EU RISK MANAGEMENT PLAN

AJOVY (Fremanezumab)

RMP version to be assessed as part of this application	
RMP version number	6.0
Data lock point for this RMP	31 December 2023
Date of final sign off	23 January 2024
Rationale for submitting an updated RMP	RMP was updated to: • Reflect completion of the commitment, from Part III, to submit the final study report of the early terminated PASS TV48125-MH-50039 (cat 3), which was replaced by PASS TV48125-MH-40217 (cat 3) in the RMP v4.0

QPPV Details	
QPPV name:	Iva Novak
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy.
QPPV/deputy signature:	The signature is available on file.

Table 1: Summary of Significant Changes in this RMP Version

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part I Product(s) overview	RMP Version 5.0 (21 December 2023)	Not applicable
Part II - Module SI Epidemiology of the indication(s) and target population(s)	RMP Version 1.4 (31 January 2019)	Not applicable
Part II - Module SII Non-clinical part of the safety specification	RMP Version 1.4 (31 January 2019)	Not applicable
Part II - Module SIII Clinical trial exposure	RMP Version 2.0 (28 November 2019)	Not applicable
Part II - Module SIV Populations not studied in clinical trials	RMP Version 2.0 (28 November 2019)	Not applicable
Part II - Module SV Post-authorisation experience	RMP Version 5.0 (21 December 2023)	Not applicable
Part II - Module SVI Additional EU requirements for the safety specification	RMP Version 1.4 (31 January 2019)	Not applicable
Part II - Module SVII Identified and potential risks	RMP Version 4.0 (12 May 2023)	Not applicable
Part II - Module SVIII Summary of the safety concerns	RMP Version 3.0 (07 April 2022)	Not applicable
Part III Pharmacovigilance plan (including post-authorisation safety studies)	RMP Version 5.0 (21 December 2023)	Completion of the commitment to submit the final CSR of the early terminated PASS TV48125-MH-50039
Part IV Plans for post-authorisation efficacy studies	RMP Version 1.4 (31 January 2019)	Not applicable
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	RMP Version 5.0 (21 December 2023)	Not applicable

Part VI Summary of the risk management plan	RMP Version 5.0 (21 December 2023)	Not applicable
Part VII Annexes	RMP Version 5.0 (21 December 2023)	Update of Annex 2 to include the completed, early terminated PASS TV48125-MH-50039 Update of Annex 8 to reflect changes introduced to RMP v6.0

Other RMP versions under evaluation	
RMP Version number	Not applicable
Submitted on	Not applicable
Procedure number	Not applicable

Details of the currently approved RMP	
Version number	5.0
Approved with procedure	EMEA/H/C/004833/IB/0046
Date of approval (opinion date)	21 December 2023

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BW	Body Weight
CDEA	Chronic Disorder with Episodic Attacks
CGRP	Calcitonin Gene-Related Peptide
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CM	Chronic Migraine
CNS	Central Nervous System
CTD	Common Technical Document
CV	Cardiovascular
DNA	Deoxyribonucleic acid
e.g.	example given
ECG	Electrocardiogram
EFD	Embryo-Fetal Development
EFNS	European Federation of Neurological Societies
ELISA	Enzyme Linked Immunosorbent Assay
EM	Episodic Migraine
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
i.e.	Id est (engl.: that means)
ICH	International Conference on Harmonization
IFN	Interferon
IgG	Immunoglobulin G
im	Intramuscular
INN	International Non-proprietary Name

ISS	Integrated Summary of Safety
iv	Intravenous
KD	Equilibrium Dissociation Constant
MedDRA	Medical Dictionary of Regulatory Affairs
N	Number of patients
NOAEL	No Observed Adverse Effect Level
PASS	Post-Authorisation Safety Study
PIP	Paediatric Investigation Plan
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
sc	Subcutaneous
SMQ	Standardised MedDRA Query
SP	Safety Population (In Clinical Trials)
SPC, SmPC	Summary of Product Characteristics
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
US(A)	United States (of America)
WHO	World Health Organisation

Part I: Product(s) Overview

Table 2: Product Overview

Active substance(s) (INN or common name)	Fremanezumab
Pharmacotherapeutic group(s) (ATC Code)	Analgesics, calcitonin gene-related peptide (CGRP) antagonists (ATC code: N02CD03)
Marketing Authorisation Holder	TEVA GmbH Graf-Arco-Str. 3 89079 Ulm Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	AJOVY®
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Fremanezumab is a humanised monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.
	Summary of mode of action: 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.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indication(s) in the EEA	**Current (if applicable)**: AJOVY is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.
	Proposed (if applicable): Not applicable.

Dosage in the EEA	**Current (if applicable)**: AJOVY should be administered by subcutaneous injection. Two dosing options are available: • 225 mg once monthly (monthly dosing) or • 675 mg every three months (quarterly dosing)
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current (if applicable)**: Solution for injection. 225 mg fremanezumab.
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication:
AJOVY is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

Incidence:

Despite an abundance of studies on the prevalence of migraine, migraine incidence studies are surprisingly scant due to its challenging aspects; as a result relatively little is known about its incidence. Besides being uncommon many of the migraine incidence studies carry some methodological concerns or confined to selected age groups such as children and adolescents (Baykan et al, 2015).

Incidence rates for people under 30 years of age vary from 1.5 to 6 per 1000 person-years in men and from 3 to 24 per 1000 person-years in women (Manzoni et al, 2003). A 12-year follow-up Danish study of the general population (1989-2001) showed that the annual incidence of migraine in persons aged 25 to 64 years was 8.1 per 1000 person-years with a male:female ratio of 1:6 (Lyngberg et al, 2005). In both males and females, the incidence decreased markedly with age. Another study of adults 18 years and older reported a cumulative incidence of migraine headaches (with or without aura) of 8.8% between 1981-1994 (Swartz et al, 2000). These findings were in line with prior longitudinal study in young adults 21-30 years of age that found an incidence of 5.0 in males and 22.0 in females per 1,000 person years in the US (Breslau et al, 1994). A more recent population-based prospective longitudinal study in Turkey estimated migraine incidence in adults (18 years and older) as 2.38 % (2.98 % in women and 1.93 % in men) per year (Baykan et al, 2015).

Prevalence:

For adult populations, the estimates of migraine prevalence range from 3.3% to 21.9% for women and 0.7% to 16.1% for men in different studies (Lipton et al, 2005).

In a US population of 40,892 men, women, and children the migraine prevalence was found to be 8.6% (males), 17.5% (females), and 13.2% (overall) and showed a bimodal distribution in both sexes (peaking in the late teens and 20s and around 50 years of age) (Victor et al, 2010).

A meta-analysis of community-based studies involving 6 million participants to study the weighted average global prevalence of migraine found a prevalence of 13.8% in females, 6.9% in males, 11.2% in urban residents, 8.4% in rural residents, and 12.4% in students. The global migraine prevalence was found to be 11.6% (95% CI 10.7–12.6%; random effects); 10.4% in Africa, 10.1% in Asia, 11.4% in Europe, 9.7% in North America and 16.4% in Central and South America. The study result showed a pattern of rising global migraine prevalence (Woldeamanuel and Cowan, 2017).

Demographics of the population in the indication and risk factors for the disease:
Overall, the prevalence of migraine is highest from ages 25 to 55 years for both men and women (Lipton et al, 2005).

Female gender, school/college goers and urban residents decreasingly are more likely to be associated with migraine compared to male gender, rural residents and the overall population. Urban residents are 1.3 times more likely to have migraine compared to rural residents. Migraine is twice as common among females compared to males (Woldeamanuel and Cowan, 2017).

Chronic migraine (CM) affects 1-2% of the general population, and about 8% of patients with migraine; it usually develops from episodic migraine (EM) at an annual conversion rate of about 3%. The chronification is reversible: about 26% of patients with CM go into remission within 2 years of chronification. The most important modifiable risk factors for CM include overuse of acute migraine medication, ineffective acute treatment, obesity, depression and stressful life events. Midlife age, female sex and low household income are the most important nonmodifiable risk factors (May and Schulte, 2016; Buse et al, 2012).

The main existing treatment options:
The goals of migraine treatment are to relieve pain, restore function, reduce headache frequency, and prevent the progression of EM to CM. Pharmacological interventions for the treatment of migraine include acute (symptomatic) treatments and daily preventive medications. The latter is indicated for patients with CM as well as for a subset of individuals with EM who have frequent or very prolonged attacks, significant disability, or contraindications to acute therapy (Lipton and Silberstein, 2015).

