PS31 Relationship Between Fremanezumab Exposure and Efficacy in Preventive Therapy of Chronic Migraine in Adults

Jill Fiedler-Kelly[1], Julie Passarell[1], Elizabeth Ludwig[1], Ronghua Yang[2], Ernesto Aycardi[2], Micha Levi[2], and Orit Cohen-Barak[3]

[1]Cognigen Corporation, a *SimulationsPlus* company, Buffalo, New York, USA; [2]Teva Pharmaceuticals, Ltd., Frazer, Pennsylvania, USA; [3]Teva Pharmaceuticals, Ltd., Netanya, Israel

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 chronic migraine (CM).
  - An exposure-efficacy response model was developed to describe the relationship between fremanezumab exposure and the reduction in the monthly moderate-to-severe (M/S) headache days in patients with CM.
  - 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 M/S headache 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-101-021: patients with CM received 1 of 3 dose treatments administered sc once monthly for 3 months: 1) monthly dosing 225 mg with a starting dose of 675 mg, 2) monthly dosing of 900 mg, or 3) monthly dosing of placebo
  - Phase 3 Study TV48125-CNS-30049: patients with CM received 1 of 3 dose treatments administered sc once monthly for 3 months: 1) monthly dosing: monthly 225 mg (with a starting dose of 675 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 M/S headache days (NONMEM, Version 7.3.0[7]) using the general form:

  Monthly M/S Headache 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, 675 mg quarterly, and 675 mg (starting dose) followed by 225 mg monthly treatment regimens to support labeling
  - 5000 virtual patients with CM 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 M/S headache 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
    - 675 mg (starting dose) followed by 225 mg once monthly

References

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RESULTS

Patient Characteristics

The dataset included 5312 measures of M/S headache days from 1361 patients; **Table 1** summarizes monthly M/S headache days at baseline in each treatment group.

Table 1. Monthly number of moderate-to-severe headache days at baseline, stratified by treatment group

Statistic	Placebo (n = 456)	Fremanezumab: Monthly Dosing 225 mg (675 mg starting dose) (n = 450)	Fremanezumab: Monthly Dosing 900 mg (n = 83)	Fremanezumab: Quarterly Dosing 675 mg (n = 372)
Mean (SD)	13.4 (5.8)	13.0 (5.9)	13.1 (5.7)	13.1 (5.4)
Median	13.0	12.0	12.4	12.9
Min, Max	0, 28	0, 28	3, 28	1, 28
n	456	450	83	372

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

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

Baseline characteristic	Statistic	Placebo (n = 456)	Fremanezumab: Monthly dose 225 mg (675 mg starting dose) (n = 450)	Fremanezumab: Monthly dose 900 mg (n = 83)	Fremanezumab: Quarterly dose 675 mg (n = 372)
Sex	%Female	87.3	86.9	85.5	87.9
Race	%White	82.0	78.4	84.3	77.7
	%Black	7.9	10.2	9.6	8.9
	%Asian	9.0	9.1	0.0	10.8
	%Other	1.1	2.2	6.0	2.7
Baseline body weight (kg)	Mean (SD)	72.35 (15.23)	73.07 (16.80)	72.99 (15.83)	72.45 (15.85)
Age (years)	Mean (SD)	41.3 (11.9)	40.7 (11.8)	41.6 (13.1)	42.0 (12.4)
Years since onset of disease	Mean (SD)	20.04 (12.88)	19.50 (11.99)	18.93 (12.42)	19.80 (12.82)
Acute medication use, days/month	Mean (SD)	5.7 (6.9)	5.5 (6.9)	5.6 (7.2)	6.4 (7.3)

n=number of patients; SD=standard deviation

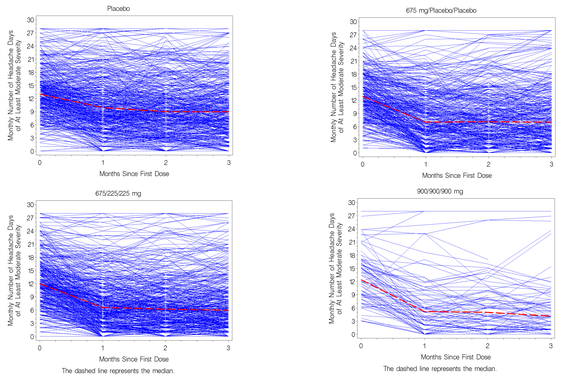
Table 3. Concomitant medication usage during the treatment period of each study, stratified by treatment group

