Brand Name: Ajovy

Generic Name: Fremanezuman-vfrm

Manufacturer: Teva Pharmaceuticals USA, Inc.

Drug Class[1,2,3,4,5]**:** Anti-migraine agent; Monoclonal antibody, Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonist; CNS Agent

Uses[1,2,3,4,5]**:**

Labeled Uses: Migraine prophylaxis in adult patients
Unlabeled Uses: none

Mechanism of Action[1,3,4,5]: Fremanezumab-vfrm is a humanized monoclonal antibody that binds to CGFP ligand and blocks its binding to the receptor

Pharmacokinetics[1,2,3,4,5]**:**

Absorption:

T_{max}	5-7 days
Vd	6 L
t ½	31 days
Clearance	0.141 L/day
Protein binding	Not reported
Bioavailability	Not reported

Metabolism: Fremanezumab is degraded by enzymatic proteolysis into small peptides and amino acids. No cytochrome P450 isoenzymes are involved in the metabolism.

Elimination: No additional information reported.

Efficacy:

Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, Loupe PS, Burstein R, Newman LC, Lipton RB. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015 Nov;14 (11):1081-90.

Study Design: Multicenter, randomized, double blind, placebo-controlled, phase 2b, parallel-group trial

Description of Study:

Methods: Two hundred ninety-seven patients with high-frequency episodic migraines were randomized to one of three treatment groups for three 28 day cycles: 225mg fremanezumab group (n=96), 675 mg fremanezumab group (n=97), and placebo group (n=104). Throughout the study, participants recorded data in diaries for the previous 24-hour period using an interactive web response system. The primary efficacy endpoint was the mean decrease from baseline in the number of migraine days during the third treatment cycle (weeks nine-twelve). The secondary endpoint was the mean decrease from baseline in the number of headache-days of any severity during the third treatment cycle. These endpoints were also analyzed at the first and second treatment cycles.

Outcome Results: The least square mean difference between 225 mg fremanezumab and placebo for the primary endpoint was -2.81 days (95% CI, -4.07 to -1.55; P=<0.0001). The least square mean difference between 675 mg fremanezumab and placebo for the primary endpoint was -2.64 days (95% CI, -3.90 to -1.38; P=<0.0001). Both fremanezumab treatment groups had statistically better outcomes for the secondary endpoint compared to placebo.

Limitations: The drug manufacturer, Teva Pharmaceuticals, funded the study, collected data, analyzed data, and wrote the article. The affiliation of the authors with Teva Pharmaceuticals included an employee, speaker of bureau, advisory member with honoraria, and recipients of personal fees or grants. It was stated that baseline demographics were similar in the three groups; however, the baseline characteristics were not statistically analyzed. It also appears that the demographics may have actually been different. Participants in the placebo group had longer years of migraine and more hours of headaches per month than either of the treatment groups. It was also stated that treatment-related adverse effects were similar, but the adverse effects were not statistically analyzed. This was a phase 2 study, which had a small amount of patients. It was not reported how data was handled for patients who were lost to follow-up. The study allowed use of other migraine prophylaxis medications and use of acute migraine medications. Specific medications used were not mentioned and the use of these other drugs was not statistically analyzed.

Conclusion: While the authors concluded that fremanezumab was safe, tolerable and efficacious for the prevention of high-frequency episodic migraine, there was potential for bias. The difference in baseline characteristics was not statistically analyzed and the differences may have confounded the results. Efficacy of the drug should be assessed further. Future studies should also assess the safety and tolerability of the drug because the adverse effects were not statistically analyzed and the study duration was only twelve weeks.

Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017 Nov 30;377 (22):2113-2122.

Study Design: Multicenter, randomized, double-blind, placebo-controlled, phase 3, parallel-group trial

Description of Study:

Methods: One-thousand, one hundred and thirty patients with chronic migraine were randomly assigned in a 1:1:1 ratio to one of three trial regimens: fremanezumab monthly (675mg at baseline and 225mg at weeks four and eight; n=379), fremanezumab quarterly (675mg at baseline and placebo at weeks four and eight; n=376), or placebo (n=375). The primary endpoint was the mean change in the mean number of headache days per month. The secondary endpoints were the mean change from baseline in mean migraine days per month, the percentage of patients with reduction of at least 50% in mean migraine days per month, and the mean change from baseline in the mean days per month in each acute headache medication used.

