31 January 2019
EMA/118499/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AJOVY

International non-proprietary name: fremanezumab

Procedure No. EMEA/H/C/004833/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibody
API	Active pharmaceutical ingredient
AR	Acceptable range
AUC	Area under the concentration-time curve
BA	Absolute bioavailability
BDS	Bulk drug substance
AMP	Cyclic adenosine monophosphate
CAPA	Corrective and preventive action
Cav	Average fremanezumab plasma concentration
CCS	Container closure system
CDC	Complement dependent cytotoxicity
CDR	Complementarity determining region
cGMP	Current Good Manufacturing Practice
CGRP	Calcitonin gene-related peptide
CHO	Chinese hamster ovary
CIPC	Critical in-process control
CL	Clearance
CL/F	Apparent clearance
CM	Chronic migraine
Cmax	Maximum drug concentration
CPP	Critical process parameter
CPV	Continued process verification
CQA	Critical quality attribute
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EM	Episodic migraine
EMEM	Eagle’s minimum essential medium
EPC	End-of-production cell
FBS	Fetal bovine serum
FcγR	Fc gamma receptors
FMEA	Failure modes and effects analysis
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IIV	Interindividual variability
INN	International Nonproprietary Name
IPC	In-process control
ISO	International Organisation for Standardization
Ka	Absorption rate constant

kDa	kiloDalton
LOQ	Limit of quantitation
mAb	Monoclonal antibody
MCB	Master cell bank
NA	Not applicable
nAb	Neutralising antibody
NMT	Not more than
NOR	Normal operating range
OC	Other concern
PD	Pharmacodynamic
PDE	Permitted daily exposure
PFS	Pre-filled syringe
Ph Eur	European Pharmacopoeia
PK	Pharmacokinetic
PP	Process parameter
PPK	Population pharmacokinetics
PPQ	Process performance qualification
PRS	Primary reference standard
PS80	Polysorbate 80
PTM	Post-translational modification
PV	Process validation
R	Accumulation ratio
SC	Subcutaneous
T1/2	Terminal half-life
TDI	Total daily intake
Tmax	Time to maximum drug concentration
TSE	Transmissible spongiform encephalopathy
USAN	United States Adopted Name
USP	United States Pharmacopoeia
V	Volume of distribution
VPC	Visual predictive check
WCB	Working cell bank
WFI	Water for injection
WRS	Working reference standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant TEVA GmbH submitted on 12 January 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for AJOVY, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: treatment of episodic and chronic migraine in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0308/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0308/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance fremanezumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 28 January 2016. The Scientific Advice pertained to the quality, non-clinical and clinical aspects of the dossier:

- **Quality**: methods to test comparability after process improvement; plans to control for excipient levels; analytical control strategy; container closure system; stability data to support shelf-life;

- **Non-clinical development**: overall agreement on the composition of the non-clinical package;

- **Clinical development**: need to conduct studies in patients with renal and hepatic impairment, drug-drug interaction studies and a dedicated QT/QTc study; plans to characterise immunogenicity; overall confirmatory trial strategy, including number of new pivotal trials to be conducted and size of the safety database; definition of a population potentially in need for prophylactic treatment; aspects of the protocols of the confirmatory studies: acceptability of primary and secondary endpoints (including PROs), dosing schedule, and comparator; protocol of the long-term follow-up study; statistical methods;.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Johann Lodewijk Hillege

The application was received by the EMA on	12 January 2018
The procedure started on	1 February 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	24 April 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 May 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 May 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 September 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanatio> to be sent to the applicant on	15 November 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 January 2019
The CHMP, in the light of the overall data submitted and the scientific	31 January 2019

discussion within the Committee, issued a positive opinion for granting a marketing authorisation to AJOVY on	

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Migraine is a neurological disorder, characterized by recurrent episodes of headaches, accompanied by associated symptoms such as nausea, vomiting, photophobia and phonophobia. The headache is often unilateral, of moderate to severe intensity, throbbing and aggravated by physical activity. An attack can be preceded by sensory warning symptoms or signs (auras), and may last for 4-72 hours. The attacks are often disabling and associated with missed activities at work, school or at home.

Migraine is conceptualized as a spectrum disorder with two categories: episodic migraine (EM) and chronic migraine (CM). EM is characterized by acute headache attacks. EM accompanied by aura is called classical migraine. Individuals with EM experience headaches on less than 15 days per month whereas CM is characterized by more than 15 headache days per month, with at least 8 days being migraine days.

2.1.2. Epidemiology

Migraine is a common neurological disorder that affects more than 10% of adults globally. The proportion of adults reporting migraine attacks in a single year is 15% in both Europe and the United States. Women are affected three times more often than men. The prevalence is highest during the peak performance years (around 30 to 50 years of age), which provides a significant burden to the sufferer, family and society. Patients with EM progress to CM at a yearly rate of around 2.5%.

2.1.3. Aetiology and pathogenesis

The calcitonin gene-related peptide (CGRP) is a neuropeptide that seems to be involved in the pathophysiology of neurovascular headaches such as migraine at both central and peripheral levels. It is extensively distributed at the trigeminal nerve endings and the trigeminal ganglion. At the peripheral level the release of CGRP leads to vasodilation and inflammation and it modulates the transmission of pain. It was shown that interictal CGRP levels are elevated in peripheral blood in both EM and CM patients. These levels were higher in CM patients.

In clinical research, small molecule CGRP receptor antagonists were initially investigated against the CGRP pathway for migraine treatment. However the molecules were found to be hepatotoxic in several studies, which led to the switch to the development of monoclonal antibodies (mAB) against the CGRP ligand or receptor. mABs bind specific to the target, have long half-lives and are not metabolized by the liver, leading to better treatment compliance and low risk for liver enzyme elevations.

2.1.4. Clinical presentation, diagnosis

Migraine is a disorder of recurrent headache attacks. A typical attack progresses through four phases. There is a prodromal phase, characterized by the presence of affective or vegetative symptoms that appear 24 to 48 hours prior to headache onset. This phase can be followed by the aura, in which one or more focal neurological symptoms are present. Though this phase does not occur in every patient, and does not necessarily have to

precede the headache, some patients experience the aura and headache combined. The headache is characterized by an often unilateral and throbbing/pulsating pain which can be accompanied by symptoms such as nausea, vomiting, photophobia or phonophobia. Once the spontaneous throbbing of the headache resolves, in the postdromal phase, the patient experiences feeling drained or exhausted or sometimes even mild elation or euphoria.

Several factors may trigger a migraine attack such as (emotional) stress, hormone levels (related to the menstrual cycle in women) or sleep disturbances.

Migraine is diagnosed based on the diagnostic criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3). A patient must have had at least 5 headache attacks that lasted 4-72 hours (untreated or unsuccessfully treated). These headaches must fulfil at least two of the following criteria: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity. During the headache at least one of the following symptoms should occur: nausea/vomiting or both, or photophobia and phonophobia.

Migraine has also been associated with ischaemic stroke and ischaemic heart disease, in particular in women and patients with aura.

Long term prognosis of migraine varies. Symptoms can gradually decrease over the years or resolve completely, they can continue with the same frequency and severity or become worse and more frequent.

2.1.5. Management

Migraine treatment can be subdivided into two categories: acute medication and prophylactic medication.

Acute medication is aimed to relieve pain and restore function during upcoming acute headache attacks. Typically used agents are non-steroidal anti-inflammatory drugs (NSAIDs), triptans with or without concomitant antiemetics.

Prophylactic treatment is intended to prevent the occurrence of attacks / headache. Several migraine prophylactic treatments are available in the European Union, though the approval varies between member states. It is recommended by the European Federation of Neurological Societies (EFNS) that first-choice prophylactic treatment are either beta-blockers (metoprolol and propranolol), calcium channel blockers (flunarizine) or anticonvulsants (topiramate and valproic acid).

Botulinum toxin A is currently the only treatment approved in some member states (including NL) for migraine prophylaxis in adults with CM who have responded inadequately or are intolerant to other prophylactic medication.

Epidemiology studies suggest that only a small proportion of patients that are candidate for prophylactic treatment currently take preventative medication. Moreover patients often switch prophylactic medication. This is likely due to the combination of titration schedules, requirement of daily dosing, side effects and delayed onset of efficacy affecting long-term compliance and/or insufficient long term efficacy.

About the product

Fremanezumab , the active substance in Ajovy, is a fully humanized immunoglobulin G2 (IgG2) Δa monoclonal antibody (mAb) derived from a murine precursor. Fremanezumab is a potent, selective calcitonin gene-related peptide (CGRP) mAb that binds to and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. Ajovy is presented in a pre-filled syringe for subcutaneous administration.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a solution for injection containing 225 mg of fremanezumab as active substance. Other ingredients are: L-histidine, L-histidine hydrochloride monohydrate, sucrose, disodium ethylenediaminetetraacetic (EDTA) acid dihydrate, polysorbate 80 and water for injections.

The product is available in a type I glass syringe with plunger stopper (bromobutyl rubber) and needle.

2.2.2. Active Substance

General Information

Fremanezumab is a monoclonal IgG2 antibody targeting both isoforms of calcitonin gene-related peptide (CGRP; α- and β-CGRP). Fremanezumab is produced in CHO cells and is N-glycosylated at position Asn298 at the heavy chain. O-glycosylation has not been reported.

Fremanezumab is comprised of two identical light chains and two identical heavy chains. Each light chain consists of 214 amino acid residues, while each heavy chain is predicted to contain 448 residues. There are a total of 36 cysteine residues in the molecule with the potential to form disulfide bonds. The C-termini of the heavy chains are primarily of the des-Lys form, which is typical of IgG molecules expressed in the Chinese hamster ovary (CHO) cell line. As such, the heavy chain actually consists of 447 residues. The molecular weight is 148 kDa.

Manufacture, process controls and characterisation

Celltrion Inc, Incheon, South Korea is responsible for manufacture and testing of the active substance.

The active substance is manufactured according to current Good Manufacturing Practices.

Description of manufacturing process and process controls

The active substance manufacturing process reflects a standard process for monoclonal antibodies. The upstream cell culture process consists of three consecutive stages (inoculum expansion, seed bioreactor expansion, and cell culture and antibody production). The upstream process ends with a bioreactor harvest and clarification step. The antibody is subsequently purified and polished using standard chromatography techniques, virus inactivation, viral filtration, and ultra-/diafiltration. The downstream process ends with the final formulation and final filtration.

An adequate batch numbering system is in place.

The applicant described the control strategy, which takes the principles laid out in ICH Q8-11 into account. Process parameters (PP) and in-process controls (IPCs) are divided into critical (i.e. CPP and CIPC) and non-critical ones.

Reprocessing is described for the virus reduction filtration step and for the final filtration step, sufficient information on the handling of a reprocessing event has been provided.

Control of materials

The applicant provided adequate information regarding the raw materials used during the manufacturing of the active substance. Compendial substances are released according to their pharmacopeial requirements. Acceptance criteria and test methods for non-compendial materials have been provided. Adequate information on the control of chromatography resins is provided.

No materials of human or animal origin are used in upstream, cell culturing, and downstream manufacturing process. Foetal bovine serum (FBS) was used in the early phase of fremanezumab cell line development. The master cell bank (MCB) and working cell bank (WCB) have been stored and cultivated in FBS-free medium.

The fremanezumab expression vector is derived from a humanized hybridoma clone. Manufacturing of the MCB and WCB has been described and was performed under GMP conditions.

Stability of the MCB and WCB has been demonstrated with regard to cell viability and growth characteristics. The MCB, WCB, and end of production cells (EPCs) have been tested in line with ICH Q5A. With the exception of the retrovirus particles and reverse transcriptase activity in EPCs, no adventitious agents were detected. The MCB has been tested for sterility, bacteriostasis and fungistasis, mycoplasma, and mycoplasmastasis.

Genetic stability of the cell banks has been addressed in line with ICH Q5B.

A procedure for generation of new working cell banks has been described.

Control of critical steps and intermediates

The CPPs, IPCs and CIPCs listed for the critical steps and intermediates are considered acceptable to control that the manufacturing process is capable of consistent and robust production of active substance meeting the fremanezumab critical quality attributes (CQAs). The limits defined for the bioburden and endotoxin levels are considered acceptable. The microbial control tests (bioburden and endotoxin) have been verified according to the respective compendia.

No intermediates are defined. In process hold times are included in the manufacturing process description.

Process validation

Manufacturing process validation was performed using three consecutive process verification lots for the active substance manufactured with the commercial process. Additionally three further active substance lots have been run as backup, which were terminated at earlier manufacturing steps. Results have been reported as supporting data. Media solution hold times have been validated. Overall, the upstream manufacturing process can be considered robust and validated.

During process verification all acceptance criteria for PPs and CPPs, as well as endotoxin levels have been met for the buffers used during downstream manufacturing.

The down-stream manufacturing process steps met all process verification acceptance criteria and demonstrated that the process can be executed in a robust and consistent manner.

The provided data support the in process hold duration and temperature for the different active substance manufacturing steps up to and including excipient addition. The final filtration and filling step was shown to be robust and consistent. All acceptance criteria have been met.

Biochemical and microbial stability data for the intermediate pool holds have been provided. Additionally, a worst case study was performed, which demonstrated that the maximal allowed hold time does not affect the tested active substance intermediate QAs. The proposed target numbers of chromatograph resin cycles are supported by small scale validation studies. It is agreed that the manufacturing scale resin lifetime study is on-going concurrently with clinical and commercial manufacturing. As stated in the dossier "If the resin lifetime

study extends beyond the manufacturer's expiration date, the maximum use period will be defined as the period from the resin manufactured date to the study end date." This is considered acceptable.

Small-scale and large-scale chromatography carry over studies have been completed or are concurrently performed, respectively. The results verify the resin cycle numbers. The approach used to monitor TFF membrane performance gives no reason for concern.

In support of the proposed reprocessing for the virus filtration step and the final filtration step, small scale validation studies are performed. No negative effect on product quality was observed in these studies. Full scale validation on a total of 3 batches will be performed if a manufacturing event necessitates reprocessing. The provided study protocol summary is acceptable.

A risk assessment for the leachables from the single-use (SU) equipment used during up- and down-stream active substance manufacturing has been performed. Medium risk components were further analysed in worst-case leachable studies. An ongoing process verification program has been implemented for the fremanezumab lifecycle.

Manufacturing process development

The manufacturing process of fremanezumab active substance has been improved during development from process 1 (1P) over 2P to the proposed commercial process 3P. The changes included scale-ups and a manufacturing site transfer.

The evaluation of comparability between 3P and 1P/2P consists of a comparison of the results of multiple tests to determine relevant product attributes (primary structure, molecular mass, secondary/higher order structure, post-translational modifications, biological activity, purity and impurities). Three 3P lots, 1 2P lot, and 1 1P lot were included in the comparison. The comparability assessment is limited in terms of number of batches that are included, but the test panel is acceptable and the results give no reason for concern. The phase 3 clinical trial has been performed with batches manufactured according to process 3P. Only minor changes are made from clinical manufacturing to process verification.

The upstream and downstream process characterisation has been described.

The PP acceptable ranges (AR) are considered acceptable. For the production bioreactor the impact of PP on product QAs and process performance attributes have been investigated. Appropriate analyses have been performed and IPCs, CIPCs and PP ranges defined.

Characterisation

A range of state-of-the-art orthogonal methods has been employed to characterise fremanezumab active substance. The primary structure, higher order structures, and the biological activity of fremanezumab were evaluated using a series of biochemical, biophysical and functional characterisation techniques.

Primary structure:

The primary structure was evaluated and 100% coverage was achieved confirming the predicted cDNA-derived primary sequence. Disulfide bonding was analysed and confirmed structural intactness of the fully bonded molecule with low levels of free thiols.

Higher order structure:

Analyses demonstrated the common mAb secondary structure distribution (mainly β-sheets, and random coils and lower amounts of α-helices, bends, and turns) of fremanezumab. Fremanezumab was shown to be temperature stable and shows three temperature transitions. A comprehensive crystal structure analyses has been performed to determine the epitope/paratope interactions between fremanezumab and its antigen CGRP.

Biological activity:

The biological activity of fremanezumab was appropriately characterised. Binding of fremanezumab to CGRP was demonstrated to be highly specific.

