Summary Report of Benefit-Risk Assessment

AJOVY SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 225MG/1.5ML

NEW DRUG APPLICATION

Active Ingredient(s)	Fremanezumab
Product Registrant	Drug Houses of Australia Pte Ltd
Product Registration Number	SIN15937P
Application Route	Abridged Evaluation
Date of Approval	08 May 2020

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A INTRODUCTION

Ajovy is indicated for the preventive treatment of migraine in adults.

The active substance, fremanezumab, is a humanised IgG2Δa/kappa monoclonal antibody that selectively binds the calcitonin gene-related peptide (CGRP) ligand and blocks both CGRP isoforms (α-and β-CGRP) from binding to the CGRP receptor, leading to migraine prevention.

Ajovy is available as a solution for injection in a pre-filled syringe containing 225mg/1.5ml of fremanezumab. Other ingredients in the pre-filled syringe are L-histidine, L-histidine hydrochloride monohydrate, sucrose, disodium ethylenediaminetetraacetic acid (EDTA) dihydrate, polysorbate 80 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Fremanezumab, is manufactured at [redacted] The drug product, Ajovy Solution for Injection in Pre-Filled Syringe 225mg/1.5ml, is manufactured at Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany.

Drug substance:

Adequate controls have been presented for the cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with compendial requirements for monoclonal antibody products. Product and process-related impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for batches manufactured by [redacted] is adequate to support the proposed storage condition and shelf life period. The packaging is polycarbonate carboys, closed with polypropylene screw cap. The drug substance is approved for storage at [redacted].

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 24 months when stored at 2 to 8 ºC and a single period of up to 14 days at a temperature up to 30ºC after removal from the refrigerator. The container closure system is pre-filled syringe with a staked needle and a bromobutyl elastomer plunger-stopper.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of fremanezumab for the preventive treatment of migraine was based primarily on two pivotal Phase III studies (TV48125-CNS-30049 and TV48125-CMS30050), and one supportive Phase III study (TV48125-CNS-30051). The studies were conducted in adult patients with chronic or episodic migraine.

The clinical efficacy of fremanezumab in adult patients with chronic migraine was supported by study TV48125-CNS-30049, which was a multicentre, randomised, double-blind, placebo-controlled, parallel group study comparing fremanezumab with placebo. Patients in the study were randomised in a 1:1:1 ratio to receive either subcutaneous fremanezumab (675mg in the first month followed by 225mg monthly, referred to as 675/225/225), subcutaneous fremanezumab (675mg in the first month followed by placebo monthly, referred to as 675/placebo/placebo) or subcutaneous placebo monthly. Patients received treatment for 12 weeks, with a run-in period of 1 month.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug. Secondary endpoints of importance were the mean change from baseline in monthly average number of migraine days and the proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity. The efficacy endpoints were appropriate in accordance with the *International Headache Society Guidelines for Preventive Treatment of Chronic Migraine in Adults*.

A total of 1130 patients were randomised in the study – 379 patients in the fremanezumab (675/225/225) arm, 376 patients in the fremanezumab (675/placebo/placebo) arm and 375 patients in the placebo arm. The efficacy analysis was conducted in the ITT population. The median duration of exposure was 85 days for all treatment arms. The patient demographics and baseline disease characteristics were well-balanced between the treatment arms. The median age was 41 years (range 18 to 71 years), the majority of subjects were female (88%) and White (79%) and the median weight was 70.4kg (range 44 to 132kg). 11% of patients were Asian. 21% of subjects were treated with prior preventive medication use, the most frequent being topiramate (30%, 340/1130). The baseline mean total number of headache and migraine days of any duration and severity was 20 days and 16 days during the 28-day run-in period, respectively.

Summary of Key Efficacy Results (Study TV48125-CNS-30049)

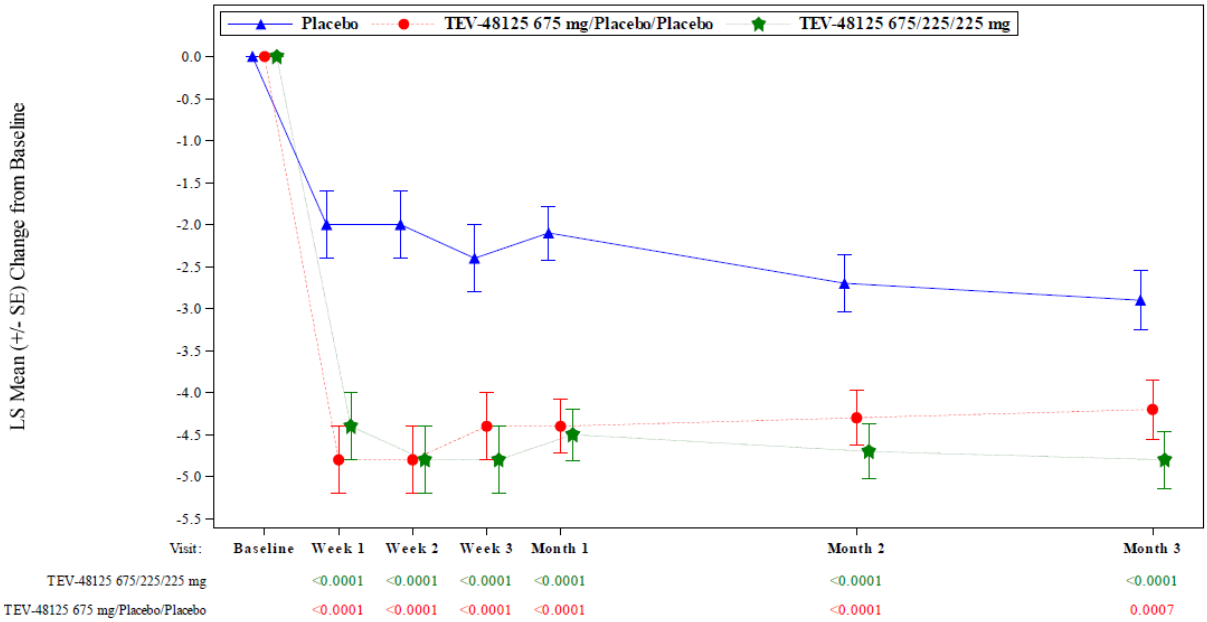
	Placebo (N=371)	Fremanezumab 675 mg/placebo/placebo (N=375)	Fremanezumab 675/225/225 mg (N=375)
Primary endpoint			
CFB in monthly average number of headache days or at least moderate severity after first dose of study drug			
LS mean (SE)	-2.5 (0.31)	-4.3 (0.31)	-4.6 (0.30)
95% CI	-3.06, -1.85	-4.87, -3.66	-5.16, -3.97
Comparison with placebo			
LS mean (SE)	-	-1.8 (0.33)	-2.1 (0.33)
95% CI	-	-2.46, -1.15	-2.76, -1.45
p-value	-	<0.0001	<0.0001
Comparison with 675 mg/placebo/placebo			
LS mean (SE)	-	-	-0.30 (0.33)
95% CI	-	-	-0.96. 0.36
Key Secondary Endpoints			
CFB in monthly average number of migraine days after first dose of study drug			
LS mean (SE)	-3.2 (0.35)	-4.9 (0.35)	-5.0 (0.35)
95% CI	-3.86, -2.47	-5.59, -4.20	-5.70, -4.33
Comparison with placebo			
LS mean (SE)	-	-1.7 (0.39)	-1.8 (0.39)
95% CI	-	-2.48. -0.97	-2.61, -1.09
p-value	-	<0.0001	<0.0001
Comparison with 675 mg/placebo/placebo			
LS mean (SE)	-	-	-0.1 (0.38)
95% CI	-	-	-0.88, 0.63
Proportion of patients with at least 50% reduction in monthly average number of headache days of at least moderate severity after first dose of study drug			
Month 1, n	370	375	374
Yes	80 (21.6%)	155 (41.3%)	150 (40.0%)
No	290 (78.2%)	220 (58.7%)	224 (59.7%)
Comparison with placebo	-	p<0.0001	p<0.0001
Month 2, n	355	365	361
Yes	90 (24.3%)	149 (39.7%)	157 (41.9%)
No	265 (71.4%)	216 (57.6%)	204 (54.4%)
Comparison with placebo	-	p<0.0001	p<0.0001
Month 3, n	342	350	345
Yes	98 (26.4%)	152 (40.5%)	167 (44.5%)
No	244 (65.8%)	198 (52.8%)	178 (47.5%)
Comparison with placebo	-	p<0.0001	p<0.0001
Overall, n	370	375	374
Yes	67 (18.1%)	141 (37.6%)	153 (40.8%)
No	303 (81.7%)	234 (62.4%)	221 (58.9%)
Comparison with placebo	-	p<0.0001	p<0.0001

