dosing regimens, PK and ADA plans is given in **Table 3** and **Table 4**.

Table 3: Studies Included in the Population Pharmacokinetic Analyses of Fremanezumab

TV48125-CNS-10141/Phase 1	A Single-Dose, Open-Label Study to Characterize the Pharmacokinetics, Safety and Tolerability of Subcutaneous Administration of Fremanezumab in Pediatric Migraine Patients	Pediatric patients (males and females, 6 to 11 years of age) with migraine (N=15) (US)	75 mg as a single sc	Include fremanezumab active dose cohorts only
TV48125-CNS-30083/Phase 3	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6 to 17 Years of Age	Pediatric patients (males and females, 6 to 17 years of age) with EM 85 sites in 9 countries	225 mg sc monthly (≥45 kg patient) 120 mg sc monthly (<45 kg patient) Placebo sc monthly (matching)	Include fremanezumab active dose cohorts only
TV48125-CNS-30084/Phase 3	A Multicenter, Open-Label Study Evaluating the Long-Term Safety, and Tolerability of Monthly Subcutaneous Administration of Fremanezumab for the Preventive Treatment of Episodic and Chronic Migraine in Pediatric Patients 6 to 17 Years of Age	Pediatric patients (males and females, 6 to 17 years of age) with CM or EM 85 sites in 9 countries	225 mg sc monthly (≥45 kg patient) 120 mg sc monthly (<45 kg patient)	Include fremanezumab active dose cohorts only

PF-04427429=TEV-48125=fremanezumab

Table 4: Dosing Regimens, Pharmacokinetic and Anti-drug Antibody Sampling Plans for Studies Included in the Population Pharmacokinetic Analyses

Study number/ Phase	Dosing regimen	Pharmacokinetic sampling	Anti-drug antibody sampling to be included in analysis
TV48125-CNS-10141/Phase 1	75 mg sc single dose	Days 1, 2, 11, 29, 85, 113	-
TV48125-CNS-30083/Phase 3	225 mg sc monthly (≥45 kg patient) for a total of 3 doses 120 mg sc monthly (<45 kg patient) for a total of 3 doses Placebo sc monthly (matching)	Pre-dose Days 1, 29, 85	Days 1, 29, 85
TV48125-CNS-30084/Phase 3	225 mg sc monthly (≥45 kg patient) for a total of 9 doses 120 mg sc monthly (<45 kg patient) for a total of 9 doses Placebo sc monthly (matching)	Pre-dose Days 1, 85, 169, 253, 393	Days 1, 85, 169, 253, 393

n=number of subjects; sc=subcutaneous

The fremanezumab pediatric population PK model was developed for describing Phase 3 pediatric PK data using previously built adult population PK model (Teva Report No. CP-18-07/01) as the starting point. A 2-compartment model with first-order absorption and elimination and weight effect on clearance and volume of distribution adequately described fremanezumab concentration-time profile. The incidence of ADA was less than 1% and hence was not an important covariate for PK.

Effect of age on Ka was identified as statistically significant covariate in the final population PK model. In addition, Study effect was a significant covariate on CL that could be explained by differences in Study demographics since younger and lower weight patients were enrolled in Phase 1 study.

Based on model-based simulation, decrease in fremanezumab PK exposure was associated with increasing baseline body weight. No significant trend was observed across age group.

Parameter estimates of the final PopPK model are shown in **Table 5**. Qualification of the final PopPK model was performed using goodness of fit plots, shown in **Figure 9**.

Furthermore, simulation of a large number of replicates with the same design using estimates of the population means and variability from the final PopPK model were overlaid with the observed data and visualized using the prediction-corrected Visual Predictive Check (pc-VPC) shown in **Figure 10** (for individual studies).

