PS47 Lack of Relationship Between Fremanezumab Exposure and Cardiovascular Adverse Events in Phase 2 and Phase 3 Data Including Chronic and Episodic Migraine Patients

Jill Fiedler-Kelly[1], Caroline Passarell[1], Julie Passarell[1], Nicola Faulhaber[2], Paul Yeung[3], Ernesto Aycardi[3], Orit Cohen-Barak[4], and Micha Levi[3]

[1]Cognigen Corporation, a *SimulationsPlus* company, Buffalo, New York, USA; [2]Teva Pharmaceuticals, Inc., Ulm, Germany; [3]Teva Pharmaceuticals, Inc., Frazer, Pennsylvania, USA; [4]Teva Pharmaceuticals, Inc., 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]
- Population-based modeling was used to evaluate the relationships between fremanezumab exposure and the probability of and time to occurrence of selected cardiovascular adverse events (AEs) in patients with episodic migraine (EM) or chronic migraine (CM).

METHODS

- Data were pooled from 2 Phase 2b and 2 Phase 3 placebo-controlled randomized studies and 1 randomized rollover study evaluating the long-term safety, tolerability, and efficacy of subcutaneous (sc) fremanezumab:
  - Phase 2b Study LBR-101-021: patients with CM received 1 of 3 dose treatments administered sc once monthly for 3 months: 1) monthly 225 mg with a starting dose of 675 mg, 2) monthly 900 mg, or 3) monthly placebo
  - Phase 2b Study LBR-101-022: patients with EM received 1 of 3 dose treatments administered sc once monthly for 3 months: 1) monthly 225 mg, 2) monthly 675 mg, or 3) monthly 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 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 placebo
- Phase 3 Study TV48125-CNS-30051: patients randomized to active treatment groups in the Phase 3 efficacy studies (Phase 3 Study TV48125 CNS 30049 and Phase 3 Study TV48125 CNS 30050) continued to receive the same treatment; patients with CM previously randomized to placebo or "new patients" (patients not rolling over from Phase 3) received 1 of 2 treatments for 12 months: monthly dosing of 225 mg (with a starting dose of 675 mg) or quarterly dosing of 675 mg; patients with EM previously randomized to placebo or "new patients" (patients not rolling over from Phase 3) received 1 of 2 treatments for 12 months: monthly dosing of 225 mg or quarterly dosing of 675 mg
- Fremanezumab exposures (average fremanezumab plasma concentration over the dosing interval [C_{av}], area under the concentration-time curve from time 0 to 28 days [AUC_{28d}], area under the concentration-time curve from time 0 to 84 days [AUC_{84d}], concentration at the end of the dosing interval [C_{trough}], and maximum drug concentration [C_{max}]) for each individual patient over the 3-month treatment period (logistic regression analysis) or each 28-day dosing interval (Kaplan-Meier plots) were generated from a population pharmacokinetic (PPK) model[6] and set to zero for placebo patients
- Exposure-response (E-R) logistic regression models of the probability of occurrence of AEs based on data from the first 3 months of treatment were developed using NONMEM, Version 7.3.0[7] for the following AEs of interest: abnormally low or high systolic or diastolic blood pressure (SBP, DBP) and abnormal heart rate (HR) based on the criteria below:

Vital sign	Criterion value	Change relative to baseline
Low SBP	≤90 mm Hg	Decrease of ≥20 mm Hg
High SBP	≥180 mm Hg	Increase of ≥20 mm Hg
Low DBP	≤50 mm Hg	Decrease of ≥15 mm Hg
High DBP	≥105 mm Hg	Increase of ≥15 mm Hg
Heart rate	≥120 beats per minute	Increase of ≥35%

  - Firth's penalized likelihood method accounting for small sample size was used where appropriate[8,9,10]
  - Final E-R models were validated using the Hosmer-Lemeshow goodness-of-fit test and area under the receiver operating characteristic curve[11,12]
- Kaplan-Meier (survival) plots were generated to describe the time to first AE occurrence versus quartiles of exposure based on all available data for patients in all 5 studies (AEs with greater than 5% incidence)

