Supplementary Online Content

Dodick DW, Silberstein SD, Bigal ME, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. *JAMA.* doi:10.1001/jama.2018.4853

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Number of Investigational Sites Per Country

Country	Number of investigational sites
Canada	5
Czech Republic	6
Finland	3
Israel	6
Japan	12
Poland	5
Russia	7
Spain	4
United States	88

eTable 2. Hierarchical Testing Sequence of Comparisons[a]

1. Mean change from baseline (pre-treatment period) in the mean number of monthly migraine days during the 12-week period after the 1st dose of study drug for monthly treatment group versus the placebo group
2. Proportion of patients reaching at least 50% reduction in mean number of monthly migraine days during 12-week period after the 1st dose of study drug for the monthly treatment group versus the placebo group
3. Mean change from baseline (pre-treatment period) in the mean number of monthly migraine days during the 12-week period after the 1st dose of study drug for the single-higher-dose treatment group versus the placebo group
4. Mean change from baseline (pre-treatment period) in the number of migraine days during the 4-week period after the 1st dose of the study drug for the single-higher-dose treatment group versus the placebo group
5. Proportion of patients reaching at least 50% reduction in mean number of monthly migraine days during 12-week period after the 1st dose of study drug for the single-higher-dose treatment group versus the placebo group
6. Mean change from baseline (pre-treatment period) in the mean number of monthly days of use of any acute headache medications during the 12-week period after the 1st dose of the study drug for the monthly treatment group versus the placebo group
7. Mean change from baseline (pre-treatment period) in the mean number of monthly days of use of any acute headache medications during the 12-week period after the 1st dose of study drug for the single-higher-dose treatment group versus the placebo group
8. Mean change from baseline (pre-treatment period) in the number of migraine days during the 4-week period after the 1st dose of the study drug for the monthly treatment group versus the placebo group
9. Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug for the monthly treatment group versus the placebo group
10. Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug for the single-higher-dose treatment group versus the placebo treatment group

11. Mean change from baseline (28-day run-in period) in the mean number of monthly migraine days during the 12-week period after the 1st dose of study drug for the monthly treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications
12. Mean change from baseline (28-day run-in period) in the mean number of monthly migraine days during the 12-week period after the 1st dose of study drug for the single-higher-dose treatment group versus the placebo treatment group in patients not receiving concomitant migraine preventive medications

[a] To control the type I statistical error rate at 0.05, a hierarchical testing procedure with a pre-planned sequence of comparisons was applied. Each comparison was interpreted inferentially at the alpha level of 0.05 only if the preceding comparison had a two-sided $P \leq 0.05$. MIDAS, Migraine Disability Assessment.

eTable 3. Sensitivity Analysis of the Primary Efficacy Endpoint with Multiple Imputation[a]

	Fremanezumab		**Placebo**
	Monthly (N = 287)	**Single Higher Dose** (N = 288)	(N = 290)
Primary endpoint			
Monthly average number of migraine days, from baseline to week 12			
Least-squares mean change (95% CI), days	–3.7 (–4.13, –3.19)	–3.5 (–3.93, –2.97)	–2.2 (–2.71, –1.78)
Difference vs placebo (95% CI)	–1.4 (–1.94, –0.89)	–1.2 (–1.73, –0.68)	
P value	<0.001	<0.001	

Abbreviations: CI, confidence interval.

[a] Efficacy analyses were conducted in the full analysis set, which included all randomized patients who received at least one dose of study drug and had had at least 10 days of post-baseline efficacy assessments on the primary endpoint. The statistics were based on 10 sets of imputed data from SAS PROC MI, where the mean is the average of the means from the 10 data sets and the standard error of the mean is adjusted based on the within-imputation variance estimates and the between-imputation variance. All statistics are adjusted for multiple imputation using PROC MIANALYZE.