In the European Union (EU), several treatment options are available for the prevention of migraine, which are either approved on a national level (mutual recognition/decentralised or national procedure) or used off label. Treatment availability and guidelines vary between EU member states (Antonaci et al, 2010, Decision Resources 2014, European Headache Federation 2007).

However, in 2009, the European Federation of Neurological Societies (EFNS) issued recommendations for prophylactic migraine medications based on scientific evidence from clinical trials and the consensus of the EFNS taskforce experts. First line treatment recommendations include 2 beta blockers (metoprolol and propranolol), 1 calcium channel blocker (flunarizine), and 2 anticonvulsants (topiramate and valproic acid) (Evers et al, 2009). Currently, onabotulinumtoxin A is the only therapy approved in some European countries for the prophylaxis of headaches in adults with CM who have responded inadequately or are intolerant to prophylactic migraine medications (Decision Resources 2014). The product failed multiple clinical studies for EM (Obermann and Diener 2009) and did not receive an indication for this disease state in Europe or elsewhere (Decision Resources 2014). This product is not consistently available in Europe because of the controversy of its benefit-risk profile, which restricted it to a second-line treatment.

Each of these medications has been established as effective in the prevention of migraine (or CM) (Aurora et al, 2010, Diener et al, 2010, Diener et al, 2002, Evers et al, 2009, Jackson et al, 2015, Silberstein 2000, Silberstein et al, 2012). However, burdensome titration schedules, the requirement for daily and sometimes twice daily dosing, side effects (tolerability issues) (BOTOX® Summary of Product Characteristics [SmPC] 2017, INDERAL® SmPC 2017,

TOPAMAX® SmPC 2017]), and delayed onset of efficacy and/or inadequate efficacy likely reduce long-term compliance and prompt many patients to discontinue these treatments (D'Amico and Lantéri-Minet 2006, D'Amico and Tepper 2008, Tfelt-Hansen and Olesen 2012).

Natural history of the indicated condition in the population, including mortality and morbidity:
Migraine is a chronic disorder with episodic attacks (CDEA). CDEAs are characterized by symptomatic attacks superimposed on an enduring predisposition to attacks. Migraine attacks may necessitate complete bed rest and interfere with occupational and educational functioning, ability to do household work and chores as well as family responsibilities, and social and leisure activities (Blumenfeld et al, 2011).

In more than 7% of migraineurs, the pain increases in frequency over time, leading to a high-frequency episodic migraine or, even worse, to a chronic disorder, when it occurs during at least 15 days per month for at least 3 months, with approximately 8 episodes per month (Pellesi et al, 2017).

CM is significantly more disabling than EM, impairing health-related quality of life and imposing a greater burden on the individual and the health care system. CM patients suffer from greater impairment in occupational, educational, family and social aspects of life, a poorer quality of life, more medical and psychiatric comorbidities, and greater perceived frustration and burden due to migraine compared to episodic migraineurs (Blumenfeld et al, 2011).

A systematic review and meta-analysis of studies investigating the association between any migraine or migraine subtypes and mortality evaluated the evidence on the association between migraine and mortality. This meta-analysis does not suggest that any migraine is associated with mortality from all-causes, cardiovascular heart disease, or coronary heart disease. However, there is heterogeneity among studies and suggestion that migraine with aura increases cardiovascular and coronary heart disease mortality (Schürks et al, 2011).

Important co-morbidities:
Migraine shows a wide spectrum of comorbidities, including cardiocerebral, vascular, psychiatric, metabolic, neurologic as well as other pathologies (Negro et al, 2010).

Migraine is highly co-morbid with a variety of psychiatric conditions. The strongest associations are between migraine, depression, and anxiety (Bergman-Bock, 2017).

Part II: Module SII - Non-Clinical Part of the Safety Specification

For the non-clinical development program, rats, rabbits and monkeys are considered relevant species.

Fremanezumab is a potent, CGRP binder that blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. Fremanezumab is highly specific for CGRP and does not bind to closely related family members amylin, calcitonin, adrenomedullin and intermedin.

CGRP is highly conserved between species and identical for humans and monkeys. Fremanezumab showed high specificity to human and monkey CGRP with binding affinity of

2.2-9.5 pM. The CGRP sequence is also highly similar for the rat, resulting in binding affinity of 740-889 pM. Additionally, the rabbit is considered a relevant species (KD ~530 pM).

Tissue cross-reactivity was in general similar between human, monkey, rabbit, and rat tissues, confirming the relevance of these species for the safety assessment. In both rats and monkeys animal models (e.g., electrical or capsaicin induced vasodilation), treatment with fremanezumab demonstrated efficacy.

Key safety findings from non-clinical studies and relevance to human usage are summarized below.

Toxicity

A comprehensive toxicological program, in accordance with the ICH M3 (R2) and ICH S6 (R1) guidelines was performed.

- Acute and repeat-dose toxicity studies:

  No mortality or morbidity was observed in any of the toxicological studies conducted following administration of high dose levels and frequent dosing, achieving high exposure. No target organs were identified or safety concern in any of the general toxicity studies.

  Perivascular inflammation around the ciliary vessel of the eye was observed in a few animals in the 3-month repeat dose toxicity study in monkeys, but no similar histological findings were noted after repeated administration at the same dose levels in a 6-month chronic toxicity study in monkeys (a longer duration study achieving higher exposure). Thus, this finding was considered incidental and not reproducible.

  The NOAEL in the 6-month repeat dose chronic toxicology study was 300 mg/kg/week, which was the highest dose tested for all repeat-dose toxicity studies, a dose that produces exposure at least 158-fold higher (based on AUC and Cmax) over the clinical exposure at 225 mg/patient monthly subcutaneous (sc) dosing.

- Reproductive/developmental toxicity:

  The reproduction and developmental toxicity package was evaluated in rats (fertility and embryo-fetal development (EFD), and pre- and postnatal development) and in rabbits (EFD). No evidence of embryofetal toxicity was noted in any of the studies. In addition, no treatment-related effects were noted on mating behavior, reproductive performance, and embryofetal survival and development at all tested dose levels.

  No toxicity was revealed in a pre-and postnatal development (PPND) study in rats.

- Genotoxicity:

  Genotoxicity studies were not conducted with fremanezumab, consistent with the ICH S6 (R1) guideline, which states that the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals.

- Carcinogenicity:

  According to the ICH S6 (R1) guideline (discussing the preclinical development of biotechnology-derived pharmaceuticals), standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals including monoclonal antibodies such as fremanezumab.

- Local tolerance in rabbits:

  No injection site reactions were observed following administration of fremanezumab at 150 mg/mL when compared to vehicle control via 5 alternate routes of administration (intravenous [iv], sc, intramuscular [im], paravenous and intra-arterial).

- Human Cytokine Release:

  Fremanezumab was tested for stimulation and release of pro-inflammatory cytokines in an exploratory non-Good Laboratory Practice (GLP) study in human whole blood. Fremanezumab did not elicit a significant cytokine release of tumor necrosis factor [TNF]-α, IL-6, interferon [IFN]-γ,) in any donor. In addition, fremanezumab is an IgG2 isotype, which is directed against a non-immunologic and soluble (not cell-bound) target and the risk of cytokine release is therefore considered to be low.

Safety Pharmacology

Consistent with the ICH S6 (R1) guideline, safety pharmacology parameters of fremanezumab were assessed in the pivotal toxicology studies, and in a separate GLP cardiovascular (CV) safety pharmacology study in male cynomolgus monkeys. The toxicology studies used both the iv and sc routes to support both possible modes of clinical administration, whereas the standalone cardiovascular safety pharmacology study used the iv route to achieve the highest exposure and to support other indications.

In addition, stand-alone studies in rats were conducted to evaluate the potential effects on the respiratory and CNS function following a single sc dose of 300 mg/kg.

These safety pharmacology studies (CV and respiratory rate in monkeys, CNS and respiratory in rats) revealed no potential for interference with critical body systems.

Immunogenicity

Fremanezumab is considered a weak immunogen in animals and only a few of the treated rats and monkeys developed Anti-Drug Antibodies (ADAs). The immunogenic response in a few animals in the 3-month toxicity study in monkeys via the sc route of administration was associated with a substantial decrease in systemic exposure. In addition, animals with an ADA positive response were noted at a high rate in control groups, casting doubt on the method specificity. Thus, a new and improved method for monkey serum samples was validated using a bridging Enzyme-Linked Immunosorbent Assay (ELISA) format which was used in the 6-month chronic toxicity study in monkeys.

Overall, the majority of the animals were not affected, allowing the successful completion of all repeat-dose toxicity studies. The immunogenicity results are important in understanding the kinetics and time related changes in the exposure and response in

animals, but are of very limited value regarding the clinical immunogenicity of fremanezumab since it is not predictive of human immunogenicity.