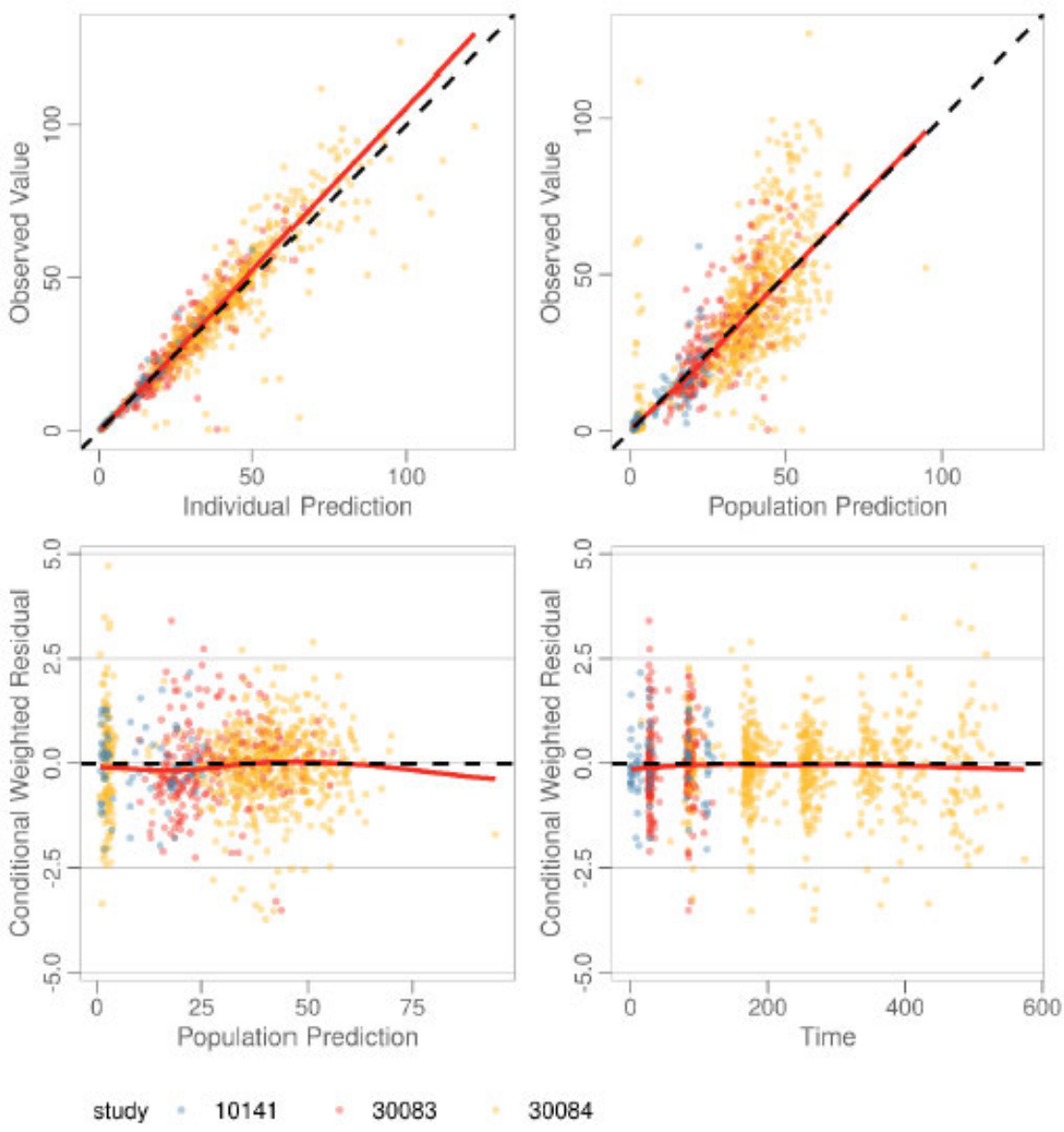
Table 5: Parameter Estimates of the Fremanezumab Final Population Pharmacokinetic Model in the Pediatric Population, Compared to Adult Final Model Parameter estimates

