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ADISINSIGHT REPORT

Fremanezumab: First Global Approval

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Abstract
Fremanezumab-vfrm (hereafter referred to as fremanezumab) [AJOVY™] is a fully humanized monoclonal antibody (IgG2Δa) developed by Teva Pharmaceuticals to selectively target calcitonin gene-related peptide (a vasodilatory neuropeptide involved in the pathophysiology of migraine). Its use has been associated with significant reductions in migraine frequency, the requirement for acute headache medication use and headache-related disability compared with placebo in multinational, phase III studies, and in September 2018 fremanezumab was approved by the US FDA for the preventive treatment of migraine in adults. A regulatory assessment for fremanezumab as a preventive treatment of migraine in adults is underway in the EU. Fremanezumab is also undergoing phase III development for the preventive treatment of cluster headache (although a phase III chronic cluster headache study has been suspended due to the results of a prespecified futility analysis) and phase II development for the preventive treatment of post-traumatic headache disorder. This article summarizes the milestones in the development of fremanezumab leading to this first approval in the USA for the preventive treatment of migraine in adults.

1 Introduction

Migraine is a complex neurological disorder with a substantial societal effect [1]. While its underlying pathophysiology is not completely understood, it is thought to involve activation of the trigeminovascular system. Such activation results in the release of various neuropeptides, including the potent vasodilator calcitonin gene-related peptide (CGRP). CGRP is present throughout the central and peripheral nervous system [1]. Its release induces vasodilation and neurogenic inflammation in leptomeningeal and extracranial vessels, resulting in the throbbing pain typical of migraine [2]. Blocking CGRP or its receptor has thus emerged as a promising option for the preventive treatment of migraine [1].

Fremanezumab-vfrm (hereafter referred to as fremanezumab) [AJOVY™] is a fully humanized monoclonal antibody (IgG2Δa) that binds to CGRP, thereby blocking its binding to the receptor [3]. It is being developed by Teva Pharmaceuticals and in September 2018 was approved by the US FDA for the preventive treatment of migraine in adults [3, 4]. The recommended dosage is 225 mg once every month or 675 mg once every 3 months (administered as three consecutive injections of 225 mg each), administered subcutaneously [3]. Fremanezumab should not be administered at the exact location of the previous injection and should not be coadministered with other injectable drugs at the same injection site [3]. A regulatory assessment for fremanezumab as a preventive treatment of migraine in adults is underway in the EU [5]. Phase III development of fremanezumab is ongoing for the preventive treatment of cluster headache [6]. However, a phase III chronic cluster headache study has been suspended due to the results of a prespecified futility analysis [6]. Fremanezumab is undergoing phase II development for the preventive treatment of post-traumatic headache disorder [7].

1.1 Company Agreements

In January 2013, Labrys Biologics acquired the worldwide rights to fremanezumab from Pfizer [8]. Under the terms of the agreement, Pfizer will be eligible to receive milestone payments and sales royalties [8]. In July 2014, Teva Pharmaceutical Industries (hereafter referred to as Teva) acquired

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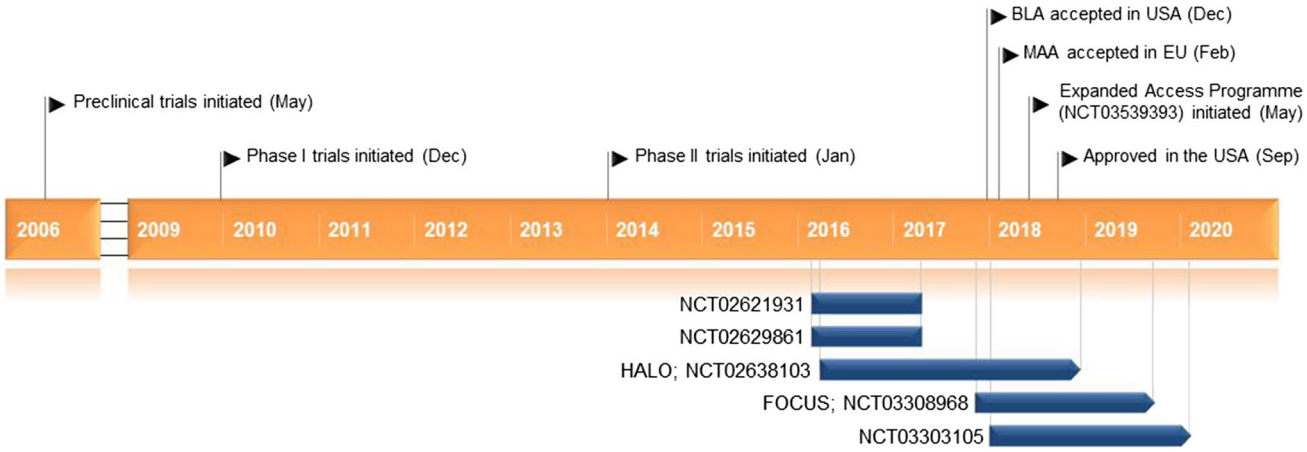

