Taiwan Food and Drug Administration

Assessment Report

Trade Name：艾久維注射液 / Ajovy solution for injection

Active Ingredient：Fremanezumab

License Number：MOHW-BI 001138

Applicant：香港商艾維斯有限公司台灣分公司

Approval Date：2020/07/27

Indication：

預防成人偏頭痛。

AJOVY is indicated for the prophylaxis of migraine in adults.

1. Background Information

Trade Name	艾久維注射液 / Ajovy solution for injection
Active Ingredient(s)	Fremanezumab
Applicant	香港商艾維斯有限公司台灣分公司
Dosage Form & Strengths	Solution for Injection 225mg/1.5mL
Indication	預防成人偏頭痛。 AJOVY is indicated for the prophylaxis of migraine in adults.
Posology	● 225 mg 每月一次，或 ● 675 mg 每 3 個月一次（每季一次）。 ● 225 mg monthly, or ● 675 mg every 3 months (quarterly), which is administered as three consecutive subcutaneous injections of 225 mg each.
Pharmacological Category **ATC Code**	N02CD03

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

Introduction

The drug product is a sterile and preservative-free solution that is aseptically filled into a type I glass syringe. Each prefilled syringe (PFS) delivers 225 mg of fremanezumab in 1.5 mL (150 mg/mL).

2.1.1 Drug substance

General Information

The drug substance “fremanezumab” is a recombinant humanized IgG2Δa/kappa monoclonal antibody produced in CHO cells. Fremanezumab binds and blocks both α- and β- calcitonin gene-related peptide (CGRP) from binding to the CGRP receptor. Fremanezumab has two identical light chains (each consists of 214 residues) and two identical heavy chains (each is predicted to contain 448 residues). The C-termini of the heavy chains are primarily of the des-Lys form. As such, the heavy chain actually consists of 447 residues. There are a total of 36 cysteine residues in the molecule with the potential to form disulfide bonds. The molecular weight of fremanezumab is about 148 kDa.

Manufacture

Fremanezumab drug substance is manufactured according to current Good Manufacturing Practices. The manufacturing process of drug substance consists of the cell culture process and the purification process.. The resulting drug substance solution is adjusted to its final

formulation and filtered into storage containers.

- *Control of material*

Sufficient details on the derivation and history of the fremanezumab cell bank development have been provided. The generation of the MCB and WCB was performed under GMP conditions. Both MCB and WCB have been extensively characterized according to ICH Q5A and ICHQ5D.

No materials of human or animal origin are used in the fremanezumab drug substance manufacturing process. The adequate information regarding the raw materials has been provided.

- *Control of critical steps and intermediates*

The process control strategy has been described. The process parameters (PPs), critical process parameters (CPPs), in-process controls (IPCs) and critical in-process controls (cIPCs) have been defined for each step in the process. The control strategy is considered appropriate and capable to ensure robust and consistent process performance and product quality.

- *Process validation*

The process validation has been conducted on 3 consecutive full scale batches using the proposed commercial process. The drug substance manufacturing process is considered successfully validated. The provided data support the maximum hold times for the in-process pools in the fremanezumab manufacturing process.

- *Manufacturing process development*

The process development history has been provided. The comparability bridging studies confirmed that drug substance lots manufactured by the commercial process are comparable to drug substance lots made by previous developmental manufacturing processes.

Characterization

Characterization studies of fremanezumab include the followings: primary structure, disulfide bonding, molecular mass, higher-order structure, biological activity, purity and post-translational modifications.

The product and process-related impurities are sufficiently described and controlled.

Control of drug substance

- *Specification*

The drug substance specification includes appearance, pH, protein concentration, identity, purity/ impurities, potency and safety tests. The proposed commercial specification for drug substance is considered adequate and acceptable.

- *Analytical methods*

The tests were performed either according to compendial methods or in-house analytical

methods. Descriptions of non-compendial analytical procedures and validation summaries have been provided.

- *Batch analysis*

The results of batch analyses meet the specifications that were in effect at the time of testing and releasing.

Reference standards

A two-tiered reference standards consisting of a primary reference standards and a working reference standards have been established. These reference materials have been qualified for their purpose.

Container closure system

Sufficient description of the container closure has been provided. The container closure system is considered safe in terms of extractables and leachables.