Parameter	**Pediatric Population** Typical value (%RSE)	**Adult Population** Typical value (%RSE)
CL/F: apparent clearance (L/day)	0.0974 (3.8)	0.0902 (1.5)
V_c/F: apparent central volume of distribution (L)	0.266 (23.9)	1.88 (3.38)
KA: absorption rate constant (1/day)	0.107 (10.7)	0.18 (12.2)
CL/F: allometric exponent on Weight (-)a	0.748 (11.9)	1.05 (4.33)
V_c/F: allometric exponent on Weight (-)a	0.851 (10.9)	1.53 (10.3)
Q: Intercompartmental Clearance (L/day)	0.153 (13.3)	0.262 FIX
V3: Peripheral Volume of Distribution (L)	2.92 (6.55)	1.72 FIX
Age on KA: KA*EXP(θ*[AGE – 13])	0.0747 (28.4) = [+/-35%]	-
Study/Phase difference on CL: CL* (1 + θ) for phase 1	0.214 (47.3)	-
IIV in CV for CL/F	0.237 (9.45)	0.234 (4.6)
IIV in CV for V_c/F	1.83 (12.6)	0.351 (19.9)
IIV in CV for KA	0.373 (20.0)	0.59 (15.8)
RV sc proportional component	0.205 (7.48)	0.0531 (4.03)
RV sc additive component	-	0.204 (25.6)

Source: Teva Report CP-18-07/01 and ../models/ MODEL04_2cmt_Vp1Q1_Theta_Fix_Covs_matchReport/ project_parameters_table.txt.
CL/F=apparent clearance; CV= coefficient of variation; IIV=interindividual variability; KA=absorption constant; RSE: relative residual error; RV=residual variability; SC=subcutaneous;V_c/F=apparent central volume of distribution

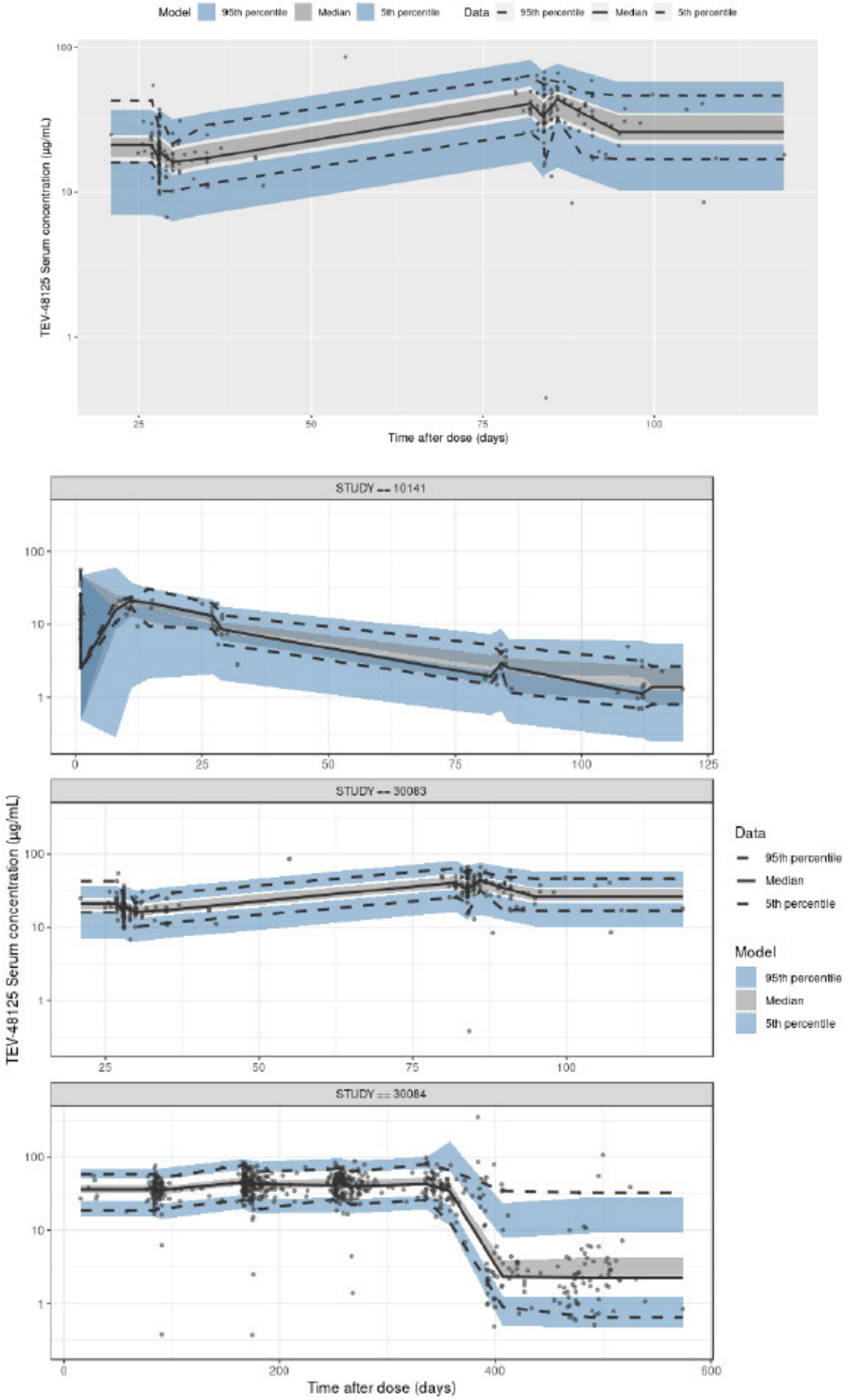
Source: Pediatric Population Pharmacokinetics and Exposure Response Report (Fremanezumab TV-48125, PMXR-2024-22), Table 7 on page 45

