

P249. Pediatric Dose Selection for Fremanezumab (AJOVY) Phase 3 Migraine Studies using Pharmacokinetic Data from a Pediatric Phase 1 Study and a Population Pharmacokinetic Model and Simulation Approach

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Objectives

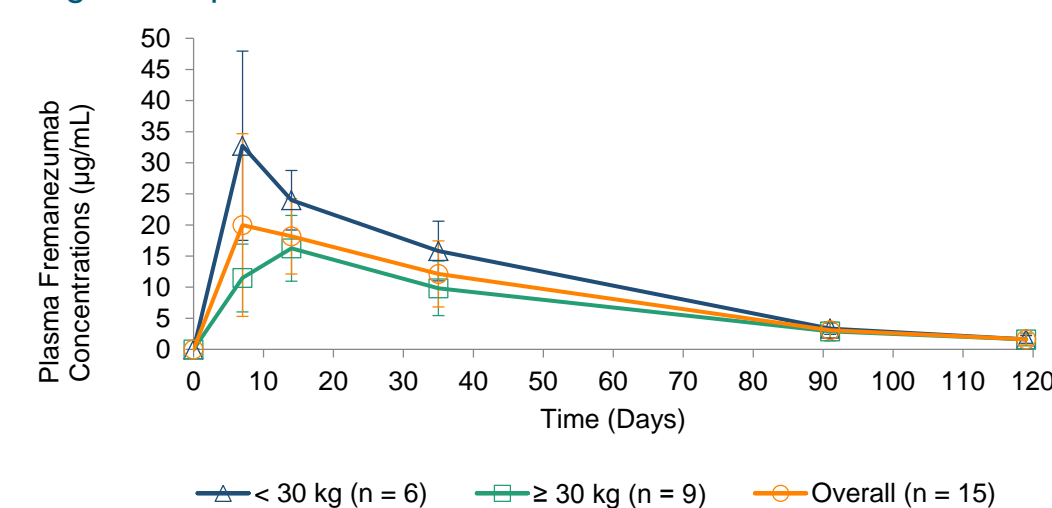
- Previous examination of the relationship between fremanezumab exposure and baseline body weight supports a weight cutoff of 45 kg for pediatric dose selection, with the approved adult dose of 225 mg monthly being appropriate for patients weighing ≥ 45 kg.
- As part of the pediatric phase 3 program for fremanezumab, the present analyses were conducted to determine the appropriate dose for migraine pediatric patients weighing < 45 kg.
- These analyses included a refinement of the adult fremanezumab population pharmacokinetic (PopPK) model using pediatric PK data from a phase 1 study (TV48125-CNS-10141) in migraine patients 6 to 11 years old and simulation

Methods & Results

Fremanezumab Phase 1 Study of Patients with Migraine Aged 6-11 Years

- In the TV48125-CNS-10141 study, 15 patients with migraine aged 6 to 11 years received a single sc injection of fremanezumab (75 mg/0.5 mL) on day 1.
- Fremanezumab concentration data were collected from all 15 patients at 6 different time-points (pre-dose and days 2, 11, 29, 85, and 113 post-dose) (Fig 1).
- Mean age was 9.3 years and mean weight was 33.63 kg. There were 6 patients in the < 30 kg group (mean weight = 25.73 kg) and 9 patients in the ≥ 30 kg group (mean weight = 38.89 kg).
- For the < 30 kg weight group, maximal concentration (C_{max}) was 2-fold higher than the ≥ 30 kg weight group (32.342 vs 15.426 $\mu\text{g/mL}$), and the corresponding median time (t_{max}) values were 1.00 day and 9.98 days, respectively. The values for cumulative exposure (AUC) were about 1.5-fold higher in the < 30 kg weight group than in the ≥ 30 kg weight group.