Analyses were performed to determine the binding affinities of fremanezumab to Fcγ-Receptors.

C1q binding (initial step CDC) was determined for fremanezumab, and shown to be negligible.

ADCC activity was not analysed for fremanezumab. This is considered acceptable because the antibody belongs to the IgG2 family and did not show significant Fcγ-RIII binding. Furthermore, fremanezumab binds to a soluble antigen, which makes a potential ADCC activity more unlikely.

Post-Translational Modifications (PTM):

Fremanezumab contains commonly seen PTMs. These are not considered to represent a safety issue as they are naturally occurring in humans.

The glycosylation pattern was shown to be similar to that commonly seen for mAbs.

Overall the characterisation of fremanezumab is considered acceptable. The process-related impurities are sufficiently described and controlled.

The applicant has appropriately characterised the active substance and product variants, and elucidated degradation pathways by forced degradation.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The control tests proposed for the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial).

The specifications for the release of the active substance are adequately justified based on release and stability data. For some parameters the applicant has committed to re-evaluate the limits when data from further batches become available.

Analytical methods

Descriptions of all analytical methods and summaries of validations thereof are provided.

The validation of the analytical procedures has been performed taking the recommendation of ICH guideline Q2 (R1) into account. The compendial tests have been validated according to their respective monographs.

For potency determination a cell-based bioassay is used. Neuroblastoma cells are cultivated in the presence of CGRP which induces cAMP formation. Addition of active substance samples (fremanezumab) prevents CGRP binding thereby inhibiting cAMP formation. Intercellular cAMP is fluorescently measured as read-out.

Batch analysis

A sufficient number of fremanezumab active substance batches have been produced. Adequate information on every batch (date of manufacturing, manufacturer/process, cell bank and use) has been provided. All batches met the acceptance criteria in place at the time of manufacturing. The batch results of the active substance batches manufactured with the proposed commercial formulation at the GMP manufacturing facility at Celltrion, Yeonsu-gu, Incheon, Republic of Korea indicate that the manufacturing process is robust.

Reference materials

During early development an interim reference standard was established. It was used as reference standard for Phase 1-3 clinical lot release and stability. During clinical Phase 3 development a two-tiered system has been established. A Phase 3 manufacturing process lot was used to create the primary reference standard (PRS). Characterisation demonstrated that the PRS is representative of batches produced under the proposed commercial manufacturing process. As a second part of the two-tiered system the working reference standard (WRS) derived from a commercial manufacturing process and process verification lot was established. The WRS was characterised side-by-side with the PRS. The results demonstrated high comparability between both standards and qualify WRS to be used as reference for commercial lot release and stability testing. Stability of

the reference standards will be monitored by predefined stability protocols. After the PRS has expired a new PRS will be qualified against the current PRS. New WRS will be qualified against a current PRS.

Container closure

The active substance is stored in carboys, with a screw cap. Sufficient description of the container closure and applied specifications has been provided. The CCS is considered safe in terms of extractables and leachables.

Stability

The active substance stability program used long-term, accelerated and stressed storage conditions as defined in ICH Q5C. Data from a sufficient number of primary and supportive stability lots have been provided. The data provided did not show significant changes in the quality attributes tested.

Considering the totality of data from primary and supportive batches, the proposed active substance shelf-life is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is provided as a solution for injection in a pre-filled syringe. The composition is shown in Table 2 below.

Sufficient information is provided on the control of excipients. The excipients used for the fremanezumab finished product are L-histidine, L-histidine hydrochloride monohydrate, sucrose, EDTA, polysorbate 80, and water for injection. All excipients are Ph. Eur. grade. No novel excipients or excipients of human or animal origin are used.

Table 1 Finished product composition

Component	Quality standard	Function
Fremanezumab	In house[a]	Active ingredient
L-histidine	JP, Ph Eur, USP	Buffering agent
L-histidine hydrochloride	JP, Ph Eur	Buffering agent
Sucrose	JP, NF, Ph Eur	Stabilizing and tonicifying agent
Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate	JP, Ph Eur, USP	Chelating agent
Polysorbate 80	JP, NF, Ph Eur	Interfacial stabilizer
Water for Injection	JP, Ph Eur, USP	Aqueous solvent

An overfill is applied to ensure each syringe can consistently meet a target label claim of 1.5 mL.

The finished product formulation is identical to the active substance formulation (150 mg/mL fremanezumab; histidine; sucrose; EDTA; PS80 at pH 5.5).

Compatibility of the finished product with the container closure system has been investigated in syringes at the recommended, accelerated and stressed conditions. The results demonstrated that under the recommended storage conditions the quality attributes did not change.

A controlled extraction and a simulation study have been performed to evaluate extractables and leachables, which might leak into the finished product under harsh and more realistic conditions, respectively. The results demonstrate that the most of the detected compounds or impurities are below the Product Quality Research Institute (PQRI) Parental and Ophthalmic Drug Product (PODP) working group's qualification threshold (QT). The compounds and impurities above that threshold have been further evaluated taking the recommendations of ICH Q3C and Q3D into account. The calculated worst-case exposures are well below the calculated permitted daily uptakes (PDE). Tungsten and Silicone have been further analysed for their effect on finished product quality attributes using spiking studies. No effect has been shown. Overall the extractable and leachable profile of fremanezumab does not raise concerns to patient safety.

The risk assessment for elemental impurities has been performed in accordance with ICH Q3D and an adequate summary is included in the dossier.

A design verification was performed to evaluate the suitability of the fremanezumab injection PFS. Functional performance has been demonstrated.

The manufacturing process of the fremanezumab finished product changed during development, from the initial process 1P over 2P to the proposed commercial process 3P. Changes during development include a manufacturing site transfer and changes to the formulation and container closure. The finished product manufacturing process is divided into two parts. The primary process consists of active substance thaw, pooling, mixing, filtration, filling and visual inspection. The secondary process encompasses assembly and packaging of the PFS. In order to evaluate the robustness of the unit operations and to define ranges for the validation studies as well as IPCs, process characterization (PC) studies have been performed. Prior to the conduct of the PC studies the control strategy has been defined and a risk assessment performed, taking the recommendations of ICH Q9 into account. Possible CQAs have been defined and a failure-mode and effects analyses (FMEA) was performed.

The PC studies are sufficiently well designed. IPC, CIPCS and PP and CPP have been defined based on the provided results. The filling process will be performed at room temperature. As this storage condition has an impact on CQA of the finished product the maximal time of filling is defined and controlled as a CPP.

Secondary packaging will be performed at room temperature. An AR and normal operating range (NOR) has been assigned based on secondary packaging capabilities, data from overall process times from process characterization studies and accelerated stability data.

The fremanezumab finished product cannot be terminally sterilized and is therefore sterile filtered and aseptically filled into sterile PFS.

Manufacture of the product and process controls

The finished product is manufactured according to current Good Manufacturing Practices (GMP). Batch release is carried out at Merckle GmbH, Ulm, Germany and Teva Pharmaceuticals Europe B.V., Haarlem, The Netherlands.

The manufacturing process of the fremanezumab finished product consists of two stages: 1) manufacturing of the pre-filled syringe (PFS); 2) secondary packaging of the PFS (combination product). The manufacturing of the PFS is performed as standard fill-and-finish process, with no addition of new excipients.

Reprocessing is not considered for the finished product manufacturing process.

The CPPs and CIPCs have been listed.

Process validation has been performed using process verification parameters and IPC results. Physico-chemical, biological and technical assays have been used as process verification parameters at the different stages of the process. The batch hold times were intentionally exceeded to prove that the assigned maximal hold times do not affect process parameters or finished product QAs. The results of 3 subsequent commercial process lots demonstrate reproducible and robust processes. All results stayed within the predefined acceptance criteria and proven acceptable ranges.

The filters used for bioreduction and sterile filtration have been validated. Extractable and Leachable studies were performed under worst-case conditions. Extractable and Leachables from the filter materials are considered to pose a low-risk regarding safety and product quality.

The filling machine is validated by media fills according to an approved standard operating procedure (SOP). Summaries of the last three media fill runs have been provided and demonstrate that the machine is capable to perform aseptic filling operations. Validation of the secondary packaging step has been performed for the three subsequent process verification batches. All CPP have been met as reported.

Product specification, analytical procedures, batch analysis

The finished product specifications are set in accordance with Ph. Eur. requirements and ICH Q6B. They are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial).

Justifications have been provided for the finished product specifications. The acceptance limits for some of the parameters are considered wide, however the applicant provided a commitment to re-evaluate these limits when data from further batches become available (see "Recommendations for future quality development").

Analytical methods

General tests for the finished product (Visible Particles, Volume in Container and Sub-Visible Particles) and safety tests (Sterility (membrane filtration)) are performed according to the Ph. Eur. Monographs. The test for container integrity is performed according to USP <1207> and a summary of test parameters is provided.

Descriptions of all analytical methods and summaries of validations thereof are provided.

A cell-based assay is used to measure the potency of fremanezumab (see active substance section).

Batch analysis

The batch results for the finished product indicate that the manufacturing process is robust. All acceptance criteria were met.

Reference materials

Please refer to the active substance section, the reference standards used for active substance and finished product are identical.

Container closure

The container closure system consists of a 2.25ml single-dose prefilled syringe. The syringe barrel and its constituent parts conform to accepted standards. Technical drawings and specifications are provided. The specifications provided are acceptable. Respective vendor certificates have been provided for the syringe and the stoppers. Both components comply with applicable monographs.

Stability of the product

The stability program for the finished product has been designed taking the recommendations of ICH Q1A and ICH Q5C into account. It includes primary, secondary packaged, and supportive lots. The lots were placed on stability at long term, accelerated, and stressed conditions. The primary batches have been manufactured from active substance batches produced at the commercial manufacturing site and are therefore considered

representative of the proposed commercial product. A sufficient number of batches, which have been secondary packaged have been included and tested for functionality.

The results show that the finished product remains stable at the recommended storage condition and no significant trends were observed. Furthermore, the finished product remains within the stability specifications upon limited exposure at accelerated and at stress conditions.

Beside the main stability study a photostability according to ICH Q1B and temperature excursion studies have been performed. The photostability study demonstrates that the finished product is sensitive to light. Hence, the finished product should be stored protected from light and this is adequately reflected in the SmPC.

Considering the data provided, the proposed finished product shelf life of 24 months at 2-8°C is acceptable.

Post approval change management protocol(s)

A post approval change management protocol (PACMP) has been included in relation to the planned addition of an additional finished product manufacturing site. To support this, an outline of the comparability assessment has been submitted.

The PACMP is considered acceptable. The applicant intends to implement the addition of the new site through a Type IB variation.

Adventitious agents

Compliance with the transmissible spongiform encephalopathy (TSE) Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The active substance is produced in a serum-free culture medium. No other material of bovine origin is added during fermentation. The MCB which has been established is free from TSE-risk substances.

The use of a serum-free medium for the fermentation process minimizes a possible contamination of adventitious viruses. The cells used for production have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB with the exception of intracellular A- and C-type retroviral particles which are well known to be present in rodent cells. This is acceptable since there is sufficient capacity within the manufacturing procedure for reduction of this type of viral particles. The purification process includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicated consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP

recommends to review some active substance and finished product specification acceptance criteria once a pre-determined number of batches will have been manufactured.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant submitted a comprehensive data package to characterise non-clinical development of fremanezumab.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Fremanezumab is a fully humanized immunoglobulin G2 (IgG2) Δa monoclonal antibody (mAb) that binds to human calcitonin gene related peptide (CGRP). CGRP is a potent vasodilator and has been shown to be important in the pathophysiology of migraine. Binding affinities of fremanezumab were determined in three different studies for human, rat and rabbit CGRP. The affinities of fremanezumab to rat and human α-CGRP are different depending on the used method.

Compared to human CGRP in which the binding affinity was high, the binding affinity is 29-400x lower for the rat and 50-244x lower for the rabbit. Since human and cynomolgus monkey CGRP have identical amino acid sequences, it is assumed that the binding affinities for both species are the same, thus lack of specific monkey data is acceptable. Based on these differences in binding affinity, rat and rabbit are relevant species, but less relevant than cynomolgus monkey. Biacore analysis further revealed that fremanezumab binds specifically to CGRP and not to the family members amylin, intermedin and calcitonin and extremely weakly to adrenomedullin.

In vitro

Cell based assays were conducted to determine the ability of fremanezumab to block activation of adenylate cyclase after stimulation with human or rat α-CGRP and to fremanezumab inhibits binding of CGRP to its receptor. It was demonstrated that fremanezumab binds equal or lower to FcγR than an IgG2 control. Also, as it was demonstrated that binding of CGRP to its receptor CGRPR1 was impaired by fremanezumab, additional ADCC or CDC assays are not deemed necessary.

In vivo

No complete animal model of migraine is available. Restriction of blood flow via inhibition of CGRP after administration of fremanezumab was assessed in several animal models, including animal models of pain. No experimental animal data exists that would support efficacy in quarterly administrations clinically. The *in vivo* evidence includes models of peripheral vasodilation and arterial vasodilation that show blockade of CGRP mediated signalling results in the inhibition of vasodilation, which can be maintained for up to 56 days. Inhibition of CGRP also results in the alleviation of symptoms associated with migraine in several animal models of disease (PoC). Fremanezumab is intended to be administered in excess to allow complete and sustained blockade of its target molecule, CGRP.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed. CGRP is a potent vasodilator with a wide expression in neuronal tissue. Given the pleiotropic activity of CGRP the applicant has provided a discussion on the role of CGRP in wound-healing and in pregnancy.

Safety pharmacology programme

In addition to the pivotal toxicology studies, three separate safety pharmacology studies were conducted.

Fremanezumab (100 mg/kg) had no meaningful effect on changes in heart rate, blood pressure, ECG recordings or body temperature in conscious telemetered monkeys. Decreases in heart rate noted during the 1-3.75 and 18-22 hours period on Days 3, 7, 10, and 14, reached statistical significance and are considered moderate. This decrease in heart rate is attributed to the moderate decreases in activity measures obtained during these same periods. It is considered likely that these decreases reflect the absence of in-room activities associated with dose administration, and not a treatment effect. Blood pressure was similarly statistically significantly and transiently reduced but without any meaningful clinical consequence. In repeat dose toxicity studies in monkeys given weekly fremanezumab doses up to 300 mg/kg, there were no notable changes in any cardiovascular parameters, confirming that the minor transient changes seen in the cardiovascular safety study are not biologically meaningful.

Fremanezumab given s.c. up to 300 mg/kg had no effect on a battery of behavioural and physiological parameters in rats, nor did it result in changes in respiratory parameters. The data suggest that, in line with other centrally acting therapeutic antibodies, fremanezumab has no adverse effect on cardiovascular, respiratory or CNS safety.

2.3.3. Pharmacokinetics

Fremanezumab pharmacokinetic profile was characterized following intravenous (iv) administration to mice, rats, rabbits and cynomolgus monkeys. Toxicokinetic profiles were characterized in rat and monkey following once weekly iv or subcutaneous (sc) dosing for a total duration of up to 3 months in rats and 6 months in monkeys. Fetal exposure was characterized as part of the Embryo-Fetal Development Study in Rabbits and in the pre- and post-natal development study (PPND) in rats.

Methods of analysis

Three different ELISA methods were used for the determination of fremanezumab in plasma. The provided validation reports demonstrate that the assays were sensitive, selective and suitable to assess fremanezumab concentrations in monkey, rabbit, mouse and/or rat plasma. For the assay used in the single dose studies, the lower and upper limits of quantitation (LLOQ and ULOQ) were 1.95 and 125 ng/ml. This assay was validated for heparin samples, whereas in the single dose rabbit and monkey studies EDTA samples were collected. This is not expected to affect the results. It is noted that no storage stability and matrix effect data were provided for the assay used for the single dose studies. For the assay used in the 1 and 3 month studies and some of the rat repro studies, the LLOQ and ULOQ were 100 and 7500 ng/ml. For the assay used in the 6 month study and newest repro studies, the LLOQ and ULOQ were 250 and 3500 ng/ml. These latter assays were adequately validated.