Conclusions

Fremanezumab has a robust pharmacological activity in both in vitro and in vivo models. Fremanezumab was well tolerated across all toxicological studies and showed a wide safety margin over clinical exposure. No toxicological concerns were identified following chronic dosing to experimental animals.

Ophthalmic events of at least moderate severity were observed as adverse events of special interest in the clinical phase 3 program based on the unconfirmed findings of mild peri-ciliary artery inflammation in a toxicity study in monkeys. However, no correlation between fremanezumab administration and ophthalmic adverse events in humans has been seen in the phase 3 studies.

″Use in pregnant women (including those at risk of pre-eclampsia)″ will be observed as missing information in the context of this RMP.

Part II: Module SIII - Clinical Trial Exposure

The evaluation of safety in the fremanezumab migraine development program focuses on 5 clinical studies comprising 2 Phase 2b studies (Study LBR-101-021 [hereafter referred to as Study 021], Study LBR-101-022 [hereafter referred to as Study 022]) and 3 Phase 3 studies (Study TV48125-CNS-30049 [hereafter referred to as Study 30049],
Study TV48125-CNS-30050 [hereafter referred to as Study 30050], and Study TV48125-CNS-30051 [hereafter referred to as Study 30051]), which were integrated into 7 cohorts as described below.

- **Cohort 1** (all patients in the placebo-controlled studies) (N=2563 [safety population]) included placebo-controlled studies in patients with EM and CM: Studies 021, 022, 30049, and 30050. The treatment groups summarized included placebo, 225 mg monthly, 675 mg quarterly, 225 mg monthly with a starting dose of 675 mg, 675 mg monthly, 900 mg monthly, and all fremanezumab.
- **Cohort 2** (all patients with CM in the placebo-controlled studies) (N=1393 [safety population]) included placebo-controlled studies in patients with CM: Studies 021 and 30049. The treatment groups summarized included placebo, 675 mg quarterly, 225 mg monthly with a starting dose of 675 mg, 900 mg monthly, and all fremanezumab.
- **Cohort 3** (all patients with EM in the placebo-controlled studies) (N=1170 [safety population]) included placebo-controlled studies in patients with EM: Studies 022 and 30050. The treatment groups summarized included placebo, 225 mg monthly, 675 mg quarterly, 675 mg monthly, and all fremanezumab.

- **Cohort 4** (all fremanezumab-treated patients) (N=2512 [safety population]) included all fremanezumab-treated patients with EM and CM: Studies 021, 022, 30049, 30050, and 30051. The treatment groups summarized included 225 mg monthly, 675 mg quarterly, 225 mg monthly with a starting dose of 675 mg, 675 mg monthly, 900 mg monthly, and all fremanezumab.
- **Cohort 5** (all fremanezumab-treated patients with CM) (N=1411 [safety population]) included all fremanezumab-treated patients with CM: Studies 021, 30049, and 30051 (patients with CM only). The treatment groups summarized included 675 mg quarterly, 225 mg monthly with a starting dose of 675 mg, 900 mg monthly, and all fremanezumab.
- **Cohort 6** (all fremanezumab-treated patients with EM) (N=1107 [safety population]) included all fremanezumab-treated patients with EM: Studies 022, 30050, and 30051 (patients with EM only). The treatment groups summarized included 225 mg monthly, 675 mg quarterly, 675 mg monthly, and all fremanezumab.
- **Cohort 7** (all patients in the pivotal studies) (N=2003 [safety population]) included patients in the placebo-controlled Phase 3 studies: Studies 30049 and 30050. The treatment groups summarized included placebo, 225 mg monthly, 675 mg quarterly, 225 mg monthly with a starting dose of 675 mg, and all fremanezumab.

Table 3: Number of Patients Included in Each of the 7 Integrated Cohorts (Safety Population)

Cohort: studies	Placebo	Fremanezumab					Total
	Monthly	225 mg monthly	675 mg quarterly	675/225 mg monthly[a]	675 mg monthly	900 mg monthly	
1: Studies 021, 022, 30049, and 30050	861	386	667	467	96	86	**2563**
2: Studies 021 and 30049	464	—	376	467	—	86	**1393**
3: Studies 022 and 30050	397	386	291	—	96	—	**1170**
4: Studies 021, 022, 30049, 30050, and 30051	—	551	1086	712	96	86	**2512**
5: Studies 021, 30049, and 30051	—	—	620	712	—	86	**1411**
6: Studies 022, 30050, and 30051	—	551	469	—	96	—	**1107**
7: Studies 30049 and 30050	668	289	667	379	—	—	**2003**

Source: Module 5.3.5.3, ISS Summary 5.1.1, ISS Summary 5.1.2, ISS Summary 5.1.3, ISS Summary 5.1.4, ISS Summary 5.1.5, ISS Summary 5.1.6, Study 30049 CSR Summary 15.1, and Study 30050 CSR Summary 15.1.

[a] Patients received fremanezumab at 225 mg monthly with a starting dose of 675 mg. Patients who received this dose in Study 30049 and rolled over to Study 30051 are summarized under this dose for both studies.

The clinical trial exposure presented below is based on cohort 4 which includes all patients with migraine who received at least 1 dose of study drug in the 2 Phase 2b and 3 Phase 3 studies.

The mean (SD) duration of exposure was 286.2 (145.71) days for the 2512 patients who received fremanezumab, total exposure in terms of patient-years was 1968.46, and the maximum patient exposure was 583 days. A total of 2290 patients (91%) received treatment with fremanezumab for ≥3 months (80% to 93% of patients in each treatment group), 1735 patients (69%) received treatment with fremanezumab for ≥6 months (64%, 80%, and 72% of patients in the 225 mg monthly, 675 mg quarterly, and 225 mg monthly with 675 mg starting dose treatment groups, respectively), and 1454 patients (58%) received treatment with fremanezumab for ≥12 months (54%, 67%, and 60% of patients in the 225 mg monthly, 675 mg quarterly, and 225 mg monthly with 675 mg starting dose treatment groups, respectively). In addition, the summary of exposure by the number of doses administered demonstrated that 93% of patients received ≥3 doses, 69% of patients received ≥6 doses, 61% of patients received ≥12 doses of study drug and 33% of patients received ≥15 doses of study drug.

Table 4: Study Drug Exposure by Treatment Group for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population)

Variable Statistic	Fremanezumab					
	225 mg monthly (N=551)	675 mg quarterly[a] (N=1086)	675/225 mg monthly[b] (N=712)	675 mg monthly (N=96)[c]	900 mg monthly (N=86)[c]	Total (N=2512)
Number of injections, n (%)						
≥1	551 (100)	1086 (100)	712 (100)	96 (100)	86 (100)	2512 (100)
≥2	527 (96)	1054 (97)	688 (97)	92 (96)	82 (95)	2425 (97)
≥3	504 (91)	1024 (94)	658 (92)	88 (92)	76 (88)	2332 (93)
≥4	370 (67)	917 (84)	543 (76)	0	0	1830 (73)
≥5	359 (65)	890 (82)	528 (74)	0	0	1777 (71)
≥6	353 (64)	867 (80)	511 (72)	0	0	1731 (69)
≥7	344 (62)	851 (78)	500 (70)	0	0	1695 (67)
≥8	335 (61)	831 (77)	490 (69)	0	0	1656 (66)
≥9	327 (59)	817 (75)	473 (66)	0	0	1617 (64)
≥10	322 (58)	804 (74)	465 (65)	0	0	1591 (63)
≥11	315 (57)	788 (73)	459 (64)	0	0	1562 (62)
≥12	309 (56)	778 (72)	448 (63)	0	0	1536 (61)
Duration of treatment (days)						
N	551	1086	712	96	86	2512
Mean	271.1	317.7	293.9	84.0	83.8	286.2
SD	151.62	129.32	141.97	16.06	13.78	145.71
25th percentile	88.0	257.0	120.5	84.0	84.0	96.0
Median	337.0	345.0	342.0	85.0	85.0	339.0
75th percentile	421.0	422.0	422.0	87.0	88.0	422.0
Min, max	1, 552	4, 583	1, 520	1, 134	22, 127	1, 583
Duration of treatment, n (%)[d]						
>0 month	551 (100)	1086 (100)	712 (100)	96 (100)	86 (100)	2512 (100)
≥1 month	547 (>99)	1078 (>99)	709 (>99)	94 (98)	85 (99)	2494 (>99)
≥2 months	528 (96)	1055 (97)	693 (97)	92 (96)	82 (95)	2432 (97)
≥3 months	489 (89)	1013 (93)	655 (92)	77 (80)	71 (83)	2290 (91)
≥6 months	355 (64)	869 (80)	510 (72)	0	0	1735 (69)
≥12 months	295 (53)	726 (67)	430 (60)	0	0	1454 (58)
Patient-years	409.02	944.72	572.91	22.09	19.73	1968.46

Source: RMP Ad Hoc Summary 1.4 (data extract 26 June 2019).