Figure 9: Goodness-of-fit Diagnostic Plots for the Final Population Pharmacokinetic Model for Fremanezumab in Pediatric Population



Source: Pediatric Population Pharmacokinetics and Exposure Response Report (Fremanezumab TV-48125, PMXR-2024-22), Figure 2 on page 50

Figure 10: Prediction-corrected Visual Predictive Check for Final Population Pharmacokinetic Model for Fremanezumab in Pediatric Population, of Total Data (upper) and Stratified by Study (lower, semi-log scale)



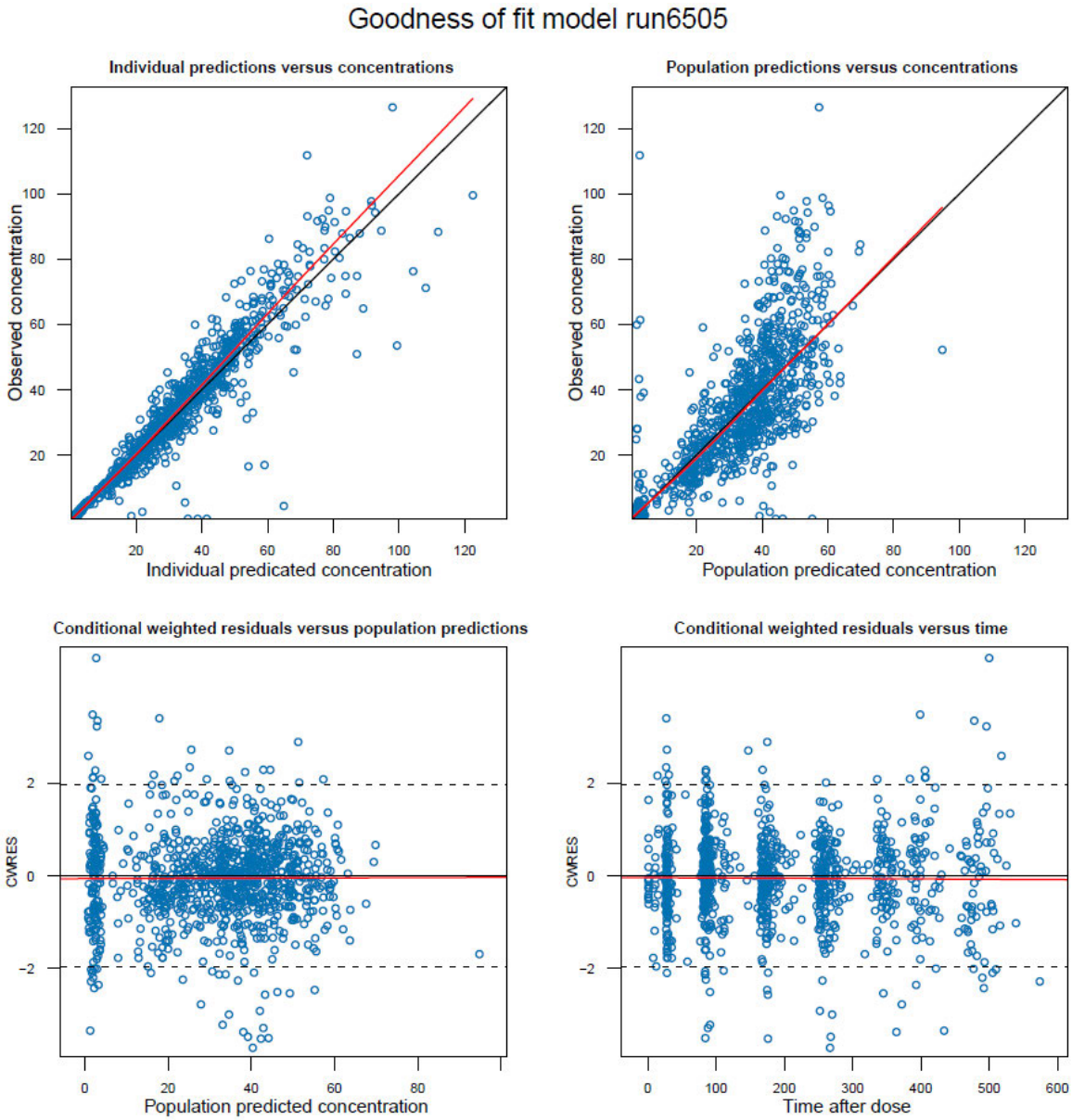
Source: Pediatric Population Pharmacokinetics and Exposure Response Report (Fremanezumab TV-48125, PMXR-2024-22), Figure 3 on page 50

Reviewer's analysis:

Table 6: Parameter Estimates of fremanezumab-vfrm Final Population Pharmacokinetic Model in Pediatric Population

Parameter	Pediatric Population Typical value (%RSE)
CL/F: apparent clerarance	0.0974 (4.0)
Vc/F: apparent central volume of distribution (L)	0.266 (30)
KA: absorption rate	0.107 (11)
CL/F: allometric exponent	0.748 (13)
Vc/F: allometric exponent on Weight	0.851 (11)
Q: Intercompartmental Clearance (L/day)	0.153 (14)
V3: Perpheral Volume of	2.92 (7)
Aage on KA	0.0747 (27)
Study/Phase difference on Cl for Phase 1	0.214 (48)
IIV in CV for CL/F	0.0237 (19)
IIV in CV for Vc/F	1.83 (23)
IIV in CV for KA	0.372 (41)
RV sc proportional component	0.204 (15)

Figure 11: Goodness-of-fit Diagnostic Plots for the Final Population Pharmacokinetic Model for Fremanezumab in Pediatric Population



The clinical pharmacology reviewer reviewed the applicant's pediatric population pharmacokinetic (popPK) model. Reviewer calculated PK parameter estimates (**Table 6**) were similar to those reported by the applicant (**Table 5**). Per applicant's and reviewer's independent analyses, the pediatric popPK model described pediatric migraine patient's data adequately (TV48125-CNS-10141, TV48125 CNS 30083 and TV48125 CNS 30084), with acceptable goodness of fit plots and visual predicted checks (**Figure 11**).