For the detection of antibodies against fremanezumab, bridging ELISA methods were developed for rat and monkey serum. The assays were selective and the sensitivity was found to be 0.8 ng/mL for the assay in rat serum (used for the 3 month study), 0.027 ng/ml for the old assay in monkey serum (used for the 3 month studies) and 28 ng/ml for the new assay in monkey serum (used in the 6 month study). In the newest assay (validated for monkey serum) drug tolerance was 336 µg/mL for fremanezumab and no interference up to 1200 ng/ml CGRP was observed. It should be noted, however, that the levels of fremanezumab in serum may be well above the drug tolerance levels leading therefore, to interfere with the assay sensitivity for ADA detection.
An assay to assess the presence of neutralizing capability of the ADA's is not provided or discussed.

Absorption

Single dose pharmacokinetic studies were performed in mice, rats, rabbits and cynomolgus monkeys, with IV doses of 10, 30 and 100 mg/kg bw. In three monkeys (1 mid dose and both high dose) and almost all rabbits, an abrupt decrease in plasma concentration was observed at 1-4 weeks after dosing, presumably due to the formation of (clearing) antibodies. For these animals, both full and truncated (excluding the plasma concentrations from the moment the abrupt decrease started) PK analyses were performed.

In general, fremanezumab showed a biphasic decline, with an initial distribution phase, followed by a slow elimination phase. The steady state volume of distribution is low, about 2–3 fold the plasma volume (i.e 0.09 – 0.14 L/kg) in rabbit, monkey, mouse and rat and in line with human (0.085 L/kg). Plasma clearance was low (i.e. 0.003-0.006 ml/min/kg) in rabbit, monkey, mouse and rat and seems to be even lower in humans (0.0013 ml/min/kg). Systemic exposure of fremanezumab increased in a dose proportional manner over the dose range of 10 to 100 mg/kg. Terminal elimination half-life (T1/2) was approximately 16 days in rats, 19 days in mice, 10 days in monkeys and 8 days in rabbits but may be influenced by ADA formation from 1 week after dosing in the latter two species.

Multiple dose pharmaco- and toxicokinetic studies were performed in rats (1 and 3 months IV and 3 months SC) and cynomolgus monkeys (1 and 3 months IV and 1, 3 and 6 months SC) upon weekly administration at dose levels of 10 - 300 mg/kg. Absorption of fremanezumab was slow after SC dosing, with Tmax at 42 h in the 3 months study in rats and 24 - 114 h in the 1, 3 and 6 months studies in monkeys. After repeated dosing, systemic exposure of fremanezumab increased in an approximately dose proportional manner over the dose range of 10 to 300 mg/kg in monkeys but less than dose proportional in the 3 month study in rats.

The mean terminal half-life (t1/2) of fremanezumab, administered SC, ranged from 14 to 18 days in the 6-month study in monkeys and was 13 days in the 3 month study in rats, compared to 35 days in humans. According to the study reports, accumulation ratios were low to moderate in the 3 months study in rats (1.8-3.7 for AUC_{0-168} for once weekly IV and 1.8 for once weekly SC, AUC week 13 compared to day 1) and moderate to high in the 6 month study in monkeys (3.2 to 9.1 for AUC_{0-168} for once weekly SC, AUC from day 176 compared to day 1). At comparable SC doses, maximal plasma concentrations in the 6 month study were higher at D85 compared to the 3 month study in cynomolgus monkeys (1.5-4x). This may be due to the different formulations of fremanezumab used in these studies.

The mean SC bioavailability of fremanezumab was approximately 65-67% and 81-89% (range 69-100%) in the 3-month studies in rats and monkeys, respectively. This is slightly higher when compared to healthy humans (~55%). There were no apparent gender differences in exposure.

It is noted that in some of the studies, fremanezumab was observed in samples from control animals (rat and monkey). According to the applicant, this cannot be explained by accidental injection of the control animals with the test substance, and that no major deviations from standard operating procedure were reported. However, since the assays were adequately validated, the observed values are unexpected.

Distribution

Consistent with the known biodistribution of monoclonal antibodies, fremanezumab has a low volume of distribution, suggesting a distribution to plasma and extravascular fluid.

Foetal exposure to fremanezumab was confirmed in Embryo-Foetal Development Studies in rats and rabbits. In rats dosed 50 - 200 mg/kg bw once weekly (sc) from GD6 to PND21, dam/pup plasma concentration ratio (measured 72 h post dose) were 1.3-1.6 at PND4 and 2.1-2.5 on PND21.

In rabbits dosed 10-100 mg/kg/week, the fetal exposure measured on GD25 was approximately 11-20% of the Cmax value measured in the dams after the last dose administered on GD18. Based on the plasma concentration time curve in the dams, it is expected that the concentration in the foetus at GD25 (168h post last dose) is in the plateau phase.

Excretion to milk has not been investigated.

Fremanezumab demonstrated similar or lower affinity to human Fc gamma receptors compared to an IgG2 control antibody and lower affinity compared to an IgG1 control antibody. This is consistent with the two mutations in the constant region of the fremanezumab heavy chain to limit Fc effector function. Binding to the FcRn receptor was similar to two control IgG2 antibodies.

Metabolism

No metabolism studies with fremanezumab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1).

Excretion

As fremanezumab is a monoclonal antibody, no renal excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion of fremanezumab were conducted. The absence of excretion studies in accordance with ICH S6(R1).

Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolize via CYP P450 enzymes. However, the mechanism of action of a drug may have an effect on CYP450 enzymes or on transporters through cytokine dependent modulation but for fremanezumab this is unlikely and no such evidence was found.

The Pharmacokinetic Drug-Drug Interactions (DDI) are assessed in the clinical PK section.

Immunogenicity

Antibodies against fremanezumab were observed in several of the studies in non-human species, which can be expected since fremanezumab is a humanized antibody. In the six month study in monkeys (SC injections once weekly) 5 out of 28 animals (17.8%) dosed with fremanezumab had treatment-related ADA response with relative low titer values, which apparently did not influence exposure, considering the fact that exposure to fremanezumab was generally similar on Days 85 and 176 in ADA-positive and negative animals. However, also in the 3 month study in monkeys and rats (IV or SC injections once weekly) and in the 1 month studies in monkeys and rats (using an older, less robust immunogenicity method) treatment related ADA's were observed and in these studies, the presence of anti-drug antibodies in the serum of animals did appear to affect exposure. In these studies there seemed to be at least some correlation between presence of antibodies and plasma concentrations of fremanezumab. Moreover, in the single dose IV studies 3/6 monkeys and almost all rabbits showed a PK profile suggesting the presence of clearing ADA's. It is noted that the anti-fremanezumab antibody data might be an underestimation since the presence of fremanezumab may inhibit detection of anti-fremanezumab antibodies and the plasma fremanezumab concentrations in the tested samples were, in general, above the provided drug-tolerance levels. The possibility of a neutralizing capability of the ADA's is not assessed. In addition, it is noted that ADAs were detected in samples from control animals as well as in pre-dose samples. Similarly, in some of the studies fremanezumab was observed in control samples. Since the assays seem to be well validated, the findings of multiple positive control samples (fremanezumab or ADA) are unexpected.

Despite the presence of ADAs, it seems that the fremanezumab in the majority of the animals remains sufficiently high to evaluate the toxicity of fremanezumab.

2.3.4. Toxicology

Repeat dose toxicity

An extensive non-clinical in vivo programme was conducted to evaluate the toxicity of fremanezumab. A single-dose toxicity study was conducted in the rat; the repeat-dose toxicity studies were performed in the cynomolgus monkey and the rat. The reproduction toxicity studies were conducted in rats and rabbits. Given the lower affinity to rat and rabbit CGRP, the cynomolgus may be considered more relevant for assessing the human risk.

Repeat-dose toxicity studies with the duration of 1 month and 3 months were conducted both in rats and monkeys; the pivotal 26-week study was only conducted in monkeys.

Toxicity studies in the rat

In rats, notable effects were decreased food consumption in all fremanezumab treated groups without corresponding decreases in weight. From 100 mg/kg/wk onwards, increased globulin was observed, which also resulted in increased total protein and decreased albumin/globulin ratio. These findings are considered non-adverse and also resolved during the recovery period.

Toxicity studies in the monkey

Fremanezumab was well tolerated in cynomolgus monkeys at weekly IV injections up to 100 mg/kg for four weeks. No adverse findings were reported.

In monkeys, in a 1 month SC study, total protein was slightly increased in the high dose group and corresponded to increased globulin levels. A minimal increase in lymphocytes was also noted at the end of treatment. None of these findings are considered to be toxicologically relevant and resolved during the recovery period. Likewise, minimal mononuclear cell infiltrates in brain are a common finding in Cynomolgus and not test article related. In the 3 month monkey study with fremanezumab, perivascular inflammation of ciliary vessels was noted in 3 animals (one 300 mg/kg/wk IV male, one 300 mg/kg/wk SC male, and one 100 mg/kg/wk IV female). The inflammation was accompanied by increased monocytes and deposition of immune complexes (C3 complement, IgG and/or IgM). These findings were not reproduced in the 6 month study. Taken together, these findings are indicative of an immune response and are typical for a hypersensitivity reaction. Although adverse, the severity was low and because these types of immune responses are not predictive for the human population, the finding is adequately characterized and not otherwise relevant. In the 6 month repeat dose toxicity study with fremanezumab in monkeys, the only notable findings were perivascular monocellular cell infiltrates of minimal severity at the injection sites in females given 100 or 300 mg fremanezumab/kg/wk and slightly increased neutrophils in males given 300 mg fremanezumab/kg/wk. These findings are not considered to be toxicologically meaningful.

All study groups were adequately exposed during the repeat dose toxicity studies. Toxicokinetic data are typical for therapeutic IgG present in excess. Anti-drug antibodies were detected in all studies and appeared to influence the clearance of fremanezumab from serum (see pharmacokinetic assessment). Nevertheless, the presence of ADA in animals assigned to study groups did not influence the safety assessment of fremanezumab. Exposure multiples (based on Cmax) varied from 2.3-43 for i.v. administrations and from 2.2-227 for s.c. administrations. It is however noted that fremanezumab levels from single doses in humans are compared to levels from multiple dose studies in animals. Since accumulation was observed in the multiple dose studies in animals (1.8-9.1x), this could result in lower safety margins than the reported.

Plasma concentrations increased approximately dose proportionally in the repeated dose toxicity studies with fremanezumab. At comparable s.c. doses, maximal plasma concentrations in the 6 month study were slightly higher (1.5-4x) compared to the 3 month study in Cynomolgus monkeys. This may be due to the different formulations of fremanezumab used in these studies.

Genotoxicity

Genotoxicity studies have not been conducted, in accordance with ICH S6(R1).

Carcinogenicity

No carcinogenicity studies have been conducted, in accordance with ICH S6(R1) and a scientific advice. However, as fremanezumab is intended for long-term treatment, in line with ICH S6(R1) a carcinogenic risk assessment was provided. Based on this review, the carcinogenic risk for CGRP inhibition is considered low.

Reproduction Toxicity

A series of reproductive toxicology studies were conducted in rats and rabbits. All animals were sufficiently exposed during the study to allow a meaningful assessment of the reproductive toxicological potential of fremanezumab, with doses up to 200 mg/kg/day in rats and 100 mg/kg/day in rabbits. There were no untoward

effects on male or female fertility and mating performance in rats, or embryofoetal development in rats and rabbits. Fremanezumab was measured in foetal rat serum, with maximal levels in the 100 mg/kg dose group being approximately 9% of the maternal Cmax. Peri and postnatal development studies in rats revealed no fremanezumab related effects in either dams or pups.

Local Tolerance

Local tolerance was evaluated in the toxicology studies and in a separate study with male rabbits. Fremanezumab was well tolerated when administered by intravenous, intra-arterial, subcutaneous, perivenous or intramuscular route

Other toxicity studies

Tissue cross-reactivity study with human, cynomolgus, rabbit and rat tissue

Specific reactions to the tissue were verified by using a negative and two positive controls. In general the staining pattern was comparable between human, cynomolgus monkey, rat and rabbit. Rather weak, specific staining of the human pituitary of one donor was detected, which was not observed in any of the animals. CGRP expression in the pituitary is supported by literature data; however, staining was cytoplasmic, thus it is unknown if fremanezumab will bind to this target *in vivo*. In addition, specific staining in cynomolgus monkey, rat and rabbit tissue was detected in parafollicular cells in the thyroid which are reported to express CGRP.

2.3.5. Ecotoxicity/environmental risk assessment

Ecotoxicity/environmental risk assessment of fremanezumab was not conducted. As a monoclonal antibody, fremanezumab is not expected to pose a risk to the environment as it is metabolised to aminoacids.

2.3.6. Discussion on non-clinical aspects

The applicant has presented non-clinical *in vitro* data to demonstrate the pharmacological mode of action for fremanezumab as a CGRP-inhibitor.

Importantly, it was demonstrated that binding of fremanezumab to FcγR is low and that binding of CGRP to CGRPR1 is impaired by fremanezumab. Thus, fremanezumab does not exhibit Fc effector functions such as ADCC and CDC. No complete *in vivo* model of migraine exists, but some mechanistic and pain models have been conducted, suggesting that fremanezumab is effective in migraine prevention.

No secondary pharmacodynamics studies were performed. CGRP is a potent vasodilator with a wide expression in neuronal tissue. The applicant acknowledged that alterations in wound healing as well as increased skin inflammatory responses at the fremanezumab injection sites could theoretically be possible consequences of CGRP blockade with fremanezumab in humans and proposes to routine pharmacovigilance surveillance. Given the limited information on the clinical effects of CGRP blockade and its role in pregnancy, the applicant proposed to conduct a post-authorisation safety study to determine the possible effect of CGRP blockade during pregnancy.

Antibodies against fremanezumab were observed in several of the studies, which, in some cases, did appear to affect exposure. The presence of clearing antibodies is also indicated by the single dose IV studies, in which 3/6

monkeys and almost all rabbits showed an abnormal PK profile suggesting the presence of clearing ADA's. There may very well be an underestimation of the ADAs present in the samples as the plasma fremanezumab concentrations in the tested samples were, in general, well above the provided drug-tolerance levels, inhibiting the detection of antibodies. The presence of neutralizing ADA's is not assessed, although this is warranted since there is no PD marker used to demonstrate sustained activity in the *in vivo* toxicology studies. In addition, there seem to be some issues with the followed procedure and/or the assays of both fremanezumab and of antibodies against fremanezumab. Although the assays seem to be well validated, the presence of fremanezumab or ADA's was observed in control and/or pre-dose samples in several of the studies. According to the applicant this could not be explained by assay variabilities nor by protocol deviations.

The applicant has discussed the presence of clearing and/or possibly neutralizing antibodies. It is agreed that the methods used to detect ADA's were adequate and the batches used in the pivotal and most recent repeated-dose as well as reproductive and developmental toxicity studies were the most relevant. In these studies, presence of ADA's seemed to be limited and exposure of fremanezumab was still sufficient. In addition, the level of ADA formation has a low predictive value for humans. Therefore, although there remain some questions with regard to the earlier studies, the assay limitations do not seem to have prevented an adequate assessment of the safety of fremanezumab in the more recent studies and the issue was considered resolved.

To support the safety of fremanezumab, a toxicology programme in cynomolgus monkeys and rats was presented, which is in accordance with current guidance and considered adequate. The main findings only observed in the 3-month repeat-dose toxicity study were perivascular infiltrates in the eye and stifle joint of cynomolgus monkeys, but are considered as a result of an immune response and not otherwise relevant. Overall, the toxicity studies provide a sufficient safety margin to the exposure at the proposed clinical dose of fremanezumab.

No carcinogenicity studies have been conducted, in accordance with ICH S6(R1) and a scientific advice. However, as fremanezumab is intended for long-term treatment, in line with ICH S6(R1) a carcinogenicity risk assessment based on review of relevant data on CGRP functions from current literature has been provided. Based on this review, the carcinogenic risk for CGRP inhibition is considered low

Reproductive and developmental toxicity was assessed in a fertility + EFD study in rats, a EFD study in rabbits and a PPND study in rats. These studies have not revealed any adverse effects on fertility and pregnancy outcome.