Stability

The stability studies have been performed according to ICH Q5C. Considering the totality of stability data, the proposed shelf life for drug substance is considered acceptable.

2.1.2 Drug product

Fremanezumab drug product is supplied as a sterile solution for subcutaneous injection in a prefilled syringe. The excipients used for the fremanezumab finished product are L-histidine, L-histidine hydrochloride monohydrate, sucrose, EDTA, polysorbate 80, and water for injection.

Pharmaceutical Development

Compatibility of the drug product with the container closure system has been demonstrated

A history of drug product development has been provided. Drug product lots produced from different processes are comparable.

Manufacture

The manufacturing process of the drug product consists of two stages: manufacturing of the PFS and secondary packaging. The manufacturing process of PFS consists of drug substance pooling and mixing, filtration, aseptic filling, stoppering and visual inspection. The secondary packaging comprises the assembly, labeling, and packaging of the PFS.

- *Control of critical step and intermediate*

The CPPs and IPCs that control the critical steps have been provided.

- *Process validation/qualification*

The process validation has been performed using 3 consecutive production batches. Overall, the validation studies have demonstrated that the fremanezumab drug product manufacturing

process is robust.

The filters used in the filtration steps of manufacturing process have been validated.

The process of aseptic filling is validated by media fill.

Control of Drug Product

- *Specification*

The batch release testing of fremanezumab includes appearance, general test, identity, purity, potency, purity/impurities, and safety tests.

The proposed release specifications for the drug product are considered acceptable.

- *Analytical procedures*

Descriptions of all analytical methods and summaries of validations have been provided.

- *Batch analyses*

The results of batch analyses meet the specifications that were in effect at the time of testing and releasing.

Control of excipients

All excipients used are tested according to compendial methods and released with compendial specifications.

Reference materials

The reference standards used for drug substance and drug product are identical.

Container closure system

The container closure system consists of a 2.25ml type I glass syringe with a staked stainless-steel needle, a plunger- stopper and a needle shield. The specifications for the syringe, needle shield, and plunger-stopper are acceptable. Overall, sufficient details of each primary packaging component have been provided.

Stability of the product

The lots were placed on stability at long term, accelerated, and stressed conditions. The data from long-term stability studies can support the proposed drug product shelf life of 24 months at 2-8℃. The photostability according to ICH Q1B and temperature excursion studies have been performed. The results of photostability study demonstrate that the drug product should be protected from light.

Adventitious agents

The MCB and WCB which have been established are free from TSE-risk substances. No raw materials of animal origin are used in the manufacturing process for drug substance.

Mycoplasma, microbial and endotoxin are controlled at appropriate stages.

Based on the results of the virus clearance studies and retroviral like particles in unprocessed

bulk observed by TEM, the estimated safety margin for potential retroviral contamination per clinical dose is considered acceptable.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

The active ingredient of Ajovy is fremanezumab. CGRP is one of the most-studied neuropeptides in the migraine field and is found at the centers of migraine processes. Fremanezumab bound (using 2 different techniques) with similar high affinity to both human and monkey α/ β CGRP, rat β CGRP, and slightly lower affinity to rat and rabbit α CGRP. Fremanezumab inhibited cAMP production induced by CGRP binding to its receptor in vitro. On the other hand, fremanezumab did not bind to similar peptides such as amylin, calcitonin, intermedin, or adrenomedullin.

In vivo pharmacology studies in animal models of induced vasodilation indicated that fremanezumab prevents the increase in blood flow in rat paw skin and the middle meningeal artery after electrical stimulation and produces a dose-dependent inhibition of the capsaicin-induced skin flare response in monkeys. Fremanezumab had low bindings to human FcγR I, FcγR IIA, FcγR IIIA (158V and 158F), and FcγR IIIB. Safety pharmacology studies to evaluate potential cardiovascular effects were performed in monkeys. The data indicated no adverse fremanezumab-related findings on vital organs after single and repeated administration for up to 6 months via once-weekly administration at the highest dose examined. Irwin test and respiratory safety pharmacology studies were conducted in rats, and the data demonstrated that fremanezumab does not induce any effects following a single subcutaneous dose of up to the highest dose examined.

