PS32 Relationship Between Fremanezumab Exposure and Efficacy in Preventive Therapy of Episodic Migraine in Adults

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OBJECTIVES

- Fremanezumab is a fully humanized IgG2Δa/kappa monoclonal antibody that selectively targets calcitonin gene-related peptide (CGRP).[1]
- Previously, fremanezumab was found to be effective and well-tolerated as a preventive treatment for migraine in 3-month Phase 2 and 3 episodic and chronic migraine studies.[2,3,4,5]
- Modeling and simulation were used to support dose selection for fremanezumab in patients with episodic migraine (EM).
  - An exposure-efficacy response model was developed to describe the relationship between fremanezumab exposure and the reduction in the monthly number of migraine days in patients with EM.
  - Simulations were performed to predict fremanezumab efficacy over 3 months, including the percent of patients with at least a 50% reduction from baseline in the number of migraine days at each month and as an average over 3 months.

METHODS

- Data were pooled from 2 placebo-controlled randomized studies:
  - Phase 2b Study LBR-101-022: patients with EM received 1 of 3 dose treatments administered sc once monthly for 3 months: 1) monthly dosing of 225 mg, 2) monthly dosing of 675 mg, or 3) monthly dosing of placebo
  - Phase 3 Study TV48125-CNS-30050: patients with EM received 1 of 3 treatments administered sc once monthly for 3 months: 1) monthly dosing of 225 mg, 2) quarterly dosing: a single dose of 675 mg every 3 months with placebo injections on months in which fremanezumab was not injected to maintain blinding, or 3) monthly dosing of placebo
- Fremanezumab exposures (average fremanezumab plasma concentration over the dosing interval [C_{av}], area under the concentration-time curve over the dosing interval [AUC_{28d}]) at each monthly visit for each individual patient were generated from a population pharmacokinetic (PPK) model[6] and assigned zero values for placebo patients
- An exposure-response (E-R) model was developed for the monthly number of migraine days (NONMEM, Version 7.3.0[7]) using the general form:

  Monthly Migraine Days = Baseline + Placebo Effect + Drug Effect

  - Placebo effect: time-course of response independent of drug
  - Drug effect: effect of fremanezumab exposure on response
    - Fremanezumab exposure measures for each patient (C_{av} and AUC_{28d}) were evaluated for statistical significance
  - Effects of the following factors on the E-R relationship were also evaluated:
    - Age, body mass index, race, sex, body weight, years since onset of disease, baseline migraine days, the number of days/month acute medications (triptans and ergot compounds), yes or no use of concomitant preventive medications, and yes or no use of concomitant analgesic medications (opioids or barbiturates)
- Visual predictive check (VPC)[8] performed to evaluate the ability of the final E-R model to accurately predict the time-course of response and the E-R relationship
- Stochastic simulations performed to compare outcomes with placebo, 225 mg monthly, and 675 mg quarterly treatment regimens to support labeling
  - 5000 virtual patients with EM generated with demographic characteristics representative of the pooled Phase 2b and Phase 3 population
  - Using the PPK model[6] and E-R model for monthly migraine days, fremanezumab exposures and efficacy endpoints were simulated over 3 months of dosing based on the following regimens:
    - Placebo once monthly
    - 225 mg once monthly
    - 675 mg once quarterly

References

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RESULTS

Patient Characteristics

The dataset included 4444 measures of migraine days from 1142 patients; **Table 1** summarizes monthly migraine days at baseline in each treatment group.

Table 1. Monthly number of migraine days at baseline, stratified by treatment group

Statistic	Placebo (n = 392)	Fremanezumab: Monthly dosing 225 mg (n = 374)	Fremanezumab: Monthly dosing 675 mg (n = 92)	Fremanezumab: Quarterly dosing 675 mg (n = 284)
Mean (SD)	9.7 (2.8)	9.5 (2.7)	11.3 (2.2)	9.2 (2.6)
Median	9.9	9.3	11.3	9.0
Min, Max	4, 20	3, 17	8, 16	4, 16

Max=maximum; Min=minimum; n=number of patients; SD=standard deviation

Table 2. Baseline patient characteristics and acute medication usage, stratified by treatment group

Baseline characteristic	Statistic	Placebo (n = 392)	Fremanezumab: Monthly Dosing 225 mg (n = 374)	Fremanezumab: Monthly dosing 675 mg (n = 92)	Fremanezumab: Quarterly dosing 675 mg (n = 284)
Sex	%Female	85.5	86.1	83.7	86.3
Race	%White	77.8	82.1	78.3	80.3
	%Black	13.3	9.4	17.4	8.8
	%Asian	6.9	7.0	0.0	9.5
	%Other	2.0	1.6	4.4	1.5
Baseline body weight (kg)	Mean (SD)	75.04 (15.98)	72.23 (15.36)	76.27 (15.21)	74.10 (15.56)
Age (years)	Mean (SD)	41.5 (11.9)	42.6 (12.6)	41.1 (12.5)	41.3 (11.4)
Years since onset of disease	Mean (SD)	20.11 (12.50)	20.50 (12.85)	16.79 (12.24)	20.12 (12.17)
Acute medication use, days/month	Mean (SD)	3.7 (4.4)	3.4 (4.1)	3.4 (4.2)	3.6 (4.0)

