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Population Pharmacokinetic Modeling of Fremanezumab in Support of Phase 3 Development for Patients with Migraine

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INTRODUCTION

Calcitonin gene-related protein (CGRP) is a well-studied neuropeptide that plays an important role in the pathophysiology of migraines, both centrally and peripherally.[1,2] Jugular levels of CGRP are increased during migraine attacks, and intravenous CGRP administration induces migraine-like headaches in most individuals with migraine.[3,4] Small-molecule CGRP receptor antagonists and anti-CGRP antibodies have demonstrated efficacy in the treatment of episodic[5,6,7,8] migraine (EM) and chronic[9] migraine (CM).

Fremanezumab (fully humanized IgG2Δa/kappa monoclonal antibody) is a selective anti-CGRP drug that is being developed for the treatment of migraines. It binds both the α- and β-CGRP isoforms and inhibits CGRP from binding to the CGRP receptor. Also, it does not bind to the closely related amylin, calcitonin, or adrenomedullin peptides. In Phase 2 and 3 studies, fremanezumab has been found to be effective and well-tolerated as a preventive treatment for episodic and chronic migraine.[8,10,11]

GOAL

The goal of these analyses was to characterize the population pharmacokinetics (PK) of fremanezumab in healthy subjects and in patients with episodic and chronic migraine and to explain sources of between-subject variability.

METHODS

Data Description and Study Design

The population PK analysis, performed using NONMEM, included data following subcutaneous administration from:

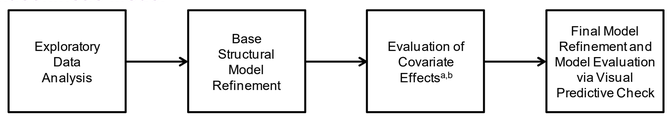
- 1 Phase 1 study
  - TV48125-PK-10078 (48 healthy subjects): 225, 675, and 900 mg single dose;
- 2 Phase 2b studies
  - LBR-101-021 (167 patients with CM): 675-225-225 mg monthly or 900 mg monthly for 3 doses
  - LBR-101-022 (186 patients with EM): 225 or 675 mg monthly for 3 doses
- 3 Phase 3 studies
  - TV48125-CNS-30049 (741 patients with CM): 675 mg followed by monthly doses of 225 mg for 3 doses or single 675 mg once quarterly
  - TV48125-CNS-30050 (567 patients with EM): 225 mg once monthly for 3 doses or single 675 mg once quarterly
  - TV48125-CNS-30051 (578 patients with CM or EM): 225 mg monthly or 675 mg followed by 225 mg monthly or 675 mg once quarterly over 12 months

In Study TV48125-PK-10078, an intensive PK sampling schedule was implemented, while the Phase 2b and 3 studies included the collection of predose (trough) samples on days 1, 29, and 57, as well as a single sample collected on day 85. Additional samples were collected in Study TV48125-CNS-30051, 3 to 10 days or 15 to 20 days after study drug administration (select subjects) and on days 169, 253, 337, and 534.

Population Pharmacokinetic Analysis

The overall procedures followed for the development and refinement of the population PK model for fremanezumab are outlined in **Figure 1**.

Figure 1. Process for the Development of the Fremanezumab Population Pharmacokinetic Model



[a] Weight, age, sex, race, albumin, creatinine clearance, and concomitant medications (acute and preventative migraine-specific medications). Anti-drug antibody (ADA) status was not tested as a covariate due to the small sample size (0.8% of total samples with ADA [excluding TV48125-CNS-30051], <10% of the overall population). Liver function category (National Cancer Institute Organ Dysfunction Working Group Liver Function Classification) was not tested as a covariate since less than 10% of the subjects were characterized with having mild or moderate hepatic impairment. In addition, analgesic medication was not tested as a covariate since less than 10% (9.1%) of the subjects had samples collected in the presence of analgesics. As such, only exploratory graphical evaluations were performed for these covariates.
[b] Stepwise forward selection (α=0.01 plus at least a 5% reduction in interindividual variability in the parameter of interest) followed by backward elimination (α=0.001) methodology was used.