[a] Placebo doses at the applicable study visits are included in the number of doses.
[b] Patients received fremanezumab at 225 mg monthly with a starting dose of 675 mg. Patients who received this dose in Study 30049 and rolled over to Study 30051 are summarized under this dose for both studies.
[c] This dose was not administered in Study 30051. Thus, the maximum number of doses a patient in this treatment group could receive was 3.
[d] 1 month=28 days.
max=maximum; min=minimum; N=number of patients; n=number of patients observed; SD=standard deviation.

Table 5: Study Drug Exposure by Age Group and Gender for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population)

Age group	**Patients**		**Patient years**	
	M	**F**	**M**	**F**
Children and adolescents (0 to 17 years)	0	0	0	0
Adults (18 to 64 years)	319	2132	243.52	1670.29
Elderly people				
65-69 years	12	40	11.18	36.32
70-74 years	0	9	0	7.16
≥75 years	0	0	0	0
Total	**331**	**2181**	**254.70**	**1713.77**

Source: RMP Ad Hoc Summary Table 2.4 (data extract 26 June 2019).
F=Female; M=Male.

Table 6: Study Drug Exposure by Race Group/Ethnicity for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population)

	Patients	Patient years
Race group		
White	2023	1583.65
Black	240	157.01
Asian	200	200.53
Other	49	27.27
Total	**2512**	**1968.46**
Ethnicity		
Hispanic or Latino	256	164.85
Not Hispanic or Latino	2247	1796.87
Not Reported	5	4.16
Unknown	4	2.57
Total	**2512**	**1968.46**

Source: RMP Ad Hoc Summary Table 2.4 (data extract 26 June 2019).

Table 7: Study Drug Exposure by Special Populations for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population)

Special populations	Patients (N=2512) n (%)	Patient-years
Patients with cardiovascular medical history (patients with at least 1 finding)	**480 (19)**	**372.27**
Cardiac disorders SOC[a]	120 (5)	88.88
Investigations SOC[b]	35 (1)	27.49
Surgical and medical procedures SOC[c]	11 (<1)	8.74
Vascular disorders SOC[d]	361 (14)	278.54
Patients receiving cardiovascular medications at baseline	**359 (14)**	**268.92**
Agents acting on the renin-angiotensin system	108 (4)	70.88
Antihypertensives	9 (<1)	6.97
Beta blocking agents	161 (6)	117.70
Calcium channel blockers	58 (2)	47.05
Cardiac therapy	13 (<1)	9.50
Diuretics	76 (3)	53.79

Special populations	Patients (N=2512) n (%)	Patient-years
Peripheral vasodilators	1 (<1)	1.60
Patients with cardiovascular or cerebrovascular risk factor[e] (patients with at least 1 risk factor)	**1405 (56)**	**1084.64**
Patients using hormonal birth control pills[f]	457 (18)	347.26
Patients who are smokers[g]	15 (<1)	10.74
Patients with abnormal ECG[h]	4 (<1)	2.51
Patients with albuminuria[i]	1 (<1)	0.24
Patients with atrial fibrillation[j]	5 (<1)	3.79
Patients with diabetes mellitus[g]	43 (2)	30.53
Patients with hypertension[g]	260 (10)	193.83
Patients with impaired glucose tolerance[g]	15 (<1)	10.34
Patients with lipid metabolism disorders[g]	227 (9)	187.36
Patients with medical history for cardiovascular disease	443 (18)	341.28
Patients with obesity (BMI ≥30 kg/m^2)[k]	689 (27)	511.75
Patients with sleep apnea syndrome[l]	60 (2)	48.94
Patients with tachycardia[h]	17 (<1)	12.97
Patients using triptans	**1313 (52)**	**1229.53**

Source: Risk Management Plan Ad Hoc Summary 2.4, MAA Ad Hoc Summary 1.1, Ad Hoc Table 1.1.37 (97ii), MAA Ad Hoc Summary 1.4, Ad Hoc Table 1.1.40 (97ii), and Ad Hoc Table 1.1.43 (97ii).

[a] Includes PTs of mitral valve prolapse, tachycardia, palpitations, sinus bradycardia, bundle branch block right, arrhythmia, bradycardia, supraventricular tachycardia, ventricular extrasystoles, atrial fibrillation, mitral valve incompetence, atrioventricular block first degree, postural orthostatic tachycardia syndrome, tachycardia paroxysmal, angina pectoris, cardiac failure congestive, sinus tachycardia, supraventricular extrasystoles, Wolff-Parkinson-White syndrome, atrial tachycardia, atrioventricular block complete, bundle branch block left, cardiac pseudoaneurysm, cardiomegaly, coronary artery dissection, extrasystoles, intracardiac mass, mitral valve disease, myocardial infarction, myocardial ischaemia, pericarditis, right atrial dilatation, and ventricular tachycardia.

[b] Includes PTs of cardiac murmur, heart rate irregular, cardiac murmur functional, blood pressure increased, angiogram, arteriogram coronary, biopsy blood vessel, cardiac stress test normal, ejection fraction decreased, ECG QRS complex prolonged, and ECG abnormal.

[c] Includes PTs of cardiac ablation, atrial septal defect repair, atrial switch operation, and mitral valve repair.

[d] Includes PTs of hypertension, hot flush, Raynaud's phenomenon, varicose vein, hypotension, orthostatic hypotension, essential hypertension, peripheral venous disease, aortic dilatation, deep vein thrombosis, flushing, lymphoedema, peripheral coldness, thrombosis, aneurysm, aortic arteriosclerosis, arteriosclerosis, embolism, haemorrhage, hyperaemia, intermittent claudication, labile blood pressure, peripheral artery stenosis, phlebitis, poor peripheral circulation, prehypertension, and thrombophlebitis.

[e] Risk factor classification is based on references identified in the following table footnotes.

[f] American Heart Association 2014, Arboix 2015, Bier 2011, Edlow and Bartz 2010, Goldstein et al 2006, Hankey 2006, Khare 2016.

[g] Benjamin 2017, O´Donnell and Elosua 2008, World Health Organization 2007.

[h] Arboix 2015, Palatini and Julius 2004, World Health Organization 2007.

[i] Arboix 2015, World Health Organization 2007.
[j] Arboix 2015, Johansson et al 2017.
[k] Goff et al 2014, World Health Organization 2007.
[l] Arboix 2015.
BMI=body mass index; ECG=electrocardiogram; MAA=Marketing Authorisation Application; N=number of patients; n=number of patients observed; NC=not calculated; PT=preferred term; SOC=system organ class.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Pregnant females	Chosen for safety reasons. The impact on fetal development is not established.	Yes	Not applicable
Nursing females	Chosen for safety reasons. The impact on developing babies through breast milk is not established.	No	Due to the very low transfer of IgG to milk and the limited uptake in the gut of the suckling child, the risk to the breast-fed child is considered minimal.
Patients over 70 years of age	The pharmacokinetics and tolerability in patients over 70 years of age is not established.	No	Clinical trial data showed that there is no correlation between the incidence of adverse events and the age of the patients.
Patients below 18 years of age	The pharmacokinetics and tolerability profile in patients below 18 years of age is not established.	No	Patients below 18 years are not included in the proposed indication.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Patients with a body mass index (BMI) of less than 17.5 kg/m^2 and total body weight below 50 kg	To ensure a homogeneous patient group and avoid outliers in the study results.	No	Fremanezumab is not considered to be a narrow therapeutic index drug. The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
Patients with a body mass index (BMI) of more than 37.5 kg/m^2 and total body weight over 120 kg	To ensure a homogeneous patient group and avoid outliers in the study results. This pre-existing condition may confound the safety profile assessment of fremanezumab.	No	The safety profile in these patients is expected to be the same as in the populations studied in the clinical trials.
History of hypersensitivity reactions to injected proteins, including monoclonal antibodies	These patients may have altered immune response confounding the assessment of hypersensitivity to fremanezumab.	No	Hypersensitivity to the active substance will remain as contraindication.
Clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator	These pre-existing conditions may confound the safety profile evaluation of fremanezumab.	No	The benefit of fremanezumab in these patients is expected to be the same as in the populations studied in the clinical trials. An additional fremanezumab induced risk increase in those patients is not established.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator	These pre-existing conditions may confound the safety profile evaluation of fremanezumab.	No	The benefit of fremanezumab in these patients is expected to be the same as in the populations studied in the clinical trials. An additional fremanezumab induced risk increase in those patients is not established.
Hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase) >1.5 × the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfilled criteria for Hy's law at screening	These pre-existing conditions may confound the safety profile evaluation of fremanezumab.	No	Since clearance of fremanezumab is believed to occur via enzymatic proteolysis, hepatic impairment is considered unlikely to affect systemic exposure to fremanezumab.
Serum creatinine >1.5 × the ULN, clinically significant proteinuria, or evidence of renal disease at screening	These pre-existing conditions may confound the safety profile evaluation of fremanezumab.	No	Since clearance of fremanezumab is believed to occur via enzymatic proteolysis, renal impairment is considered unlikely to affect systemic exposure to fremanezumab.