Table 7 shows popPK model predicted fremanezumab-vfrm exposures at steady state from adult and pediatric patients (≥ 45 kg) analyzed by the applicant. **Table 8** shows popPK model predicted fremanezumab exposures at steady state analyzed by the reviewer. As shown in **Table 7** and **Table 8**, predicted fremanezumab PK exposures are comparable between the applicant and the reviewer.

Table 9 shows applicant's predicted fremanezumab exposures at steady state between adult and pediatric patients ≥ 45 kg. Differences in fremanezumab PK exposures are described in Section 12.3 *Pharmacokinetics* of the proposed label. **Table 10** shows reviewer's predicted fremanezumab PK exposures at steady state between adult and pediatric patients ≥ 45 kg. As shown in **Table 9** and **Table 10**, predicted fremanezumab PK exposures at steady state are comparable between the applicant and the reviewer. Therefore, the reviewer agreed with the applicant's proposed labeling language as shown below.

Labeling text:

Following subcutaneous administration of 225 mg fremanezumab monthly in pediatric population weighing at least 45 kg, predicted steady state exposures (maximum plasma concentration [Cmax], area under the plasma concentration-time curve [AUC], average plasma concentration [Cav]) of fremanezumab generally overlapped with those of adults, with 31% higher mean Cmax and approximately 4% higher mean AUC and Cavg in the pediatric population.

Table 7: Comparison of Model Predicted Fremanezumab Exposures at Steady State from the Adult and Pediatric Population Pharmacokinetic Models by Dosing Regimen (Applicant's analysis)

Statistic	Predicted exposures for 225 mg sc monthly dosing regimen by Population					
	Adult Population (N=2474)			Paediatric Population (*N=174000)		
	$C_{max,ss(0-28d)}$ (µg/mL)	$AUC_{ss(0-28d)}$ (µg×day/mL)	$C_{av,ss(0-28d)}$ (µg/mL)	$C_{max,ss(0-28d)}$ (µg/mL)	$AUC_{ss(0-28d)}$ (µg×day/mL)	$C_{av,ss(0-28d)}$ (µg/mL)
Mean	71.2	1670	59.7	93.50	1744.3	62.30
SD	20.8	522	18.6	12.10	234.1	8.34
%CV	29.2	31.2	31.2	12.94	13.42	13.42
5th percentile	40.8	928	33.1	73.53	1318.3	47.08
Median	69.8	1640	58.5	95.56	1775.4	63.41
95th percentile	108	2590	92.4	111.1	2058.8	73.53

Source: Adult exposure: Teva Report CP-18-07, Table 19; ..\outputs\04_popPK_simulation\exposure_summary.csv.

*Pediatric post-hoc exposure calculated from simulation of 87 subjects over 2000 simulated trials.

%CV=coefficient of variation expressed as a percent; AUCss(0-28d)=area under the fremanezumab plasma concentration versus time curve from time 0 to 28 days at steady state; AUCss(0-84d)=area under the fremanezumab plasma concentration versus time curve from time 0 to 84 days at steady state; Cav,ss(0-28d)=average fremanezumab plasma concentration from time 0 to 28 days at steady state; Cav,ss(0-84d)=average fremanezumab plasma concentration from time 0 to 84 days at steady state; Cmax,ss(0-28d)=maximum drug concentration from time 0 to 28 days at steady state; Cmax,ss(0-84d)=maximum drug concentration from time 0 to 84 days at steady state; sc=subcutaneous; SD=standard deviation.

Source: Pediatric Population Pharmacokinetics and Exposure Response Report (Fremanezumab TV-48125, PMXR-2024-22), Table 9 on page 47

Table 8: Comparison of Model Predicted Fremanezumab Exposures at Steady State from the Adult and Pediatric Population Pharmacokinetic Models by Dosing Regimen (Reviewer's analysis)