Assessment of Effects of Covariates on Fremanezumab Exposure

Individual Bayesian estimates for patients from the Phase 2b and 3 studies and dosing regimens of 225 mg once monthly (12 doses) and 675 mg once quarterly (4 doses) were used to assess the effects of body weight, race, age, sex, albumin, preventative medications, acute medications, analgesic medications, liver function, and ADAs. The effect of patient status was evaluated using the subjects from Phase 1, Phase 2b, and Phase 3.

Simulations

The final PK model estimates were used along with the subject characteristics resampled from the Phase 3 studies to simulate concentration-time data for 1000 virtual subjects at each of the following dosing regimens:

- 225 mg once monthly for 12 doses
- 675 mg starting dose followed by 225 mg once monthly for a total of 12 doses
- 675 mg quarterly for 4 doses

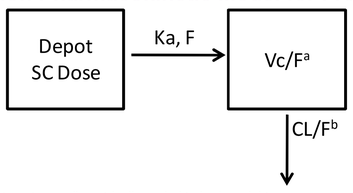
Simulated steady-state exposures were presented graphically stratified by covariate group (discrete covariates) or quartiles (continuous covariates). Individual measures of fremanezumab exposures (maximum drug concentration [C_{max}] after each dose, area under the concentration-time curve from time 0 to 28 days [$AUC_{0\text{-}28}$], and AUC from time 0 to 84 days [$AUC_{0\text{-}84}$] up until the 12th dose [for monthly doses] or 4th dose [for quarterly doses]) were calculated. The model-based terminal half-life and accumulation ratio were also calculated using steady-state exposures.

RESULTS

Population Pharmacokinetic Analysis

A total of 8346 fremanezumab concentrations from 2287 individuals were used for the population PK modeling. A 1-compartment model with first-order absorption and elimination adequately fit the pooled Phase 1/2b/3 data (**Figure 2**).

Figure 2. Population Pharmacokinetic Model for Fremanezumab

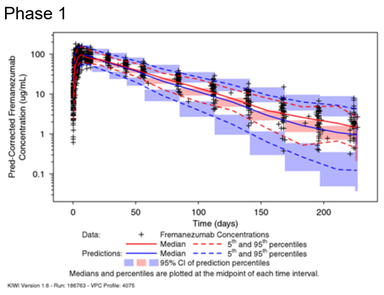


[a] Volume of the central compartment was allometrically scaled to body weight.
[b] Clearance was allometrically scaled to body weight.
CL/F=apparent clearance; F=bioavailability fraction; Ka=first-order absorption rate constant; SC=subcutaneous; Vc/F=apparent central volume of distribution

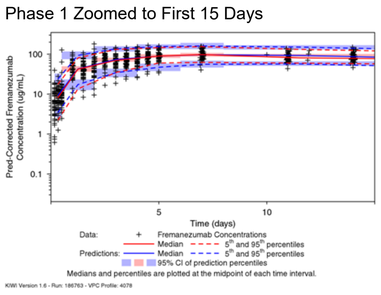
All fixed and random effect parameters were estimated with good precision and visual predictive check diagnostics indicated a good fit of the model to the data (**Figure 3**). The model characterized the overall PK data well, particularly during the period ranging from time 0 to approximately 29 or 85 days, where the bulk of the concentration data were observed. In addition, the model accurately captured the central tendency and shape of the multiple-dose PK data. The typical values for apparent clearance (CL/F) (0.141 L/day) and apparent central volume of distribution (V_c/F) (6.28 L) were generally consistent with the previously reported values for IgG antibodies.[12,13] As generally observed with monoclonal antibodies, weight was a significant covariate in the model with respect to both CL/F and V_c/F, where higher weight was associated with increased CL/F and V_c/F (**Table 1**). The effects of other covariates evaluated (race, sex, albumin, age, creatinine clearance, and acute and preventative medications) were not found to statistically significantly influence the PK of fremanezumab.