Concomitant Medication Use	Statistic	Placebo (n = 456)	Fremanezumab: Monthly Dose 225 mg (675 mg starting dose) (n = 450)	Fremanezumab: Monthly Dose 900 mg (n = 83)	Fremanezumab: Quarterly Dose 675 mg (n = 372)
Days/month acute medications (triptan and ergot compounds)	Mean (SD)	5.1 (6.7)	3.8 (5.8)	3.4 (5.4)	4.7 (6.4)
Preventive medications	%Yes	25.8	23.9	36.2	19.7
Analgesic medications	%Yes	10.6	11.2	8.3	10.2

n=number of patients; SD=standard deviation

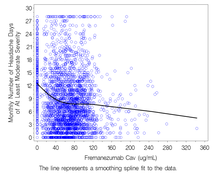
Effect of Fremanezumab Dose and Exposure on Monthly M/S Headache Days During Fremanezumab Studies

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



These plots illustrate the magnitude of observed between- and within-patient variability in the time-course of M/S headache days. In general, a larger reduction in M/S headache days from baseline to month 1 is observed in fremanezumab-treated patients as compared to patients receiving placebo, which is maintained at the same level in month 2 and month 3 in all groups. There was somewhat greater reduction in monthly number of M/S headache days for higher doses of fremanezumab, particularly 900 mg monthly.

Figure 2. Monthly number of moderate-to-severe headache days versus fremanezumab C_{av}



As fremanezumab C_{av} increases, the number of M/S headache days decreases until an apparent plateau is achieved with C_{av}>80 µg/mL.

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, 675 mg quarterly, and 675 mg starting dose followed by 225 mg monthly 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, 675/225/225 mg once-monthly, and 675 mg once-quarterly regimens over 12 months

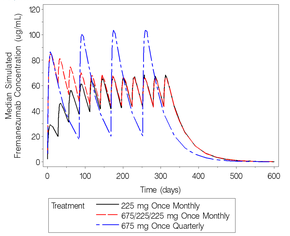


Table 4. Comparison of calculated median exposures for 225 mg once-monthly, 675/225/225 mg once-monthly, and 675 mg once-quarterly regimens

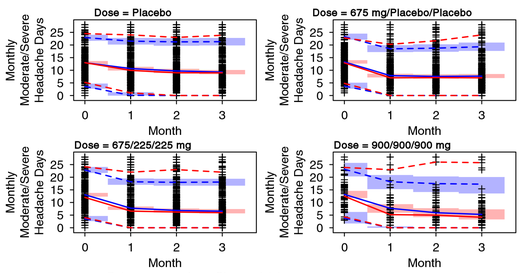
	Treatment group	AUC_{84d} (µgxday/mL)	C_{av} (µg/mL)
Months 1 - 3	225 q1m	3130	37.2
	675/225/225 q1m	5730	68.2
	675 q3m	4010	47.7
Months 10 - 12	225 q1m	4800	57.1
	675/225/225 q1m	4740	56.4
	675 q3m	4800	57.1

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 Moderate-to-Severe Headache Days in Chronic Migraine

- The time-course of reduction in monthly M/S headache days due to placebo response was described by a sigmoid inhibitory function.
- When evaluated as a predictor of response, both fremanezumab C_{av} and AUC_{28d} had a significant effect on the reduction of M/S headache days, with C_{av} having a greater effect.
- The effect of fremanezumab was described by a power function of C_{av}, with parameters estimating the drug effect intercept and the power (exponent) due to C_{av}.
- Placebo treatment was predicted to result in a maximal reduction in monthly M/S headache days of 6.24 from a baseline of 11.7 days, with 50% of response expected by 1.76 months.
- An additional 11.6%, 15.7%, and 20.7% maximal reduction in monthly M/S headache days from baseline due to drug effect was predicted at the median month 3 C_{av} for 675 mg quarterly, 675/225/225 mg monthly, and 900 mg monthly regimens, respectively.
- Greater acute medication use at baseline was the only statistically significant covariate effect and was predictive of higher baseline M/S headache days.
  - Baseline was related to the number of days per month of acute medication use at baseline (>5) [slope = 0.460] in a linear manner.
- No other covariates were found to significantly influence variability in response.
- As shown in **Figure 4**, the CM E-R model accurately predicts the response at the median response in all treatment groups, with the exception of month 1 in the 900 mg fremanezumab arm where the drug effect is underpredicted; in all treatment groups, several patients with 28 headache days per month of at least moderate severity at all months (ie, who exhibit no reduction in M/S headache days) result in an apparent overprediction bias in the predicted responses for the upper 95th percentile.