Statistics	Predicted exposures for 225 mg sc monthly dosing regimen by Population					
	Adult Population			Pediatric Population (≥ 45 kg)		
	Cmax,ss(0-28d)(µg/ml)	AUC,ss(0-28d) (µg*day/ml)	Cavg,ss(0-28d)(µg/ml)	Cmax,ss(0-28d)(µg/ml)	AUC,ss(0-28d) (µg*day/ml)	Cavg,ss(0-28d)(µg/ml)
Mean	73.2	1675.6	59.8	85.0	1828.0	65.3
SD	22.8	519.2	18.5	43.3	658.3	23.5
%CV	31.2	31.0	31.0	51.0	36.0	35.9
5th percentile	41.9	952.7	34.0	29.8	827.8	29.7
Median	70.0	1601.7	57.2	77.7	1805.4	64.5
95th percentile	114.8	2633.6	94.1	160.1	2974.1	106.2

Table 9: Predicted Fremanezumab Exposures at Steady State between Adults and Pediatrics ≥ 45 kg (Applicant's analysis)

Applicant's Analysis	Adults	Pediatrics ≥ 45 kg
Cmax,ss (0-28d)(µg/ml)	71.2	93.5
AUC,ss (0-28d)(µg*day/ml)	1670	1744.3
Cavg,ss (0-28d)(µg*day/ml)	59.7	62.3

Table 10: Predicted Fremanezumab Exposures at Steady State between Adults and Pediatrics ≥ 45 kg (Reviewer's analysis)

Reviewer's Analysis	Adults	Pediatrics ≥ 45 kg
Cmax,ss (0-28d)(µg/ml)	73.2	85
AUC,ss (0-28d)(µg*day/ml)	1675.6	1828
Cavg,ss (0-28d)(µg*day/ml)	59.8	65.3

4. Appendices

4.1 Summary of bioanalytical and immunogenicity method validation

Bioanalytical method validation:

The PK samples were analyzed according to the validated ELISA method SOP-015503. The ELISA method SOP-015503 was validated and used in the original BLA submission. The ELISA method SOP-015503 was considered adequate in the original clinical pharmacology review. Please refer to CONSULT REV-CLINPHARM-01 (General Consult Review), Date 03/19/2018 for more details.

Two Addendum Method Validation Reports, 1) SOP-015503-AVR-01-ADDENDUM 2 and 2) SOP-015503-AVR-01-ADDENDUM 3, were submitted in this supplemental BLA. Method Validation Report SOP-015503-AVR-01-ADDENDUM 2 demonstrated that study samples were stable for up to 41 months when stored in a -20°C or ≤-65°C freezer. Method Validation Report SOP-015503-AVR-01-ADDENDUM 3 lists partial method validation data. All acceptance criteria outlined in the Addendum Method Validation Reports 02 and 03 were met (Appendix 1). Method SOP-015503 was adequate to quantify fremanezumab-vfrm concentrations in pediatric plasma samples.

Bioanalytical Study Report TV48125-CNS-10141-PK-BAR-01 (Sequence 0778): Performance of standards and QCs indicate that the bioanalytical ELISA method was accurate and precise for the analysis of fremanezumab concentrations in the clinical study (TV48125-CNS-10141). The longest sample storage duration from the date of collection to the date of analysis was 11 months (11 Jul 2018 to 20 Jun 2019); therefore, the established long-term sample storage stability of 41 months covered the time of sample storage before analysis.

Bioanalytical Study Report TV48125-CNS-30083-PK-BAR-01: Performance of standards and QCs indicate that the bioanalytical ELISA method was accurate and precise for the analysis of fremanezumab concentrations in the clinical study (TV48125-CNS-30083). The longest sample storage duration from the date of collection to the date of analysis was 24 months (25 November 2020 to 22 November 2022); therefore, the established long-term sample storage stability of 41 months covered the time of sample storage before analysis.

Bioanalytical Study Report TV48125-CNS-30084-PK-BAR-01 Interim 01: Performance of standards and QCs indicate that the bioanalytical ELISA method was accurate and precise for the analysis of fremanezumab concentrations in the clinical study (TV48125-CNS-30084). The longest sample storage duration from the date of collection to the date of analysis was 21 months (15 July 2022 to 11 April 2024); therefore, the established long-term sample storage stability of 41 months covered the time of sample storage before analysis.