CFB: change from baseline; LS: least squares; SE: standard error; CI: confidence interval

Treatment with fremanezumab resulted in a clinically meaningful reduction of about 2 headache days per month compared to placebo on average over the 12-week treatment period. The LS mean change from baseline in the monthly average number of headache days of at least moderate severity between fremanezumab compared to placebo was -2.1 days (95% CI -2.76, -1.45) and -1.8 days (95% CI -2.46, -1.15) for fremanezumab 675/225/225 and 675/placebo/placebo, respectively. The differences were statistically significant in both fremanezumab arms compared to placebo (p<0.0001). The difference between the monthly and quarterly treatments was not statistically tested, but the monthly treatment was numerically better compared to the quarterly treatment in reducing headaches– the difference was -0.30 (95% CI -0.96, 0.36). Both fremanezumab treatment regimens also resulted in statistically

significant reductions in the average number of headache days of at least moderate severity compared with placebo treatment as early as 1 month after administration of the first dose and this effect was maintained throughout the rest of the 12-week treatment period. The subgroup analyses demonstrated consistent benefit in terms of reducing headache days in the subgroups studied, including age, race and sex.

Change from Baseline in the Monthly Number of Headache Days of At Least Moderate Severity by Treatment Group (Full Analysis Set; Study TV48125-CNS-30049)



The benefit of fremanezumab over placebo was observed to be consistent between the primary and secondary endpoints. In particular, the LS mean change from baseline in monthly average number of migraine days, showed statistically significant changes of -1.8 (95% CI 2.61, -1.09) and -1.7 (95% CI -2.48, -0.97) for fremanezumab 675/225/225 and 675/placebo/placebo, respectively. In addition, the proportion of patients reaching at least 50% reduction in the monthly average number of headache days was greater in both fremanezumab treatment arms compared to placebo, with all comparisons between the fremanezumab and placebo arms showing statistically significant differences (overall $p<0.0001$). The clinical effect of both fremanezumab treatment regimens appeared to be similar.

The clinical efficacy of fremanezuamb in adult patients with episodic migraine was supported by Study TV48125-CNS-30050, which was a multicentre, randomised, double-blind, placebo-controlled, parallel group comparing fremanezumab with placebo. Patients in the study were randomised in a 1:1:1 ratio to receive either subcutaneous fremanezumab (675mg in the first month followed by placebo monthly, represented as 675/placebo/placebo), subcutaneous fremanezumab (225mg monthly, represented as 225/225/225) or subcutaneous placebo monthly. The study design was otherwise the same as that of study TV48125-CNS-30049.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of study drug. Secondary endpoints included the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days after the first dose of the study drug.

A total of 875 patients were randomised – 291 patients to fremanezumab (675/placebo/placebo), 290 patients to fremanezumab 225/225/225 and 294 patients to placebo. The efficacy analysis was conducted in the ITT population. The median duration of exposure was 85 days for all treatment arms. The patient demographics and baseline disease characteristics were well-balanced between the treatment arms. The median age was 42 years (range 18 to 70 years), the majority of subjects were female (85%) and White (80%) and the median weight was 72.1kg (range 43 to 120kg). 9% of patients were Asian. 21% of subjects were treated with prior preventive medication use, the most frequent being topiramate (19%, 168/875). The baseline mean number of migraine days was 9.1 days.

Summary of Key Efficacy Results (Study TV48125-CNS-30050)