Key milestones in the development of fremanezumab for the preventive treatment of migraine in adults, focussing on phase III trials. *BLA* Biologics License Application, *MAA* Marketing Authorisation Application

Labrys Biologics (and the fremanezumab programme) for an upfront payment of US$200 million and contingent payments of up to US$625 million (subject to the achievement of certain development milestones) [9, 10]. In May 2017, Teva and Otsuka Pharmaceuticals (hereafter referred to as Otsuka) entered into a development and commercialization agreement [11]. Under the terms of this agreement, Otsuka acquires exclusive rights to fremanezumab and will fund clinical studies in Japan, while Teva receives a payment of US$50 million and will be eligible for milestone payments upon filing and regulatory approval in Japan and upon the achievement of revenue targets [11].

2 Scientific Summary

2.1 Pharmacodynamics

Fremanezumab is a fully humanized monoclonal antibody (IgG2Δa) that selectively targets both the α and β isoforms of CGRP (a 37 amino acid neuropeptide involved in the pathophysiology of migraine) [3, 12]. By binding to CGRP, fremanezumab prevents CGRP binding to its receptor [3]. However, the relationship between the pharmacodynamic activity and the mechanism(s) by which fremanezumab exerts its clinical effects is not yet known [3].

In vitro, fremanezumab blocked the CGRP-induced dilation of human intracranial (cerebral cortical and middle meningeal) and abdominal arteries [13].

2.2 Pharmacokinetics

Fremanezumab exhibited dose proportionality over a 225–900 mg dose range, according to a population pharmacokinetic (PPK) analysis [3]. Following the administration of a single subcutaneous 225, 675 and 900 mg dose, the median time to the maximum fremanezumab concentration was 5 to 7 days. Steady state was reached at ≈ 6 months and the median accumulation ratio was ≈ 2.3 and 1.2 following therapy with subcutaneous fremanezumab 225 mg once every month and subcutaneous fremanezumab 675 mg once every 3 months [3]. Fremanezumab (with an apparent volume of distribution of ≈ 6 L) appears to be minimally distributed to the extravascular tissues [3]. As with other monoclonal antibodies, fremanezumab is degraded into small peptides and amino acids by enzymatic proteolysis. Its estimated half-life is ≈ 31 days [3].

The pharmacokinetic parameters of fremanezumab 225, 675 and 900 mg were similar between Japanese and Caucasian healthy volunteers, according to a phase I study [14].

Interactions with concomitant medications that are inducers, inhibitors or substrates of CYP enzymes are considered unlikely (as fremanezumab is not metabolized by CYP enzymes) [3]. According to a PPK analysis, acute treatment medications (specifically analgesics, ergots, and triptans) did not affect fremanezumab exposure [3].

2.3 Therapeutic Trials

Therapy with fremanezumab was associated with significant reductions in migraine frequency, the requirement for acute headache medication use and headache-related disability compared with placebo in adults (aged 18–70 years) with episodic migraine [15] and chronic migraine [16] participating in two randomized, double-blind, multinational, phase III studies [NCT02629861 (Study 30050) [15]; NCT02621931 (Study 30049) [16]].