Figure 3. Prediction-corrected Visual Predictive Check for Final Pooled Phase 1/2b/3 Fremanezumab Population Pharmacokinetic Model Overlaid with the Observed Data

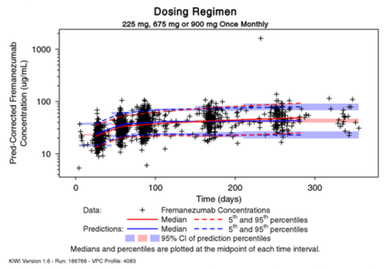
Phase 1



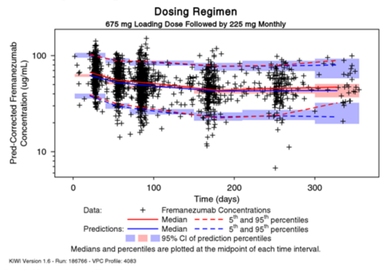
Phase 1 Zoomed to First 15 Days



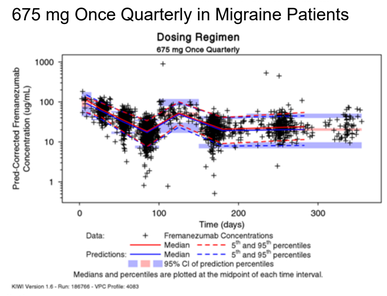
225, 675, 900 mg Once Monthly in Migraine Patients



675 mg Starting Dose Followed by 225 mg Monthly in Migraine Patients



675 mg Once Quarterly in Migraine Patients



CI=confidence interval; Pred=prediction

Table 1. Parameter Estimates and Standard Errors for Fremanezumab Pooled Phase 1/2b/3 Final Pharmacokinetic Model: Including TV48125-CNS-30051

Parameter	Final parameter estimate		Interindividual variability / residual variability[a]	
	Typical value	%RSE	Magnitude	%RSE
CL/F: apparent central clearance (L/day)[b]	0.141	0.742	29.0 %CV	3.64
CL/F: allometric exponent for weight (-)[b]	1.20	2.48		
V_c/F: apparent central volume of distribution (L)[c]	6.28	0.880	22.7 %CV	9.29
V_c/F: allometric exponent for weight (-)[c]	0.892	4.16		
k_a: absorption rate constant (1/day)	0.379	5.93	54.8 %CV	22.0
cov(IIV in V_c/F, IIV in CL/F)[d]	0.0462	7.00	NA	NA
Residual variability (log unit)	0.0268	8.75	0.164 SD	NA
Minimum value of the objective function = -15075.843				