2.2.2 Toxicological Studies

In 3- and 6-month repeat-dose toxicity studies in rats and monkeys, no adverse fremanezumab-related changes were noted up to the highest dose examined. Anti-drug antibodies were detected in some animals. In 3-month repeat-dose toxicity studies in monkeys, eye and joint inflammation were observed, which may result from an immune-mediated reaction (a species-specific response due to immunogenic response to a humanized monoclonal antibody).

The reproductive and developmental toxicity was evaluated in rats (fertility, embryo-fetal development, and pre- and postnatal development) and rabbits (embryo-fetal development). No evidence of embryo-fetal toxicity was noted in any of the studies. The results revealed no fremanezumab-related effects on mating behavior, reproductive performance, and embryo-fetal survival and development at all tested dose levels. A carcinogenicity assessment of fremanezumab indicated that the carcinogenic potential of fremanezumab is low.

In addition to the injection site reaction observed in the repeat-dose toxicity studies, a

stand-alone local tolerance study in rabbits showed no adverse changes for the intra-arterial, intramuscular perivenous, subcutaneous, and intravenous routes of administration. Tissue cross-reactivity studies, cytokine release assay, or hemolysis test demonstrated no potential safety concern of fremanezumab under the experimental condition.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Fremanezumab is a fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand. Fremanezumab is indicated for prophylaxis of migraine in adults. The recommended dosage is 225 mg monthly or 675 mg every 3 months (quarterly) by subcutaneous administration.

After single subcutaneous administrations of 225 mg and 675 mg fremanezumab, median time to 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 53.8% and 57.2%, respectively. Dose proportionality, based on population pharmacokinetics, was observed between 225 mg to 900 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 2.3 and 1.2, respectively.

Fremanezumab has an apparent volume of distribution of approximately 6 liters, suggesting minimal distribution to the extravascular tissues. Similar to other monoclonal antibodies, fremanezumab is degraded by enzymatic proteolysis into small peptides and amino acids. The apparent clearance of fremanezumab was approximately 0.141 L/day. And fremanezumab was estimated to have a half-life of approximately 31 days.

Site of administration (abdomen, thigh and back of the arm) was not found to be a significant covariate of fremanezumab exposure based on population PK analysis.

2.3.2 Interaction Studies

Fremanezumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. The effects of medications for the acute treatment (specifically analgesics, ergots, and triptans) and preventive treatment of migraine were evaluated in a population PK model, and found not to influence fremanezumab exposure.

2.3.3 Special Populations

A population PK analysis assessing effects of age, race, sex, and weight was conducted on data from 2287 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 to131.8 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.

Exploratory analyses demonstrated no indication of reduced exposure to fremanezumab in patients who developed antibodies to fremanezumab (ie, were ADA positive). Due to the low occurrence of ADA formation, these results should be interpreted with caution.

Since monoclonal antibodies are not known to be eliminated via renal pathways or metabolized in the liver, renal and hepatic impairment are not expected to impact the pharmacokinetics of fremanezumab. Population pharmacokinetic analysis of integrated data from the fremanezumab clinical studies did not reveal a difference in the pharmacokinetics of fremanezumab in patients with mild to moderate renal impairment or mild hepatic impairment relative to those with normal renal or hepatic function. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) have not been studied. There were only 4 patients with moderate hepatic impairment, and no patient with severe hepatic impairment in fremanezumab clinical studies. No dedicated hepatic/renal impairment studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of fremanezumab.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Sponsor provided two Phase III studies (30049 and 30050) to support the efficacy of Ajovy solution for injection (Fremanezumab) for the claimed indication. The efficacy findings for two studies are summarized below.

- **Study [30049]**

Study 30049 was a phase III, 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the safety, tolerability, and efficacy of 2 dosing regimens of subcutaneous fremanezumab and placebo in adults (18 through 70 years of age) with chronic migraine (CM).

The primary efficacy endpoint was the mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug.

Results showed that 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 1st dose of study drug, for both fremanezumab doses, demonstrated statistically significant differences from placebo (Fremanezumab 675 mg/placebo/placebo vs. Placebo: LS mean difference: -1.8, 95% CI:-2.46, -1.15, p<0.0001; Fremanezumab 675/225/225 mg vs. Placebo: LS mean difference: -2.1, 95% CI:-2.76, -1.45, p<0.0001).

The secondary endpoints showed a consistent beneficial effect with treatment and indicated a clinically significant beneficial impact based on the aggregate improvement in all endpoints (Table 2.4.1-1).