In Study 30050 [15], patients with episodic migraine received subcutaneous injections of fremanezumab 225 mg once every month (i.e. monthly fremanezumab) [$n = 287$],

Features and properties of fremanezumab	
Alternative names	AJOVY; anti-calcitonin gene-related peptide monoclonal antibody; anti-CGRP monoclonal antibody; fremanezumab-vfrm; LBR-101; PF-04427429; PF-4427429; RN-307; TEV-48125
Class	Antimigraines; monoclonal antibodies
Mechanism of action	Calcitonin gene-related peptide antagonist
Route of administration	Subcutaneous injection
Pharmacodynamics	Fully humanized monoclonal IgG2 antibody; by specifically binding to the potent neuropeptide vasodilator calcitonin gene-related peptide (CGRP), fremanezumab prevents CGRP binding to its receptor
Pharmacokinetics	Exhibited dose proportionality over a 225–900 mg dose range; median time to maximum concentration of 5 to 7 days, with steady state reached in ≈ 6 months Estimated half-life of ≈ 31 days
Most frequent adverse events	Injection-site reactions
ATC codes	
WHO ATC code	N02C (antimigraine preparations)
EphMRA ATC code	N2C (anti-migraine preparations)
Chemical name	Immunoglobulin G2, anti-(human alpha-calcitonin gene-related peptide/beta-calcitonin gene-related peptide) (human-mus musculus monoclonal TEV-48125 heavy chain), disulfide with human-mus musculus monoclonal TEV-48125 light chain, dimer

fremanezumab 675 mg once every 3 months (i.e. quarterly fremanezumab) [$n = 288$] or placebo ($n = 290$) for 3 months. The least-squares mean (LSM) change from baseline at month 3 in the mean number of monthly migraine days (primary endpoint) was significantly lower with monthly fremanezumab [− 3.7 vs. − 2.2; between-group difference of − 1.5 (95% CI − 2.0 to 0.93); $p < 0.001$] and quarterly fremanezumab [− 3.4 vs. − 2.2; between-group difference of − 1.3 (95% CI − 1.79 to − 0.72); $p < 0.001$] than placebo. At baseline, the mean number of monthly migraine days was 8.9, 9.2, and 9.1 in the respective groups. A significantly ($p < 0.001$) higher proportion of patients receiving monthly fremanezumab and quarterly fremanezumab than placebo achieved a ≥ 50% reduction from baseline at month 3 in the mean number of monthly migraine days (47.7 and 44.4 vs. 27.9%). Moreover, the LSM change from baseline at month 3 in the mean number of monthly days requiring acute headache medication use was significantly lower with monthly fremanezumab [− 3.0 vs. − 1.6; between-group difference of − 1.4 (95% CI − 1.84 to − 0.89); $p < 0.001$] and quarterly fremanezumab [− 2.9 vs. − 1.6; between-group difference of − 1.3 (95% CI − 1.76 to − 0.82); $p < 0.001$] than placebo. At baseline, the mean number of monthly days requiring acute headache medication use was 7.7, 7.9 and 7.7 in the respective groups. The LSM change from baseline at month 1 in the mean number of monthly migraine days was significantly lower with monthly fremanezumab [− 3.5 vs. − 1.7; between-group difference of − 1.8 (95% CI − 2.43 to − 1.18); $p < 0.001$] and quarterly fremanezumab [− 3.3 vs. − 1.7; between-group difference of − 1.6 (95% CI − 2.22 to − 0.97); $p < 0.001$] than placebo, indicating an early treatment benefit. Both monthly fremanezumab and quarterly fremanezumab were also significantly ($p \leq 0.002$) more effective than placebo in terms of the LSM change from baseline at month 3 in the mean number of monthly migraine days in patients not receiving concomitant migraine preventive medication and the Migraine Disability Assessment (MIDAS) score. At baseline, 21% of patients were using preventive medications. Sensitivity analyses demonstrated that the results of the primary analyses were robust [15].