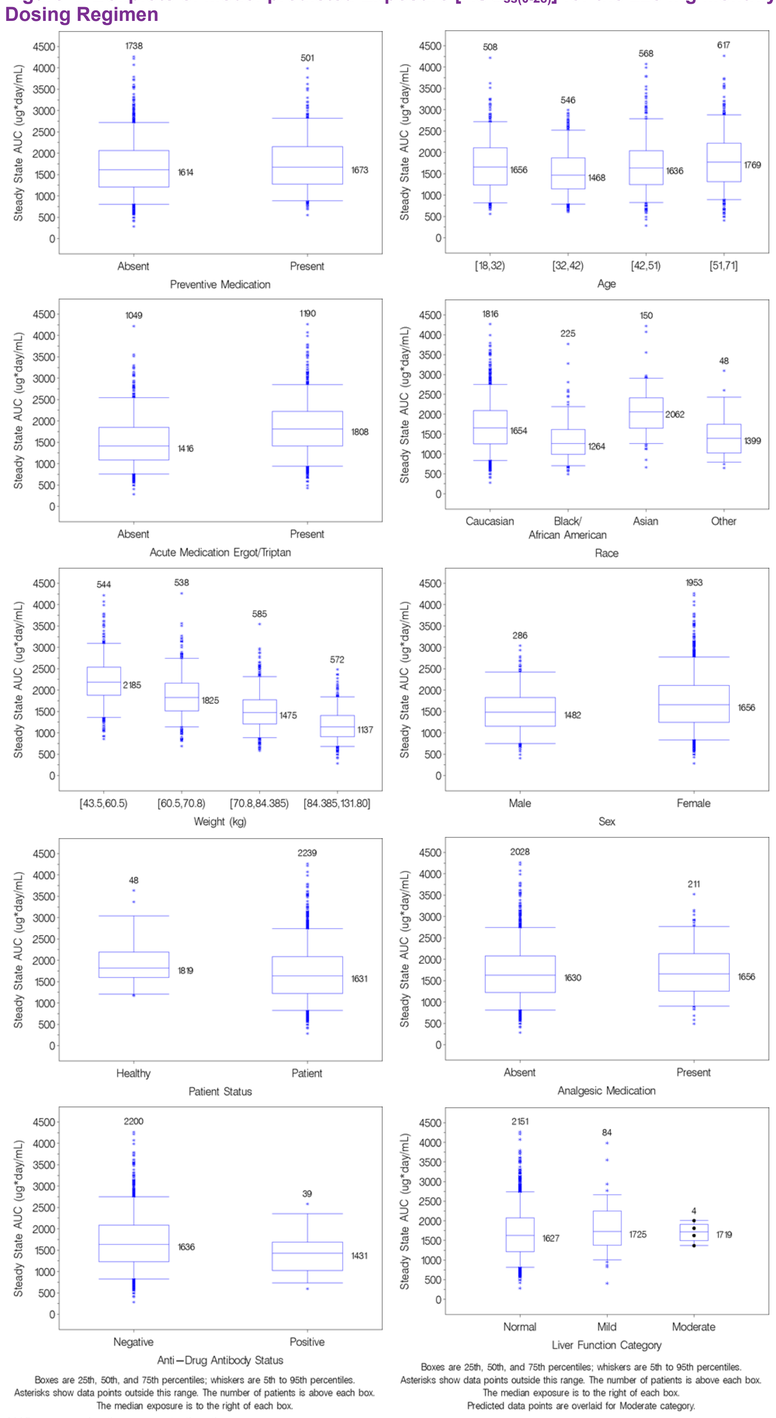
For the effect of weight, relative to a 71-kg subject (the median weight in the population), a 51-kg subject and a 101-kg subject (corresponding to the 5th and 95th percentiles of body weight observed in the analysis dataset) are expected to have approximately 32% lower and 52% higher CL/F and 25% lower and 36% higher V_c/F, respectively.
[a] ETA shrinkage: eta CL/F: 6.23%; eta V_c/F: 27.9%; eta k_a: 52.0%; epsilon shrinkage: 17.6%.
[b] *Typical Value for* $CL/F = 0.141 \times (Weight/71)^{1.20}$
[c] *Typical Value for* $V_c/F = 6.28 \times (Weight/71)^{0.892}$
[d] The calculated correlation coefficient (r^2) of the off-diagonal omegas was 0.491 for cov(IIV in V_c/F, IIV in CL/F).
%CV=coefficient of variation expressed as a percent; IIV=interindividual variability; NA=not applicable; SD=standard deviation; %RSE=relative standard error expressed as a percent

Assessment of Effects of Covariates on Fremanezumab Exposure

Based on graphical exploration of covariates (**Figure 4**), predicted exposures in the presence or absence of preventive migraine-specific medications were comparable. Fremanezumab exposures were slightly higher, but generally overlapping, in the presence of acute migraine-specific medication (ergotamine/triptan) use compared to the absence of use. In addition, exposures were also consistent across each age quartile. Exposures were somewhat higher in the Asian subjects compared to the other groups, but the overall range of exposures overlapped with the predicted range in the much larger group of Caucasian subjects. Across the range of body weight, a decrease in fremanezumab exposure was evident with increasing body weight across the quartiles. Exposures were marginally higher in females, but the overall range of exposures in male subjects overlapped with the predicted range in the much larger group of female subjects. Boxplots of exposures for fremanezumab in healthy subjects versus patients with chronic migraine or episodic migraine indicate similarity in exposures between these 2 populations.

Analgesic medication, ADA, and liver function were solely evaluated on an exploratory basis due to limited sample size within respective categories. The results show no indication of ADA status or analgesic medication having an impact on fremanezumab exposure. Although the median exposures were slightly higher in patients with mild liver function impairment, the range of exposures in these groups was encompassed in the range of predicted exposures in the subjects with normal liver function. There were only 4 subjects with moderate impairment, as shown in the boxplots, precluding making any conclusion for this category.