Outcome Results: The least square mean (±SE) number of monthly headache days reduced by 4.3±0.3 days in the quarterly group, 4.6±0.3 days in the monthly group, and 2.5±0.3 days in the placebo group ($P<0.001$ for both comparisons). Both fremanezumab treatment groups had statistically better outcomes for each of the secondary endpoints compared to placebo.

Limitations: Teva Pharmaceuticals, the manufacturer of the study drug, funded the study, performed data analysis, and assisted with manuscript writing. All the authors were affiliated with Teva Pharmaceuticals via being an employee or receiving consulting fees and/or grants from Teva Pharmaceuticals. The conflicts may have led to potential for bias in how the results were presented. It is reported that baseline characteristics are similar between the two groups; however, the baseline demographics were not statistically analyzed. The efficacy endpoints were reported as the mean number of days ±SEM instead of ±SD. It is possible that the authors reported SEM instead of SD in order to report a smaller number of variability. Adverse effects were not statistically analyzed in the study. The study allowed use of other migraine prophylaxis medications and use of acute migraine medications. Specific medications used were not mentioned and the use of these other drugs was not statistically analyzed.

Conclusion: The duration of the study was too short at only twelve weeks and the adverse effects were not statistically analyzed; therefore, the safety of the drug should be further evaluated. The study focused specifically on patients with chronic migraine, which was defined as at least 15 headache days a month. It could be arguable that decreasing the number of headache days per month by 1.8 to 2.1 days in that population is not clinically significant.

Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018 May 15;319 (19):1999-2008.

Study Design: Multicenter, randomized, double-blind, placebo-controlled, phase 3, parallel-group trial

Description of Study:

Methods: Eight-hundred seventy-five patients meeting diagnostic criteria for migraines were randomized 1:1:1 to receive one of three treatments. The first treatment was 225mg of fremanezumab at baseline and weeks four and eight (n= 290). The second treatment was 675mg of fremanezumab at baseline and placebo at weeks four and eight (n=291). The third treatment was placebo at baseline and at weeks four and eight (n=294). The primary endpoint was mean change from baseline in the mean number of monthly migraine days during the twelve-week period after the first injection. Secondary endpoints included the proportion of patients that achieved at least 50% reduction in the mean number of monthly migraine days from baseline to week twelve, the mean change from baseline to week twelve in the monthly mean number of days of acute headache medications, the mean change from baseline to week four in the number of migraine days, the mean change from baseline to week twelve in the mean number of monthly migraine days in patients not receiving concomitant migraine prevention medications, and the mean change in the Migraine Disability Assessment Score (MIDAS).

Outcome Results: The primary outcome was statistically lower for the monthly dosing vs. placebo at -1.5 days (95% CI, -2.01 to -0.93 days; P-<0.001). It was also statistically lower for the single higher dose vs. placebo at -1.3 days (95% CI, -1.79 to -0.72 days; P=<0.001). Both fremanezumab treatment groups had statistically better outcomes for each of the secondary endpoints compared to placebo.

Limitations: The drug manufacturer, Teva Pharmaceuticals, funded the study, was involved in the design, collected data, analyzed data, and prepared the manuscript. Each of the authors were affiliated with Teva Pharmaceuticals via employment, received grants and/or personal fees, and received compensation for serving on advisory boards and/or consulting with the company. The conflicts may have led to potential bias within the article and how the results were reported. The baseline characteristics were described as similar between all groups; however, no statistical tests were performed on the differences between the baseline demographics. In the results section, it was stated that treatment-related adverse events were higher in the fremanezumab treatment groups than the placebo group, but the discussion states that there was “no clinically significant pattern of adverse events or drug-related serious adverse events.” The adverse effects were not statistically analyzed. The study duration was short at only 12 weeks. The study allowed use of other migraine prophylaxis medications and use of acute migraine medications. Specific medications used were not mentioned and the use of these other drugs was not statistically analyzed.

Conclusion: The study showed a benefit of fremanezumab in the prevention of migraines compared to placebo. There were many conflicts of interest and potential for bias within the study. For the primary endpoint, the difference in reduction of mean migraine days per month of 1.3 to 1.5 less compared to placebo may not be clinically significant. Further evaluation of the safety, efficacy and tolerability of this drug needs to be completed. Future studies should be longer in duration and exclude, or at least statistically analyze, the use of other migraine prophylaxis medications.

Contraindications[1,2,3,4,5]**:** Serious hypersensitivity to fremanezumab or to any component of the drug.