Fig 1. Mean (SD) Plasma Concentration of Fremanezumab by Weight Group



Re-estimating the Adult Fremanezumab PopPK Model with Pediatric Data

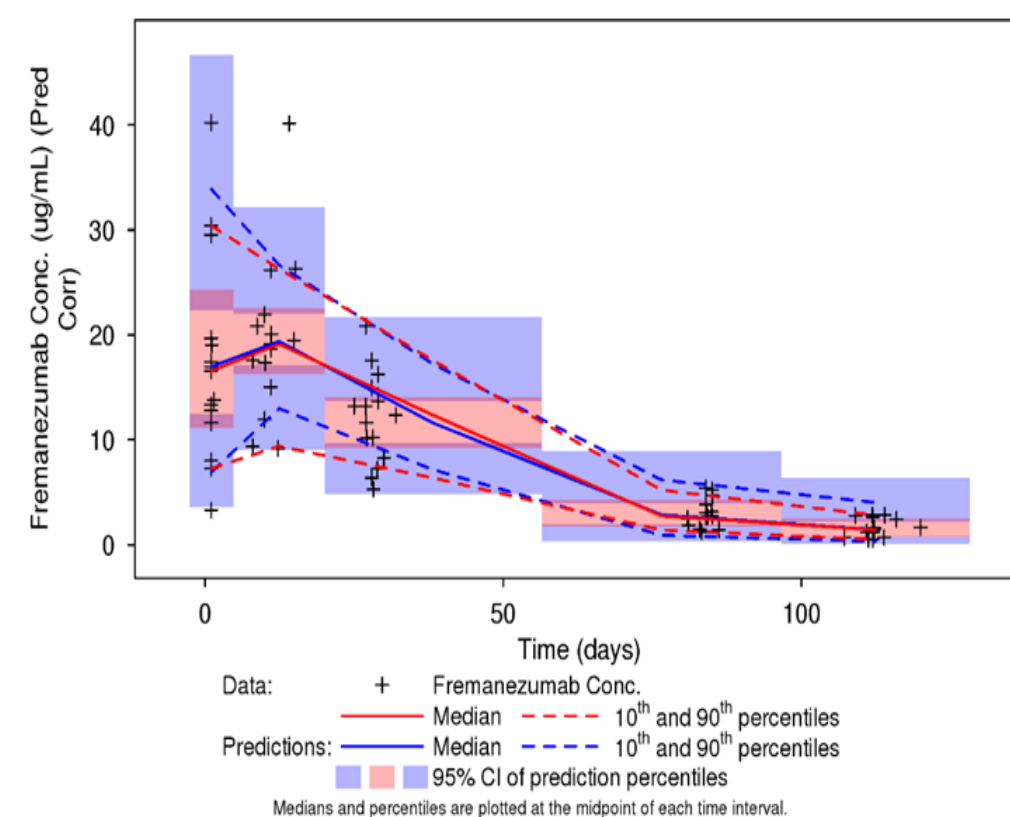
- The base model was a two-compartment model with first-order absorption and elimination. Covariates already included in the previously developed adult PopPK model¹ (allometric weight scaling on clearance and central volume) were reevaluated as well as age and sex.
- Model evaluation was performed throughout the modeling steps using prediction-corrected visual predictive check (pcVPC), which provided a graphical assessment of the agreement between the time course of observed and model-predicted concentrations (Fig 2).
- In the re-estimation of the adult PopPK model using the pediatric data, the final PK parameter estimates, with the exception of absorption rate k_a and the allometric exponents for clearance CL and central volume V_c , were comparable between adult and pediatric patients (Table 1).

Table 1. Parameter Estimates for Fremanezumab Comparing Adult PopPK Model with Updated Pediatric PopPK Model