Figure 4. Boxplots of Model-predicted Exposure [$AUC_{ss(0\text{-}28)}$] for the 225 mg Monthly Dosing Regimen



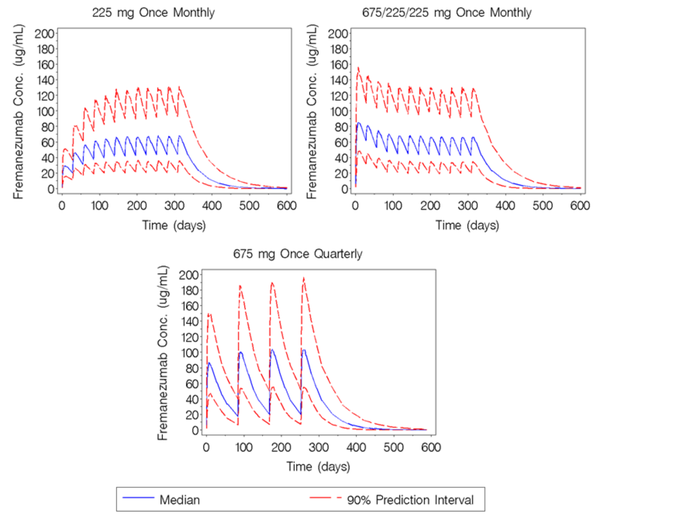
Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of patients is above each box.
The median exposure is to the right of each box.
Predicted data points are overlaid for Moderate category.

AUC=area under the concentration-time curve
Similar results were observed for the 675 mg once-quarterly dosing.

Simulation Results

The calculated, model-based median half-life was approximately 31 days (independent of dose or dose regimen). Based on predicted exposure levels, steady state is expected to be achieved by approximately 168 days (about 6 months; **Figure 5**). The C_{max} values in the 675 mg once-quarterly dosing regimen were consistently higher when compared to the 225 mg monthly or subsequent 225 mg monthly doses in the 675-225-225 mg monthly dosing regimen; as expected, the use of a starting dose of 675 mg resulted in a slightly higher exposure in month 1 than that observed at steady state (**Figure 6**). Comparison of the fremanezumab exposure ($AUC_{0\text{-}28}$, C_{max}) following the final dose (dose 12) of 225 mg monthly to a single 225-mg dose resulted in a median accumulation ratio of 2.34 for both AUC and C_{max} (**Table 2**). Comparison of the exposures following the final dose (dose 12) of 225 mg to the 675 mg starting dose resulted in a median ratio of 0.78 (**Table 2**). For the 675 mg once-quarterly dosing regimen, the exposure ($AUC_{0\text{-}84}$, C_{max}) after dose 4 (final dose) compared to dose 1 resulted in a median accumulation ratio of 1.20 and 1.19 for AUC and C_{max}, respectively (**Table 3**).

Figure 5. Simulated Concentration-Time Profiles for the Doses Used in the Phase 3 Clinical Trials Administered Over 12 Months



Conc=concentration

Figure 6. Comparison of Simulated Median Concentration Versus Time Profiles by Dosing Regimen

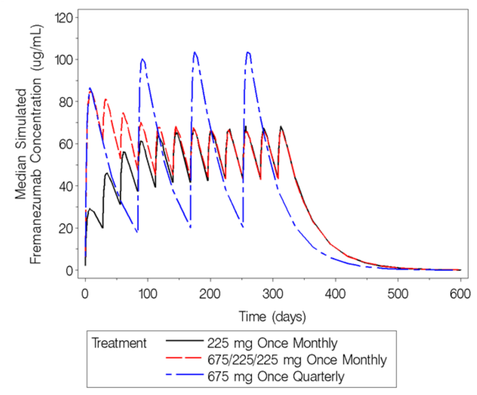


Table 2. Summary of Accumulation Ratios: 225 mg Once Monthly

Percentile	AR_{AUC}[a]	AR_{Cmax}[b]	$AR_{Loading\ Dose}$[c]
5th	2.21	2.25	0.730
50th	2.34	2.34	0.782
95th	2.60	2.57	0.863