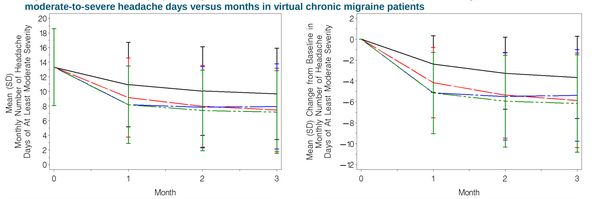
Figure 4. Visual predictive check model evaluation for the final exposure-response model for monthly moderate-to-severe headache days in chronic migraine, response over time by treatment group



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

- Similar separation between the active regimens and placebo is evident over 3 months, as shown in **Figure 5**, with mean differences of approximately 2 days between response in all treatment groups and placebo
- All fremanezumab regimens separate from placebo by month 1, with a smaller reduction associated with the 225 mg once-monthly regimen as compared to the regimens with a 675 mg dose in the first month; at month 3, when exposure drops in the 675 mg once-quarterly regimen, reduction in M/S headache is plateauing in comparison to the sustained reduction achieved with the 675/225/225 mg and 225 mg monthly regimens

Figure 5. Simulated mean (SD) monthly number of moderate-to-severe headache days and change from baseline in moderate-to-severe headache days versus months in virtual chronic migraine patients

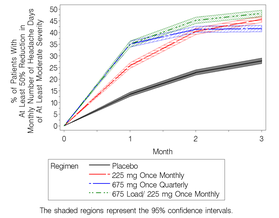


The bars represent the mean ± one standard deviation.

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

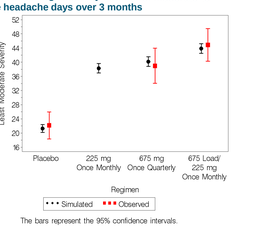
- **Figure 6** shows that in the first month, a larger percentage of virtual patients who received an initial dose of 675 mg achieved a 50% reduction compared to patients given 225 mg and both were substantially higher than the group receiving placebo. By the second month, a similar percentage of patients achieve at least a 50% reduction with the 225 mg once-monthly and 675 mg once-quarterly regimens, while slightly more patients achieve at least a 50% reduction with the 675/225/225 mg regimen; by the third month, a plateauing of response with the quarterly dose regimen is predicted while the percentage of patients achieving at least a 50% reduction with the 225 mg once monthly and 675/225/225 mg fremanezumab treatment groups increase slightly over month 2.
- For the average response over 3 months, as shown in **Figure 7**, a similar percentage of virtual patients (approximately 38% to 44%) achieved at least a 50% reduction from baseline with all 3 active treatments of fremanezumab, and all were well above the predicted percentage for the placebo group (21%). The regimen showing the largest percentage of patients achieving at least a 50% reduction from baseline was the 225 mg once monthly with a starting dose of 675 mg, followed by 675 mg once quarterly and 225 mg once monthly that demonstrated similar effect.
- Since the 225 mg once-monthly regimen was evaluated in simulations only, and not studied in patients with CM, no observed percentage of patients is available. For the regimens evaluated in the clinic (ie, placebo, 675 mg once quarterly, and 225 mg once monthly with a starting dose of 675 mg), there is very good concordance between the model-based predictions and the observed percentages of patients achieving at least a 50% reduction from baseline.

Figure 6. Simulated percentage of virtual patients with chronic migraine with at least a 50% reduction from baseline in monthly moderate-to-severe headache 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 moderate-to-severe headache days over 3 months



The bars represent the 95% confidence intervals.

CONCLUSIONS

- Higher fremanezumab C_{av} is predictive of greater reduction in monthly M/S headache days.
- A clear trend towards a greater percentage of virtual patients with at least a 50% reduction is evident with all fremanezumab dose regimens compared to placebo treatment by the first month that continues throughout the 3-month period. It is notable that higher month 1 exposure with the 675 mg starting dose results in higher response.
- Due to the higher overall exposure, the regimen showing a slightly higher 3-month average response is the 675 mg starting dose followed by 225 mg sc monthly vs. the other 2 active arms.
- Fremanezumab 225 mg sc monthly and 675 mg sc quarterly regimens achieve similar higher 3-month average response versus placebo in CM due to the similarity in drug exposure over 3 months for these 2 dose regimens.