In Study 30049 [16], patients with chronic migraine received subcutaneous injections of monthly fremanezumab (consisting of a 675 mg dose at baseline followed by 225 mg doses at months 1 and 2) [$n = 375$], quarterly fremanezumab (consisting of a 675 mg dose once every 3 months) [$n = 375$] or placebo ($n = 371$) for 3 months. The LSM change from baseline at month 3 in the average number of monthly headache days (primary endpoint) was significantly lower with monthly fremanezumab (− 4.6 vs. − 2.5; between-group difference of − 2.1; $p < 0.001$) and quarterly fremanezumab (− 4.3 vs. − 2.5; between-group difference of − 1.8; $p < 0.001$) than placebo. At baseline in the respective groups, the mean number of headache days was 12.8, 13.2 and 13.3 and the mean number of days with headache of any severity or duration was 20.3, 20.4 and 20.3. Monthly fremanezumab (− 5.0 vs. − 3.2; between-group difference of − 1.8; $p < 0.001$) and quarterly fremanezumab (− 4.9 vs. − 3.2; between-group difference of − 1.7; $p < 0.001$) were associated with a significantly lower LSM change from baseline at month 3 in the average number of monthly migraine days than placebo. At baseline, the mean number of migraine days was 16.0, 16.2 and 16.4 in the respective groups. A significantly ($p < 0.001$) higher proportion of patients receiving monthly fremanezumab and quarterly fremanezumab than placebo achieved a ≥ 50% reduction from baseline at month 3 in the average number of monthly headache days (40.8 and 37.6 vs. 18.1%). Moreover, the LSM change from baseline at month 3 in the average number of monthly days requiring

Key clinical trials of fremanezumab

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Fremanezumab, placebo	Migraine prevention	II	Completed	USA	NCT02021773 (LBR-101-021)	Teva Pharmaceutical Industries
Fremanezumab, placebo	Migraine prevention	II	Completed	USA	NCT02025556 (LBR-101-022)	Teva Pharmaceutical Industries
Fremanezumab, placebo	Post-traumatic headache prevention	II	Recruiting	USA	NCT03347188 (Study 20024)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab, placebo	Migraine prevention	II/III	Recruiting	Japan	NCT03303079 (406-102-00001; JapicCTI-173723)	Otsuka Pharmaceutical Co., Ltd.
Fremanezumab, placebo	Migraine prevention	II/III	Recruiting	Japan	NCT03303092 (406-102-00002; JapicCTI-173725)	Otsuka Pharmaceutical Co., Ltd.
Fremanezumab, placebo	Migraine prevention	III	Completed	Multinational	NCT02629861 (Study 30050)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab, placebo	Migraine prevention	III	Completed	Multinational	NCT02621931 (Study 30049)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab, placebo	Migraine prevention	III	Active, not recruiting	Multinational	NCT02638103 (Study 30051; HALO)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab, placebo	Migraine prevention	III	Active, not recruiting	Multinational	NCT03308968 (Study 30068; FOCUS)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab	Cluster headache prevention	III	Enrolling by invitation	Multinational	NCT03107052 (Study 30058; ENFORCE)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab	Migraine prevention	III	Recruiting	Japan	NCT03303105 (406-102-00003; JapicCTI-173726)	Otsuka Pharmaceutical Co., Ltd.
Fremanezumab, placebo	Episodic cluster headache prevention	III	Recruiting	Multinational	NCT02945046 (Study 30056)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab, placebo	Cluster headache prevention	III	Terminated	Multinational	NCT02964338 (Study 30057)	Teva Branded Pharmaceutical Products, R&D Inc.
Fremanezumab	Migraine, cluster headache	Expanded access	Available	Not available	NCT03539393	Teva Branded Pharmaceutical Products, R&D Inc.

acute headache medication use was also significantly lower with monthly fremanezumab (− 4.2 vs. − 1.9; between-group difference of − 2.3; $p < 0.001$) and quarterly fremanezumab (− 3.7 vs. − 1.9; between-group difference of − 1.8; $p < 0.001$) than placebo. The LSM change from baseline at month 1 in the average number of monthly headache days was significantly lower with monthly fremanezumab (− 4.5 vs. − 2.1; between-group difference of − 2.4; $p < 0.001$) and quarterly fremanezumab (− 4.4 vs. − 2.1; between-group difference of − 2.3; $p < 0.001$) than placebo, indicating an early treatment benefit. Both monthly fremanezumab and quarterly fremanezumab were also significantly ($p < 0.001$) more effective than placebo in terms of the LSM change from baseline in other secondary endpoints [average number of monthly headache days at month 3 in patients not receiving concomitant migraine preventive medication and six-item Headache Impact Test (HIT-6) score]. At baseline, 21% of patients were using preventive medications [16].