Pharmacokinetic Parameter	Adult Patients	Pediatric Patients
	Population Estimate (%RSE)	
CL: central clearance (L/day) ^a	0.0902 (1.50)	0.0905 (0.0937)
CL: allometric exponent for weight (-) ^b	1.05 (4.33)	0.245 (32.7)
V_c : central volume of distribution (L) ^{a,c}	1.88 (3.38)	1.89 (0.213)
V_c : allometric exponent for weight (-) ^d	1.53 (10.3)	1.20 (32.7)
k_a : absorption rate constant (1/day)	0.180 (12.2)	0.252 (14.8)
Q: inter-compartmental clearance (L/day) ^a	0.262 (FIXED)	0.262 (FIXED)
V_p : peripheral volume of distribution (L) ^a	1.72 (FIXED)	1.72 (FIXED)
ALAG1: lag time (day)	0.0803 (FIXED)	NE
F1: bioavailability	0.658 (FIXED)	Apparent (F1=1)
Magnitude of inter-individual variability (%RSE)		
Inter-individual variability in CL	23.4 %CV (4.60)	34.2 %CV (53.2)
Inter-individual variability in V_c	35.1 %CV (19.9)	79.9 %CV (49.6)
Inter-individual variability in k_a	59.0 %CV (15.8)	NE
Parameter estimate (%RSE)		
Residual variability proportional component	0.0531 (4.03)	0.0338 (43.7)
Residual variability additive component	0.204 (25.6)	NE

^aCV = coefficient of variation expressed as a percent; NE = not estimated; %RSE = relative standard error expressed as a percent; sc = subcutaneous; ^bIn pediatric patients, parameters are apparent; ^cTypical value for CL from pediatric model = 0.0905-(Weight/71)^{0.245}; ^dCentral volume of distribution, sc from adult model; ^eTypical value for V_c from pediatric model = 1.89 × (Weight/71)^{1.20}

Fig 2. pcVPC for Fremanezumab Pediatric PopPK Model



Simulations to Support Pediatric Phase 3 Dose Selection

- A virtual population of 2400 pediatric patients (6 to 17 years old, 200 patients per year of age) was generated and used along with the final pediatric PopPK model estimates to simulate concentration-time profiles for monthly fremanezumab sc doses ranging from 60 to 225 mg.
- Weight was determined by the Centers for Disease Control and Prevention growth chart (CDC 2009; <https://www.cdc.gov/growthcharts/zscore.htm>) using a random number to determine the Z score (percentile of body weight) for each simulated age. Among the 2400 virtual pediatric patients, 1453 had a body weight < 45 kg. The median baseline body weight for these patients was 29.0 kg (range 17.0 to 44.8 kg).
- Simulated exposure measures (i.e., cumulative exposure represented by the area under the concentration-time curve from time 0 to 28 days [AUC_{28d}], and maximum drug concentration [C_{max}]) were calculated at steady-state for the virtual pediatric patients and compared to simulated exposure measures at steady-state in the adult population receiving fremanezumab 225 mg sc monthly.

Dose Selection for Pediatric Patients Weighing < 45 kg

- For virtual pediatric patients (aged 6 to 17 with body weight < 45 kg) administered 120 mg sc monthly, the simulated AUC_{28d} distribution is nearly identical to the adult patient distribution following 225 mg sc monthly (Fig 3). Very similar patterns are observed for C_{av} and C_{min}.
- The simulated C_{max} distribution following 120 mg sc monthly in the pediatric population suggests slightly higher C_{max} than that achieved in the adult population with 225 mg, however overall the upper exposure range extends only slightly above the upper range of the adult distribution (Fig 4).
- When comparing the simulated C_{max} distribution following 120 mg sc monthly in the pediatric population with the adult C_{max} by weight quartile, the C_{max} distribution for the pediatric population is comparable to that of the two lower body weight quartiles of the adult population (Fig 5).

Fig 3. Simulated AUC_{28d} by Dose for Pediatric Patients 6 to 17 Years < 45 kg compared to adults