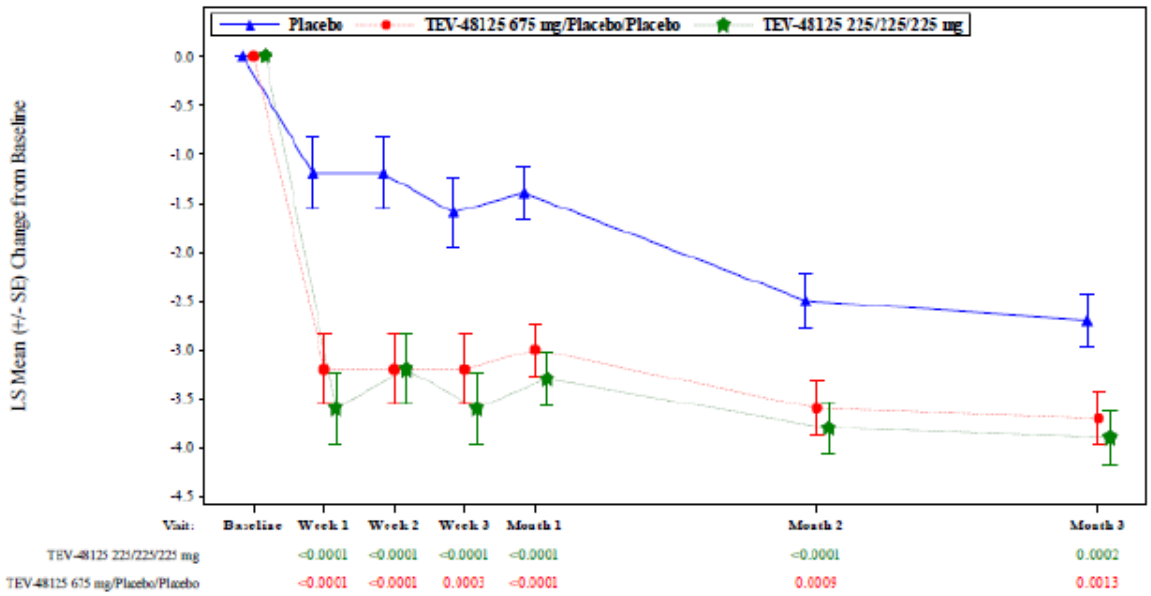
	Placebo (N=290)	**Fremanezumab 675 mg/placebo/placebo (N=288)**	**Fremanezumab 225/225/225 mg (N=287)**
Primary endpoint			
CFB in monthly average number of migraine days after the first dose of the study drug			
LS mean (SE)	-2.2 (0.24)	-3.4 (0.25)	-3.7 (0.25)
95% CI	-2.68, -1.71	-3.94, -2.96	-4.15, -3.18
Comparison with placebo			
LS mean (SE)	-	-1.3 (0.27)	-1.5 (0.28)
95% CI	-	-1.79, -0.72	-2.01, -0.93
p-value	-	<0.0001	<0.0001
Comparison with 675 mg/placebo/placebo			
LS mean (SE)	-	-	-0.2 (0.28)
95% CI	-	-	-0.75, 0.33
Secondary Endpoint			
Proportion of patients with ≥ 50% reduction in monthly average number of migraine days after the first dose of study drug			
Month 1, n	290	288	287
Yes	73 (25.2%)	127 (44.1%)	135 (47.0%)
No	217 (74.8%)	161 (55.9%)	152 (53.0%)
Comparison with placebo	-	<0.0001	<0.0001
Month 2, n	274	274	274
Yes	101 (34.8%)	135 (46.9%)	139 (48.4%)
No	173 (59.7%)	139 (48.3%)	135 (47.0%)
Comparison with placebo	-	0.0032	0.0010
Month 3, n	268	269	263
Yes	108 (37.2%)	141 (49.0%)	147 (51.2%)
No	160 (55.2%)	128 (44.4%)	116 (40.4%)
Comparison with placebo	-	0.0048	0.0003
Overall, n	290	288	287
Yes	81 (27.9%)	128 (44.4%)	137 (47.7%)
No	209 (72.1%)	160 (55.6%)	150 (52.3%)
Comparison with placebo	-	<0.0001	<0.0001

CFB: change from baseline; LS: least squares; SE: standard error; CI: confidence interval

Treatment with fremanezumab resulted in a clinically meaningful reduction of about 1.5 migraine days per month compared to placebo on average over the 12-week treatment period. The LS mean change from baseline in the monthly average number of migraine days between fremanezumab compared to placebo were -1.3 days (95% CI -1.79, -0.72) and -1.5 days (95% CI -2.01, -0.93) for fremanezumab 675/placebo/placebo and fremanezumab 225/225/225, respectively. The differences were statistically significant in both fremanezumab arms compared to placebo (p< 0.0001). Both fremanezumab treatment regimens also resulted in statistically significant reductions in the average number of migraine days compared with placebo treatment as early as 1 month after administration of the first dose and this effect was maintained throughout the rest of the 12-week treatment period. The difference between the

monthly and quarterly treatments was not statistically tested, but the monthly treatment was numerically better compared to the quarterly treatment in reducing headache – the difference was -0.20 (95% CI -0.75, 0.33) .The subgroup analyses demonstrated consistent benefit in terms of reducing migraine days in the subgroups studied, including age, race and sex.

Change from Baseline in the Monthly Number of Migraine Days by Treatment Group (Full Analysis Set; Study TV48125-CNS-30050)



The benefit of fremanezumab over placebo was observed to be consistent between the primary and secondary endpoints in this study. The proportion of patients reaching at least 50% reduction in the monthly average number of migraine days was greater in both fremanezumab treatment arms compared to placebo, with all comparisons between the fremanezumab and placebo arms showing statistically significant differences (overall p<0.0001).

A post-hoc analysis in Study TV48125-CNS-30050 was performed in the subgroup of patients with ≥ 12 headache days per month, and this was considered to be a surrogate of the chronic migraine population. The results showed that the LS mean change from baseline in the monthly average number of migraine days during the 12-week period between fremanezumab compared to placebo was -1.6 days (95% CI -2.56, -0.74) for fremanezumab 675/placebo/placebo and -1.6 days (95% CI -2.49, -0.71) for freumanezumab 225/225/225. When both fremanezumab arms were statistically compared, the difference was 0.0 days (95% CI -0.88, 0.97; p = 0.9227), indicating that the loading dose of fremanezumab 675mg from the 675/225/225 treatment regimen did not significantly contribute to the reduction in the monthly number of migraine days. Between the three fremanezumab treatment regimens considered for the population with chronic migraine (675 mg quarterly, 675mg followed by 225 mg monthly and 225 mg monthly), the differences in effect size (-0.1 to -0.2) were small and not clinically meaningful. In addition, the mechanism of action of fremanezumab is not expected to differ for chronic and episodic migraine. Therefore, the proposed dosing regimen of fremanezumab 225mg monthly or 675mg quarterly for the preventive treatment of chronic migraine is considered acceptable.

Additional supportive data were available from Study TV48125-CNS-30051, which was an exploratory multicentre, randomised, double-blind, parallel-group study evaluating the long-term safety and efficacy of fremanezumab in adult patients with chronic and episodic migraine.

The study consisted patients who completed studies TV48125-CNS-30049 or TV48125-CNS-30050, and new patients. Patients with chronic migraine were randomised in a 1:1 ratio to receive subcutaneous fremanezumab as 675mg in the first month followed by 225 mg monthly or 675 mg every 3 months for 12 months. Patients with episodic migraine were randomised in a 1:1 ratio to receive subcutaneous fremanezumab as 225 mg monthly or 675mg every 3 months for 12 months.

The study endpoints included the mean change from baseline in the monthly number of migraine days and headache days of at least moderate severity. Statistical analyses were not performed due to the exploratory nature of this study. A total of 1890 patients were randomised in the study – 1110 patients with chronic migraine and 780 patients with episodic migraine. There were 312 new patients and 1578 patients who transitioned from the previous studies. The median duration of exposure was 337 days on average for all treatment arms. The patient demographics and baseline disease characteristics were well-balanced between the treatment arms for both chronic and episodic migraine populations. As of data cut-off (30 May 2018), a total of 666 patients completed the study.