2.3.7. Conclusion on the non-clinical aspects

The submitted non-clinical data were reviewed and deemed acceptable by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

The clinical efficacy of fremanezumab was evaluated in 3 Phase 3 studies, 2 highly similar double-blind, placebo-controlled studies (study 30049 in chronic migraine and study 30050 in episodic migraine) and 1 long-term, double-blind safety study (study 30051), the latter ongoing at the time of submission of this Marketing Authorization Application.

Supportive data come from 2 double-blind, placebo-controlled Phase 2b studies (study 021 and study 022).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 Tabular overview of clinical studies

Study ID (status) **Study phase** **Number of study centers** **Location(s)**	**Study start (first patient randomized)** **Study completion** **Total randomized (goal)**	**Design control type**	**Study and control drugs (doses, route, and regimens)**	**Number of patients by group** **Total treated/ completed**	**Treatment duration**	**Sex M/F** **Median age (years) (range)**	**Study population** **Inclusion criteria**	**Primary efficacy variable and endpoint (primary analysis)**
Pivotal (confirmatory) efficacy studies								
Study TV48125-CNS-30049 (completed) Phase 3 132 Global	22 March 2016 11 April 2017 1130 (1020)	Randomized, double-blind, placebo-controlled, parallel-group study	PBO/PBO/PBO sc fremanezumab 675 mg/PBO/PBO[a] sc fremanezumab 675/225/225 mg[b]	PBO/PBO/PBO: 375/342 fremanezumab 675 mg/PBO/PBO: 376/349 fremanezumab 675/225/225 mg: 379/343	12 weeks	139/991 41.0 (18, 71)	M/F patients, 18-70 years of age, with CM[c], up to 30% of patients were permitted to use no more than 1 concomitant preventive medication	Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week treatment period (ANCOVA)
Study TV48125-CNS-30050 (completed) Phase 3 123 Global	23 March 2016 10 April 2017 875 (768)	Randomized, double-blind, placebo-controlled, parallel-group study	sc PBO/PBO/PBO sc fremanezumab 675 mg/PBO/PBO[a] sc fremanezumab 225/225/225 mg[d]	PBO/PBO/PBO: 294/265 fremanezumab 675 mg/PBO/PBO: 291/264 fremanezumab 225/225/225 mg: 290/262	12 weeks	133/742 42.0 (18, 70)	M/F patients, 18-70 years of age, with EM[e] up to 30% of patients were permitted to use no more than 1 concomitant preventive medication	Mean change from baseline in the monthly average number of migraine days during the 12-week treatment period (ANCOVA)

Study ID (status) **Study phase** **Number of study centers** **Location(s)**	**Study start (first patient randomized)** **Study completion** **Total randomized (goal)**	**Design control type**	**Study and control drugs (doses, route, and regimens)**	**Number of patients by group** **Total treated/ completed**	**Treatment duration**	**Sex M/F** **Median age (years) (range)**	**Study population** **Inclusion criteria**	**Primary efficacy variable and endpoint (primary analysis)**
Study TV48125-CNS-30051 (ongoing)[f] Phase 3 134 Global	25 March 2016 Ongoing 1889 (1842)	Randomized, double-blind, parallel-group study	monthly sc fremanezumab at 225 mg for 12 months (Note: New patients with CM and patients with CM who received placebo in Study 30049 and are randomized to the 225 mg monthly treatment group receive a starting dose of 675 mg.) quarterly sc fremanezumab at 675 mg for 12 months for a total of 4 doses	fremanezumab 225 mg monthly with initial 675 mg starting dose[g]: 558/16 fremanezumab 225 mg monthly[h]: 386/2 fremanezumab 675 mg quarterly[i]: 943/14	12 months	CM: 132/977 43 (18, 71) EM: 113/677 45 (18, 71)	Rollover: All patients who complete Study 30049 or Study 30050 without major protocol violations. New: M/F patients, 18-70 years of age, with CM or EM; permitted to use no more than 2 concomitant preventive medications	NA

Study ID (status) Study phase Number of study centers Location(s)	Study start (first patient randomized) Study completion Total randomized (goal)	Design control type	Study and control drugs (doses, route, and regimens)	Number of patients by group Total treated/ completed	Treatment duration	Sex M/F Median age (years) (range)	Study population Inclusion criteria	Primary efficacy variable and endpoint (primary analysis)
Supportive studies in patients with migraine								
Study LBR-101-021 (completed) Phase 2b 53 USA	10 January 2014 12 January 2015 264 (240)	Randomized, double-blind, double-dummy, placebo-controlled, parallel-group study	PBO/PBO/PBO sc fremanezumab 675/225/225 mg[b] sc fremanezumab 900/900/900 mg	PBO/PBO/PBO: 89/77 fremanezumab 675/225/225 mg: 88/72 fremanezumab 900/900/900 mg: 86/76	12 weeks	37/227 41.5 (18.0, 65.0)	M/F patients, 18-65 years of age, with CM[c] patients were allowed to use up to 2 different preventive medications or interventions/devices for migraine if the dose and regimen were stable for at least 2 months before the run-in period	Mean change from baseline in the number of headache hours of any severity during month 3 (MMRM)
Study LBR-101-022 (completed) Phase 2b 63 USA	09 January 2014 17 February 2015 297 (300)	Randomized, double-blind, placebo-controlled, parallel-group study	PBO/PBO/PBO sc fremanezumab 225/225/225 mg[d] sc fremanezumab 675/675/675 mg	PBO/PBO/PBO: 104/98 fremanezumab 225/225/225 mg: 96/83 fremanezumab 675/675/675 mg: 96/88	12 weeks	36/261 42.0 (18.0, 65.0)	M/F patients, 18-65 years of age, with HFEM[i]; patients were allowed to use up to 1 preventive medication or intervention/device for migraine if the dose and regimen were stable for at least 2 months before the run-in period	Mean change from baseline in the number of migraine days during month 3 (MMRM)

2.4.2. Pharmacokinetics

The proposed clinical dose of fremanezumab is 225 mg once monthly (monthly dosing) or 675 mg every three months (quarterly dosing) as per patients preference.

Of the seven studies contributing to the characterization of the pharmacokinetics of fremanezumab, two phase 1 studies in healthy volunteers with dense PK sampling were primarily designed as clinical pharmacology studies. In study LBR-101-011, fremanezumab was administered both iv and sc to render information on bioavailability. In all other studies, fremanezumab was solely administered via the sc route. Pharmacokinetics in episodic and chronic migraine patients were investigated in two phase 2 efficacy and safety studies in patients with CM or EM (studies LBR-101-021 and LBR-101-022) and three phase 3 efficacy and safety studies (studies TV48125-CNS-30049, TV48125-CNS-30050 and TV48125-CNS-30051). In these studies, only sparse PK sampling was performed. In the studies with intensive PK data, non-compartmental PK analysis was conducted, while for the sparse PK data in migraine patients a population PK model was developed.

Absorption

Absolute bioavailability of fremanezumab after sc administration was approximately 54% to 57% from non-compartmental comparison of iv and sc administration of 225 mg and 900 mg single doses to healthy subjects. Based on the stepwise update of PPK modelling, bioavailability was estimated based on the same intensive PK data (Study LBR-101-011) to 65.8% in a model-based way. This value was fixed before adding further PK data from migraine patients. The applicant revised the wording on fremanezumab absolute bioavailability (F) in the Summary of Product Characteristics (SmPC) to be based on both non-compartmental (NCA) and population pharmacokinetic (PPK) analyses. Due to the sparse data PK base, the characterization of absorption in terms of ka (high shrinkage and IIV) remains complex.

Distribution and elimination

Fremanezumab displayed PK parameters typical for therapeutic antibodies. Volume of distribution over F (Vc/F) was in the range of 5.7 – 6.4 L, indicating limited tissue penetration and distribution mainly in serum after sc administration. Fremanezumab half-life was estimated to 30 days and linear clearance over F (CL/F) was estimated to 0.141 L/day. Since monoclonal antibodies are known to be mainly eliminated via intracellular proteolysis, renal or hepatic elimination pathways are negligible.

The updated population PK analysis resulted in a rough estimate of 66% for bioavailability based on limited data for healthy subjects. Assuming that this model-derived estimate holds for the patient population, the volume of distribution was 3.6 L and central clearance was 0.09 L/day for a typical subject following subcutaneous administration of 225 mg, 675 mg and 900 mg of fremanezumab.

Dose proportionality and time dependencies

In the single dose studies in healthy subjects, slightly greater than dose-proportional increases in fremanezumab exposure with increasing doses was shown. However, the deviation was minimal and patient numbers quite small. The PPK analysis subsequently revealed overlapping dose-normalized AUC and Cmax for the different fremanezumab doses investigated, thereby indicating dose-proportionality.

After multiple dosing of fremanezumab, the median accumulation ratios for once-monthly and once-quarterly dosing regimen were estimated to 2.34-fold and 1.2-fold, respectively. Exposure simulations indicated that steady state following both 225 mg monthly and 675 mg quarterly dosing was reached after 168 days, which approx. corresponds to 5 half-lifes of fremanezumab.

Variability

Estimated IIV was larger for ka (54.8 %SEM) compared to CL/F (29.0 %SEM) and Vc/F (22.7 %SEM). Large IIV for the absorption rate is acceptable as mainly sparse PK samples and few iv data have been included in the population PK analysis data set.

Overall, VPC plots indicate no major deviation. The high variability of the data is captured in the model. The variability however remains unexplained as besides body weight, no other covariate could be identified by population PK data analysis including injection sites.

The Applicant provided information on the inter-individual variation and calculated the intra-individual variability in Cmax,ss, Cav,ss, and AUCss following dosing with 225 mg fremanezumab once monthly and 675 mg

fremanezumab every 3 months. There was no difference in inter-individual variation between the once monthly and once quarterly dosing regimen. The intra-individual variability in Cmax,ss; Cav,ss and AUCss was low, as expected for monoclonal antibodies injected via the SC route.

Special populations

Fremanezumab is not expected to be eliminated via renal or hepatic pathways and therefore no studies in subjects with impaired renal or hepatic function are obligatory.

In the PPK model, body weight was demonstrated to have a significant influence on CL and V:
Relative to a 71-kg subject (the median weight in the population), a 51-kg subject and a 101-kg subject (corresponding to the 5th and 95th percentile of body weights observed in the analysis dataset) are expected to have approximately 32% lower and 52% higher CL/F and a 25% lower and 36% higher Vc/F, respectively.

No other significant covariates were identified, concluding that no relevant differences in fremanezumab exposure were detected among different sex, race or age groups.

Pharmacokinetic interaction studies

No drug interaction studies have been performed with fremanezumab, which was formerly agreed to by both FDA and EMA, since interaction with CYP450 enzymes is considered unlikely with monoclonal antibodies of high molecular weight.

In the PPK analysis, the impact of concomitantly administered migraine medications on fremanezumab exposure was investigated. Overall, exposure ranges were demonstrated to be comparable in the presence or absence of co-medication. Ergotamine/triptan use was not found to be a significant covariate in the PPK analysis.

2.4.3. Pharmacodynamics

Mechanism of action

Fremanezumab is a potent, selective anti-CGRP monoclonal antibody. It blocks both the α- and β-CGRP isoforms from binding to the CGRP receptor and does not bind to the closely related amylin, calcitonin, or adrenomedullin peptides. Introduction of 2 mutations into the constant region of the fremanezumab heavy chain limits antibody effector functions, thereby preventing fremanezumab from stimulating antibody-dependent cell-mediated cytotoxicity and triggering complement-mediated lysis (Armour 1999, Zeller 2008).

Primary and Secondary pharmacology

The binding of fremanezumab to its targets (CGRP) has been characterized in non-human models.
Fremanezumab prevents in vitro cyclic adenosine monophosphate production induced by CGRP while not binding to similar peptides such as amylin, calcitonin, or adrenomedullin.

Three studies addressing cardiac safety have been conducted and have collected ECGs in a well-controlled environment in rigorous fashion within the therapeutic dosing range. No specific PD studies regarding efficacy endpoints have been provided. Thus, pharmacodynamic endpoints with regard to efficacy evaluated in terms of monthly number of migraine days are difficult to be precisely correlated with fremanezumab exposure. Based on the chosen study program and achieved PK/PD results, the rationale for dose selection remains vague.

Regarding exposure-efficacy analysis, exploratory analyses and exposure-response models have been provided relating Cav and change from baseline migraine days for both patient groups EM and CM.

Overall, no clear relationship between doses/exposure and response is indicated. Following fremanezumab treatment, an additional but comparable decrease in migraine days in addition to a quite strong placebo response could be detected from the data and model-based analyses.

Bodyweight was shown to have an appreciable impact on fremanezumab PK. According to simulation results, in each of the dosing regimen, except for placebo treatment, there was a trend in greater efficacy in CM patients at lower body weight. No trend was indicated regarding EM patients.

Exposure response analysis based von Phase 2 and Phase 3 data with regard to the safety endpoints abnormal heart rate and abnormal systolic and diastolic blood pressure did not indicate a clinical relevant relationship between exposure metrics and safety endpoints.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In total, 7 studies were conducted in support of the characterization of the PK properties of fremanezumab.

The analytical methods used for detection of fremanezumab and anti-drug antibodies in human serum were adequately validated and in line with the recent guidance.

A population PK model was developed for the characterization of fremanezumab PK in migraine patients. No major deviations were identified and the model can be considered adequate. The PK parameters estimates deriving from the PPK analysis were mainly consistent with findings from previous analyses of fremanezumab pharmacokinetics in healthy subjects and other monoclonal antibodies. As an update of population PK description, iv and long term PK data were included in the modelling process. In this line, a two-compartment model has been selected and F was estimated based on limited iv and sc PK data.

Steady state exposure estimated for migraine patients was demonstrated to be comparable to PK in in healthy subjects. Similarly, half-life estimated by PPK analysis was similar to half-life determined after single dose administration of fremanezumab in healthy subjects. However, for the 675 mg quarterly dose regimen, median AUCinf determined by non-compartmental analysis in healthy subjects appears to be twice as high as median AUC(0-84d) estimated in the PPK model. In response, the applicant clarified there was a unit error and the values presented for the PPK model were for AUC0-28d instead of AUC0-84d.

The PK of fremanezumab was described to be dose-proportional without any indication of time-dependent changes.

The impact of liver function on fremanezumab exposure was investigated in the PPK model, revealing no significant differences in exposure of patients with normal liver function vs. mild or moderate liver function

impairment. However, given the possibility that monoclonal antibodies may be cleared by damaged kidneys due to proteinurea, section 5.2 of the SmPC includes a statement that patients with severe renal impairment have not been studied.

The body weight effect on fremanezumab exposure is reflected in the SmPC, although body weight did not seem to have an effect on clinical efficacy in patients with body weight up to 132 kg. Since no data are available on patients with body weight > 132 kg, it is unknown whether the plasma levels in these patients are sufficiently high to have a clinically significant effect. This uncertainty was reflected in the SmPC.

Immunogenicity of fremanezumab in both healthy subjects and migraine patients was very low (0.4 – 1.6%), which was confirmed by long-term data from the extension study.

No analysis of primary or secondary pharmacology (e.g. CGRP, capsaicin-induced dermal blood flow) was conducted. Conclusively, the pharmacodynamic proof of concept in humans was not demonstrated in clinical studies.

The exposure-efficacy analysis revealed no clear relationship between average fremanezumab concentration achieved with different dose regimen and respective reduction in monthly number of migraine/headache days. Thus, the rationale for dose selection from this perspective remains vague. In addition, long-term data beyond 3 months of treatment are required to elucidate the presence or absence of changes in response after reaching a steady state fremanezumab concentration.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics of fremanezumab has been adequately characterized. PK and immunogenicity data from the long-term roll-over extension study were provided.

Although the PK data set for PPK analyses has been enlarged, the new PPK model structure, parameter estimates, and the necessity of fixing of central PK parameters indicate some model deficiencies in describing iv and sc data simultaneously.

The only data provided regarding pharmacodynamic properties of fremanezumab was the exposure-efficacy analysis which investigated the effect of fremanezumab exposure on reduction of monthly number of migraine/headache days. The absence of further PD measures is considered adequately justified.