Exclusion criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism	The purpose of this exclusion was to study patients whose primary medical concern was migraine and who were otherwise medically stable.	No	"Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension" will be observed as an important potential risk. Further data will be collected through a post authorisation safety study.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as very rare adverse reactions.

In the migraine development program (Cohort 4) a total of 1454 patients received treatment with fremanezumab for ≥12 months and a total of 700 patients received treatment for ≥15 months. There has been no opportunity to observe ADRs that might occur with prolonged exposure or prolonged latency.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 8: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Women who were pregnant were excluded from all clinical studies. 15 pregnancies with patients on fremanezumab had been reported in patients/subjects participating in studies that compose the migraine clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase) >1.5 × the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfilled criteria for Hy's law at screening were not included in the clinical development program.
• Patients with renal impairment	Patients with serum creatinine >1.5 × the ULN, clinically significant proteinuria, or evidence of renal disease at screening were not included in the clinical development program.
• Patients with cardiovascular impairment	A total of 480 patients (372.27 patient years) had a medical history with at least 1 cardiovascular finding (see Table 9).
• Immunocompromised patients	Not included in the clinical development program.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Population with relevant different ethnic origin</td><td>
<table>
<tr><th>Race group</th><th>Patients</th><th>Patient years</th></tr>
<tr><td>White</td><td>2023</td><td>1583.65</td></tr>
<tr><td>Black</td><td>240</td><td>157.01</td></tr>
<tr><td>Asian</td><td>200</td><td>200.53</td></tr>
<tr><td>Other</td><td>49</td><td>27.27</td></tr>
<tr><td>Total</td><td>2512</td><td>1968.46</td></tr>
</table>
<table>
<tr><th>Ethnicity</th><th>Patients</th><th>Patient years</th></tr>
<tr><td>Hispanic or Latino</td><td>256</td><td>164.85</td></tr>
<tr><td>Not Hispanic or Latino</td><td>2247</td><td>1796.87</td></tr>
<tr><td>Not Reported</td><td>5</td><td>4.16</td></tr>
<tr><td>Unknown</td><td>4</td><td>2.57</td></tr>
<tr><td>Total</td><td>2512</td><td>1968.46</td></tr>
</table>
</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development program.</td></tr>
</table>

Part II: Module SV - Post-Authorisation Experience

SV.1.1 Method Used to Calculate Exposure

Estimation of cumulative exposure from post-marketing sources was calculated based on data collected from Teva. Patient exposure was calculated in patient-years by using the monthly dose of 225 mg (twelve doses per year).

SV.1.2 Exposure

Estimation of Patient Exposure (Data Lock Point 13 March 2023)		
Period	**Monthly doses sold**	**Estimation of patient-years**
Cumulative	6,064,540	505,378

Source: Addendum to Clinical Overview No. 656/03/23 submitted and approved as part of the marketing authorisation renewal application (procedure EMEA/H/C/004833/R/0044).

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The potential for misuse for illegal purposes of fremanezumab is unlikely, given the mechanism of action and lack of penetration of the blood-brain barrier due to its large molecular size.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Summary of Safety Concerns in the initial approved RMP (version 1.4; approval date 28 March 2019)	
Important identified risks	• None
Important potential risks	• Severe hypersensitivity reactions • Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension
Missing information	• Long-term safety • Use in pregnant women (including those at risk of pre-eclampsia)

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Not applicable

Potential risks that do not impact the risk-benefit profile:

- Not applicable

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Not applicable

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Not applicable

Known risks that do not impact the risk-benefit profile:

- Injection site pain
- Injection site induration
- Injection site erythema
- Injection site pruritus
- Injection site rash

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Potential Risk:

Important Potential Risk	Risk-benefit impact
Severe hypersensitivity reactions	Severe hypersensitivity reactions are regarded as a potential risk for fremanezumab based on the following considerations: Type I hypersensitivity or allergic reactions (eg, shortness of breath, urticaria, anaphylaxis, angioedema) are theoretically possible with any injected protein, and type III hypersensitivity reactions may occur as a consequence of an antibody response to the injected protein, resulting in immune complex formation. Mild and moderate drug hypersensitivity events were observed in the clinical development programme but no anaphylaxis or severe hypersensitivity reactions were seen. However, it cannot be excluded that severe events may occur in the future.
Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension	Patients with significant cardiovascular disease were excluded from the fremanezumab clinical studies. In clinical studies there were no clinically relevant differences in cardiovascular adverse events between placebo and fremanezumab treated groups, regardless of the presence of cardiovascular medical history at baseline. However, due to the clinical trial exclusion criteria and that these comorbidities are rare in the migraine population, limited data are available in this patient group. CGRP is a potent vasodilator. Due to the theoretical concern of vasoconstriction with anti-CGRP drugs, the safety in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension will be observed as an important potential risk.

Missing Information

Missing Information	Risk-benefit impact
Long-term safety	In the migraine development program (Cohort 4) a total of 2,512 patients received at least 1 dose of fremanezumab with the mean (standard deviation [SD]) duration of exposure of 286.2 (145.71) days. A total of 1454 patients (58%) received treatment with AJOVY for ≥ 12 months. Based on available long-term data no potential long-term safety risks in humans have been identified.
Use in pregnant women (including those at risk of pre-eclampsia)	There is a limited amount of data from the use of fremanezumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure it is preferable to avoid the use of AJOVY during pregnancy. There is a theoretical concern that inhibition of CGRP effects could have adverse effects on the blood pressure and fetoplacental development in pregnancy. However, based on the events reported to date no potential risk in humans has been identified.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

“Severe hypersensitivity reactions” previously classified as an important potential risk was removed from the list of safety concerns in RMP v3.0.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Table 10: Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risks: None	
Important Potential Risk: Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension	
Potential mechanisms	Due to its mechanism of action CGRP inhibitors are considered as having a theoretical potential to increase the risk for hypertension/ hypertensive crisis, cardiovascular and cerebrovascular disease, as well as for peripheral arterial disorder. In this respect it is important to recognize, that patients with migraine per se have an increased risk for cardiovascular or cerebrovascular diseases. The conducted phase 2/3 studies allowed the inclusion of subjects with vascular risk factors. However, patients with a history of significant cardiovascular and cerebrovascular disease, as well as patients with a history of thromboembolic events had been excluded from trial participation.
Evidence source(s) and strength of evidence	Due to the clinical trial exclusion criteria limited data are available in this patient group. Based on the data on cardiovascular safety in clinical studies there is no clear trend or signal that suggests an increased risk of cardiac disorders in patients with fremanezumab. In clinical studies the safety profile of fremanezumab was comparable across age groups without specific safety signals for patients with cardiovascular risk factors.
Characterisation of the risk	Most cardiovascular events occurred in only 1 or 2 patients which accounts for less than 1% of the total population treated with fremanezumab. Palpitations were the only AE reported for 2% of patients (n=2) in the 675 mg monthly group but was not reported for patients in the fremanezumab 900 mg monthly group, making it less likely that there is a causative or dose-dependent relationship. However, patients with major cardiovascular disease were excluded from clinical studies, so no safety data is available for these patients. In patients with elevated systolic or diastolic blood pressure at baseline, there was a decrease in mean blood pressure in all treatment arms in all the double-blind studies with fremanezumab.
Risk factors and risk groups	Unknown
Preventability	Unknown
Impact on the risk-benefit balance of the product	The impact on the risk-benefit balance is currently considered to be not significant.
Potential public health impact of safety concern	The frequency and thus the number of possibly affected patients cannot be predicted.