Treatment with fremanezumab resulted in a numerical decrease in monthly migraine days relative to baseline. The mean change from baseline to month 6 and month 12 in the chronic migraine population was -7.6 and -8.1 days, respectively, in the 675/225mg monthly treatment arm, and -6.5 and -7.2 days, respectively, in the 675mg quarterly treatment arm. The mean change from baseline to month 6 and month 12 in the episodic migraine population was -4.9 and -5.1 days, respectively, in the 225mg monthly treatment arm, and -5.0 and -5.2 days, respectively, in the 675mg quarterly treatment arm. In the chronic migraine population, the monthly number of headache days of at least moderate severity was seen to decrease relative to baseline. The mean change from baseline to month 6 and 12 was -6.5 and -6.8 months, respectively, in the 225mg monthly treatment arm, and -5.7 and -6.4 days, respectively, in the 675mg quarterly treatment arm.

In general, persistence of effect of fremanezumab in reducing migraine/headache days was observed. Efficacy responses were achieved at 1 month and maintained for at least 6 months of the treatment period. The exploratory results supported the positive effect of fremanezumab treatment observed in the pivotal studies.

Overall, the results of study TV28125-CBS-30049 were consistent in meeting the primary and secondary efficacy endpoints and demonstrated robustness. This was further supported by study TV48125-CNS-30051. The results adequately supported the efficacy of fremanezumab in both dosing regimens proposed for the preventive treatment of migraine in adults.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety data supporting the use of fremanezumab for the requested indication comprised a total of 3373 patients (2512 in the fremanezumab arm and 861 in the placebo arm) who were enrolled in studies TV48125-CNS-30049, TV48125-CNS-30050, TV48125-CNS-30051, LBR-101-021 and LBR-101-022. The safety analysis was conducted in two cohorts, i.e. Cohort 1 (all subjects in the placebo-controlled studies) and Cohort 4 (all fremanezumab-treated patients). In Cohort 1, the median duration of exposure was 85 days for patients treated with fremanezumab and placebo. The duration of exposure was similar across the individual fremanezumab treatment groups. In Cohort 4, the median duration of exposure was 339 days.

Overview of Safety Profile: All Patients in the Placebo-Controlled Studies (Cohort 1)

	Placebo	Fremanezumab		
AE	**Monthly (N = 861)**	**225mg Monthly (N = 386)**	**675mg Quarterly (N = 667)**	**675/225mg Monthly (N = 467)**
Any AE	505 (59%)	236 (61%)	458 (69%)	317 (68%)
Treatment-related AE	307 (36%)	164 (42%)	323 (48%)	219 (47%)
SAE	14 (2%)	5 (1%)	6 (<1%)	6 (1%)
Treatment-related SAE	2 (<1%)	1 (<1)	0	0

Overview of Safety Profile: All Fremanezumab-Treated Patients (Cohort 4)

	Fremanezumab		
AE	**225mg Monthly (N = 551)**	**675mg Quarterly (N = 1086)**	**675/225mg Monthly (N = 712)**
Any AE	423 (77%)	936 (86%)	613 (86%)
Treatment-related AE	311 (56%)	658 (61%)	437 (61%)
SAE	25 (5%)	60 (6%)	40 (6%)
Treatment-related SAE	2 (<1%)	4 (<1%)	4 (<1%)

The most frequently reported treatment-emergent adverse events (AEs) were injection site pain, injection site induration and injection site erythema. Mild to moderate injection site reactions are expected adverse events. In the majority of cases, the adverse events were of mild to moderate intensity. The overall incidences of AEs were comparable across the fremanezumab treatment arms and were generally comparable to placebo. The safety profile in Cohort 4 was comparable to that of Cohort 1.

The most commonly reported fremanezumab/placebo-related AEs with higher incidences in the fremanezumab arm compared to the placebo arm were injection site pain (23% vs 21%), injection site induration (17% vs 13%), injection site erythema (16% vs 12%), and injection site pruritus (2% vs <1%).

The incidence of serious adverse events (SAEs) and treatment-related SAEs reported were low in cohorts 1 and 4. In Cohort 1, SAEs occurred in 21 patients (1%) who received fremanezumab and 14 patients (2%) who received placebo. In Cohort 4, SAEs occurred in ≤6% of all fremanezumab-treated patients. The most commonly reported SAEs among all fremanezumab-treated patients were migraine, status migrainosus, basal cell carcinoma and pneumonia (4 patients per SAE). In both Cohorts, the incidence of treatment related SAE was <1%, including one case each of pneumonia, generalised tonic-clonic seizure, central nervous system lesion, papillary thyroid cancer, depression and suicidal ideation, and 3 cases of status migrainosus. As most SAEs occurred in a single patient each, a safety signal was not identified. The incidence of SAEs or treatment-related SAEs were similar in patients with chronic migraine and those with episodic migraine.

AEs leading to discontinuation from fremanezumab occurred in 35 patients in Cohort 1 and 111 patients in Cohort 4. Most events leading to discontinuation had resolved and were mild to moderate in intensity.

Adverse Events Leading to Discontinuation Occurring in At Least 2 Patients Total in Fremanezumab Treatment Groups – Cohort 1

SOC MedDRA PT	Fremanezumab Number of patients (%)			
	Placebo Monthly N = 861	225mg Monthly N = 386	675mg Quarterly N = 667	675/225mg Monthly N = 467
Patients with at least 1 AE leading to discontinuation	14 (2)	9 (2)	10 (1)	11 (2)
Gastrointestinal disorders	0	0	3 (<1)	0
Abdominal pain	0	0	2 (<1)	0
Diarrhoea	0	0	2 (<1)	0
General disorders and administration site	4 (<1)	5 (1)	7 (1)	4 (<1)
Injection site erythema	0	1 (<1)	4 (<1)	1 (<1)
Injection site rash	0	1 (<1)	2 (<1)	2 (<1)
Injection site induration	0	1 (<1)	1 (<1)	0
Injection site pain	1 (<1)	1 (<1)	0	1 (<1)
Injection site pruritus	0	0	2 (<1)	0
Infections and infestations	1 (<1)	1 (<1)	0	2 (<1)
Investigations	0	1 (<1)	0	1 (<1)
Nervous system disorders	2 (<1)	1 (<1)	1 (<1)	0
Migraine	2 (<1)	1 (<1)	1 (<1)	0
Psychiatric disorders	2 (<1)	0	2 (<1)	1 (<1)
Depression	0	0	2 (<1)	0
Anxiety	0	0	2 (<1)	0
Skin and subcutaneous tissue	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Pruritus	0	1 (<1)	1 (<1)	0
Vascular disorders	0	1 (<1)	0	1 (<1)

Overall, 3 deaths were reported. All 3 patients received the fremanezumab 675mg quarterly treatment regimen. The causes of death were found to be unrelated to fremanezumab.

Cardiovascular effects and immunogenicity were identified as AEs of special interest associated with fremanezumab. However, an association of cardiovascular events with fremanezumab treatment could not be confirmed and the development of anti-drug antibody was low, even with long-term use of fremanezumab. The AEs of special interest have been adequately described in the proposed package insert.