Exposure response analysis based von Phase 2 and Phase 3 data with regard to the safety endpoints abnormal heart rate and abnormal systolic and diastolic blood pressure did not indicate a clinical relevant relationship between exposure metrics and safety endpoints.

2.5. Clinical efficacy

The clinical efficacy of fremanezumab was evaluated in 3 Phase 3 studies, hereof 2 highly similar designed double-blind, placebo-controlled studies (study 30049 in chronic migraine and study 30050 in episodic migraine) and 1 long-term, double-blind safety study (study 30051), the latter ongoing at the time of submission of this Marketing Authorization Application.

Supportive data come from 2 double-blind, placebo-controlled Phase 2b studies (study 021 and study 022).

2.5.1. Dose response study

Study 021 was a phase 2b study in patients with chronic migraine (CM). 264 patients were randomly assigned to receive 3 monthly sc doses of either:

- placebo

- fremanezumab 900 mg or

- fremanezumab 225 mg (with a starting dose of 675 mg).

As the phase 3 studies, study 021 consisted of a 28-day run-in period and a 12-week treatment period, including a final evaluation at week 12. Baseline characteristics were similar between treatment groups. Main duration of migraine diagnosis was 20.4, 15.8, and 18.8 years for placebo, fremanezumab 675/225/225 mg, and fremanezumab 900/900/900 mg, respectively. A slight majority of patients was not using migraine preventive medication (57%, 60%, and 62% for placebo, fremanezumab 675/225/225 mg, and fremanezumab 900/900/900 mg, respectively). The average age of patients was 40.8 years (range 18 to 65 years), with the majority of patients being women (86%) and White. Based on this distribution of age, disease history and female preponderance, the study population is considered representative for the group of patients with migraine being candidates for preventive migraine treatment.

Primary endpoint of this study was change in monthly cumulative headache hours of any severity, assessed at week 12. This choice of endpoint is agreed for a population with CM. Chronic headaches often become more featureless over time, and patients with CM -in addition to typical migraine attacks- may present with headache attacks that do not fulfil the criteria of migraine. This is why the definition of CM is based on headaches on at least 15 days per month of which more than eight are migrainous.

Indeed, the primary endpoint (cumulative headache hours of any severity) was found to be reduced at week 12 in all three treatment groups, but in favour of the two fremanezumab regimens over placebo (MMRM results): -37.10, -59.84, and -67.51 hours for placebo, fremanezumab 675/225/225, and fremanezumab 900/900/900, respectively. The difference from placebo was statistically significant for both fremanezumab treatment groups. Superiority in this endpoint was also found for month 1 and month 2, indicating a rapid onset of treatment effect. However, despite statistical significance, a difference over placebo of 22.74 hours (fremanezumab 675/225/225 mg), and 30.41 hours (fremanezumab 900/900/900 mg) equate approximately one day and is not considered a really huge treatment effect given the absolute number of headache hours at baseline in this population.

A statistical significant, but in clinical terms moderate treatment effect over placebo was also found with the secondary efficacy endpoint "number of headache days of at least moderate severity (-4.2, -6.04, and -6.16 days at week 12 for placebo, fremanezumab 675/225/225/, and fremanezumab 900/900/900 mg, respectively [FAS], indicating a difference of less than 2 days).

The primary analysis indicated a slightly better treatment effect of fremanezumab 900/900/900 mg compared with the lower dose of 675/225/225 mg.

2.5.2. Main studies

A multicentre, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of 2 dose regimens of subcutaneous administration of fremanezumab (TEV-48125) versus placebo for the preventive treatment of chronic migraine

A multicentre, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of 2 dose regimens of subcutaneous administration of fremanezumab (TEV-48125) versus placebo for the preventive treatment of episodic migraine

Methods

TV48125-CNS-30049 (Chronic Migraine) and roll-over in study TV48125-CNS-30051

Study schematic for patients with CM

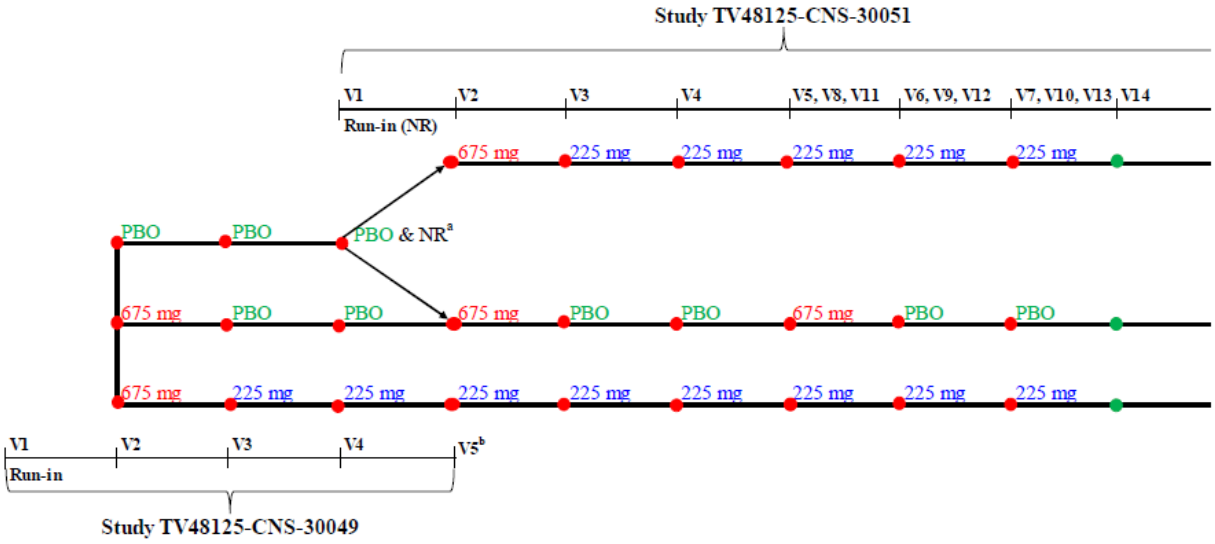


Figure 1

a Patients not rolling over from the pivotal efficacy study who met eligibility criteria after completing a 28-day run-in period and patients rolling over from the pivotal efficacy study who received placebo were blindly randomized in a 1:1 ratio at visit 2 to receive a starting dose of fremanezumab at 675 mg followed by monthly fremanezumab at 225 mg or quarterly fremanezumab at 675 mg.

b For patients who began this study (visit 2) on the same day as the EOT visit (visit 5) of the pivotal efficacy studies, the EOT visit procedures/assessments for the pivotal efficacy study were completed before beginning visit 2 procedures/assessments.

EOT=end-of-treatment; NR=nonrollover patients; PBO=placebo; V=visit.

TV48125-CNS-30050 (Episodic Migraine) and roll-over in study TV48125-CNS-30049

Study schematic for patients with EM

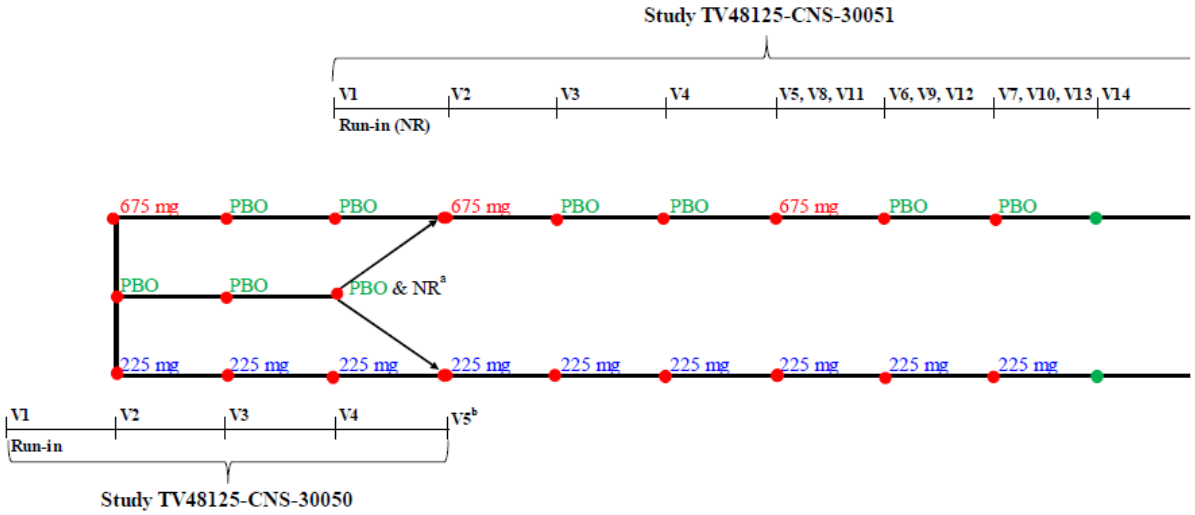


Figure 2

a Patients rolling over from the pivotal efficacy study who received placebo and patients not rolling over from the pivotal efficacy study who met eligibility criteria after completing a 28-day run-in period were blindly randomized in a 1:1 ratio at visit 2 to receive quarterly fremanezumab at 675 mg or monthly fremanezumab at 225 mg.

b For patients who began this study (visit 2) on the same day as the EOT visit (visit 5) of the pivotal efficacy study, the EOT visit procedures/assessments for the pivotal efficacy study were completed before beginning visit 2 procedures/assessments.

EOT=end-of-treatment; NR=nonrollover patients; PBO=placebo; V=visit.

Study Participants

TV48125-CNS-30049 (Chronic Migraine)

This study included female and male patients, aged 18 to 70 years, inclusive, with a history of migraine for at least 12 months and CM (as defined by ICHD-3 criteria [Headache Classification Committee of the IHS 2013]). The diagnosis was prospectively confirmed via a review of headache data recorded daily during a 28-day run-in period in an electronic headache diary device.

A subset of patients (specified in the protocol not to exceed 30%) were allowed to use 1 concomitant migraine preventive medication, and no changes in these medications were allowed until the last study assessments were completed. All other patients were not using concomitant preventive migraine medications at the time of the screening visit, and they were not allowed to initiate these medications after study start. Patients were allowed to use acute medications to treat acute migraine attacks as needed.

TV48125-CNS-30050 (Episodic Migraine)

The study population was composed of men and women, 18 to 70 years of age (inclusive), with a history of migraine (as defined by ICHD-3 criteria [Headache Classification Committee of the IHS 2013]) for at least 12

months prior to screening and EM prospectively documented via a review of headache data recorded daily during a 28-day run-in period in an electronic headache diary device.

TV48125-CNS-30051 (LTS)

The study included female and male patients 18 through 70 years of age with CM and EM who completed the pivotal efficacy studies (Studies TV48125-CNS-30049 and TV48125-CNS-30050) and approximately 300 patients (approximately half of whom had a diagnosis of CM and half of whom had a diagnosis of EM as defined by International Classification of Headache Disorders, 3rd edition [ICHD-3] criteria [Headache Classification Committee of the IHS 2013]) who had not participated in the pivotal efficacy studies. In addition, patients who had not completed the pivotal efficacy studies and patients who completed the pivotal efficacy studies but did not wish to continue treatment during this long-term safety, tolerability, and efficacy study could attend a follow-up visit during this study for the purpose of ADA assessment approximately 7.5 months after their last dose of study drug during the pivotal efficacy study.

Treatments

TV48125-CNS-30049 (Chronic Migraine)

Study drug was administered every 28 days for a total of 3 doses, as follows:

- Patients who were randomized to receive fremanezumab 675/225/225 mg received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) at visits 3 and 4 (referred to as the 675/225/225-mg treatment group hereafter).
- Patients who were randomized to receive fremanezumab 675 mg/placebo/placebo received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2 and placebo as a single 1.5-mL injection at visits 3 and 4 (referred to as the 675-mg/placebo/placebo treatment group hereafter).
- Patients who were randomized to receive placebo received three 1.5-mL placebo injections at visit 2 and a single 1.5-mL placebo injection at visits 3 and 4.

TV48125-CNS-30050 (Episodic Migraine)

Study drug was administered every 28 days for a total of 3 doses, as follows:

- Patients randomized to receive monthly fremanezumab at 225 mg received 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) and two 1.5-mL placebo injections at visit 2 and 225 mg of fremanezumab as 1 active injection (225 mg/1.5 mL) at visits 3 and 4 (referred to as the 225/225/225-mg treatment group hereafter).
- Patients randomized to receive fremanezumab at 675 mg/placebo/placebo received 675 mg of fremanezumab as 3 active injections (225 mg/1.5 mL) at visit 2 and placebo as a single 1.5-mL injection at visits 3 and 4 (referred to as the 675-mg/placebo/placebo treatment group hereafter).
- Patients randomized to receive placebo received three 1.5-mL placebo injections at visit 2 and a single 1.5-mL placebo injection at visits 3 and 4.

TV48125-CNS-30051 (LTS)

Patients who rolled over from the pivotal efficacy studies and received placebo or new patients (not rolling over) were randomly assigned in a 1:1 ratio using interactive response technology (IRT) as follows:

- Patients with CM received sc fremanezumab at 675 mg (loading dose) followed by 11 monthly sc doses of fremanezumab at 225 mg or sc fremanezumab at 675 mg once every 3 months for 12 months for a total of 4 doses.
- Patients with EM received monthly sc fremanezumab at 225 mg for 12 months or quarterly sc fremanezumab at 675 mg for 12 months for a total of 4 doses.

Study drug was administered by qualified study personnel as sc injections every 4 weeks (28 days).

Objectives

TV48125-CNS-30049 (Chronic Migraine)

Primary objectives

- to demonstrate the efficacy of 2 dose regimens of fremanezumab, as assessed by the decrease 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 relative to the baseline period
- to evaluate the safety and tolerability of 2 dose regimens of fremanezumab in the preventive treatment of CM

Key secondary objectives

- to demonstrate the efficacy of fremanezumab, as assessed by the reduction of the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period
- to evaluate the proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity with fremanezumab during the 12-week period after the 1st dose of study drug relative to the baseline period

TV48125-CNS-30050 (Episodic Migraine)

Primary objectives

The primary objectives are identical to the ones evaluated in study 30049, namely:

- to demonstrate the efficacy of 2 dose regimens of fremanezumab, as assessed by the decrease in the monthly average number of migraine days during the 12-week period after the 1st dose of study drug relative to the baseline period
- to evaluate the safety and tolerability of 2 dose regimens of fremanezumab in the preventive treatment of EM

Secondary objectives

- to evaluate the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days with fremanezumab during the 12-week period after the 1st dose of study drug relative to the baseline period
- to demonstrate the efficacy of fremanezumab, as assessed by the reduction 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 relative to the baseline period

TV48125-CNS-30051 (LTS)

Primary objective

The primary objective of the study was to evaluate the long-term safety and tolerability of sc fremanezumab in the preventive treatment of migraine.

Secondary objective

There were no secondary objectives.

Outcomes/endpoints

TV48125-CNS-30049 (Chronic Migraine) and TV48125-CNS-30050 (Episodic Migraine)

Primary efficacy variable

Primary efficacy variables of the two pivotal studies were monthly average number of headache days of at least moderate severity (study 30049), and monthly average number of migraine days (study 30050), respectively. Data were derived from headache information collected daily using an electronic headache diary device.

Secondary efficacy variables

The secondary variables including monthly average number of migraine days, average number of headache days, average number of headache days of at least moderate severity, and monthly average number of days of use of use of any acute headache medications, migraine related disability were also derived from daily collected information using the electronic headache diary.

Study 30049:

The HIT-6, a short form for assessing the adverse headache impact in clinical practice (social functioning, role functioning, vitality, cognitive functioning, and psychological distress) was conducted at pre-specified time points. Scores range from 36 to 78, where a higher score indicates a greater impact of headache on the daily life of the patient, i.e., scores $\leq$49 represent little or no impact, scores between 50 and 55 represent some impact, scores between 56 and 59 represent substantial impact; and scores $\geq$60 indicate severe impact (Bayliss and Batenhorst 2002).

Study 30050:

Headache-related disability was assessed using the MIDAS questionnaire, a 5-item instrument based on lost days of activity in 3 domains (work, household work, and non-work) over the previous 3 months (Stewart et al 1999). The total of the scores of the first 5 questions is used for grading of disability, with scores of 0 to 5, 6 to 10, 11 to 20, and ≥21 interpreted as disability grades 1 (little or no disability), 2 (mild disability), 3 (moderate disability), and 4 (severe disability), respectively.