Patients in Studies 30050 [15] and 30049 [16] had a ≥ 12-month history of migraine and had experienced episodic migraine (defined as a headache occurring on 6–14 days, with a migraine occurring on ≥ 4 days) [15] or chronic migraine (defined as a headache occurring on ≥15 days, with a migraine occurring on ≥8 days) [16] during the 28-day pre-treatment period (i.e. baseline). Patients who had previously failed ≥ 3 months' treatment of episodic or chronic migraine with ≥ 2 clusters of preventive medications were among those excluded [15, 16]. At baseline, 96% of 875 patients [15] and 95% of 1130 patients [16] were using acute headache medications. Endpoints were evaluated in a hierarchical manner [15, 16]. A migraine day was defined as a day in which headache pain (which met the criteria for migraine with or without aura, or probable migraine) lasted for ≥ 2 h [15] or ≥ 4 h [16], or a day in which headache pain (of any duration) was treated with acute migraine-specific medication (triptans or ergots). A headache day was defined as a day in which headache pain lasted for ≥ 4 h and had at least a moderate peak severity, or a day in which headache pain (of any duration) was treated with acute migraine-specific medication [16]. The MIDAS [15] and HIT-6 [16] questionnaires assess headache-related disability. Analyses were conducted in the modified intent-to-treat population [15, 16].

Results from Studies 30050 and 30049 are supported by those from two randomized, double-blind, placebo-controlled, multicentre, phase IIb studies in adults (aged 18–65 years) with episodic migraine (NCT02025556; $n = 294$) [17] and chronic migraine (NCT02021773; $n = 261$) [18]. In these studies, patients received subcutaneous injections of monthly fremanezumab (consisting of a 225 or 675 mg dose at baseline and months 1 and 2 [17]; consisting of a 675 mg dose at baseline followed by 225 mg doses at months 1 and 2, or a 900 mg dose at baseline and months 1 and 2 [18]) for 3 months. Compared with placebo, both fremanezumab regimens in each study met the primary endpoint (LSM change from baseline during the last month of treatment in the number of migraine days [17] or the number of headache hours of any severity [18]). A migraine day was defined as a day in which migraine with or without aura, or probable migraine (lasting for ≥ 4 h, or any duration if acute migraine-specific medication was administered) occurred [17].

Preliminary data (available as abstracts) from an ongoing, randomized, double-blind, multinational, phase III study (NCT02638103; HALO) suggested that reductions in migraine frequency were maintained during longer-term (up to 12 months) therapy with fremanezumab [19–21]. In this longer-term study, patients (who had completed Study 30050 or Study 30049, or were directly enrolled) received subcutaneous injections of monthly fremanezumab [consisting of a 225 mg (patients with episodic migraine) or 675 mg (patients with chronic migraine) dose at baseline followed by 225 mg doses at months 1 and 2)] or quarterly fremanezumab (consisting of a 675 mg dose once every 3 months) [19]. In the monthly and quarterly fremanezumab groups, the mean change from baseline (of the core studies, where applicable) at 6 months in the number of monthly migraine days was − 4.9 and − 5.0 days in patients with episodic migraine ($n = 780$) and − 7.9 and − 6.5 days in patients with chronic migraine ($n = 1180$) [19]. Moreover, in the respective groups, 61 and 65% of patients with episodic migraine achieved a ≥ 50% reduction from baseline at month 6 in the average number of monthly migraine days [20] and 56 and 51% of patients with chronic migraine achieved a ≥ 50% reduction from baseline at month 6 in the average number of monthly headache days of at least moderate severity [21].

2.4 Adverse Events

At least one treatment-emergent adverse event (TEAE) was reported in 66.2, 66.3 and 58.4% of patients receiving monthly fremanezumab, quarterly fremanezumab and placebo ($n = 290$, 291 and 293), respectively, in Study 30050 [15], with ≥ 1 TEAE occurring in a significantly ($p = 0.03$) higher proportion of patients receiving monthly fremanezumab, but not quarterly fremanezumab, than placebo in Study 30049 (71.2 and 70.5 vs. 64.0%) [$n = 379$, 376 and 375] [16]. Most TEAEs were mild or moderate in severity [15, 16]. Treatment-related adverse events occurred in 47.6, 47.1 and 37.2% of patients receiving monthly fremanezumab, quarterly fremanezumab and placebo, respectively, in Study 30050 [15] and in 51.2, 49.5 and 42.4% of patients, respectively, in Study 30049 [16].