Overall, fremanezumab at all doses tested were found to be generally well tolerated in migraine patients. Fremanezumab-related AEs are mostly manageable and the safety profile was consistent with that observed in other CGRP inhibitors, such as galcanezumab.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard of care for preventive migraine therapy includes treatment with topiramate, clostridium botulinium toxin type A, and most recently approved galcanezumab. Commonly used prophylactic treatment options are known to be associated with undesired side effect profiles and dosing regimens leading to non-compliance. Therefore, new therapeutic options are required to improve outcomes by reducing the frequency of migraine headaches.

Fremanezumab was shown to show treatment benefit in terms of a statistically significant reductions in the average number of migraine/headache days per month in both episodic and chronic migraine populations. In the chronic migraine population, this was -2.1 days (95% CI -2.76, -1.45) and -1.8 days (95% CI -2.46, -1.15) for fremanezumab 675/225/225 and 675/placebo/placebo, respectively, and in the episodic migraine population, the change was -1.3 days (95% CI -1.79, -0.72) and -1.5 days (95% CI -2.01, -0.93) for fremanezumab 675/placebo/placebo and fremanezumab 225/225/225, respectively. The differences of effect between fremanezumab to placebo were shown to be consistent across primary and secondary endpoints. Persistence of effect of fremanezumab was observed throughout the 12-week treatment period in the pivotal studies and maintained at least 6 months in the long-term safety study.

The safety profile of fremanezumab at all doses tested were generally well tolerated in migraine patients. The most common AEs were injection site reactions. The identified risks have been adequately described in the local package insert, reflected under warnings and precautions for use and undesirable effects.

Overall, the benefit-risk profile of fremanezumab indicated for preventive treatment of migraine in adults was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of fremanezumab for the preventive treatment of migraine in adults was deemed favourable and approval of the product registration was granted on 08 May 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

AJOVY pre-filled syringe 225 mg/1.5ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 225 mg fremanezumab.

Fremanezumab is a humanised monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to opalescent, colourless to slightly yellow solution with a pH of 5.5 and an osmolality of 300-450 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AJOVY is indicated for the preventive treatment of migraine in adults.

4.2 Posology and method of administration

The treatment should be initiated by a physician experienced in the diagnosis and treatment of migraine.

Posology

Two dosing options are available:

- 225 mg once monthly (monthly dosing) or
- 675 mg every three months (quarterly dosing)

When switching dosing regimens, the first dose of the new regimen should be administered on the next scheduled dosing date of the prior regimen.

When initiating treatment with fremanezumab, concomitant migraine preventive treatment may be continued if considered necessary by the prescriber (see section 5.1).

The treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter.

Missed dose
If a fremanezumab injection is missed on the planned date, dosing should resume as soon as possible on the indicated dose and regimen. A double dose must not be administered to make up for a missed dose.

Special Populations

Elderly
There is limited data available on the use of fremanezumab in patients ≥65 years of age. Based on the results of population pharmacokinetic analysis, no dose adjustment is required (see section 5.2).

Renal or hepatic impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment or hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of AJOVY in children and adolescents below the age of 18 years have not yet been established. No data are available.

Method of administration

Subcutaneous use.

AJOVY is for subcutaneous injection only. It should not be administered by the intravenous or intramuscular route. AJOVY can be injected into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. For multiple injections, injection sites should be alternated.

Patients may self-inject if instructed in subcutaneous self-injection technique by a healthcare professional. For further instructions on administration, please refer to the patient information leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

Hypersensitivity reactions were reported with fremanezumab in less than 1% of patients in clinical trials. If a hypersensitivity reaction occurs, discontinuation of fremanezumab administration should be considered and appropriate therapy should be initiated.

Major cardiovascular diseases

Patients with certain major cardiovascular diseases were excluded from clinical studies (see section 5.1). No safety data are available in these patients.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical drug interaction studies have been performed with AJOVY. No pharmacokinetic drug interactions are expected based on the characteristics of fremanezumab. Furthermore, concomitant use of acute migraine treatments (specifically analgesics, ergots, and triptans) and migraine preventive medicinal products during the clinical studies did not affect the pharmacokinetics of fremanezumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of AJOVY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of AJOVY during pregnancy.

Breast-feeding

It is unknown whether fremanezumab is excreted in human milk. Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of fremanezumab could be considered during breast-feeding only if clinically needed.

Fertility

There are no fertility data in humans. Available non-clinical data do not suggest an effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

AJOVY has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

A total of over 2,500 patients (more than 1,900 patient years) have been treated with AJOVY in registration studies. More than 1,400 patients were treated for at least 12 months.

Commonly reported adverse drug reactions (ADRs) were local reactions at the injection site (pain [24%], induration [17%], erythema [16%] and pruritus [2%]).

Tabulated list of adverse reactions

ADRs from clinical studies are presented according to MedDRA system organ classification. Within each system organ class, ADRs are ranked by frequency, most frequent reactions first. Within each frequency grouping, ADRs are presented in the order of decreasing seriousness. Frequency categories are based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

The following ADRs have been identified in the AJOVY clinical development programme (Table 1).

Table 1: Adverse reactions in clinical studies

MedDRA System Organ Class	Frequency	Adverse Reaction
General disorders and administration site conditions	Very common	Injection site pain
		Injection site induration
		Injection site erythema
	Common	Injection site pruritus
	Uncommon	Injection site rash

Description of selected adverse reactions

Injection site reactions
The most frequently observed local reactions at the injection site were pain, induration and erythema. All local injection site reactions were transient and predominantly mild to moderate in severity. Pain, induration and erythema were typically observed immediately after injection while pruritus and rash appeared within a median of 24 and 48 hours, respectively. All injection site reactions resolved, mostly within a few hours or days. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Immunogenicity
In placebo-controlled studies, 0.4 % of patients (6 out of 1,701) treated with fremanezumab developed anti-drug antibodies (ADA). The antibody responses were of low titer. One of these 6 patients developed neutralising antibodies. To date, 1,494 patients have completed 12 months of treatment with fremanezumab in the ongoing long-term Study 3. ADA were detected in 2% of the patients (38 out of 1,888). The safety and efficacy of fremanezumab were not affected by ADA development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Doses up to 2,000 mg have been administered intravenously in clinical trials without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and given appropriate symptomatic treatment if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcitonin gene-related peptide (CGRP) antagonists.
ATC code: N02CD03.

Mechanism of action

Fremanezumab is a humanised IgG2Δa/kappa monoclonal antibody derived from a murine precursor. Fremanezumab selectively binds the calcitonin gene-related peptide (CGRP) ligand and blocks both CGRP isoforms (α-and β-CGRP) from binding to the CGRP receptor. While the precise mechanism of action by which fremanezumab prevents migraine attacks is unknown, it is believed that prevention of migraine is obtained by its effect modulating the trigeminal system. CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief.

Fremanezumab is highly specific for CGRP and does not bind to closely related family members (e.g., amylin, calcitonin, intermedin and adrenomedullin).