Patients completed the MIDAS questionnaire at pre-specified time points

Exploratory efficacy measures and variables

Exploratory efficacy variables (monthly average number of headache days of at least moderate severity, monthly average number of headache days of any severity, monthly average number of migraine days, monthly average number of headache hours of any severity, monthly average number of headache hours of at least moderate severity, monthly average number of days of use of migraine-specific acute headache medications, monthly average number of days with nausea or vomiting, and monthly average number of days with photophobia and phonophobia) were also derived from headache information collected daily using the electronic headache diary.

Additional exploratory variables included changes in quality of life, health status, depression status, work productivity and activity impairment, and patient satisfaction with treatment. Measures for these exploratory efficacy variables included the MSQOL, EQ-5D-5L, PHQ-2/PHQ-9, WPAI, and PGIC.

TV48125-CNS-30051 (LTS)

There was no primary or secondary efficacy measure in this study.

Exploratory efficacy measures and variables

Exploratory efficacy variables (monthly average number of migraine days, headache days of at least moderate severity, headache days of any severity, days of use of any acute headache medications, headache hours of at least moderate severity, headache hours of any severity, days with nausea or vomiting, and days with photophobia and phonophobia during the 4-week periods after visits 2, 3, 4, 7, and 13 for months 1, 2, 3, 6, and 12) were derived from headache information collected daily using the electronic headache diary.

Additional exploratory variables included changes in quality of life, health status, adverse headache impact on daily living, headache related disability, depression status, work productivity and activity impairment, and patient satisfaction with treatment. Measures for these exploratory efficacy variables included the HIT, MIDAS, MSQOL, EQ-5D-5L, PHQ-2/PHQ-9, WPAI, and PGIC.

Sample size

TV48125-CNS-30049 (Chronic Migraine)

In a Phase 3 study in CM patients, a treatment difference of 1.7 days of monthly average headache days of at least moderate severity between the TEV-48125 675/225/225 mg and placebo treatment groups was observed at month 3. A sample size of 867 patients (i.e., 289 evaluable patients completing the study per treatment group) results in at least 90% power for the study to succeed (assuming a common standard deviation [SD] of

6.29 days) at an alpha level of 0.05. Assuming a 15% discontinuation rate, 340 patients per treatment group were to be randomized.

TV48125-CNS-30050 (Episodic Migraine)

A total of 768 patients were planned to be randomized in this study to have 675 completers (225 completers per treatment group); a 12% drop-out rate was anticipated. A sample size of 675 patients (ie, 225 evaluable patients completing the study per treatment group) will provide 90% power to detect a 1.6 difference in migraine days between an active arm (monthly TEV-48125 225mg or TEV-48125 675mg followed by monthly placebo) and placebo arm at an alpha level of 0.05, assuming a common standard deviation (SD) of 5.2 days.

TV48125-CNS-30051 (LTS)

There are no statistical considerations for this sample size. A total of 1842 patients (867 patients from Study TV48125-CNS-30049, 675 patients from Study TV48125-30050, and approximately 300 patients who did not participate in the pivotal efficacy studies) were planned for enrolment, and a 30% drop-out rate was anticipated.

Randomisation

TV48125-CNS-30049 (Chronic Migraine)

Eligible patients were to be randomized in a 1:1:1 ratio to receive a loading dose of TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg, TEV-48125 at 675 mg followed by monthly placebo, or monthly placebo. Randomization was to be stratified by gender, country, and baseline preventive medication use (yes, no).

TV48125-CNS-30050 (Episodic Migraine)

Eligible patients were to be randomized in a 1:1:1 ratio to receive 1 of the 2 TEV-48125 dose regimens or placebo with stratification based on gender, country, and baseline preventive medication use (yes, no).

Long-Term Study TV48125-CNS-30051 (Chronic Migraine & Episodic Migraine)

Patients rolling over from the pivotal efficacy studies who were randomized to the active treatment groups were to be continue receiving the same treatment throughout the study. Patients rolling over from the pivotal efficacy studies who received placebo and patients not rolling over will be randomly assigned in a 1:1 ratio to receive quarterly TEV-48125 at 675 mg or monthly TEV-48125 at 225 mg (Note: Patients with CM will receive a 675-mg loading dosing at visit 2 and TEV-48125 at 225 mg at each subsequent visit.). Patients were to be stratified by gender, country, and baseline preventive medication use (yes, no) during the pivotal efficacy studies or this study if they are not rolling over from the pivotal efficacy study.

Blinding (masking)

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients were to be blinded to treatment assignment. The personnel responsible for bioanalysis were not to have access to clinical safety and efficacy data and were to provide concentration data to other personnel in a manner that would not identify individual patients (ie, a dummy patient identifier was to be linked to an individual patient's concentration data).

- **Statistical methods**

Efficacy studies (TV48125-CNS-30049 - Chronic Migraine & TV48125-CNS-30050 - Episodic Migraine)

Analysis sets

In both studies, four analysis sets were defined: ITT set (all randomized patients, as randomized), safety set (patients who received at least one dose, as treated), FAS (ITT set with at least one dose and 1 post-baseline efficacy assessment), and PP set (completers without any violations of the inclusion/exclusion criteria or any violations or omissions of the drug administration).

The FAS was to be the primary analysis set for efficacy analyses.

Statistical analyses

In Study 30049 (Chronic Migraine), the primary efficacy endpoint (PE) was defined as 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. The primary endpoint was to be analysed using an analysis of covariance method. The model included treatment, gender, country, and baseline preventive medication use as fixed effects and baseline number of headache days of at least moderate severity and years since onset of migraines as covariates. Ninety-five percent confidence intervals will be constructed for the least squares mean differences between each TEV-48125 group and the placebo group. A hierarchical procedure was to be used to control type 1 error rate. The primary comparison is between the monthly TEV-48125 dose and placebo.

In Study 30050 (Episodic Migraine), the primary efficacy endpoint (PE) 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. The primary endpoint was to be analysed using the same analysis of covariance method as specified for chronic migraine. A hierarchical procedure was to be used to control type 1 error rate. However, the primary comparison was not specified in the protocol.

For both studies, a MMRM model for monthly migraine days was specified in the SAP as supplemental analysis. The MMRM model was to include baseline value, treatment, sex, region, baseline preventive migraine medication use (yes/no), years since onset of migraines, month and treatment-by-month interaction as fixed effects, and patient in the repeated statement as a random effect. The unconstructed covariance structure (sic!) was to be used for the repeated observations within a patient. LS means for the treatment groups, LS means for the treatment differences (TEV-48125 - placebo), and corresponding 95% confidence intervals and associated p-values were to be calculated by month and for the overall treatment period.

Missing values

Per the SAP, missing values were to be neglected if more than 10 observations existed. In detail, if a patient had ≥10 days of the e-diary data after 1st dose of the study drug, his/her monthly average number of days/hours of efficacy variables during the 12-week period were to be prorated to 28 days and set to missing otherwise. For monthly efficacy values, the same algorithm was to be used if ≥ 10 / < 10 entries within the respective month existed.

Long-Term Safety Study (TV48125-CNS-30051 - Chronic Migraine & Episodic Migraine)

The same analysis sets as for the pivotal efficacy studies were used with an additional ADA only data set containing all patients rolling over from the pivotal efficacy studies for ADA assessment only.

This study is a long-term safety study. Efficacy is an exploratory endpoint and as such only analysed descriptively. Missing values will be treated as in the pivotal efficacy studies.

Results

Participant flow

Study 30049 (Chronic Migraine)

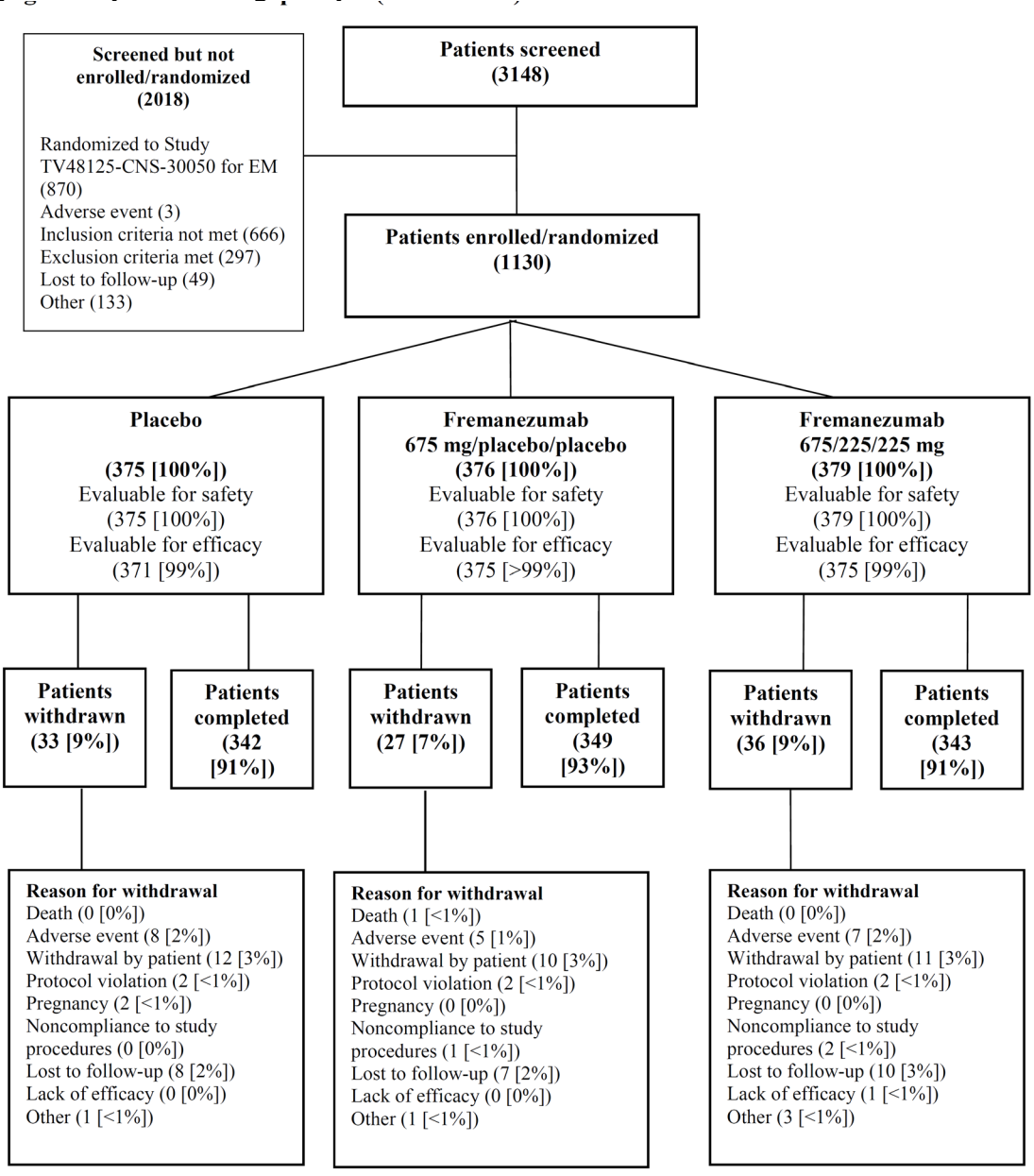


Figure 3 Patient disposition (30049)

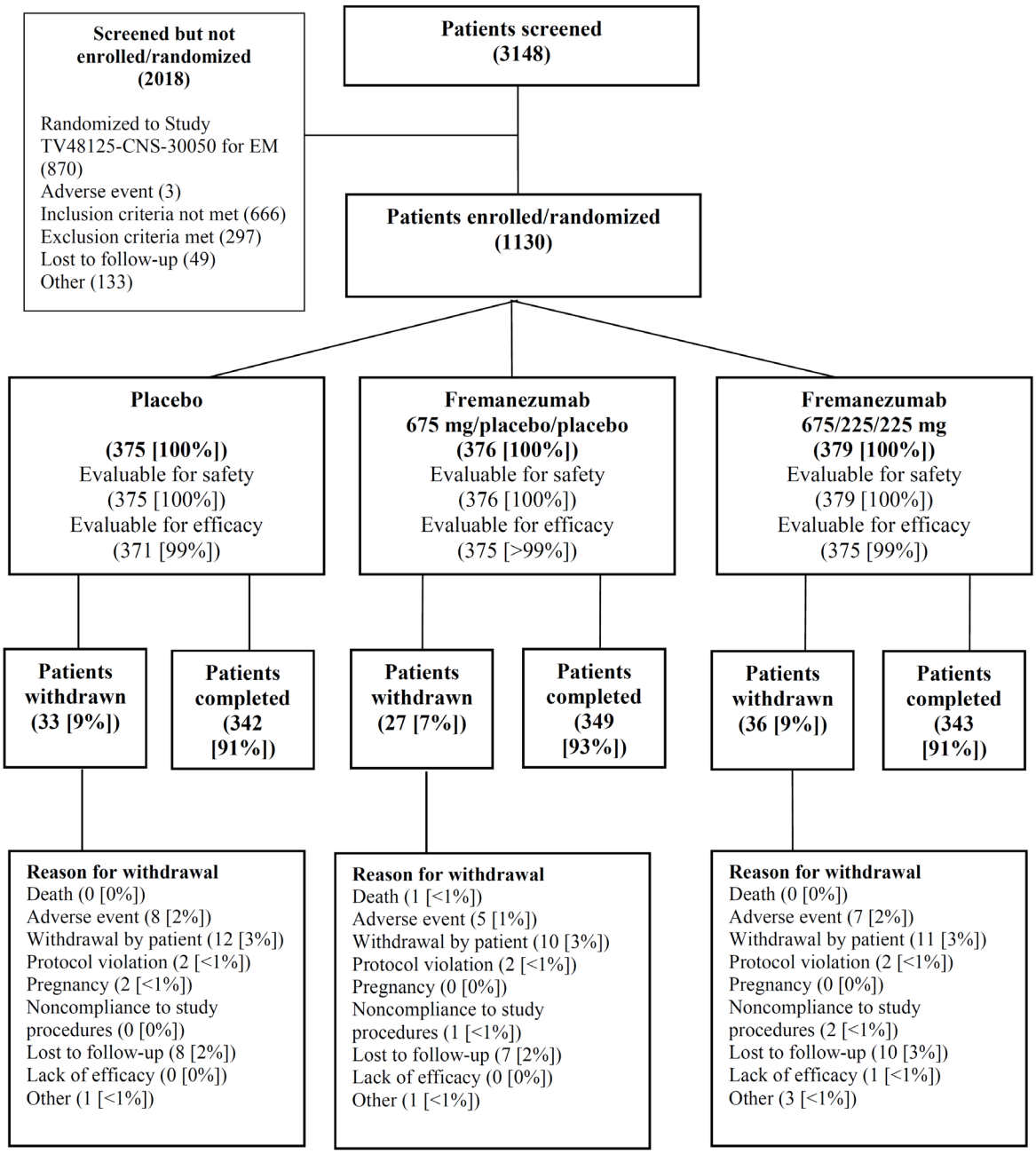


Figure 5 Patient disposition (30049)

Study 30050 (Episodic Migraine)

Figure 2: Patient Disposition (All Patients)

