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

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OBJECTIVES

Fremanezumab is a 94-kDa humanized IgG1 monoclonal antibody that selectively targets calcitonin gene-related peptide. Preliminary fremanezumab was found to be effective and well tolerated as a prevention treatment for migraine in 3-month Phase 2 and 3 trials in episodic and chronic migraine patients. Fremanezumab is dosed once monthly for 1 year, and a randomized rollover study is planned to assess long-term efficacy and safety. Fremanezumab is anticipated to provide a treatment option for patients who are not adequately treated with their current prophylactic regimen. We aimed to evaluate the cardiovascular safety in the Phase 2 and Phase 3 studies for patients treated with fremanezumab, with a focus on vital sign AEs.

METHODS

Data were from the Phase 2 and 3 Phase 2b/pooled Phase 3 randomized trials and 1 multicenter, investigator-initiated, 1-year follow-up study evaluating the long-term safety, tolerability, and efficacy of fremanezumab in episodic migraine.

- Phase 2b study: CTR-111181 (181 patients with migraine received 675 mg at onset and 225 mg monthly for 12 months; 120 placebo recipients received placebo monthly for 12 months. Vital sign monitoring: in-clinic visits at 0, 1, 2, 6 months, then every 6 months)
- Phase 2a study: CTR-111181 (123 patients with migraine received 675 mg at onset and 225 mg monthly for 12 months; 120 placebo recipients received placebo monthly for 12 months. Vital sign monitoring: in-clinic visits at 0, 1, 2, 6 months, then every 6 months)
- Phase 3 study: CTR-111117 (500 patients with migraine received 675 mg every 2 months and 675 mg at onset and 225 mg monthly for 12 months; 198 placebo recipients received placebo monthly for 12 months. Vital sign monitoring: in-clinic visits at 0, 1, 2, 6, 12 months, then annually)

Phase 2 and 3 studies were conducted in 40 centers and 675.center in the United States and 88 centers in 12 countries.

RESULTS

Of the 1090 patients enrolled in the 4-month safety evaluation of episodic migraine, 806 patients were from Study LBR-2113-004, 290 patients were from Study LBR-2113-002, and 72 patients were from Study TV48125. The mean age was 38.5 years (range 18-72) and the mean body mass index (BMI) was 29.1 kg/m² (range 16.4-46.8). The proportion of women was 64% (658/1027). There were 675 mg from months 1 to 9 and 225 mg from months 10 to 24 and 795 mg from month 1 to month 12. The primary endpoint was the number of patients with and time to occurrence of selected cardiovascular adverse events (CVAEs). None of the exposure measures evaluated were found to be statistically significant predictors (α = 0.05) of the probability of occurrence of CVAEs, as shown in Figure 3a, Figure 3b, and Figure 5a.

CONCLUSIONS

- None of the fremanezumab exposure measures evaluated (Cmax, AUC, Cmax*Ct, Cmax*Ct) were found to be statistically significant predictors (α = 0.05) of the probability of occurrence of CVAEs. The trend toward an increase in CVAEs for each quartile of exposure was not significant, indicating a similar probability of occurrence for each quartile of exposure, as shown in Figure 3b.

- None of the patients enrolled in the 4-month safety evaluation of episodic migraine experienced abnormal heart rate (HR) versus fremanezumab exposure (a) or abnormal increase in HR (b) versus fremanezumab exposure (c). The trend toward an increase in CVAEs for each quartile of exposure was not significant, indicating a similar probability of occurrence for each quartile of exposure, as shown in Figure 3b.