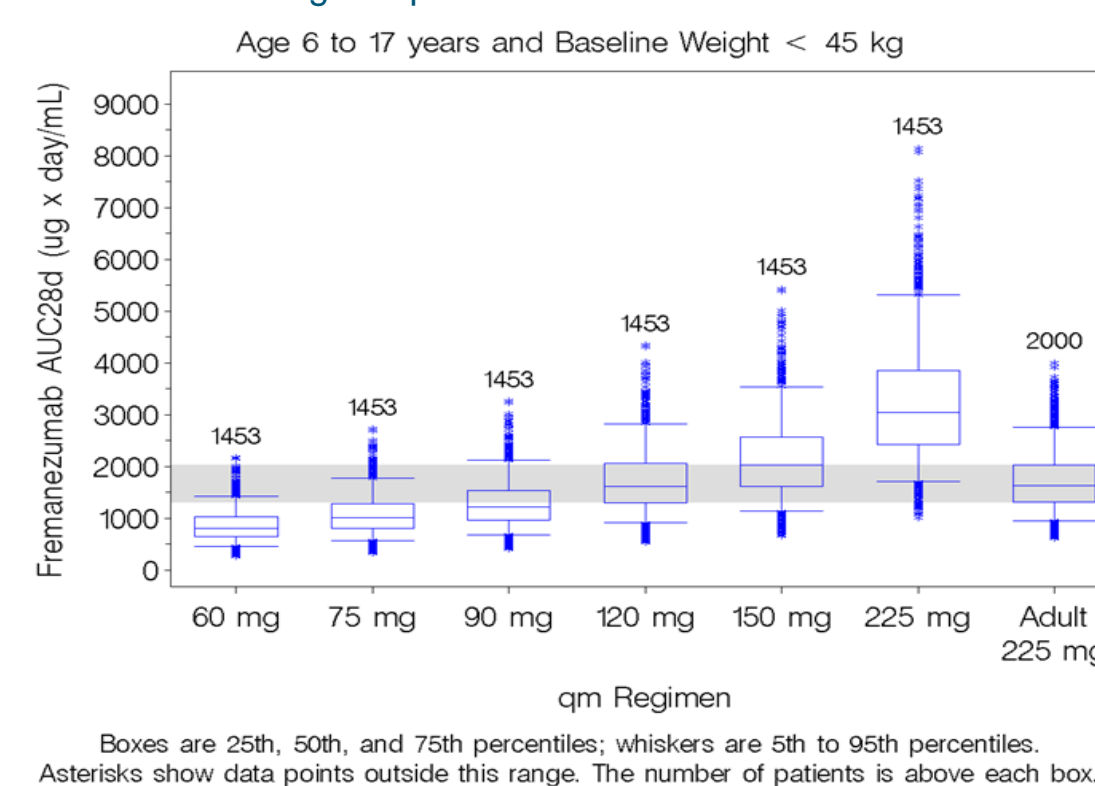


Fig 4. Simulated C_{max} by Dose for Pediatric Patients 6 to 17 Years < 45 kg Compared to Adults