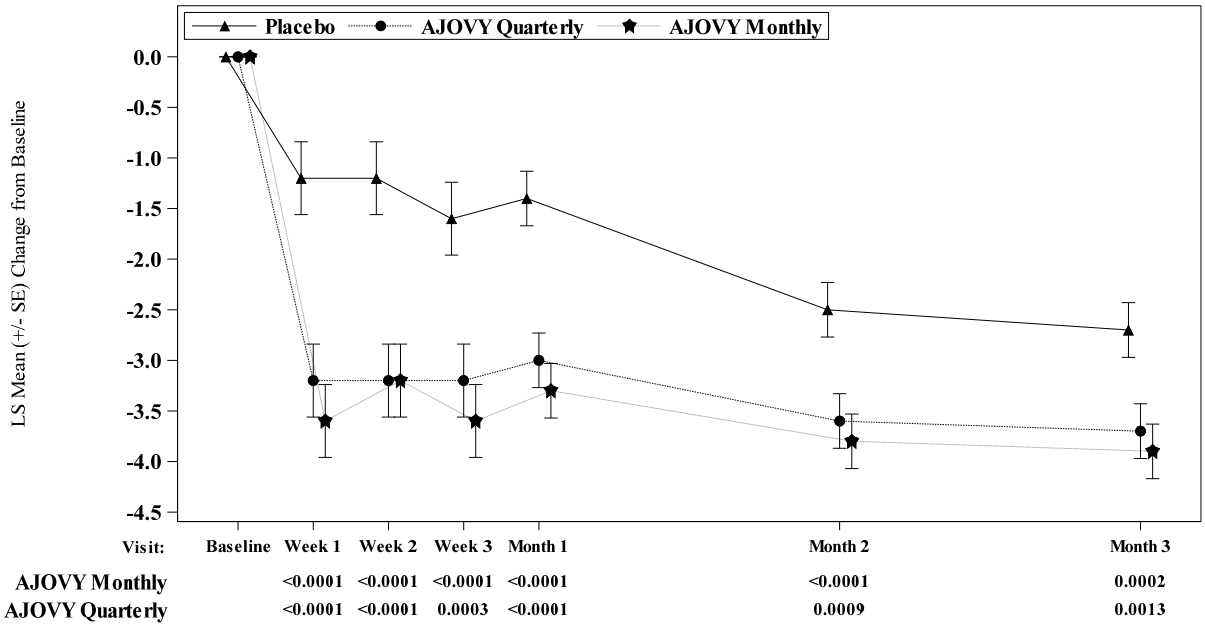
Clinical efficacy and safety

The efficacy of fremanezumab was assessed in two randomised, 12-week, double-blind, placebo-controlled phase III studies in adult patients with episodic (Study 1) and chronic migraine (Study 2). The patients enrolled had at least a 12-month history of migraine (with and without aura) according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria. Elderly patients (>70 years), patients using opioids or barbiturates on more than 4 days per month, and patients with pre-existing myocardial infarction, cerebrovascular accident, and thromboembolic events were excluded.

Episodic migraine study (Study 1)
The efficacy of fremanezumab was evaluated in episodic migraine in a randomised, multicentre, 12-week, placebo-controlled, double-blind study (Study 1). Adults with a history of episodic migraine (less than 15 headache days per month) were included in the study. A total of 875 patients (742 females, 133 males) were randomised into one of three arms: 675 mg fremanezumab every three months (quarterly, n=291), 225 mg fremanezumab once a month (monthly, n=290), or monthly administration of placebo (n=294) administered via subcutaneous injection. Demographics and baseline disease characteristics were balanced and comparable between the study arms. Patients had a median age of 42 years (range: 18 to 70 years), 85% were female, and 80% were white. The mean migraine frequency at baseline was approximately 9 migraine days per month. Patients were allowed to use acute headache treatments during the study. A sub-set of patients (21%) was also allowed to use one commonly used concomitant, preventive medicinal product (beta-blockers, calcium channel blocker/benzocycloheptene, antidepressants, anticonvulsants). Overall, 19% of the patients had previously used topiramate. A total of 791 patients completed the 12-week double-blind treatment period.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 12-week treatment period. Key secondary endpoints were the achievement of at least 50% reduction from baseline in monthly migraine days (50% responder rate), mean change from baseline in the patient reported MIDAS score, and change from baseline in monthly average number of days of acute headache medicinal product use. Both monthly and quarterly dosing regimens of fremanezumab demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo for key endpoints (see Table 2). The effect also occurred from as early as the first month and sustained over the treatment period (see Figure 1).

Figure 1: Mean Change from Baseline in the Monthly Average Number of Migraine Days for Study 1



Mean at baseline (monthly average number of migraine days): Placebo: 9.1, AJOVY Quarterly: 9.2, AJOVY Monthly: 8.9.

Table 2: Key Efficacy Outcomes in Study 1 in Episodic Migraine

Efficacy Endpoint	**Placebo** (n=290)	**Fremanezumab 675 mg quarterly** (n=288)	**Fremanezumab 225 mg monthly** (n=287)
MMD			
Mean change[a] (95% CI)	-2.2 (-2.68, -1.71)	-3.4 (-3.94, -2.96)	-3.7 (-4.15, -3.18)
TD (95% CI)[b]	-	-1.2 (-1.74, -0.69)	-1.4 (-1.96, -0.90)
Baseline (SD)	9.1 (2.65)	9.2 (2.62)	8.9 (2.63)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
MHD			
Mean change[a] (95% CI)	-1.5 (-1.88, -1.06)	-3.0 (-3.39, -2.55)	-2.9 (-3.34, -2.51)
TD (95% CI)[b]	-	-1.5 (-1.95, -1.02)	-1.5 (-1.92, -0.99)
Baseline (SD)	6.9 (3.13)	7.2 (3.14)	6.8 (2.90)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
50% Responder Rate MMD			
Percentage [%]	27.9%	44.4%	47.7%
P-value (vs. placebo)	-	*p<0.0001*	*p<0.0001*
75% Responder Rate MMD			
Percentage [%]	9.7%	18.4%	18.5%
P-value (vs. placebo)	-	*p=0.0025*	*p=0.0023*
MIDAS total			
Mean change[a] (95% CI)	-17.5 (-20.62, -14.47)	-23.0 (-26.10, -19.82)	-24.6 (-27.68, -21.45)
Baseline (SD)	37.3 (27.75)	41.7 (33.09)	38 (33.30)
P-value (vs. placebo)[a]	-	*p=0.0023*	*p<0.0001*
MAHMD			
Mean change[a] (95% CI)	-1.6 (-2.04, -1.20)	-2.9 (-3.34, -2.48)	-3.0 (-3.41, -2.56)
TD (95% CI)[b]	-	-1.3 (-1.73, -0.78)	-1.3 (-1.81, -0.86)
Baseline (SD)	7.7 (3.60)	7.7 (3.70)	7.7 (3.37)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*

CI = confidence interval; MAHMD = monthly acute headache medication days; MHD = monthly headache days of at least moderate severity; MIDAS = Migraine Disability Assessment; MMD = monthly migraine days; SD = standard deviation; TD = treatment difference

[a] For all endpoints mean change and CIs are based on the ANCOVA model that included treatment, gender, region, and baseline preventive medication use (yes/no) as fixed effects and corresponding baseline value and years since onset of migraine as covariates.