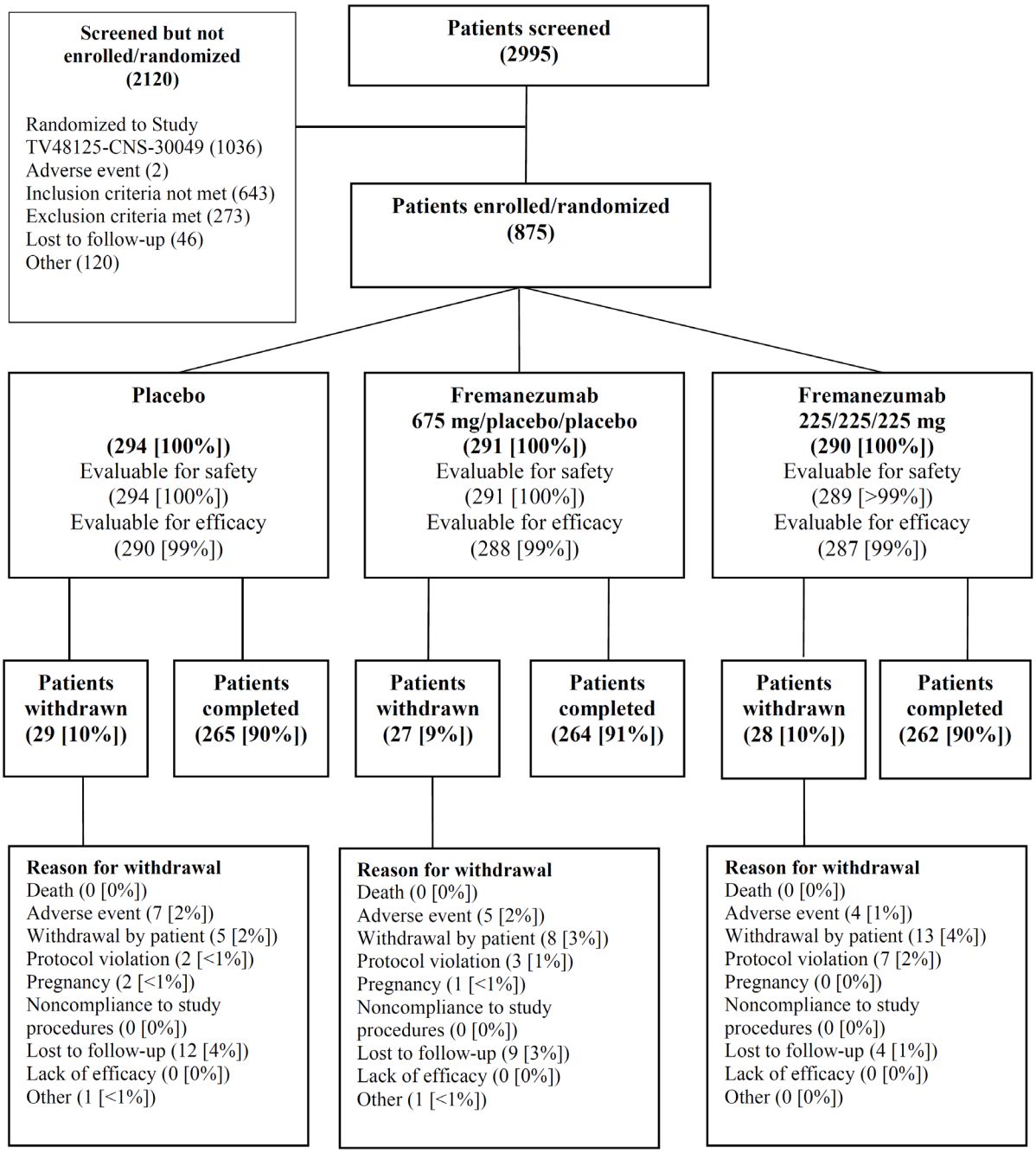


Figure 4 Patient disposition (All patients) study 30050

Study 30051 Long-term study (chronic and episodic migraine)

Figure 3: Patient Disposition (All Patients)

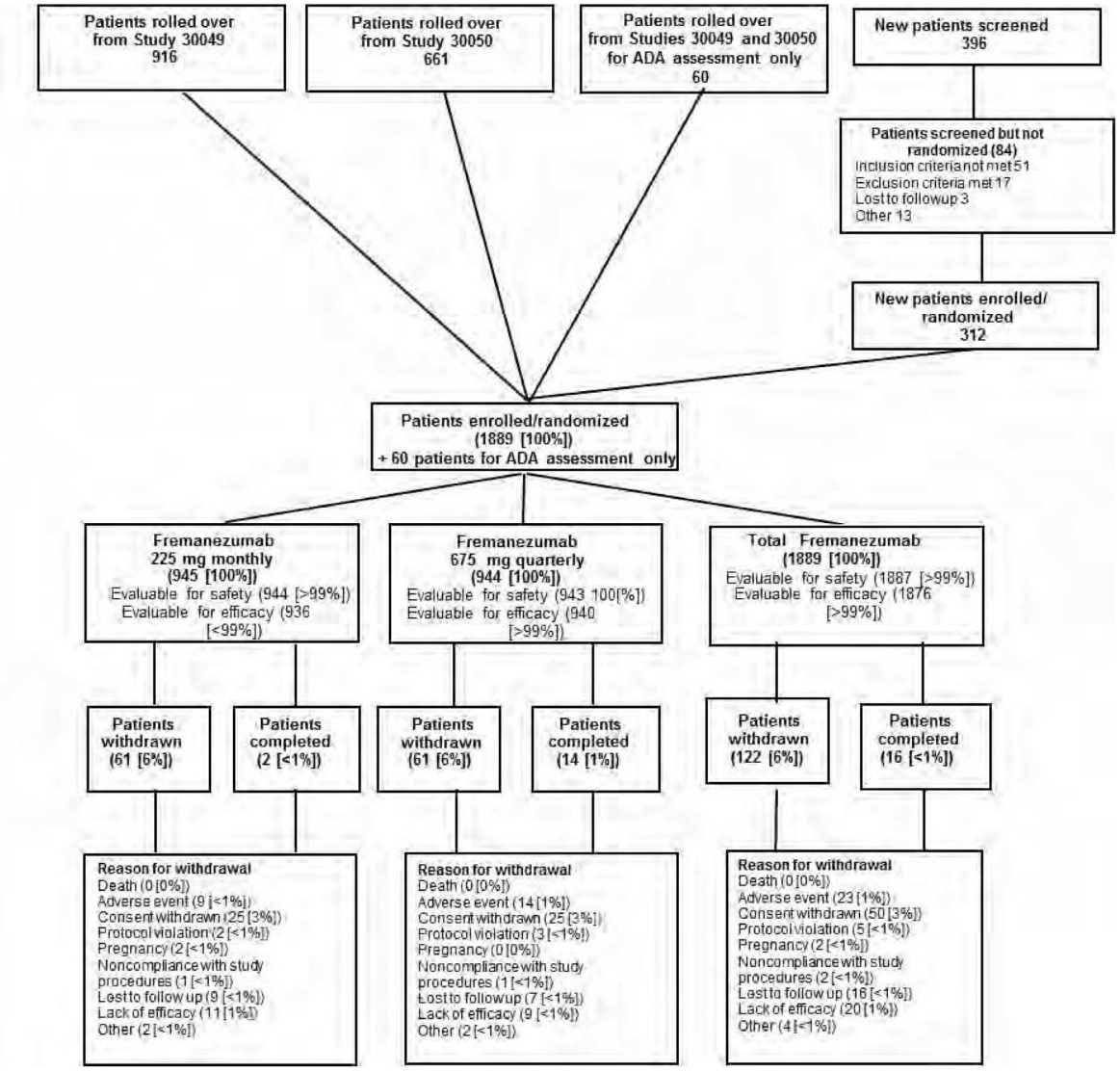


Figure 5 Patient disposition (All patients) study 30051

Recruitment

TV48125-CNS-30049 (Chronic Migraine)

Of the 1130 subjects in the ITT population (i.e., who were randomized and received at least 1 dose of IP), 1121 patients (>99%) were evaluable for efficacy. 1034 patients (92%) completed the study. The mean age of the patients was 41.3 years (range 18 to 71 years). The majority of patients were White (79%) and women (88%).

First patient enrolled on 22 March 2016, last patient completed the double-blind phase on 11 April 2017.

TV48125-CNS-30050 (Episodic Migraine)

Of the 874 subjects in the ITT population (i.e., who were randomized and received at least 1 dose of IP), 865 patients (99%) were evaluable for efficacy. 791 patients (90%) completed the study and 686 patients (78%) rolled into the long-term safety study 30051. The mean age of the patients was 41.8 years (range 18 to 70 years). The majority of patients were White (80%) and women (85%).

First patient enrolled on 23 March 2016, last patient completed the double-blind phase on 10 April 2017.

Long-Term Study TV48125-CNS-30051 (Chronic Migraine & Episodic Migraine)

Of the 1889 subjects in the ITT population (i.e., who were randomized and received at least 1 dose of IP), 1887 patients (>99%) were evaluable for safety. AT the time of the data cut-off only 16 patients (<1%)n hereof 8 with CM and 8 with EM completed the study. The mean age of the patients was 43.1 years (range 18 to 71 years). The majority of patients were White (81%) and women (88%).

First patient enrolled on 25 March 2016, study cut-off date: 31 May 2017.

Baseline data

TV48125-CNS-30049 (Chronic Migraine) and TV48125-CNS-30050 (Episodic Migraine)

In both studies, patients were predominantly female (CM:88%, EM: 85%), White (CM: 79, EM:80%) with a mean age of 41.3 years (CM), and 41.8 years (EM) respectively. The demographic characteristics of sex, age, race, and weight were generally similar across treatment groups.

The average number of years since initial migraine diagnosis was similar across treatment groups (19.1 years to 19.7 years) as was the proportion of patients using concomitant preventive migraine medication (21% to 22%).

The majority (95% to 97%) of patients received acute medications for migraine prior to study entry. Migraine/headache medications most frequently used by patients before and during the study included sumatriptan (609 patients [32%]), ibuprofen (605 patients [32%]), and acetaminophen-aspirin- caffeine (454 patients [24%]).

Demographics, ITT population

Table 3

	Study 30049				Study 30050			
	Placebo	Fremanezumab		Total (N=1130)	Placebo	Fremanezumab		Total (N=875)
Demographic variable	Monthly (N=375)	675 mg quarterly (N=376)	675/225 mg monthly (N=379)		Monthly (N=294)	675 mg quarterly (N=291)	225 mg monthly (N=290)	
Age, years								
n	375	376	379	1130	294	291	290	875
Mean (SD)	41.4 (12.03)	42.0 (12.37)	40.6 (11.95)	41.3 (12.12)	41.3 (12.04)	41.1 (11.41)	42.9 (12.67)	41.8 (12.06)
Median (min, max)	41.0 (19, 70)	43.0 (18, 71)	40.0 (18, 70)	41.0 (18, 71)	41.0 (18, 70)	42.0 (18, 69)	43.0 (18, 70)	42.0 (18, 70)
Age group, n (%)								
≤65 years	372 (99)	367 (98)	371 (98)	1110 (98)	286 (97)	288 (99)	283 (98)	857 (98)
>65 years	3 (<1)	9 (2)	8 (2)	20 (2)	8 (3)	3 (1)	7 (2)	18 (2)
Sex, n (%)								
Men	45 (12)	45 (12)	49 (13)	139 (12)	47 (16)	40 (14)	46 (16)	133 (15)
Women	330 (88)	331 (88)	330 (87)	991 (88)	247 (84)	251 (86)	244 (84)	742 (85)
Race, n (%)								
White	303 (81)	293 (78)	297 (78)	893 (79)	225 (77)	232 (80)	243 (84)	700 (80)
Black	29 (8)	33 (9)	37 (10)	99 (9)	40 (14)	28 (10)	18 (6)	86 (10)
Asian	40 (11)	40 (11)	41 (11)	121 (11)	25 (9)	27 (9)	25 (9)	77 (9)
American Indian or Alaskan Native	0	4 (1)	2 (<1)	6 (<1)	0	1 (<1)	3 (1)	4 (<1)
Pacific Islander	1 (<1)	2 (<1)	0	3 (<1)	0	1 (<1)	0	1 (<1)
Other	2 (<1)	4 (1)	2 (<1)	8 (<1)	4 (1)	2 (<1)	1 (<1)	7 (<1)
Race group, n (%)								
Caucasian	303 (81)	293 (78)	297 (78)	893 (79)	225 (77)	232 (80)	243 (84)	700 (80)
Non-Caucasian	72 (19)	83 (22)	82 (22)	237 (21)	69 (23)	59 (20)	47 (16)	175 (20)

	Study 30049				Study 30050			
	Placebo	Fremanezumab		Total (N=1130)	Placebo	Fremanezumab		Total (N=875)
Demographic variable	Monthly (N=375)	675 mg quarterly (N=376)	675/225 mg monthly (N=379)		Monthly (N=294)	675 mg quarterly (N=291)	225 mg monthly (N=290)	
Ethnicity, n (%)								
Not Hispanic or Latino	343 (91)	352 (94)	338 (89)	1033 (91)	267 (91)	251 (86)	252 (87)	770 (88)
Hispanic or Latino	32 (9)	22 (6)	41 (11)	95 (8)	27 (9)	39 (13)	37 (13)	103 (12)
Unknown	0	1 (<1)	0	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)
Missing	0	1 (<1)	0	1 (<1)	0	0	0	0
Region, n (%)								
North America	276 (74)	279 (74)	280 (74)	835 (74)	229 (78)	233 (80)	231 (80)	693 (79)
Europe[a]	63 (17)	62 (16)	61 (16)	186 (16)	41 (14)	32 (11)	34 (12)	107 (12)
Japan	36 (10)	35 (9)	38 (10)	109 (10)	24 (8)	26 (9)	25 (9)	75 (9)
Weight (kg)								
n	375	376	377	1128	294	291	290	875
Mean (SD)	72.6 (15.58)	72.4 (15.79)	72.5 (16.36)	72.5 (15.90)	75.3 (16.01)	74.2 (15.42)	72.1 (15.77)	73.9 (15.77)
Median (min, max)	71.2 (45, 119)	70.5 (45, 132)	69.8 (44, 119)	70.4 (44, 132)	74.3 (43, 118)	73.0 (45, 120)	69.3 (45, 119)	72.1 (43, 120)
Time since initial migraine diagnosis (years)								
n	375	376	379	1130	294	291	290	875
Mean (SD)	19.9 (12.86)	19.7 (12.84)	20.1 (11.98)	19.9 (12.55)	19.9 (11.87)	20.0 (12.14)	20.7 (12.85)	20.2 (12.28)
Median (min, max)	17.0 (1, 57)	18.0 (1, 61)	18.0 (1, 55)	18.0 (1, 61)	17.5 (1, 51)	19.0 (1, 65)	19.0 (0, 58)	18.0 (0, 65)
Concomitant preventive medication use, n (%)								
Yes	77 (21)	77 (20)	85 (22)	239 (21)	62 (21)	58 (20)	62 (21)	182 (21)
Topiramate use for migraine in the past, n (%)								
Yes	117 (31)	106 (28)	117 (31)	340 (30)	53 (18)	51 (18)	64 (22)	168 (19)

	Study 30049				Study 30050			
	Placebo	Fremanezumab		Total (N=1130)	Placebo	Fremanezumab		Total (N=875)
Demographic variable	Monthly (N=375)	675 mg quarterly (N=376)	675/225 mg monthly (N=379)		Monthly (N=294)	675 mg quarterly (N=291)	225 mg monthly (N=290)	
OnabotulinumtoxinA use for migraine in the past, n (%)								
Yes	49 (13)	66 (18)	50 (13)	165 (15)	9 (3)	15 (5)	16 (6)	40 (5)
Triptans/ergot use for migraine during baseline, n (%)								
Yes	192 (51)	208 (55)	187 (49)	587 (52)	137 (47)	152 (52)	148 (51)	437 (50)
Any acute headache medication use, n (%)								
Yes	358 (95)	359 (95)	360 (95)	1077 (95)	280 (95)	281 (97)	279 (96)	840 (96)
No	17 (5)	17 (5)	19 (5)	53 (5)	13 (4)	10 (3)	9 (3)	32 (4)
Missing	0	0	0	0	1 (<1)	0	2 (<1)	3 (<1)