Table 11: Presentation of the Missing Information

Missing information: Long-term safety	
Evidence source	In the migraine development program (Cohort 4) a total of 2,512 patients received at least 1 dose of fremanezumab with the mean (standard deviation [SD]) duration of exposure of 286.2 (145.71) days. A total of 1454 patients (58%) received treatment with AJOVY for ≥ 12 months and a total of 700 patients (28%) received treatment with fremanezumab for ≥ 15 months. Based on available long-term data no potential long-term safety risks in humans have been identified.
Population in need of further characterisation	Adult patients with migraine on long-term treatment with fremanezumab.
Missing information: Use in pregnant women (including those at risk of pre-eclampsia)	
Evidence source	There is a limited amount of data from the use of fremanezumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure it is preferable to avoid the use of AJOVY during pregnancy. There is a theoretical concern that inhibition of CGRP effects could have adverse effects on the blood pressure and fetoplacental development in pregnancy. However, based on the events reported to date no potential risk in humans has been identified.
Population in need of further characterisation	Pregnant women, infants exposed during pregnancy.

Part II: Module SVIII - Summary of the Safety Concerns

Table 12: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension
Missing information	• Long-term safety • Use in pregnant women (including those at risk of pre-eclampsia)

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires

Table 13: Description of Enhanced Routine PhV Activities

Areas requiring confirmation or further investigation	Proposed routine PhV activities	Objectives
Use during pregnancy and pregnancy/foetal outcomes	**Pregnancy follow-up questionnaire: "Standard Form for Initial and FU Post Marketing Pregnancy Report".** Specific questionnaire distribution will be triggered in case of spontaneously received pregnancy reports directly from healthcare professionals and patients/consumers. Follow-up questionnaire will be used to follow-up pregnancy outcome after expected delivery date. Evaluation of pregnancy reports will be done at PSUR intervals and presented in PSUR.	To follow-up and collect in more details information from spontaneous reports to further characterise this safety concern
Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension	**Specific cardiovascular follow-up questionnaire.** Follow-up questionnaire will be sent only to the stakeholders who have the knowledge/background to provide the information as requested in the questionnaire (see questionnaire in Annex 4 of the RMP). Trigger terms: • MedDRA SMQ (narrow) "Ischaemic central nervous system vascular conditions" • MedDRA SMQ (narrow) "Myocardial infarction"	To follow-up and collect in more details information from spontaneous reports to further characterise this safety concern.

III.2 Additional Pharmacovigilance Activities

Table 14: PASS summary table

Study short name and title		Rationale and study objectives	Study design	Study population	Milestones
1	Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Registry (Study TV48125-MH-50037)	The overall aim of this study is to assess major adverse maternal, fetal, and infant outcomes during pregnancy and up to 1 year after birth by comparing women exposed to AJOVY before or during pregnancy to comparison groups unexposed to AJOVY. The primary objective is to estimate the risk of major congenital malformations in infants of women exposed to AJOVY compared to the comparison groups unexposed to AJOVY. The secondary objectives are to estimate the risk of the following outcomes in women exposed to AJOVY and their infants compared to the comparison groups unexposed to AJOVY: • Minor congenital malformations • Pregnancy complications, including preeclampsia and eclampsia • Pregnancy outcomes, including spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and low birth weight • Other adverse outcomes, including postnatal growth and development abnormalities	Comparative, prospective observational Pregnancy Registry	Female patients with migraine aged 18-45 years	Submission of protocol to PRAC: 9 months after MAA approval Final report of study results: 12 months after end of data collection
2	Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Database Study (Study TV48125-MH-50038)	The objective of this study is to assess the risk of major congenital malformations, spontaneous abortions, stillbirths, preeclampsia, eclampsia, preterm delivery, low birth weight, and small-for-gestational age births in women exposed to AJOVY during pregnancy compared to comparison populations unexposed to AJOVY. The primary objective is to estimate the prevalence of major congenital malformations in women exposed to AJOVY during the first trimester of pregnancy compared to comparison groups unexposed to AJOVY during the first trimester of pregnancy. The secondary objectives are: • To estimate the prevalence of major congenital malformations in women exposed to AJOVY anytime during pregnancy compared to comparison groups unexposed to AJOVY anytime during of pregnancy;	Comparative observational cohort study	Female patients aged 15 through 49 years who had delivery of live-born infants, stillbirth, or spontaneous abortion and continuous health plan membership/ enrollment for at least 6 months prior to the estimated start of pregnancy and throughout pregnancy	Submission of protocol to PRAC: 9 months after MAA approval Final report of study results: 12 months after end of data collection

Study short name and title		Rationale and study objectives	Study design	Study population	Milestones
		• To estimate the prevalence of spontaneous abortions, stillbirths, preeclampsia, eclampsia, preterm delivery, low birth weight, and small-for-gestational age births in women exposed to AJOVY any time during pregnancy compared to comparison groups unexposed to AJOVY during the same time period.			
3	A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe (Study TV48125-MH-40217)	To collect additional long-term safety (LTS) data, including cardiovascular (CV) safety data, in patients with migraine treated with fremanezumab in a real-world setting using secondary data. The four primary objectives of this study are: • To compare the incidence of new onset of hypertension in patients treated with fremanezumab to other groups of migraine patients not treated with fremanezumab. • To compare the incidence of worsening of hypertension in patients treated with fremanezumab with pre-existing hypertension to other groups of migraine patients not treated with fremanezumab. • To compare the LTS of fremanezumab in patients with migraine without a history of hypertension or CV disease (CV uncompromised patients) to other groups of migraine patients not treated with fremanezumab. • To compare the LTS of fremanezumab in patients with migraine and a history of CV disease and/or hypertension (CV compromised patients) to other groups of migraine patients not treated with fremanezumab.	Long-term, multi-national (United States, Germany), observational, new-user comparative cohort study using secondary data from electronic healthcare records (EHR) and claims databases. EHR and claims data for the US, and claims data only for Germany will be used.	Patients with a diagnosis of migraine (including CV compromised patients) but without epilepsy, whose data were recorded in claims databases (US, Germany) and an EHR database (US).	Interim report: Q2 2025. Final report of study results: Q4 2027.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 15: Ongoing and Planned Additional Pharmacovigilance Activities

Study *(study short name, and title)* **Status** *(planned/ongoing)*	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Registry (Study TV48125-MH-50037) Status: Ongoing	The overall aim of this study is to assess major adverse maternal, fetal, and infant outcomes during pregnancy and up to 1 year after birth by comparing women exposed to AJOVY before or during pregnancy to comparison groups unexposed to AJOVY. The primary objective is to estimate the risk of major congenital malformations in infants of women exposed to AJOVY compared to the comparison groups unexposed to AJOVY. The secondary objectives are to estimate the risk of the following outcomes in women exposed to AJOVY and their infants compared to the comparison groups unexposed to AJOVY: • Minor congenital malformations • Pregnancy complications, including preeclampsia and eclampsia • Pregnancy outcomes, including spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and low birth weight • Other adverse outcomes, including postnatal growth and development abnormalities	• Use in pregnant women (including those at risk of pre-eclampsia)	Submission of protocol to PRAC	9 months after MAA approval
			Final report of study results	12 months after end of data collection

Study *(study short name, and title)* **Status** *(planned/ongoing)*	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Database Study (Study TV48125-MH-50038) Status: Ongoing	The objective of this study is to assess the risk of major congenital malformations, spontaneous abortions, stillbirths, preeclampsia, eclampsia, preterm delivery, low birth weight, and small-for-gestational age births in women exposed to AJOVY during pregnancy compared to comparison populations unexposed to AJOVY. The primary objective is to estimate the prevalence of major congenital malformations in women exposed to AJOVY during the first trimester of pregnancy compared to comparison groups unexposed to AJOVY during the first trimester of pregnancy. The secondary objectives are: • To estimate the prevalence of major congenital malformations in women exposed to AJOVY anytime during pregnancy compared to comparison groups unexposed to AJOVY anytime during of pregnancy; • To estimate the prevalence of spontaneous abortions, stillbirths, preeclampsia, eclampsia, preterm delivery, low birth weight, and small-for-gestational age births in women exposed to AJOVY any time during pregnancy compared to comparison groups unexposed to AJOVY during the same time period.	• Use in pregnant women (including those at risk of pre-eclampsia)	Submission of protocol to PRAC	9 months after MAA approval
			Final report of study results	12 months after end of data collection
A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe (Study TV48125-MH-40217) Status: Planned	The four primary objectives of this study are: • To compare the incidence of new onset of hypertension in patients treated with fremanezumab to other groups of migraine patients not treated with fremanezumab. • To compare the incidence of worsening of hypertension in patients treated with fremanezumab with pre-existing hypertension to other groups of migraine patients not treated with fremanezumab. • To compare the LTS of fremanezumab in patients with migraine without a history of hypertension or CV disease (CV uncompromised patients) to other groups of migraine patients not treated with fremanezumab.	• Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension • Long-term safety	Interim report	Q2 2025
			Final report of study results	Q4 2027

Study *(study short name, and title)* **Status** *(planned/ongoing)*	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
	• To compare the LTS of fremanezumab in patients with migraine and a history of CV disease and/or hypertension (CV compromised patients) to other groups of migraine patients not treated with fremanezumab.			