n=number of patients; SD=standard deviation

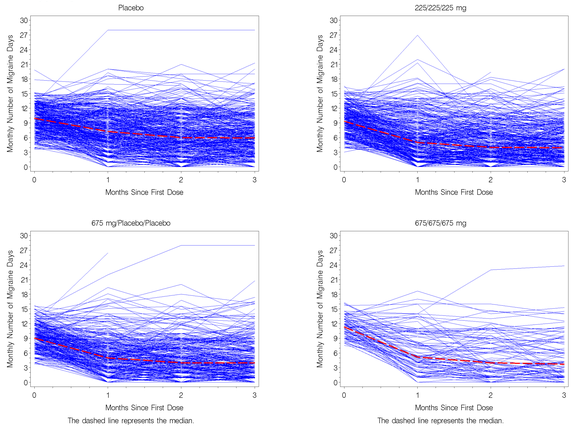
Table 3. Concomitant medication usage during the treatment period of each study, stratified by treatment group

Concomitant Medication Use	Statistic	Placebo (n = 392)	Fremanezumab: Monthly dosing 225 mg (n = 374)	Fremanezumab: Monthly dosing 675 mg (n = 92)	Fremanezumab: Quarterly dosing 675 mg (n = 284)
Days/month of acute medications (triptans and ergots)	Mean (SD)	3.3 (4.3)	2.2 (3.5)	2.0 (3.3)	2.3 (3.4)
Preventive medications	%Yes	303 (19.9)	336 (23.2)	103 (28.3)	207 (18.8)
Analgesic medications	%Yes	109 (7.1)	102 (7.0)	20 (5.5)	65 (5.9)

n=number of patients; SD=standard deviation

Effect of Fremanezumab Dose and Exposure on Monthly Migraine Days During Fremanezumab Studies

Figure 1. Individual monthly numbers of migraine days versus months since first dose, stratified by treatment group (central tendency joining the median values at each visit is in red)

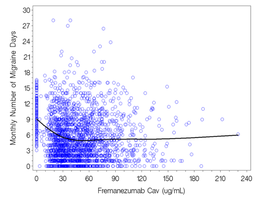


The dashed line represents the median.

These plots illustrate the magnitude of observed between- and within-patient variability in the time-course of migraine days. In general, a larger reduction in migraine days from baseline to month 1 is observed in fremanezumab-treated patients as compared to patients receiving placebo, with a slightly lesser decrease at month 2 and month 3 in all groups.

Figure 2. Monthly number of migraine days versus fremanezumab C_{av}

As fremanezumab C_{av} increases, the number of migraine days decreases until an apparent plateau is achieved with C_{av}>50 µg/mL.



The line represents a smoothing spline fit to the data.

Fremanezumab Exposure Simulations Based on Population Pharmacokinetic Model

Figure 3 and **Table 4** illustrate the expected differences in drug exposure during the first 3 months of fremanezumab 225 mg monthly and 675 mg quarterly regimens simulated for 12 months, and the similarity between AUC_{84d} and C_{av} over the last 3 months of treatment.

Figure 3. Simulated fremanezumab median concentration-time profiles for 225 mg once-monthly and 675 mg once-quarterly regimens over 12 months

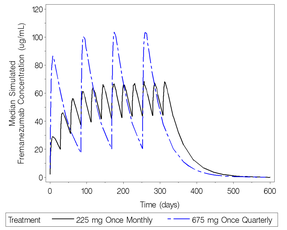


Table 4. Comparison of calculated median exposures for 225 mg once-monthly and 675 mg once-quarterly regimens

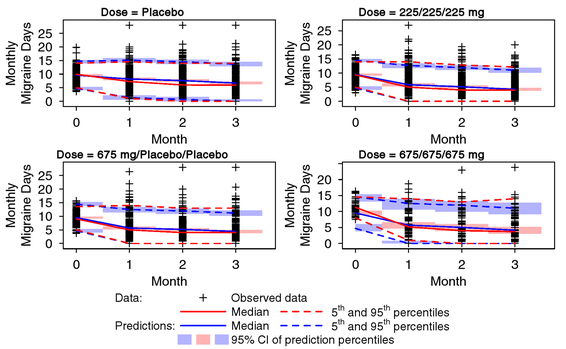
	Treatment group	AUC_{84d} (µgxday/mL)	C_{av} (µg/mL)
Months 1 - 3	225 q1m	3130	37.2
	675 q3m	4010	47.7
Months 10 - 12	225 q1m	4800	57.1
	675 q3m	4800	57.1

AUC_{84d}=area under the concentration-time curve over the dosing interval; C_{av}=average fremanezumab plasma concentration over the dosing interval; q1m=once monthly; q3m=once quarterly