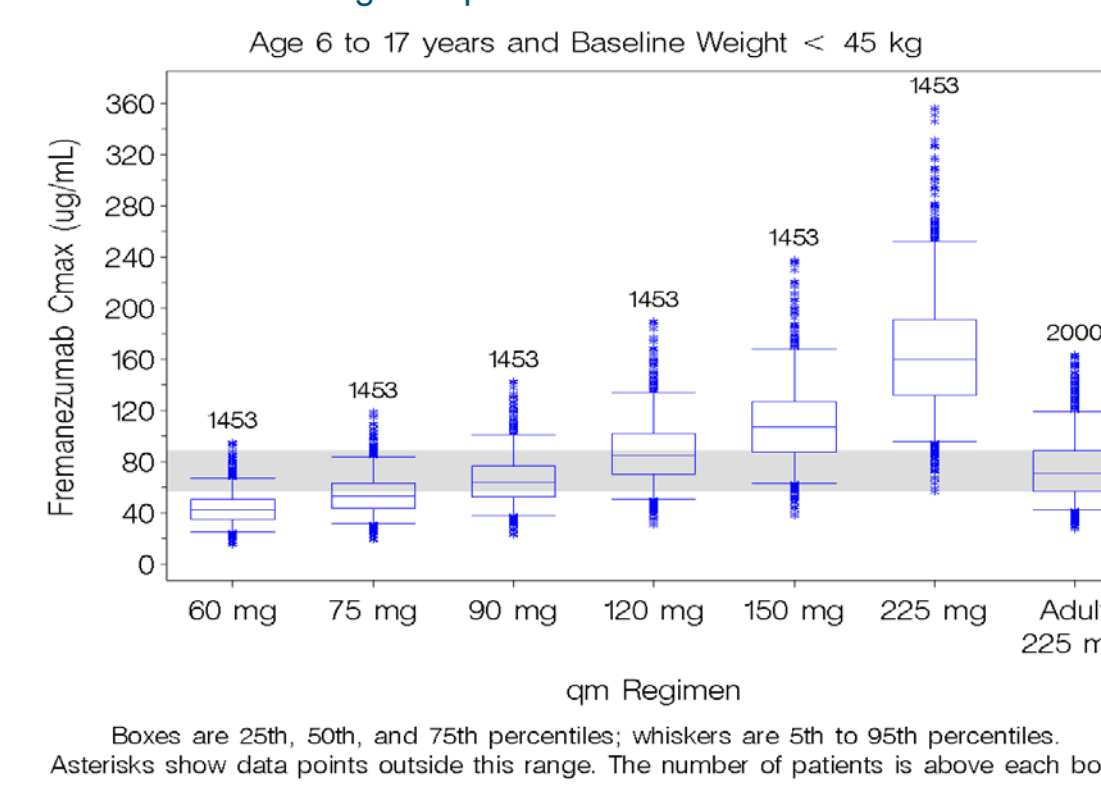
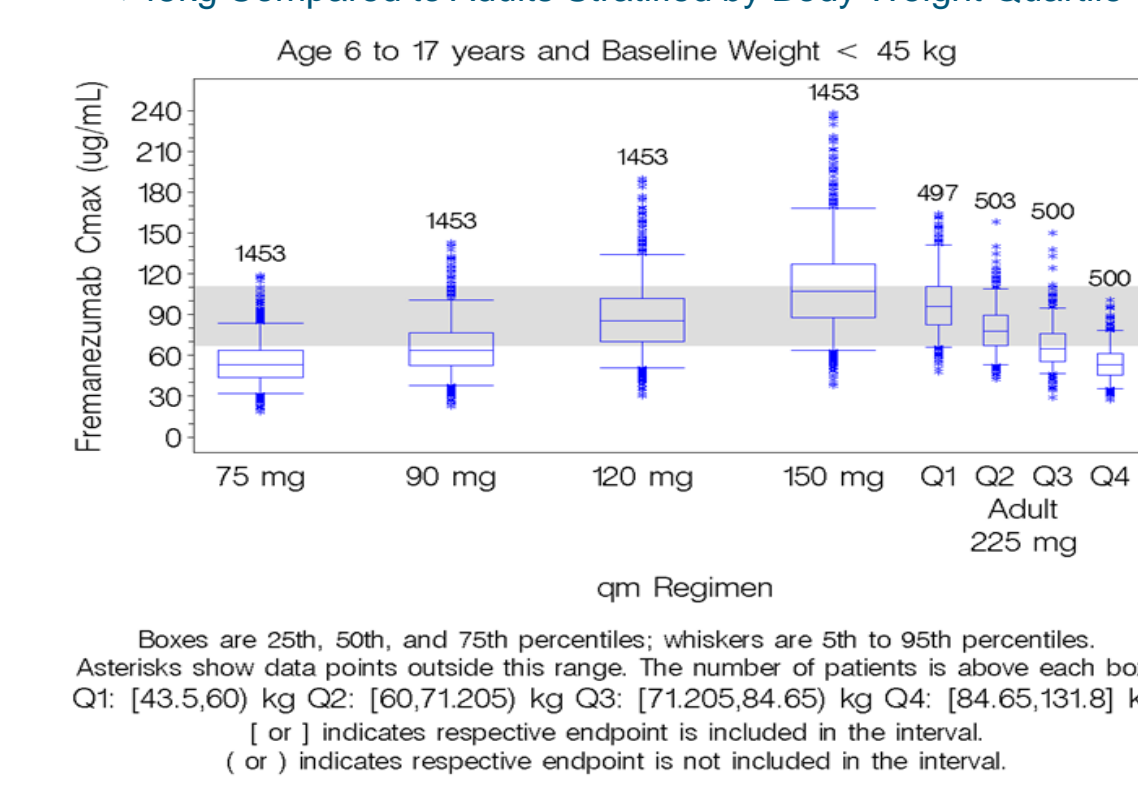