In a pooled analysis of Study 30050 [15] and Study 30049 [16], the most frequently reported [occurring in ≥ 2% of patients in either the monthly ($n = 669$) or quarterly ($n = 667$) fremanezumab groups and with a numerically higher incidence in the fremanezumab groups than the placebo group ($n = 668$)] adverse reactions (during the 3-month treatment period and 1-month follow-up period) were injection-site reactions (43 and 45 vs. 38%) [3]. In the monthly fremanezumab, quarterly fremanezumab and placebo groups, respectively, of Study 30050 [15], pain occurred in 30.0, 29.6 and 25.9% of patients, induration in 24.5, 19.6 and 15.4%, erythema in 17.9, 18.9 and 14.0% and injection-site haemorrhage in 1.0, 3.1 and 2.0%. In the respective groups of Study 30049 [16], pain occurred in 26.1, 30.3 and 27.7% of patients, induration in 23.7, 19.7 and 18.1%, erythema in 19.8, 21.3 and 16.0% and haemorrhage in 2.1, 1.9 and 2.7%.

The incidences of serious TEAEs and TEAEs resulting in discontinuation were low (< 3%) and similar across the treatment groups [15, 16]. One quarterly fremanezumab recipient in each study died (from suicide [15] and chronic obstructive pulmonary disease [16]), with each death considered to be unrelated to the study medication [15, 16]. In Study 30050 [15], there were no clinically relevant changes in laboratory parameters (including liver function tests); in Study 30049 [16], an alanine transaminase or aspartate aminotransferase level ≥ 3 × the upper limit of normal (ULN), a total bilirubin level ≥ 2 × ULN or an international normalized ratio > 1.5 each occurred in < 1% of patients in each treatment group. Results (available as an abstract) from pooled data ($n = 2512$) from four placebo-controlled studies suggests that fremanezumab has no cardiovascular safety signal [22]. At the data cut-off date of 26 September 2017 (mean duration of exposure of 244.8 days), cardiovascular TEAEs had occurred infrequently, with a similar incidence seen between patients receiving fremanezumab and placebo. The most frequently reported (occurring in ≥ 10 patients) cardiovascular TEAEs reported in patients receiving fremanezumab were hypertension (2%), hot flush (< 1%) and palpitations (< 1%) [22].

Longer-term (up to 12 months) therapy with fremanezumab appears to be generally safe and well tolerated, according to preliminary data (available as an abstract) from the ongoing HALO study [19]. At the time of the interim analysis, the most frequently reported TEAEs were mild to moderate injection-site reactions and pruritus, only 4% of patients had discontinued the study due to adverse events and no deaths had been reported [19].

In 3-month placebo-controlled studies, treatment-emergent anti-drug antibody (ADA) responses were seen in 6 (< 1%) of 1701 patients receiving fremanezumab, with 1 patient developing anti-fremanezumab neutralizing antibodies (at

day 84) [3]. In the ongoing longer-term open-label study, ADAs were detected in 30 (1.6%) of 1888 patients receiving fremanezumab, with 17 demonstrating neutralizing activity in their post-dose samples [3].

2.5 Ongoing Clinical Trials

There are several ongoing phase II/III (NCT03303079; NCT03303092) and III [NCT03303105; NCT02638103 (HALO); NCT03308968 (FOCUS)] studies of fremanezumab for the preventive treatment of migraine. NCT03303079, NCT03303092 and NCT03303105 are currently recruiting patients in Japan. HALO and FOCUS are both randomized, double-blind, placebo-controlled, multinational studies; HALO has enrolled 1890 patients and is evaluating the long-term (74–78 weeks) efficacy, safety and tolerability of fremanezumab, while FOCUS has enrolled 838 patients with an inadequate response to prior preventive treatments and is evaluating the short-term (12 weeks) efficacy and safety of fremanezumab.

3 Current Status

Fremanezumab received its first global approval on 14 September 2018 in the USA for the preventive treatment of migraine in adults [3].