Exposure-Response Model for Monthly Migraine Days in Episodic Migraine

- The time-course of reduction in monthly migraine days due to placebo response was described by an exponential function.
- When evaluated as a predictor of response, both fremanezumab C_{av} and AUC_{28d} had a significant effect on the reduction of migraine days, with C_{av} having a greater effect.
- The effect of fremanezumab was described by a maximum pharmacologic effect of C_{av} as a fraction of baseline, and C_{av50}, the C_{av} associated with 50% of the maximum response.
- Placebo treatment was predicted to reduce monthly migraine days by 2.94 (32.7%) at 3 months from a baseline of 9 days.
- An additional 25.2% maximal reduction from baseline was due to drug effect.
- The C_{av} associated with half-maximal response for active treatment was 3.60 µg/mL, well below the median C_{av} at any month for any treatment regimen, resulting in similar predicted responses with 225 mg once monthly and 675 mg once quarterly.
- Greater acute medication use at baseline was the only statistically significant covariate effect and was predictive of higher baseline migraine days.
  - Baseline was related to the number of days per month of acute medication use at baseline (>5) [slope = 0.438] in a linear manner.
- No other covariates were found to significantly influence variability in response.
- As shown in **Figure 4**, the EM E-R model slightly underpredicts the placebo response at months 1 and 2 at the median level, but is reasonable at month 3; the drug effect is predicted well except for a slight underprediction at month 2 for 225 mg once monthly and 675 mg once quarterly.

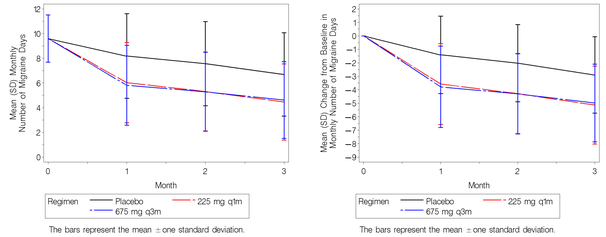
Figure 4. Visual predictive check model evaluation for the final exposure-response model for monthly migraine days in episodic migraine, response over time by treatment group



Medians and percentiles are plotted at the median month of the data observed within each month interval.

- Both dosing regimens separate from placebo by month 1 and continue with similar separation over 3 months, as shown in **Figure 5**, with mean differences of approximately 2 days between response in both treatment groups and placebo

Figure 5. Simulated mean (SD) monthly number of migraine days and change from baseline in migraine days versus months in virtual episodic migraine patients

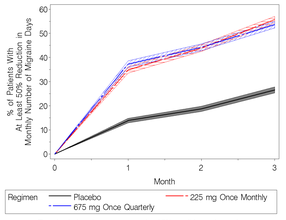


The bars represent the mean ± one standard deviation.

q1m=once monthly; q3m=once quarterly; SD=standard deviation

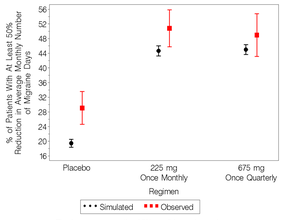
- Consistent with the simulated response over time shown in **Figure 5**, **Figure 6** shows a substantially higher percentage of patients with at least a 50% reduction in monthly number of migraine days with the fremanezumab treatment regimens (both demonstrate similar effects) compared to placebo treatment by the first month and this trend continues throughout the 3-month period

Figure 6. Simulated percentage of virtual patients with episodic migraine with at least a 50% reduction from baseline in monthly migraine days at each month



The shaded regions represent the 95% confidence intervals.

Figure 7. Simulated and observed mean percentage of virtual patients with at least a 50% reduction from baseline in average monthly number of migraine days over 3 months



The bars represent the 95% confidence intervals.

- For the average response over 3 months, a similar percentage of virtual patients (approximately 45%) are predicted by the model to achieve at least a 50% reduction from baseline with fremanezumab 675 mg once quarterly and 225 mg once monthly, well above the predicted percentage for the placebo group (19%)
- The observed percentages of responders are higher than the model-predicted percentages in all groups with the biggest difference in the placebo group (where the VPC results indicated a slight underprediction of placebo effect by the model)

CONCLUSIONS

- Higher fremanezumab C_{av} is predictive of greater reduction in monthly migraine days.
- The fremanezumab regimens of 225 mg sc monthly and 675 mg sc quarterly significantly reduced monthly migraine days in a similar fashion during month 1 compared to placebo treatment, an effect which continued during the 3-month treatment.
- For the 3-month average response, fremanezumab 225 mg sc monthly and 675 mg sc quarterly regimens achieve similar higher response versus placebo in EM due to the similarity in drug exposure over 3 months for these 2 dose regimens.

Presented at American Headache Society 60th Annual Scientific Meeting
June 28-July 1, 2018; San Francisco, CA, USA.
Support for this study was provided by Teva Pharmaceuticals, Ltd., Israel.