[b] Treatment difference is based on the MMRM analysis with treatment, gender, region, and baseline preventive medication use (yes/no), month, and treatment month as fixed effects and corresponding baseline value and years since onset of migraine as covariates.

In patients on one other concomitant, migraine preventive medicinal product, the treatment difference for the reduction of monthly migraine days (MMD) observed between fremanezumab 675 mg quarterly and placebo was -1.8 days (95% CI: -2.95, -0.55) and between fremanezumab 225 mg monthly and placebo -2.0 days (95% CI: -3.21, -0.86).

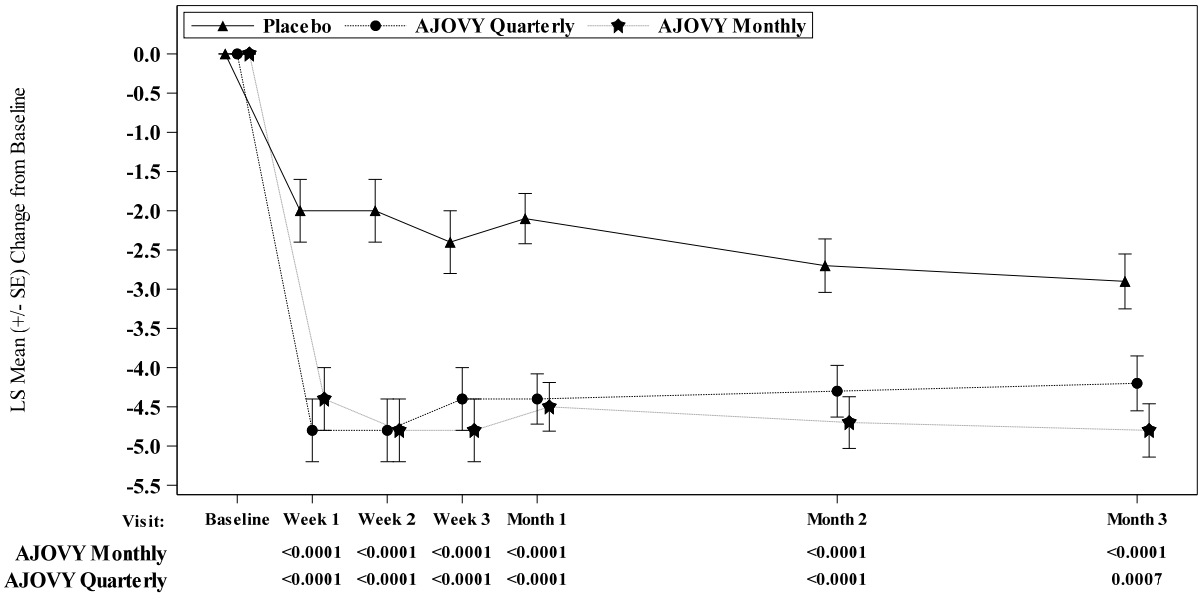
In patients who had previously used topiramate the treatment difference for the reduction of monthly migraine days (MMD) observed between fremanezumab 675 mg quarterly and placebo was -2.3 days (95% CI: -3.64, -1.00) and between fremanezumab 225 mg monthly and placebo -2.4 days (95% CI: -3.61, -1.13).

Chronic migraine study (Study 2)

Fremanezumab was evaluated in chronic migraine in a randomised, multicentre, 12-week, placebo-controlled, double-blind study (Study 2). The study population included adults with a history of chronic migraine (15 headache days or higher per month). A total of 1,130 patients (991 females, 139 males) were randomised into one of three arms: 675 mg fremanezumab starting dose followed by 225 mg fremanezumab once a month (monthly, n=379), 675 mg fremanezumab every three months (quarterly, n=376), or monthly administration of placebo (n=375) administered via subcutaneous injection. Demographics and baseline disease characteristics were balanced and comparable between the study arms. Patients had a median age of 41 years (range: 18 to 70 years), 88% were female, and 79% were white. The mean headache frequency at baseline was approximately 21 headache days per month (of which 13 headache days were of at least moderate severity). Patients were allowed to use acute headache treatments during the study. A sub-set of patients (21%) was also allowed to use one commonly used concomitant, preventive medicinal product (beta-blockers, calcium channel blocker/benzocycloheptene, antidepressants, anticonvulsants). Overall, 30% of the patients had previously used topiramate and 15% onabotulinumtoxin A. A total of 1,034 patients completed the 12-week double-blind treatment period.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week treatment period. Key secondary endpoints were the achievement of at least 50% reduction from baseline in monthly headache days of at least moderate severity (50% responder rate), mean change from baseline in the patient reported HIT-6 score, and change from baseline in monthly average number of days of acute headache medicinal product use. Both monthly and quarterly dosing regimens of fremanezumab demonstrated statistically significant and clinically meaningful improvement from baseline compared to placebo for key endpoints (see Table 3). The effect also occurred from as early as the first month and sustained over the treatment period (see Figure 2).

Figure 2: Mean Change from Baseline in the Monthly Average Number of Headache Days of At Least Moderate Severity for Study 2



Mean at baseline (monthly average number of headache days of at least moderate severity): Placebo: 13.3, AJOVY Quarterly: 13.2, AJOVY Monthly: 12.8.

Table 3: Key Efficacy Outcomes in Study 2 in Chronic Migraine

Efficacy Endpoint	**Placebo** (n=371)	**Fremanezumab 675 mg quarterly** (n=375)	**Fremanezumab 225 mg monthly with 675 mg starting dose** (n=375)
MHD			
Mean change[a] (95% CI)	-2.5 (-3.06, -1.85)	-4.3 (-4.87, -3.66)	-4.6 (-5.16, -3.97)
TD (95% CI)[b]	-	-1.8 (-2.45, -1.13)	-2.1 (-2.77, -1.46)
Baseline (SD)	13.3 (5.80)	13.2 (5.45)	12.8 (5.79)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
MMD			
Mean change[a] (95% CI)	-3.2 (-3.86, -2.47)	-4.9 (-5.59, -4.20)	-5.0 (-5.70, -4.33)
TD (95% CI)[b]	-	-1.7 (-2.44, -0.92)	-1.9 (-2.61, -1.09)
Baseline (SD)	16.3 (5.13)	16.2 (4.87)	16.0 (5.20)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*
50% Responder Rate MHD			
Percentage [%]	18.1%	37.6%	40.8%
P-value (vs. placebo)	-	*p<0.0001*	*p<0.0001*
75% Responder Rate MHD			
Percentage [%]	7.0%	14.7%	15.2%
P-value (vs. placebo)	-	*p=0.0008*	*p=0.0003*
HIT-6 total			
Mean change[a] (95% CI)	-4.5 (-5.38, -3.60)	-6.4 (-7.31, -5.52)	-6.7 (-7.71, -5.97)
Baseline (SD)	64.1 (4.79)	64.3 (4.75)	64.6 (4.43)
P-value (vs. placebo)[a]	-	*p=0.0001*	*p<0.0001*
MAHMD			
Mean change[a] (95% CI)	-1.9 (-2.48, -1.28)	-3.7 (-4.25, -3.06)	-4.2 (-4.79, -3.61)
TD (95% CI)[b]	-	-1.7 (-2.40, -1.09)	-2.3 (-2.95, -1.64)
Baseline (SD)	13.0 (6.89)	13.1 (6.79)	13.1 (7.22)
P-value (vs. placebo)[a]	-	*p<0.0001*	*p<0.0001*