References

1. Walter S, Bigal ME. Curr Pain Headache Rep. 2015 Mar;19(3):6.
2. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Lancet Neurol. 2015 Nov;14(11):1081-1090.
3. Bigal ME, Edvinsson L, Rapoport AM, Lipton RB, Spierings ELH, Diener HC, et al. Lancet Neurol. 2015 Nov;14(11):1091-1100.
4. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. N Engl J Med. 2017 Nov 30;377(22):2113-2122.
5. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. JAMA. 2018 May;319(19):1999-2008.
6. Morris D, Fiedler-Kelly J, Levi M, Cohen-Barak O. Population pharmacokinetic modeling of fremanezumab in support of phase 3 development for patients with migraine. Poster presented at PAGE 2018; Montreux, Switzerland.
7. Beal SL, Sheiner LB, Boeckmann AJ, Bauer RJ (eds). NONMEM 7.3.0 Users Guides. (1989-2013). ICON Development Solutions, Hanover, MD.
8. Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993 Mar;80(1):27-38.
9. Heinze G. Stat Med. 2006 Dec;25(24):4216-4226.
10. Heinze G, Schemper M. Stat Med. 2002 Aug;21(16):2409-2419.
11. Hosmer DW, Jr, Lemeshow S. Applied logistic regression. 2nd ed. New York, NY: John Wiley & Sons; 2000. 375 p.
12. Rana S, Midi H, Sarkar SK. Validation and performance analysis of binary logistic regression model: proceedings of the WSEAS international conference on environment, medicine and health sciences [Internet]. United States Branch of the World Scientific and Engineering Academy and Society Web site. Page 51-55 [cited 2012 March 28]; Accessed from: http://www.wseas.us/e-library/conferences/2010/Penang/EMEH/EMEH-09.pdf.

RESULTS

- Of the 2829 patients included in the E-R safety analyses of vital sign AEs, 256 patients were from Study LBR-101-021 (CM), 290 patients were from Study LBR-101-022 (EM), 1115 patients were from Study TV48125-CNS-30049 (CM), 860 patients were from Study TV48125-CNS-30050 (EM), and 308 patients were from Study TV48125-CNS-30051.
- The population was primarily white (80.6%) with a median age of 42 (range of 18 to 71 years) and a median baseline body weight of 71.6 kg (range of 43.1 to 131.8 kg).
- Relationships between each of the fremanezumab exposure measures (C_{max}, C_{av}, AUC_{84d}, and C_{trough}) and the probability of each vital sign AE were explored, with similar findings for all exposure measures; none of the exposure measures were found to be statistically significant predictors of the probability of high or low systolic or diastolic blood pressure or abnormal heart rate.

High Diastolic Blood Pressure

- 8.9% of patients (n = 250) experienced high DBP
  - 8.7% of the patients (n = 75) receiving placebo experienced high DBP
  - 8.9% of the patients (n = 175) receiving active treatment experienced high DBP
- None of the exposure measures evaluated were found to be statistically significant predictors (α = 0.05) of the probability of high DBP, as shown in **Figure 1a**, **Figure 1b**, and **Figure 1c**

Figure 1. (a) Boxplots of fremanezumab exposure versus the occurrence of high diastolic blood pressure and (b) observed percentage of patients with high diastolic blood pressure versus fremanezumab exposure

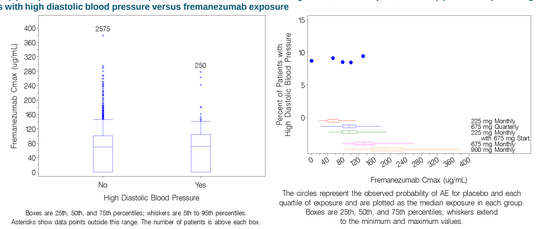
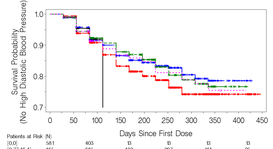