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 16: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
IMPORTANT IDENTIFIED RISK	
None	Not applicable
IMPORTANT POTENTIAL RISK	
Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension	**Routine risk communication:** Safety concern is addressed in the SmPC section 4.4 and in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
MISSING INFORMATION	
Long-term safety	**Other routine risk minimisation measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.
Use in pregnant women (including those at risk of pre-eclampsia)	**Routine risk communication:** Safety concern is addressed in SmPC section 4.6 and in PL section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation to avoid the use of fremanezumab during pregnancy in SmPC section 4.6 and in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Legal status: Medicinal product subject to restricted medical prescription.

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of Risk Minimisation Measures

Table 17: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT IDENTIFIED RISK		
None	Not applicable	Not applicable
IMPORTANT POTENTIAL RISK		
Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension	**Routine risk minimisation measures:** • SmPC section 4.4 • PL section 2 • Medicinal product subject to restricted medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific cardiovascular follow-up questionnaire. **Additional pharmacovigilance activities:** • A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe (Study TV48125-MH-40217) Final study report due date: Q4 2027
MISSING INFORMATION		
Long-term safety	**Routine risk minimisation measures:** • Medicinal product subject to restricted medical prescription	**Additional pharmacovigilance activities:** • A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe (Study TV48125-MH-40217) Final study report due date: Q4 2027
Use in pregnant women (including those at risk of pre-eclampsia)	**Routine risk minimisation measures:** • SmPC section 4.6 • PL section 2 • Medicinal product subject to restricted medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Pregnancy follow-up questionnaire: “Standard Form for Initial and FU Post Marketing Pregnancy Report”. **Additional pharmacovigilance activities:** • Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Registry. Final study report due date: 12 months after end of data collection • Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Database Study. Final study report due date: 12 months after end of data collection

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for AJOVY (fremanezumab)

This is a summary of the risk management plan (RMP) for AJOVY (herein after also referred to as fremanezumab). The RMP details important risks of AJOVY, how these risks can be minimised, and how more information will be obtained about AJOVY´s risks and uncertainties (missing information).

AJOVY's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how AJOVY should be used.

This summary of the RMP for AJOVY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of AJOVY´s RMP.

I. The Medicine and What It is used for

AJOVY is authorised for prophylaxis of migraine in adults who have at least 4 migraine days per month (see SmPC for the full indication). It contains fremanezumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of AJOVY's benefits can be found in AJOVY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/ajovy

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of AJOVY, together with measures to minimise such risks and the proposed studies for learning more about AJOVY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Updated Report (PSUR) assessment so that

immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of AJOVY is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of AJOVY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AJOVY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 18: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension
Missing information	• Long-term safety • Use in pregnant women (including those at risk of pre-eclampsia)

II.B Summary of Important Risks

Table 19: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important Identified Risks: None	
Important Potential Risk: Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension	
Evidence for linking the risk to the medicine	Due to its mechanism of action CGRP inhibitors are considered as having a theoretical potential to increase the risk for hypertension/ hypertensive crisis, cardiovascular and cerebrovascular disease, as well as for peripheral arterial disorder. Patients with a history of significant cardiovascular and cerebrovascular disease, as well as patients with a history of thromboembolic events had been excluded from trial participation. Due to the clinical trial exclusion criteria limited data are available in this patient group. Based on the data on cardiovascular safety in clinical studies there is no clear trend or signal that suggests an increased risk of cardiac disorders in patients with fremanezumab. In clinical studies the safety profile of fremanezumab was comparable across age groups without specific safety signals for patients with cardiovascular risk factors.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures • SmPC sections 4.4 • PL section 2 • Medicinal product subject to restricted medical prescription
Additional pharmacovigilance activities	• A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe
Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures • Medicinal product subject to restricted medical prescription
Additional pharmacovigilance activities	• A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe
Missing information: Use in pregnant women (including those at risk of pre-eclampsia)	
Risk minimisation measures	Routine risk minimisation measures • SmPC section 4.6 • PL section 2 • Medicinal product subject to restricted medical prescription
Additional pharmacovigilance activities	• Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Registry • Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Database Study

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of fremanezumab.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study name	Purpose of the study
Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Registry	The overall aim of this study is to assess major adverse maternal, fetal, and infant outcomes during pregnancy and up to 1 year after birth by comparing women exposed to AJOVY before or during pregnancy to comparison groups unexposed to AJOVY.
Assessment of pregnancy outcomes in patients treated with fremanezumab: Pregnancy Database Study	The objective of this study is to assess the risk of major congenital malformations, spontaneous abortions, stillbirths, preeclampsia, eclampsia, preterm delivery, low birth weight, and small-for-gestational age births in women exposed to AJOVY during pregnancy compared to comparison populations unexposed to AJOVY.
A Long-Term Observational, Retrospective Cohort Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice in the United States and Europe	The study aims to evaluate the incidence of new onset hypertension and the worsening of preexisting hypertension in patients treated with fremanezumab in addition to the long-term safety of fremanezumab in both cardiovascular compromised and cardiovascular uncompromised patients in comparison to migraine patients treated with other prophylactic migraine medication.

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Overview of included Follow-up Forms

• Pregnancy Follow-up Questionnaire: “Standard Form for Initial and FU Post Marketing Pregnancy Report”
• Fremanezumab Cardiovascular Follow-up Questionnaire

Standard Form for Initial and FU Post Marketing Pregnancy Report

(For mother, child and father exposure reports)

1. GENERAL DETAILS (for Teva internal use only)				
Source (multiple selection is allowed): ☐ Spontaneous; ☐ Solicited; ☐ Literature; ☐ Health Authority; ☐ Patient/Consumer; ☐ Other (specify)_____				
Report version: ☐ Initial ☐ Follow- up FU number:____	Safety Database ID# (LRN/ Arisg number):	Local reference number (for internal use only):	Receiver's Name:	Date Received by Teva group (DD-MMM-YYYY):

2. REPORTER DETAILS			
Reporter Type: ☐ Consumer/ non-Health care professional; ☐ Pharmacist; ☐ Physician; ☐ Other Health care professional; Occupation:_____			
Reporter Name:	Tel. No:	Address (includes country):	Does the company have the patient's permission to contact the reporter in the future for follow-up information? ☐ YES ☐ NO

3. PATIENT DETAILS					
Who does this report concern? ☐ MOTHER / ☐ CHILD*; Did Father take the Suspect product? ☐ YES* ☐ NO **Please complete section 5: PARENT DETAILS*					
Patient Initials:	Date of Birth (DD-MMM-YYYY):	Age:	Gender:	Weight:	Height:

4. RELEVANT PATIENT MEDICAL HISTORY / LABS	
Chronic diseases (i.e. diabetes, hypertension, asthma, etc.):	
Other diseases/ labs:	
Tobacco smoking:	☐ YES ☐ NO ; number of cigarettes per day:_____
Alcohol drinking:	☐ YES ☐ NO

5. PARENT DETAILS					
Parent:	Initials:	Date of Birth (DD-MMM-YYYY):	Age:	Weight:	Height:
Mother (please fill this section for child report only)					
Father (please fill this section for father exposure report only)					

6. PREGNANCY INFORMATION				
Is the patient still pregnant? ☐ Yes ☐ No	Last menstrual period date (DD-MMM-YYYY):	**Pregnancy Outcome** (multiple selection is allowed): ☐ Normal (No fetal anomaly) ☐ Live birth with fetal AEs ☐ Congenital Malformation ☐ Spontaneous abortion ☐ Induced abortion ☐ Elective Abortion ☐ Ectopic pregnancy ☐ Fetal death (stillbirth) ☐ Other:_____		
Number of fetuses:	Expected delivery date (DD-MMM-YYYY):	Delivery Date (DD-MMM-YYYY):	Child birth weight (kg):	Is the patient breast- feeding? ☐ Yes ☐ No If Yes, Start Date:_____ ; Stop Date: _____

In case of abnormal current pregnancy outcome, please complete section 7.