Compliance with Ethical Standards

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Conflicts of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the author on the basis of scientific completeness and accuracy. Sheridan Hoy is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

References

1. Maasumi K, Michael RL, Rapoport AM. CGRP and migraine: the role of blocking calcitonin gene-related peptide ligand and receptor in the management of migraine. Drugs. 2018;78(9):913–28.
2. Silberstein SD, Edvinsson L. Is CGRP a marker for chronic migraine? Neurology. 2013;81(14):1184–5.
3. Teva Pharmaceuticals Inc. AJOVY™ (fremanezumab-vfrm) injection, for subcutaneous use: US prescribing information. 2018. http://www.fda.gov/. Accessed 18 Sep 2018.
4. Teva Pharmaceutical Industries Ltd. Teva announces US approval of AJOVY™ (fremanezumab-vfrm) injection, the first and only anti-CGRP treatment with both quarterly and monthly dosing for the preventive treatment of migraine in adults [media release]. 14 Sep 2018. http://www.tevapharm.com/.
5. Teva Pharmaceutical Industries Ltd. European Medicines Agency (EMA) accepts fremanezumab Marketing Authorization Application [media release]. 2 Feb 2018. http://www.tevapharm.com/.
6. Teva Pharmaceutical Industries Ltd. Teva provides update on clinical trial of fremanezumab for use in chronic cluster headache [media release]. 15 June 2018. http://www.tevapharm.com/.
7. Teva Pharmaceutical Industries Ltd. FDA accepts Biologics License Application for fremanezumab with priority review for prevention of migraine and grants fast track designation for cluster headache development program [media release]. 18 Dec 2017. http://www.tevapharm.com.
8. Labrys Biologics Inc. Labrys Biologics secures $31 million Series A financing from venture capital firms; acquires phase 2 ready antibody for chronic migraine from Pfizer [media release]. 3 Jan 2013. http://www.prnewswire.com.
9. Teva Pharmaceutical Industries Ltd. Teva completes acquisition of Labrys: opens door to a strong and novel migraine prevention and treatment franchise within its CNS portfolio [media release]. 21 July 2014. http://www.tevapharm.com.
10. Teva Pharmaceutical Industries Inc. Teva to acquire Labrys Biologics, Inc.: novel migraine prophylaxis treatment adds significant new dimension to Tevas growing pain care franchise [media release]. 3 June 2014. http://www.tevapharm.com.
11. Otsuka Pharmaceutical. Otsuka and Teva sign licensing agreement for Japan on prophylactic migraine drug candidate fremanezumab (TEV-48125) [media release]. 15 May 2017. http://www.otsuka-us.com.
12. Walter S, Bigal ME. TEV-48125: a review of a monoclonal CGRP antibody in development for the preventive treatment of migraine. Curr Pain Headache Rep. 2015;19(3):6.
13. Ohlsson L, Kronvall E, Stratton J, et al. Fremanezumab blocks CGRP induced dilatation in human cerebral, middle meningeal and abdominal arteries. J Headache Pain. 2018;19(1):66.
14. Cohen-Barak O, Weiss S, Rasamoelisolo M, et al. A phase 1 study to assess the pharmacokinetics, safety, and tolerability of fremanezumab doses (225 mg, 675 mg and 900 mg) in Japanese and Caucasian healthy subjects. Cephalalgia. 2018. https://doi.org/10.1177/0333102418771376.
15. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA. 2018;319(19):1999–2008.
16. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017;377(22):2113–22.
17. Bigal ME, Dodick DW, Rapoport AM, et al. 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;14(11):1081–90.
18. Bigal ME, Edvinsson L, Rapoport AM, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015;14(11):1091–100.
19. Goadsby P, Yeung PP, Blankenbiller T, et al. Fremanezumab long-term efficacy and safety: interim results of a one-year study. [abstract no. PS30]. Headache. 2018;58(Suppl 2):166.
20. Brandes J, Yeung PP, Cohen JM, et al. Long-term impact of fremanezumab on response rates, acute headache medication use, and disability in patients with episodic migraine: interim results of a one-year study [abstract no. PS35]. Headache. 2018;58(Suppl 2):170.
21. McAllister P, Yeung PP, Cohen JM, et al. Long-term impact of fremanezumab on response rates, acute headache medication use, and disability in patients with chronic migraine: interim results of a one-year study [abstract no. PF14]. Headache. 2018;58(Suppl 2):86–7.
22. Ning X, Faulhaber N, Lang N, et al. Fremanezumab cardiovascular safety profile: pooled data from placebo-controlled and long-term studies [abstract no. PS41]. Headache. 2018;58(Suppl 2):174–5.