Figure 1. (c) Kaplan-Meier plot of time to first high diastolic blood pressure event versus time, by quartiles of fremanezumab exposure



N=number of patients; P=probability
Note: [or] indicates value is included in the interval and (or) indicates value is not included in the interval.
Note: The survival probability for the placebo group stops at 112 days when the studies including placebo treatment end as specified in the protocols.

High Systolic Blood Pressure

- 8.2% of patients (n = 231) experienced high SBP
  - 7.4% of the patients (n = 64) receiving placebo experienced high SBP
  - 8.5% of the patients (n = 167) receiving active treatment experienced high SBP
- None of the exposure measures evaluated were found to be statistically significant predictors (α = 0.05) of the probability of high SBP, as shown in **Figure 2a**, **Figure 2b**, and **Figure 2c**

Figure 2. (a) Boxplots of fremanezumab exposure versus the occurrence of high systolic blood pressure and (b) observed percentage of patients with high systolic blood pressure versus fremanezumab exposure

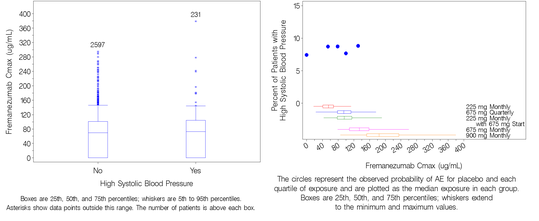
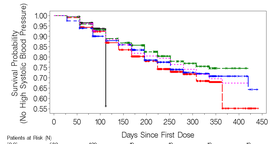


Figure 2. (c) Kaplan-Meier plot of time to first high systolic blood pressure event versus time, by quartiles of fremanezumab exposure



N=number of patients; P=probability
Note: [or] indicates value is included in the interval and (or) indicates value is not included in the interval.
Note: The survival probability for the placebo group stops at 112 days when the studies including placebo treatment end as specified in the protocols.

Low Diastolic Blood Pressure

- 8.5% of patients (n = 239) experienced low DBP
  - 8.4% of the patients (n = 72) receiving placebo experienced low DBP
  - 8.5% of the patients (n = 167) receiving active treatment experienced low DBP
- None of the exposure measures evaluated were found to be statistically significant predictors (α = 0.05) of the probability of low DBP, as shown in **Figure 3a**, **Figure 3b**, and **Figure 3c**

Figure 3. (a) Boxplots of fremanezumab exposure versus the occurrence of low diastolic blood pressure and (b) observed percentage of patients with low diastolic blood pressure versus fremanezumab exposure

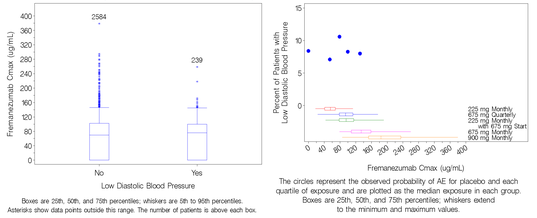
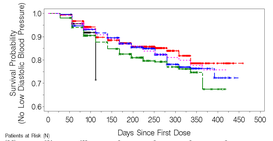


Figure 3. (c) Kaplan-Meier plot of time to first low diastolic blood pressure event versus time, by quartiles of fremanezumab exposure

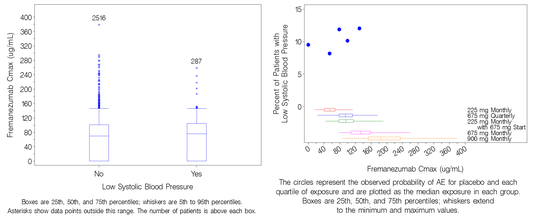


N=number of patients; P=probability
Note: [or] indicates value is included in the interval and (or) indicates value is not included in the interval.
Note: The survival probability for the placebo group stops at 112 days when the studies including placebo treatment end as specified in the protocols.