7. PREGNANCIES HISTORY INFORMATION (for past pregnancies)

Past pregnancies outcomes (number of pregnancies):

☐ Normal (____);
☐ Abortion(____); Specify:_____
☐ Birth defect/ Congenital abnormality; Specify:_____
☐ Fetal death (stillbirth); Specify:_____
☐ Other(____); Specify:_____

☐ Is there Family history of birth defects / congenital abnormalities? ☐ YES ☐ NO
Specify:_____

8. ADVERSE EVENT/ SPECIAL SITUATION DETAILS DURING /AFTER PREGNANCY						
Adverse Event (s):	Onset Date (DD-MMM-YYYY):	End Date (DD-MMM-YYYY):	Outcome*: *(please use the legend below)*	Serious ?	Seriousness criteria**: *(please use the legend below)*	Reporter Causality***: (please specify which suspect drug the causality concerns) *(please use the legend below)*
				☐ YES ☐ NO		Suspect Drug 1_____ Suspect Drug 2_____ Suspect Drug 3_____
				☐ YES ☐ NO		Suspect Drug 1_____ Suspect Drug 2_____ Suspect Drug 3_____
				☐ YES ☐ NO		Suspect Drug 1_____ Suspect Drug 2_____ Suspect Drug 3_____

***Outcome:** Recovered/ resolved =1; Recovering/Resolving =2; Not recovered/ not resolved =3; Recovered/ resolved with sequel =4; Fatal=5; Unknown =6.

****Seriousness criteria:** Death =1; Disability or permanent damage =2; Important Medical Event =3; Life threatening = 4; Congenital anomaly/Birth Defect =5; Hospitalization =6.

*****Causality:** Possible =1; Not related =2; Not assessable =3; Not reported =4.

9. SUSPECT DRUG(s) INFORMATION											
Brand Name:	Active Ingredient:	Admin Route:	Unit Dose:	Frequency:	Daily Dose:	Start Date (DD-MMM-YYYY):	Stop Date (DD-MMM-YYYY):	Batch No.:	Indication:	Trimester Exposed*: *(please use the legend below)*	Action Taken**: *(please use the legend below)*

***Trimester Exposed:** Stopped before conception =0; First =1; Second =2; Third =3 (it may be more than one trimester)

****Action Taken:** Dosage maintained=1; Drug discontinued =2; Dose increased=3; Dose reduced=4; Not applicable=5; Unknown=6.

10. CONCOMITANT / PAST DRUG(s) DETAILS						
Brand name:	Active ingredient:	Dosing regimen:	Start date:	Stop date:	Indication:	Action Taken:

11. NARRATIVE

12. LINKED CASES (i.e. Child-Mother, Twins, for use by LSO)

Appendix #1

List of definitions

Last menstrual period date[1] - Last menstrual period (abbreviation LMP): according to international consensus, the Gestational age is measured from the first day of the LMP.

Gestational age or length[1] - the duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed days or completed weeks (e.g. events occurring 280 to 286 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation).

Expected delivery date[2] - An estimate of the date on which a baby will be born. This is an arbitrary calculation based on a statistical average gestation period of 266 days, counted as 280 days from the date of the first day of the last menstrual period.

Congenital Malformation[1] - Congenital malformation: a morphological defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process.

Congenital abnormality[1] - Congenital abnormality (structural birth defect, sometimes congenital malformation, foetal defect): a consequence of error of morphogenesis, i.e. structural-morphological defect, grossly or microscopically present at birth whether detected at birth or not.

Spontaneous Abortion (miscarriage)[3,4] - Termination of pregnancy by expulsion of embryo/foetus before 22 weeks of gestation (measured from the first day of LMP – last menstrual period - or 20 weeks from conception) or below 500 grams of weight.

Termination of pregnancy[1] (induced abortion, elective abortion) - artificial interruption of pregnancy.

Ectopic pregnancy[1] - extrauterine pregnancy, early foetal death most often in the Fallopian tube.

Foetal death (stillbirth)[1] - (intrauterine death, in utero death): death prior to complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the foetus does not show any evidence of life (WHO ICD 10). Early foetal death (before 22 completed weeks of gestation) comprises ectopic pregnancy and miscarriage and late foetal death (after 22 completed weeks of gestation) is known as stillbirth.

Live birth[1] - the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy which, after such separation, breathes or shows any evidence of life.

Child birth weight[1] - the initial weight of the infant at birth.

[1]EMEA/CHMP/313666/2005 - Guideline on the Exposure to the Medicinal Products during Pregnancy (14-Nov-2005)

[2]http://medical-dictionary.thefreedictionary.com
[3]Definitions and Indicators in Family Planning Maternal & Child Health and Reproductive Health – World Health Organization – March 1999 & January 2001
[4] Reviewer Guidance: Evaluating the risk of drug exposure in human pregnancies; CDER/CBER (Apr. 2005)

Fremanezumab - Cardiovascular Follow-up Questionnaire

- Supplement to the (S)AE Form -

Date:..... Local Case#: [Case No.]

1. REPORTER INFORMATION:

Name and title:.....
Affiliation:.....
Address:.....
Phone number:..... e-mail:.....
.....Date.....

2. PATIENT INFORMATION:

Name/initials (*confidential*):..... Age... Date of Birth (dd/mm/yyyy)
Gender: ☐ M ☐ F Pregnant: ☐ Y ☐ N Weight.....kg/.....lbs

3. REPORTED DRUG INFORMATION

Product:..... Batch number:..... Exp. date (mm/yy):.....
.....
Exposure to Fremanezumab at the time the adverse event occurred: ☐ No ☐ Yes
Indication for which Fremanezumab was used:.....
.....
Fremanezumab dosage:.....
Therapy start date (dd/mm/yy):.....
☐ Therapy end date (dd/mm/yy):..... ☐ Ongoing
Dates of any previous Fremanezumab exposure prior to the current treatment: (dd/mm/yy):
.....
Action taken with Fremanezumab:
☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug withdrawn
If Drug stopped: Has there been any improvement after stopping Fremanezumab?
☐ Yes ☐ No ☐ Not applicable
If Drug stopped: Was Fremanezumab restarted after the adverse event?
☐ Yes ☐ No ☐ Not applicable
If yes, did the adverse event reappear after reintroduction of Fremanezumab?
☐ Yes ☐ No ☐ Not applicable

4. ADVERSE EVENT DATA

Reported event:.....
.....
List specific details (clinical presentation (incl. signs and symptoms), clinical findings, precise sequence of events and results of all assessments that support the diagnosis or the causality:
……
……
……
……

Event onset date (dd/mm/yy):..... Event end date (dd/mm/yy):.....
Fremanezumab exposure prior to onset of event:..... (days/months/years)
Did the patient experience any other adverse event? ☐ No ☐ Yes
If yes, please specify:.....

What was the severity of the event?
☐ Mild ☐ Moderate ☐ Severe
☐ Was the event life-threatening?
☐ Did the event result in death ?(Date of death (dd/mm/yy):)

Adverse event **treatment**: .....
v .....
Location of adverse event treatment
☐ home ☐ clinic, ☐ emergency room, ☐ hospital, ☐ other (please specify):……
……

Event outcome
If recovered/ resolved, please specify the time from onset of symptoms until recovery (in minutes, hours, or days): .....
If recovered with sequelae/ not resolved, please specify details:.....
.....
.....
If the outcome was **fatal**, please specify if the death was related to Fremanezumab:
☐ No ☐ Yes
Cause of death:.....

5. MEDICAL HISTORY / ADDITIONAL DETAILS

Patient history
Does the patient have any additional relevant (past/ concomitant) medical history? Please check all that apply and provide details:
☐ Myocardial infarction: .....
☐ Cerebrovascular accident: .....
☐ Transient ischemic attack: .....
☐ Unstable angina: .....
☐ Stable angina: .....
☐ Hypertension: .....
☐ Diabetes: .....
☐ Smoker: .....

Relevant laboratory/ diagnostic tests data

Test	Date (dd/mm/yy)	Result
Total Cholesterol		…… (mmol/L)
HDL Cholesterol		…… (mmol/L)
LDL Cholesterol		…… (mmol/L)
Systolic Blood Pressure		…….. (mm Hg)

Concomitant drugs

Did the patient take any relevant concomitant medications at the time when fremanezumab was used? ☐ No ☐ Yes

If yes, please provide the following information for each concomitant medication used in the patient's treatment:

Product Name (and active substance)	**Route of admin.**	**Posology** (dose; e.g. mg/kg, mcg)	**Drug Start Date** (dd/mm/yy)	**Drug Stop Date** (dd/mm/yy)	**Indication**	**Possible Causal relationship with the event?** (Yes/No)

Narrative (provide clinical presentation (incl. signs and symptoms), treatment provided and patient status at resolution of the event. If applicable, please provide discharge summary.

.....
.....
.....
.....
.....

6. COMMENTS

Contact details of the **specialist** to whom the patient was referred for further evaluation of the reported event(s):

Name:.....

Address:.....

Phone number:.....

Please give **any additional information** or comments you consider relevant and have not been covered by the questionnaire:

.....
.....
.....
.....
.....

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Not applicable.