Precautions[1,2,3,4,5]**:** Hypersensitivity reactions including rash, pruritus, drug hypersensitivity, and urticaria have been reported. Reports have occurred from hours to one month after administration of Ajovy. If hypersensitivity reaction occurs, consider discontinuation and institute appropriate therapy.

Adverse Effects[1,2,3,4,5]**:**

- Injection site reaction
  - Incidence: 43%-45%
- Antibody development
  - Incidence: 0.6% to 1.6%
- Hypersensitivity reaction

Drug Interactions[1,2,3,4,5]**:** There are no known significant drug interactions with fremanezumab.

Dosing/Administration[1,2,3,4,5]**:**

- Dosage
  - 225mg subcutaneously once monthly OR 675mg subcutaneously once every 3 months (given as three consecutive 225mg injections)
  - If switching dosage options, administer first new dose on the next scheduled date of administration.
- Administration
  - Ajovy is for subcutaneous use only.
  - Healthcare professionals, patients, and/or caregivers may administer Ajovy.
  - Prior to use of Ajovy, remove from the refrigerator and allow it to sit at room temperature for 30 minutes protected from direct sunlight. Do not use Ajovy if it has been left at room temperature for 24 hours or longer.
  - Do not use if the solution appears cloudy, discolored, or contains particles.
  - Administer Ajovy in the abdomen, thigh, or upper arm subcutaneously.
  - Store in the original carton under refrigeration between 2 and 8 degrees Celsius. Do not expose to heat or direct sunlight.
  - If a dose of Ajovy is missed, administer as soon as possible. Adjust schedule from date that the dose was given.

Use in special circumstances[1,2,3,4,5]**:**

- Renal Impairment
    - No dosage adjustments are provided. Renal impairment is not expected to affect the pharmacokinetics of fremanezumab.
- Hepatic Impairment
    - No dosage adjustments are provided. Hepatic impairment is not expected to affect the pharmacokinetics of fremanezumab.
- Geriatric
    - No dosage adjustment necessary.
- Pediatrics
    - Safety and efficacy has not been established in the pediatric population.
- Pregnancy
    - There is no data on the risks associated with Ajovy use in pregnant women. After the administration of fremanezumab to pregnant rats and rabbits at 2-3 times the plasma exposure compared to healthy, non-pregnant humans, no adverse effects on the pre or post-natal development were observed. The long half-life of Ajovy should be considered in women who are pregnant or plan to become pregnant.
- Lactation
    - There is no data on the presence of fremanezumab in human milk, the effects on breastfed infants, or the effects on milk production. The developmental benefits of breastfeeding, the mother's clinical need for Ajovy, and potential adverse effects to the infant should be considered.

Conclusion: Ajovy (fremanezumab-vfrm) is a monoclonal antibody specific for calcitonin gene-related peptide (CGRP) that has been recently FDA approved for migraine prophylaxis. Studies have shown statistically significant reduction in mean migraine days per month compared to placebo for patients with chronic and episodic migraines. The studies had several limitations including significant conflicts of interest and potential for bias. The studies also were very similar in design and only lasted for twelve weeks. The adverse effects appear to be minimal, but were not statistically analyzed in the clinical trials. Future studies need to be completed to analyze the long-term safety, tolerability, and efficacy of fremanezumab. All data points, including baseline characteristics and adverse effects, should be statistically analyzed when comparing the treatment group(s) and placebo group. Cost should be considered before using this medication. The average wholesale price for a single dose of Ajovy is $690.00, which is higher than other medications used for migraine prophylaxis (9). The average wholesale price for a one-month supply of metoprolol, topiramate, and propranolol is approximately $15.00, $360.00, and $69.00 respectively (9). Currently, Ajovy is not first-line for migraine prophylaxis and should be reserved for patients that fail other prophylactic medications.

Recommended References:

1. Ajovy (fremanezumab-vfrm) [package insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; Issued: 09/2018.

2. Fremanezumab. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2009. Available at: http://www.clinicalpharmacology.com Accessed: November 27, 2018.
3. Fremanezumab. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: November 27, 2018.
4. Fremanezumab. Lexi-Drugs [database online]. Lexi-Comp, Inc; November 27, 2018.
5. Fremanezumab. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: November 27, 2018.
6. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, Loupe PS, Burstein R, Newman LC, Lipton RB. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015 Nov;14 (11):1081-90.
7. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017 Nov 30;377 (22):2113-2122.
8. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018 May 15;319 (19):1999-2008.
9. Redbook. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: November 27, 2018.

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