Table 2.4.1-1 Results of the secondary efficacy endpoints (Study 30049, FAS)

Sequence	Endpoint	Hypothesis testing	p-value LS mean difference (95% CI)
1	Mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug	Fremanezumab 675/225 mg monthly vs placebo	p<0.0001 -1.8 (-2.61, -1.09)
2	Mean change from baseline (28-day run-in period) in the number of headache days of at least moderate severity during the 4-week period after the 1st dose of study drug	Fremanezumab 675/225 mg monthly and fremanezumab 675 mg quarterly vs placebo	p<0.001 -2.3 (-2.95, -1.73)
3	Proportion of patients with at least 50% reduction in monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug	Fremanezumab 675/225 mg monthly vs placebo	p<0.0001 Fremanezumab: 153 (40.8%) Placebo: 67 (18.1%)
4	Mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 -1.8 (-2.46, -1.15)
5	Mean change from baseline (28-day run-in period) in the monthly average number of use of any acute headache medications during the 12-week period after the 1st dose of study drug	Fremanezumab 675/225 mg monthly vs placebo	p<0.0001 -2.3 (-2.97, -1.67)
6	Proportion of patients with at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 Fremanezumab: 141 (37.6%) Placebo: 67 (18.1%)
7	Mean change from baseline (28-day run-in period) in the monthly average number of use of any acute headache medications during the 12-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 -1.8 (-2.43, -1.12)
8	Mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 -1.7 (-2.48, -0.97)
9	Mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose in patients not receiving concomitant preventive migraine medications	Fremanezumab 675/225 mg monthly vs placebo	p<0.0001 -2.0 (-2.86, -1.10)
10	Mean change from baseline (28-day run-in period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the 1st dose in patients not receiving concomitant preventive migraine medications	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 -1.8 (-2.68, -0.93)
11	Mean change from baseline (day 0) in disability score (HIT-6) at 4 weeks after administration of the 3rd dose of study drug	Fremanezumab 675/225 mg monthly vs placebo	p<0.0001 -2.4 (-3.32, -1.38)
12	Mean change from baseline (day 0) in disability score (HIT-6) at 4 weeks after administration of the 3rd dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p=0.0001 -1.9 (-2.90, -0.96)

- **Study [30050]**

Study 30050 was a phase III, 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the safety, tolerability, and efficacy of 2 dosing regimens of subcutaneous fremanezumab and placebo in adults (18 through 70 years of age) with episodic migraine (EM).

The primary efficacy endpoint was the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug.

Results showed that the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug for both fremanezumab doses, demonstrated statistically significant differences from placebo (Fremanezumab 675 mg/placebo/placebo vs. Placebo: LS mean difference: -1.3, 95% CI:-1.79, -0.72, p<0.0001; Fremanezumab 225/225/225 mg vs. Placebo: LS mean difference: -1.5, 95% CI:-2.01, -0.93, p<0.0001).
The secondary endpoints showed a consistent beneficial effect with treatment and indicated a clinically significant beneficial impact based on the aggregate improvement in all endpoints (Table 2.4.1-2).

Table 2.4.1-2 Results of the secondary efficacy endpoints (Study 30050, FAS)

Sequence	Endpoint	Hypothesis testing	p-value LS mean difference (95% CI)
1	Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug	Fremanezumab 225 mg monthly vs placebo	p<0.0001 Fremanezumab: 137 (47.7%) Placebo: 81 (27.9%)
2	Mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 -1.3 (-1.79, -0.72)
3	Mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 -1.6 (-2.22, -0.97)
4	Proportion of patients reaching at least 50% reduction in the monthly number of migraine days during the 12-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 Fremanezumab:128 (44.4%) Placebo: 81 (27.9%)
5	Mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug	Fremanezumab 225 mg monthly vs placebo	p<0.0001 -1.4 (-1.84, -0.89)
6	Mean change from baseline (28-day run-in period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the 1st dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p<0.0001 -1.3 (-1.76, -0.82)
7	Mean change from baseline (28-day run-in period) in the number of migraine days during the 4-week period after the 1st dose of the study drug	Fremanezumab 225 mg monthly vs placebo	p<0.0001 -1.8 (-2.43, -1.18)
8	Mean change from baseline (day 0) in disability	Fremanezumab 225 mg	p<0.0001