CI = confidence interval; HIT-6 = Headache Impact Test; MAHMD = monthly acute headache medication days; MHD = monthly headache days of at least moderate severity; MMD = monthly migraine days; SD = standard deviation; TD = treatment difference

[a] For all endpoints mean change and CIs are based on the ANCOVA model that included treatment, gender, region, and baseline preventive medication use (yes/no) as fixed effects and corresponding baseline value and years since onset of migraine as covariates.

[b] Treatment difference is based on the MMRM analysis with treatment, gender, region, and baseline preventive medication use (yes/no), month, and treatment month as fixed effects and corresponding baseline value and years since onset of migraine as covariates.

In patients on one other concomitant, migraine preventive medicinal product, the treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity observed between fremanezumab 675 mg quarterly and placebo was -1.3 days (95% CI: -2.66, 0.03) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.0 days (95% CI: -3.27, -0.67).

In patients who had previously used topiramate the treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity observed between fremanezumab 675 mg quarterly and placebo was -2.7 days (95% CI: -3.88, -1.51) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.9 days (95% CI: -4.10, -1.78). In patients who had previously used onabotulinumtoxin A the treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity observed between fremanezumab 675 mg quarterly and placebo was -1.3 days (95% CI: -3.01, -0.37) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.0 days (95% CI: -3.84, -0.22).

Approximately 52% of the patients in the study had acute headache medication overuse. The observed treatment difference for the reduction of monthly headache days (MHD) of at least moderate severity between fremanezumab 675 mg quarterly and placebo in these patients was -2.2 days (95% CI: -3.14, -1.22) and between fremanezumab 225 mg monthly with 675 mg starting dose and placebo -2.7 days (95% CI: -3.71, -1.78).

Long-term study (Study 3)

For all episodic and chronic migraine patients, efficacy was sustained for up to 12 additional months in the long-term study (Study 3), in which patients received 225 mg fremanezumab monthly or 675 mg quarterly. 79% of patients completed the 12-month treatment period of Study 3. Pooled across the two dosing regimens, a reduction of 6.6 monthly migraine days was observed after 15 months relative to Study 1 and Study 2 baseline. 61% of patients completing Study 3 achieved a 50% response in the last month of the study. No safety signal was observed during the 15-month combined treatment period.

Intrinsic and extrinsic factors

The efficacy and safety of fremanezumab was demonstrated regardless of age, gender, race, use of concomitant preventive medicinal products (beta-blockers, calcium channel blocker/benzocycloheptene, antidepressants, anticonvulsants), use of topiramate or onabotulinumtoxin A for migraine in the past, and acute headache medication overuse.
There is limited data available on the use of fremanezumab in patients ≥65 years of age (2% of the patients).

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

After single subcutaneous administrations of 225 mg and 675 mg fremanezumab, median time to maximum concentrations (t_{max}) in healthy subjects was 5 to 7 days. The absolute bioavailability of fremanezumab after subcutaneous administration of 225 mg and 900 mg in healthy subjects was 55% (±SD of 23%) to 66% (±SD of 26%). Dose proportionality, based on population pharmacokinetics, was observed between 225 mg to 675 mg. Steady state was achieved by approximately 168 days (about 6 months) following 225 mg monthly and 675 mg quarterly dosing regimens. Median accumulation ratio, based on once monthly and once quarterly dosing regimens, is approximately 2.4 and 1.2, respectively.

Distribution

Assuming the model-derived estimated bioavailability of 66% (±SD of 26%) holds for the patient population, the volume of distribution for a typical patient was 3.6 L (35.1% CV) following subcutaneous administration of 225 mg, 675 mg and 900 mg of fremanezumab.

Biotransformation

Similar to other monoclonal antibodies, fremanezumab is expected to be degraded by enzymatic proteolysis into small peptides and amino acids.

Elimination

Assuming the model-derived estimated bioavailability of 66% (±SD of 26%) holds for the patient population, central clearance for a typical patient was 0.09 L/day (23.4% CV) following subcutaneous administration of 225 mg, 675 mg and 900 mg of fremanezumab. The formed small peptides and amino acids may be re-used in the body for de novo synthesis of proteins or are excreted by the kidney. Fremanezumab has an estimated half-life of 30 days.

Special populations

A population pharmacokinetic analysis looking at age, race, gender, and weight was conducted on data from 2,546 subjects. Approximately twice as much exposure is expected in the lowest body weight quartile (43.5 to 60.5 kg) compared to the highest body weight quartile (84.4 to 131.8 kg). However, body weight did not have an observed effect on the clinical efficacy based on the exposure-response analyses in episodic and chronic migraine patients. No dose adjustments are required for fremanezumab. No data on exposure-efficacy relationship in subjects with body weight >132 kg is available.

Renal or hepatic impairment
Since monoclonal antibodies are not known to be eliminated via renal pathways or metabolised in the liver, renal and hepatic impairment are not expected to impact the pharmacokinetics of fremanezumab. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) have not been studied. Population pharmacokinetic analysis of integrated data from the AJOVY clinical studies did not reveal a difference in the pharmacokinetics of fremanezumab in patients with mild to moderate renal impairment or hepatic impairment relative to those with normal renal or hepatic function (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

As fremanezumab is a monoclonal antibody, no genotoxicity or carcinogenicity studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the pre-filled syringe(s) in the outer carton in order to protect from light.
AJOVY may be stored unrefrigerated for up to 14 days at a temperature up to 30°C. AJOVY must be discarded if it has been out of the refrigerator for longer than 14 days.

6.5 Nature and contents of container

1.5 mL solution in a 2.25 mL Type I glass syringe with plunger stopper (bromobutyl rubber) and needle.

Pack sizes of 1 or 3 pre-filled syringes. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

The detailed instructions for use provided in the patient information leaflet must be followed step-by-step carefully.
The pre-filled syringe is for single use only.
AJOVY should not be used if the solution is cloudy or discoloured or contains particles.
AJOVY should not be used if the solution has been frozen.
The pre-filled syringe should not be shaken.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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Germany

8. DATE OF REVISION OF THE TEXT

04-2020