Low Systolic Blood Pressure

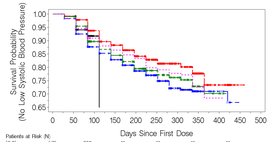
- 10.2% of patients (n = 287) experienced low SBP
  - 9.5% of the patients (n = 81) receiving placebo experienced low SBP
  - 10.6% of the patients (n = 206) receiving active treatment experienced low SBP
- None of the exposure measures evaluated were found to be statistically significant predictors (α = 0.05) of the probability of low SBP, as shown in **Figure 4a**, **Figure 4b**, and **Figure 4c**

Figure 4. (a) Boxplots of fremanezumab exposure versus the occurrence of low systolic blood pressure and (b) observed percentage of patients with low systolic blood pressure versus fremanezumab exposure



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.

Figure 4. (c) Kaplan-Meier plot of time to first low systolic blood pressure event versus time, by quartiles of fremanezumab exposure



N=number of patients; P=probability
Note: [or] indicates value is included in the interval and (or) indicates value is not included in the interval.
Note: The survival probability for the placebo group stops at 112 days when the studies including placebo treatment end as specified in the protocols.

Abnormal Increase in Heart Rate

- 3.8% of patients (n = 108) experienced abnormal HR
  - 4.5% of the patients (n = 39) receiving placebo experienced abnormal HR
  - 3.5% of the patients (n = 69) receiving active treatment experienced abnormal HR

Figure 5. (a) Boxplots of fremanezumab exposure versus the occurrence of abnormal heart rate and (b) observed percentage of patients with abnormal heart rate versus fremanezumab exposure

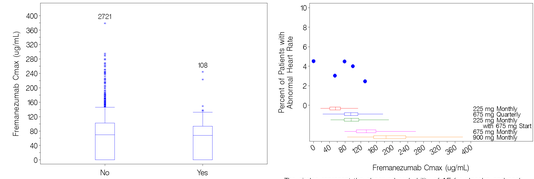
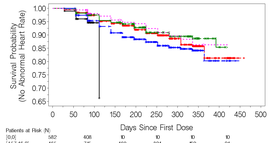


Figure 5. (c) Kaplan-Meier plot of time to first abnormal heart rate event versus time, by quartiles of fremanezumab exposure



N=number of patients; P=probability
Note: [or] indicates value is included in the interval and (or) indicates value is not included in the interval.
Note: The survival probability for the placebo group stops at 112 days when the studies including placebo treatment end as specified in the protocols.

- Due to the low rate of occurrence for abnormal HR, no formal E-R modeling was performed.
- The observed incidence of abnormal HR was slightly lower with active treatment as compared to placebo and, therefore, no clear trend for a dose-response relationship was observed, as shown in **Figure 5a** and **Figure 5b**.
- Considering the time to abnormal HR versus fremanezumab exposure, there is overlap between the survival curves for each quartile of exposure during this time, indicative of a lack of E-R, as shown in **Figure 5c**.

CONCLUSIONS

- None of the fremanezumab exposure measures evaluated (C_{av}, AUC_{84d}, C_{trough}, C_{max}) were found to be statistically significant predictors (α = 0.05) of the probability of low or high SBP or DBP. No clear trend for an exposure response relationship was observed for abnormal increase in HR.
- For the first 4 months of the treatment period, placebo and each quartile of fremanezumab exposure demonstrate overlap between the survival curves for each blood pressure and HR AE, indicating a similar probability of survival (ie, not experiencing the AE).
- Overall, this study showed no E-R relationship between fremanezumab exposure and selected AEs including abnormal low or high SBP and DBP and abnormal increase HR at the clinically relevant studied doses.