	score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug	monthly vs placebo	-7.0 (-10.51, -3.53)
9	Mean change from baseline (day 0) in disability score, as measured by the MIDAS questionnaire, at 4 weeks after administration of the last (3rd) dose of study drug	Fremanezumab 675 mg quarterly vs placebo	p=0.0023 -5.4 (-8.90, -1.93)
10	Mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications	Fremanezumab 225 mg monthly vs placebo	p<0.0001 -1.3 (-1.92, -0.70)
11	Mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug in patients not receiving concomitant migraine preventive medications	Fremanezumab 675 mg quarterly vs placebo	p=0.0002 -1.1 (-1.75, -0.54)

2.4.2 Safety Results

Major treatment-emergent adverse events are injection site reactions, including pain, induration, erythema and pruritus, and hypersensitivity. Because CGRP is a vasodilator, cardiovascular effects, including medication-induced hypertension are of potential safety concern with CGRP inhibition. Patients with certain major CV diseases were excluded from clinical trials, and the safety profile has not been explored in this population. Therefore, there is uncertainty about the potential CV risks of fremanezumab in these patients and the information should be adequately described in the label.

2.5 Bridging Study Evaluation

The bridging study evaluation of fremanezumab has been done. The effect of race on the PK of fremanezumab was assessed with healthy Japanese and Caucasian subjects with a single subcutaneous dose of fremanezumab at a dose of 225, 675, or 900 mg. The study result showed that, at each dose level, C_{max} and AUCs were similar for Japanese and Caucasian subjects. Both peak and overall exposures increased with increase in dose level. The T_{max} was also similar between Japanese and Caucasian subjects at the 225 mg (7 days) and 675 mg (5 days) dose levels, respectively, and comparable at the 900 mg dose level (11 and 7 days, respectively). The $t_{1/2}$, CL/F and V_z/F values were also similar across all dose levels and race/ethnic groups. Besides, no subject developed ADAs after fremanezumab administration.

In addition, the effect of race (Caucasian, Black, Asian, and other races) was not found to be a significant covariate in the population PK analysis.

There were few East Asian subjects enrolled in pivotal studies (9%), the sponsor supplemented the preliminary results of Japanese studies (406-102-00001, 406-102-00002 and 406-102-00003) in this NDA submission.

In Study 406-102-00001, 540 subjects of chronic migraine (from Japan and Korea) were randomized to fremanezumab 675 mg at Day 0 then 225 mg QM (675/225/225),

fremanezumab 675 mg at Day 0 then placebo QM (675 mg/PLB/PLB) or placebo treatment. The primary efficacy endpoint, mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period, was -4.12 days for fremanezumab 675/225/225 mg group, -4.14 days for fremanezumab 675 mg/PLB/PLB group and -2.45 days for placebo group; the difference from placebo was statistically significant for both fremanezumab groups (p=0.0002 for 675/225/225 mg and p=0.0001 for 675 mg/PLB/PLB by ANCOVA).

In Study 406-102-00002, 330 subjects of episodic migraine (from Japan and Korea) were randomized to fremanezumab 225/225/225 mg, fremanezumab 675 mg/PLB/PLB or placebo treatment. The primary efficacy endpoint, mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period, was -4.00 days for fremanezumab 225/225/225 mg group, -4.02 days for fremanezumab 675 mg/PLB/PLB group and -1.02 days for placebo group; the difference from placebo was statistically significant for both fremanezumab groups (p<0.0001 by ANCOVA).

The common TEAEs are injection site reactions such as erythema, hemorrhage, induration, pain, pruritus and swelling. The safety profile was apparently similar to that of global results. In summary, the efficacy results and safety profile in Asian population were comparable to those observed in overall population.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. Two adequate and well controlled clinical studies were provided with two proposed dose regimens to demonstrate the efficacy of fremanezumab for the prophylaxis of migraine in adults. The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required. In conclusion, the overall benefit/risk ratio is favorable to support regular approval of the claimed indications.

3. Post-Marketing Requirements

The sponsor should submit the results of the following studies once available.

(1) Submission of the study reports (or synopsis) of Japanese pivotal studies (406-102-00001, 406-102-00002 and 406-102-00003).
(2) Prospective pregnancy exposure cohort analyses requested by US FDA.

Routine pharmacovigilance should be conducted.