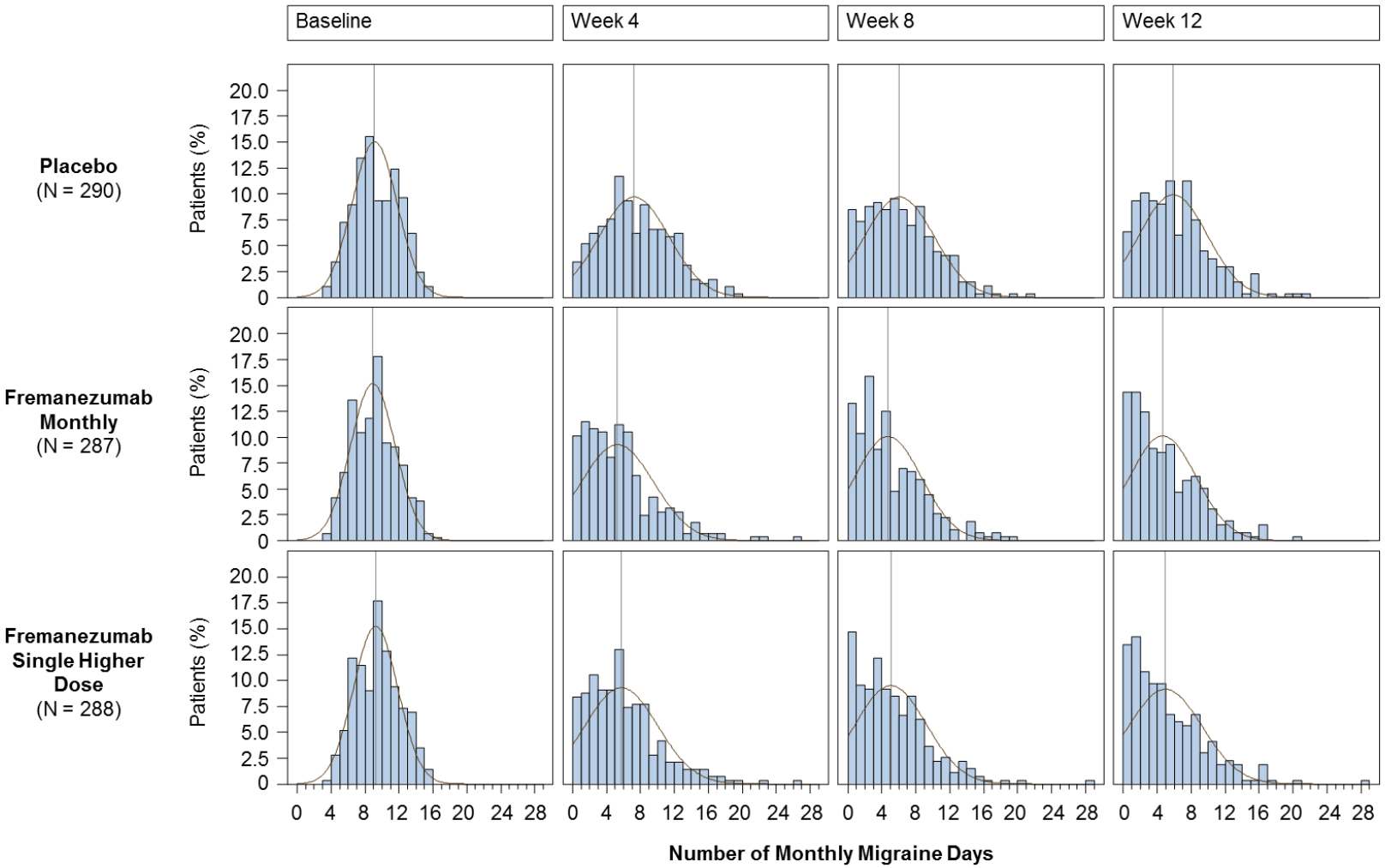
eTable 4. Sensitivity Analysis of the Primary Efficacy Endpoint Using Mixed-effect Model with Country as a Random Effect[a]

	Fremanezumab		Placebo
	Monthly (N = 287)	**Single Higher Dose** (N = 288)	(N = 290)
Primary endpoint			
Monthly average number of migraine days, from baseline to week 12			
Least-squares mean change (95% CI), days	–3.1 (–4.04, –2.19)	–2.9 (–3.83, –1.98)	–1.6 (–2.56, –0.74)
Difference vs placebo (95% CI)	–1.5 (–2.00, –0.93)	–1.3 (–1.79, –0.72)	
P value	<0.001	<0.001	

Abbreviations: CI, confidence interval.

[a] Efficacy analyses were conducted in the full analysis set, which included all randomized patients who received at least one dose of study drug and had had at least 10 days of post-baseline efficacy assessments on the primary endpoint. The mixed-effect model includes treatment, sex, and baseline preventive medication use as fixed effects and baseline number of migraine days and years since onset of migraine as covariates. This analysis included country as a random effect.

eFigure. Histograms of Migraine Days at Each Time Point[a]



[a] Efficacy analyses were conducted in the full analysis set, which included all randomized patients who received at least one dose of study drug and had had at least 10 days of post-baseline efficacy assessments on the primary endpoint. Histograms show the percentage of subjects experiencing 0–28 headache days. Vertical lines indicate the mean number of monthly migraine days. Fitted normal distribution curves are also shown.

eTable 5. Other Safety Measures

Variable	Fremanezumab		Placebo
	Monthly (N = 290)	**Single Higher Dose** (N = 291)	(N = 293)
Clinically significant abnormal vital signs – no. of patients (%)			
Hypertension	1 (0.3)	1 (0.3)	0
QTc interval length ≥500 ms at 1 or more time points	1 (0.3)	0	1 (0.3)
Immunogenicity – no. of patients (%)			
Fremanezumab antibody response	4 (1.4)	0	0

Abbreviations: QTc, corrected QT interval.