Bioanalytical Study Report TV48125-BE-10145-ADA-BAR-01 (Sequence 0153) has been reviewed previously. The sample analyses for Study TV48125-BE-10145 were considered acceptable. Please refer to the clinical pharmacology review (DARTTS: 09/16/2019) for more details about the sample analyses.

Immunogenicity assay validation:

The anti-drug antibody (ADA) analysis of fremanezumab in human serum was performed using a validated bridging enzyme linked immunosorbent assay (ELISA). The

neutralizing antibody (NAb) analysis against fremanezumab in human serum was quantified using a validated competitive ligand binding ELISA method. The same immunogenicity assays (ADA and Nab) were used in the supplemental BLA as the original BLA. No additional immunogenicity validation report was submitted in the supplemental BLA. The original immunogenicity assays were found adequate during the original QUALITY ASSESSMENTS.

Appendix 1:

Table 11: Summary of the Validation Results (Addendum 02)

Validation Parameters or Acceptance Criteria	Results	Pass/Fail criteria
Long term stability: Accuracy must be between 80-120% of nominal values		
32 months	-20±5°C 3/3 HQC have accuracy between 95-99% 3/3 LQC have accuracy between 103-105%	Pass
	≤ -65°C 3/3 HQC have accuracy between 87-102% 3/3 LQC have accuracy between 96-107%	
37 months	-20±5°C 3/3 HQC have accuracy between 103-107% 3/3 LQC have accuracy between 86-89%	Pass
	≤ -65°C 3/3 HQC have accuracy between 91-103% 3/3 LQC have accuracy between 81-84%	
41 months	-20±5°C 3/3 HQC have accuracy between 98-104% 3/3 LQC have accuracy between 87-100%	Pass
	≤ -65°C 3/3 HQC have accuracy between 95-105% 3/3 LQC have accuracy between 94-100%	
Dilution on automation vs. manual dilution		
Intra-day %CV must be ≤20% (automation data)	CV≤ 14%	Pass
Inter-day % CV must be ≤20% (automation data)	CV≤ 14%	Pass

Validation Parameters or Acceptance Criteria	Results	Pass/Fail criteria
% variability in concentrations between manual and automation must be within 30%	Excluding the mock sample with <LLOQ, 24/24 spiked samples have % difference between -17 to 13%	Pass
1 % Casein in PBS vs. 2% Casein in PBS blocking buffer		
% variability in concentrations between 1% Casein in PBS vs 2% Casein in PBS must be within 30%	Excluding the mock sample with <LLOQ, 24/24 spiked samples have % difference between - 18 to 9%	Pass

Table 12: Summary of the Validation Results (Addendum 03)

Parameter	Target acceptance criteria	Observed result
Selectivity	Pooled matrix spiked at low level should have recovery (%AR) within (b) (4)% of nominal	Recovery of pooled matrix spiked at low level was 102%
	(b) (4)% of individual spiked samples at low level should have recovery within (b) (4)% of nominal	Six out of 7 individuals (86% of samples) spiked at low level recovered between 93-105% of nominal
	Pooled matrix spiked at high level and further dilutions should have median recoveries within (b) (4)% of nominal	Recovery of pooled matrix spiked at high level and further dilutions have median recoveries of 106% of nominal
	(b) (4)% of individual spiked samples at high level and further dilutions should have median recoveries within (b) (4)% of nominal	Seven out of 7 individuals (100% of samples) spiked at high level recovered between 92-98% of nominal and further dilutions median recovery ranged from 95-97% of nominal
	(b) (4)% of the unspiked sample's mean results must be below the limit of quantification level	Seven out of 7 (100% of samples) of unspiked samples recovered below the limit of quantification level

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PING DU
07/29/2025 01:48:42 PM

ADARSH S GANDHI
07/29/2025 03:19:48 PM
On behalf of Poonam Delvadia

VENKATESH A BHATTARAM
07/29/2025 03:22:22 PM

MEHUL U MEHTA
07/29/2025 03:26:23 PM