Fig 5. Simulated C_{max} by Dose for Pediatric Patients 6 to 17 Years < 45 kg Compared to Adults Stratified by Body Weight Quartile



Evaluation of Body Weight Cutoff

- Based on the significant effect of body weight on fremanezumab, the scatterplot of simulated AUC_{28d} predicted slightly higher exposures with lower body weight (Fig 6).
- Despite this relationship, it is notable that the range and central tendency of the simulated exposures are similar for body weights between 17 and 45 kg.
- As shown in Fig 7, the distribution of exposures for pediatric patients is nearly identical in both body weight categories (17 to < 30 kg and 30 to < 45 kg) while matching the exposures in adults at the effective dose of 225 mg sc monthly. Based on the similarity in exposures over this body weight range, no additional body weight cutoff value < 45 kg was deemed necessary.

Fig 6. Simulated Fremanezumab AUC_{28d} Versus Body Weight

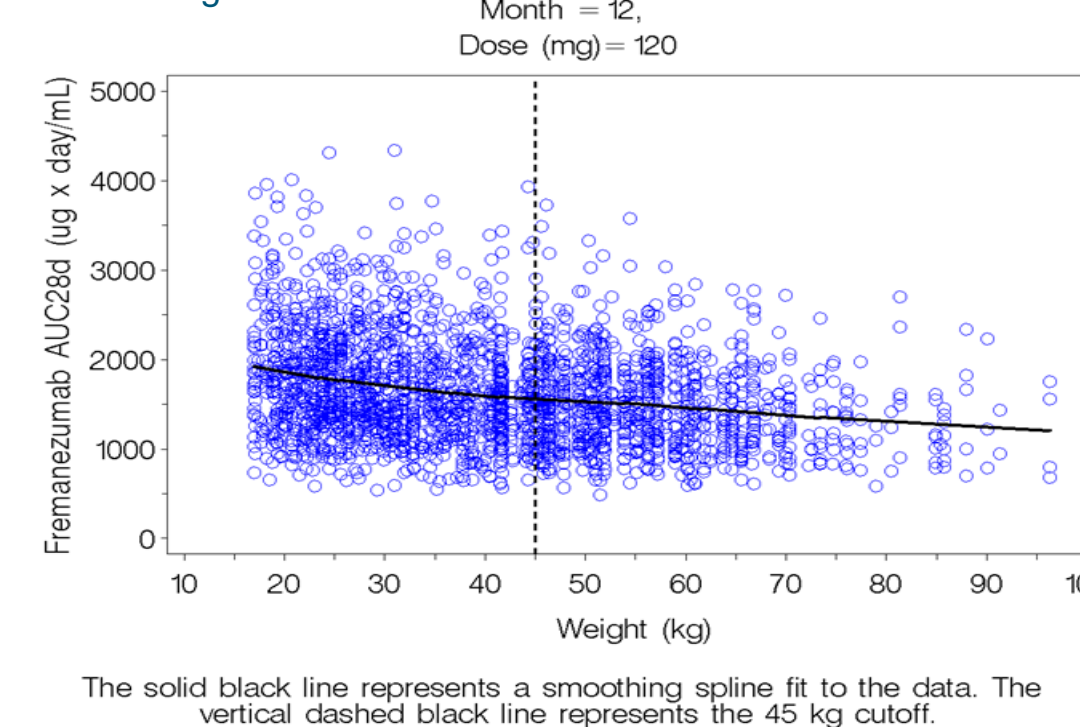


Fig 7. Predicted Exposures by Body Weight Categories