[a] $AUC_{(0\text{-}28,\ 225\ mg\ 12^{th}\ Dose)}/AUC_{(0\text{-}28,\ 225\ mg\ 1^{st}\ Dose)}$.
[b] $C_{max(225\ mg\ 12^{th}\ Dose)}/C_{max(225\ mg\ 1^{st}\ Dose)}$.
[c] $AUC_{(0\text{-}28,\ 225\ mg\ 12^{th}\ Dose)}/AUC_{(0\text{-}28,\ 675\ mg\ 1^{st}\ Dose)}$.
AR=accumulation ratio; AUC=area under the concentration-time curve; C_{max}=maximum drug concentration

Table 3. Summary of Accumulation Ratios: 675 mg Once Quarterly

Percentile	AR_{AUC}[a]	AR_{Cmax}[b]
5th	1.16	1.17
50th	1.20	1.19
95th	1.29	1.31

[a] $AUC_{(0\text{-}84,\ 675\ mg\ 4^{th}\ Dose)}/AUC_{(0\text{-}84,\ 675\ mg\ 1^{st}\ Dose)}$.
[b] $C_{max(675\ mg\ 4^{th}\ Dose)}/C_{max(675\ mg\ 1^{st}\ Dose)}$.
AR=accumulation ratio; AUC=area under the concentration-time curve; C_{max}=maximum drug concentration

CONCLUSIONS

- A 1-compartment model with first-order absorption and elimination and weight effect on CL/F and V_c/F adequately described the fremanezumab concentration-time data.
- Higher weight was associated with increased clearance and central volume of distribution resulting in a decrease of fremanezumab exposure with increasing body weight. Age, albumin levels, creatinine clearance, sex, race, as well as acute and preventative medications were also tested as covariates and not found to be statistically significant predictors of variability in PK.
- There is no indication of reduced exposure to fremanezumab in patients with positive ADA status.
- The median model-based estimate of half-life is approximately 31 days (independent of dose or dose regimen).
- Based on simulated data, steady state is expected to be achieved by approximately 168 days for monthly and quarterly doses. The use of a starting dose of 675 mg followed by 225 mg monthly resulted in faster achievement of plasma concentrations within the steady-state range.
- The median accumulation ratio, based on once-monthly and once-quarterly clinically relevant dosing regimens, is approximately 2.34 and 1.20, respectively.

REFERENCES

1. Eftekhari S, Edvinsson L. Possible sites of action of the new calcitonin gene-related peptide receptor antagonists. Ther Adv Neurol Disord. 2010 Nov;3(6):369-378.
2. Edvinsson L, Ekman R, Goadsby PJ. Measurement of vasoactive neuropeptides in biological materials: problems and pitfalls from 30 years of experience and novel future approaches. Cephalalgia. 2010 Jun;30(6):761-766.
3. Ashina M, Bendtsen L, Jensen R, Schifter S, Jansen-Olesen I, Olesen J. Plasma levels of calcitonin gene-related peptide in chronic tension-type headache. Neurology. 2000 Nov 14;55(9):1335-1340.
4. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia. 2010 Oct;30(10):1179-1186.
5. Olesen J, Diener HC, Husstedt IW, Goadsby PJ, Hall D, Meier U, et al. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med. 2004 Mar 11;350(11):1104-1110.
6. Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet. 2008 Dec 20;372(9656):2115-2123.
7. Hewitt DJ, Aurora SK, Dodick DW, Goadsby PJ, Ge YJ, Bachman R. Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. Cephalalgia. 2011 Apr;31(6):712-722.
8. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015 Nov;14(11):1081-1090.
9. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings EL, Diener HC, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015 Nov;14(11):1091-1100.
10. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017 Nov 30;377(22):2113-2122.
11. Bigal ME, Dodick DW, Krymchantowski AV, VanderPluym JH, Tepper SJ, Aycardi E, et al. TEV-48125 for the preventive treatment of chronic migraine: efficacy at early time points. Neurology. 2016 Jul 5;87(1):41-48.
12. Davies B, Morris T. Physiological parameters in laboratory animals and humans. Phar Res 1993;10(7):1093-1095.
13. Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2010 Oct;49(10):633-659.

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