Baseline efficacy variables by treatment group, electronic headache diary data

Table 4

	Study 30049				Study 30050			
	Placebo	Fremanezumab		Total (N=1130)	Placebo	Fremanezumab		Total (N=875)
Variable Statistic	Monthly (N=375)	675 mg quarterly (N=376)	675/225 mg monthly (N=379)		Monthly (N=294)	675 mg quarterly (N=291)	225 mg monthly (N=290)	
Number of headache days of at least moderate severity								
n	375	376	379	1130	293	291	288	872
Mean (SD)	13.3 (5.82)	13.2 (5.47)	12.8 (5.80)	13.1 (5.70)	6.9 (3.12)	7.2 (3.14)	6.8 (2.90)	7.0 (3.06)
Median (min, max)	12.6 (0, 28)	13.0 (1, 28)	12.0 (0, 28)	12.6 (0, 28)	7.0 (0, 15)	7.0 (0, 16)	6.5 (0, 15)	7.0 (0, 16)
Number of migraine days								
n	375	376	379	1130	293	291	288	872
Mean (SD)	16.4 (5.15)	16.2 (4.88)	16.0 (5.19)	16.2 (5.07)	9.1 (2.65)	9.3 (2.65)	8.9 (2.63)	9.1 (2.64)
Median (min, max)	15.5 (7, 28)	15.9 (7, 28)	15.4 (5, 28)	15.7 (5, 28)	9.0 (4, 15)	9.0 (4, 17)	9.0 (3, 16)	9.0 (3, 17)
Number of days of use of any acute headache medications								
n	375	376	379	1130	293	291	288	872
Mean (SD)	13.0 (6.92)	13.1 (6.79)	13.1 (7.20)	13.1 (6.96)	7.7 (3.60)	7.8 (3.74)	7.7 (3.37)	7.8 (3.57)
Median (min, max)	13.5 (0, 28)	14.0 (0, 28)	13.6 (0, 28)	13.8 (0, 28)	8.0 (0, 15)	8.0 (0, 16)	7.7 (0, 15)	8.0 (0, 16)
Number of headache days of any duration and any severity								
n	375	376	379	1130	293	291	288	872
Mean (SD)	20.3 (4.19)	20.4 (3.93)	20.3 (4.26)	20.3 (4.13)	11.2 (2.45)	11.1 (2.42)	11.0 (2.49)	11.1 (2.45)
Median (min, max)	19.3 (11, 28)	20.0 (13, 28)	19.0 (8, 28)	19.6 (8, 28)	11.7 (6, 16)	11.0 (6, 18)	11.2 (6, 17)	11.4 (6, 18)
Number of headache hours of any severity								
n	375	376	379	1130	293	291	288	872
Mean (SD)	127.2 (86.03)	119.1 (73.23)	129.0 (88.62)	125.1 (82.95)	55.7 (26.47)	57.1 (29.97)	57.1 (30.04)	56.7 (28.84)
Median (min, max)	103.6 (22, 672)	104.1 (24, 672)	108.0 (21, 672)	105.2 (21, 672)	50.0 (9, 192)	50.0 (8, 206)	51.7 (9, 211)	50.2 (8, 211)

Long-Term Study TV48125-CNS-30051 (Chronic Migraine & Episodic Migraine)

Overall, patients were predominantly female (CM:88%, EM: 86%), White (CM+EM:81%) with a mean age of 43.1 years (CM)/44 years (EM). The demographic characteristics of sex, age, race, and BMI were generally similar across treatment groups.

The majority (99%) of patients received medications for migraine prior to study entry. Migraine/headache medications most frequently used by patients before and during the study included sumatriptan (609 patients [32%]), ibuprofen (605 patients [32%]), and acetaminophenaspirin- caffeine (454 patients [24%]).

Numbers analysed

TV48125-CNS-30049 (Chronic Migraine)

Of the 1130 patients who were randomized, 1130 were included in the ITT population, 1130 in the safety population, 1121 in the FAS, and 959 in the PP analysis set.

TV48125-CNS-30050 (Episodic Migraine)

Of the 875 patients who were randomized and included in the ITT population, 874 patients were included in the safety population, 865 in the FAS, and 747 in the PP analysis set.

Long-Term Study TV48125-CNS-30051 (Chronic Migraine & Episodic Migraine)

Of the 1889 patients who were enrolled/randomized, 1889 were included in the ITT population, 1887 in the safety population, 1876 in the FAS, and an additional 60 patients in the ADA only analysis set.

Outcomes and estimation

TV48125-CNS-30049 (Chronic Migraine)

Primary variable

Table 5 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 – ANCOVA Results and Wilcoxon Rank Sum Test (FAS)

Statistic	Placebo (N=371)	Fremanezumab 675 mg/placebo/placebo (N=375)	Fremanezumab 675/225/225 mg (N=375)
LS mean (SE)	-2.5 (0.31)	-4.3 (0.31)	-4.6 (0.30)
95% confidence interval	-3.06, -1.85	-4.87, -3.66	-5.16, -3.97
Comparison with placebo			
LS mean (SE)	--	-1.8 (0.33)	-2.1 (0.33)
95% confidence interval	--	-2.46, -1.15	-2.76, -1.45
p-value	--	<0.0001	<0.0001
Comparison with 675 mg/placebo/placebo			
LS mean (SE)	--	--	-0.3 (0.33)
95% confidence interval	--	--	-0.96, 0.36
Non-parametric analysis			
25% percentile	-5.6	-7.7	-7.8
Median	-2.5	-4.2	-4.5
75% percentile	0.0	-1.7	-1.7
Wilcoxon rank-sum test (p-value vs. placebo)	--	<0.0001	<0.0001

ANCOVA=analysis of covariance; FAS=full analysis set; LS=least squares; N=number of patients; SE=standard error

Change from baseline in the monthly average number of headache days of at least moderate severity

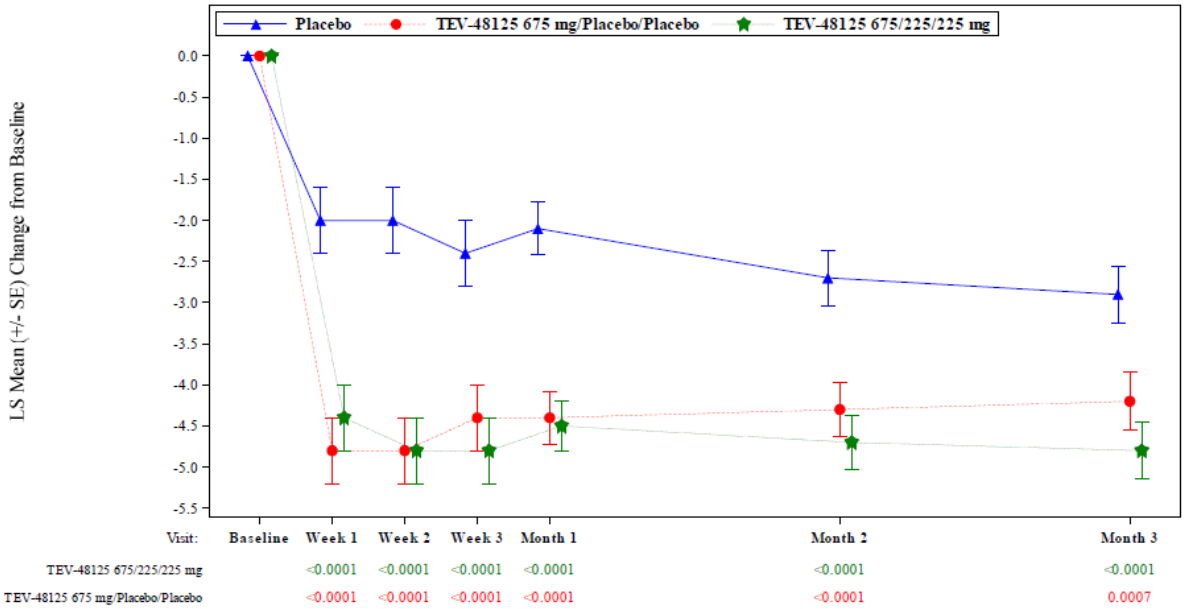


Figure 6

FAS=full analysis set; LS=least squares; MMRM=mixed-effects model for repeated measures; SE=standard error; TEV-48125=fremanezumab.

Key Secondary variables

Table 6 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 –ANCOVA Results (FAS)

	Placebo (N=371)	Fremanezumab 675 mg/placebo/placebo (N=375)	Fremanezumab 675/225/225 mg (N=375)
LS mean (SE)	-3.2 (0.35)	-4.9 (0.35)	-5.0 (0.35)
95% confidence interval	-3.86, -2.47	-5.59, -4.20	-5.70, -4.33
Comparison with placebo			
LS mean (SE)	--	-1.7 (0.39)	-1.8 (0.39)
95% confidence interval	--	-2.48, -0.97	-2.61, -1.09
p-value	--	<0.0001	<0.0001
Comparison with 675 mg/placebo/placebo			
LS mean (SE)	--	--	-0.1 (0.38)
95% confidence interval	--	--	-0.88, 0.63

ANCOVA=analysis of covariance; FAS=full analysis set; LS=least squares; N=number of patients; SE=standard error of the mean.

Change from baseline in the monthly number of migraine days by month and treatment group using MMRM (FAS)

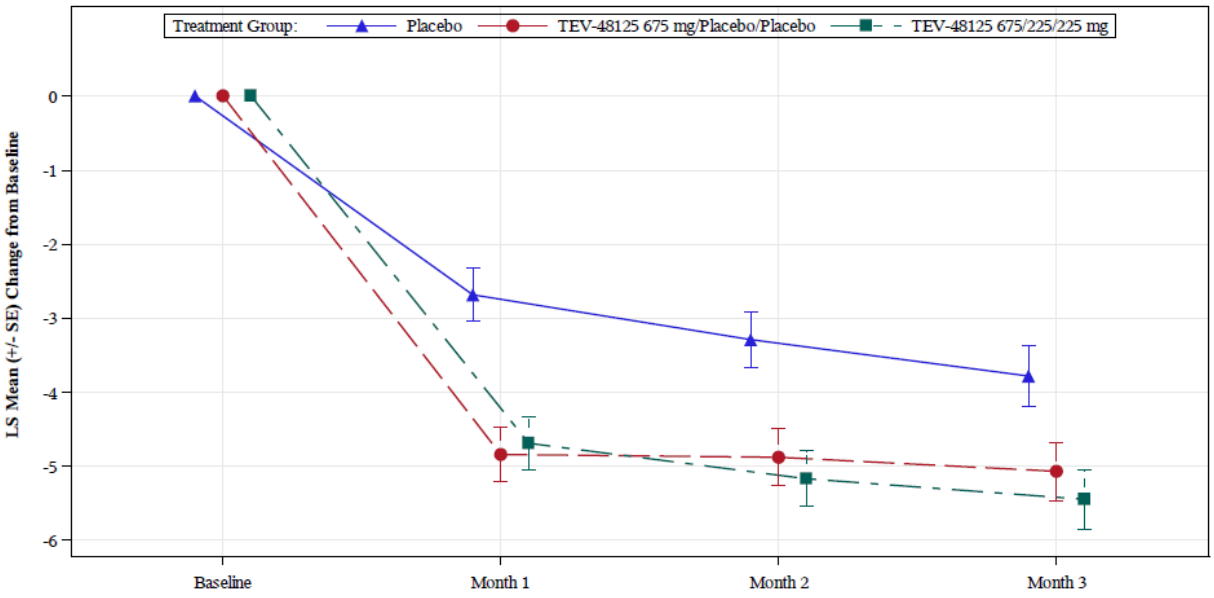


Figure 7

Table 7 Proportion of patients reaching 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 (FAS)

	Placebo (N=371) n (%)	Fremanezumab 675 mg/ placebo/placebo (N=375) n (%)	P-value fremanezumab 675 mg/placebo/ placebo vs placebo	Fremanezumab 675/225/225 mg (N=375) n (%)	P-value fremanezumab 675/225/225 mg vs placebo
Month 1, n	370	375	--	374	--
Yes	80 (21.6)	155 (41.3)	--	150 (40.0)	--
No	290 (78.2)	220 (58.7)	<0.0001	224 (59.7)	<0.0001
Month 2, n	355	365	--	361	--
Yes	90 (24.3)	149 (39.7)	--	157 (41.9)	--
No	265 (71.4)	216 (57.6)	<0.0001	204 (54.4)	<0.0001
Month 3, n	342	350	--	345	--
Yes	98 (26.4)	152 (40.5)	--	167 (44.5)	--
No	244 (65.8)	198 (52.8)	<0.0001	178 (47.5)	<0.0001
Overall[a], n	370	375	--	374	--
Yes	67 (18.1)	141 (37.6)	--	153 (40.8)	--
No	303 (81.7)	234 (62.4)	<0.0001	221 (58.9)	<0.0001

FAS=full analysis set; N=number of patients; n=number of patients with data available.

Notes: P-value based on Cochran-Mantel-Haenszel test stratified by baseline preventive medication use. For the overall analysis, patients who discontinued early were considered non-responders.

Other secondary variables

Change from baseline in the monthly number of days of use of any acute headache medications by months and treatment group using MMRM (FAS)

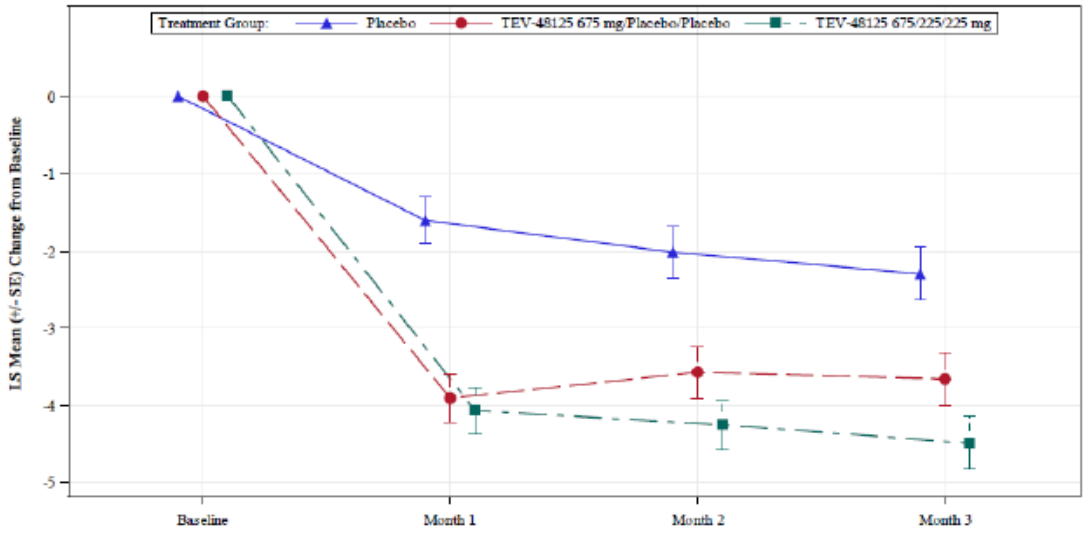


Figure 8

FAS=full analysis set; LS=least squares; MMRM=mixed-effects model for repeated measures; SE=standard error.

Note: Nominal p≤0.0007 for all comparisons vs placebo at all time points.

TV48125-CNS-30050 (Episodic Migraine)

Primary variable

Table 8 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 – ANCOVA Results and Wilcoxon Rank-Sum Test (FAS)

Time point statistic	Placebo (N=290)	Fremanezumab 675 mg/placebo/placebo (N=288)	Fremanezumab 225/225/225 mg (N=287)
LS mean (SE)	-2.2 (0.24)	-3.4 (0.25)	-3.7 (0.25)
95% confidence interval	(-2.68, -1.71)	(-3.94, -2.96)	(-4.15, -3.18)
Comparison with placebo			
LS mean (SE)	—	-1.3 (0.27)	-1.5 (0.28)
95% confidence interval	—	(-1.79, -0.72)	(-2.01, -0.93)
p-value	—	<0.0001	<0.0001
Comparison with 675 mg/placebo/placebo			
LS mean (SE)	—	—	-0.2 (0.28)
95% confidence interval	—	—	(-0.75, 0.33)
Non-parametric analysis			
25% percentile	-4.7	-6.4	-6.2
Median	-2.7	-4.0	-4.2
75% percentile	-0.5	-1.9	-2.0
Wilcoxon rank-sum test p-value (vs. placebo)	—	<0.0001	<0.0001

ANCOVA=analysis of covariance; FAS=full analysis set; LS=least squares; N=number of patients; n=number of patients with observations; SE=standard error.

Change from baseline in the monthly number of migraine days by treatment group using MMRM (FAS)

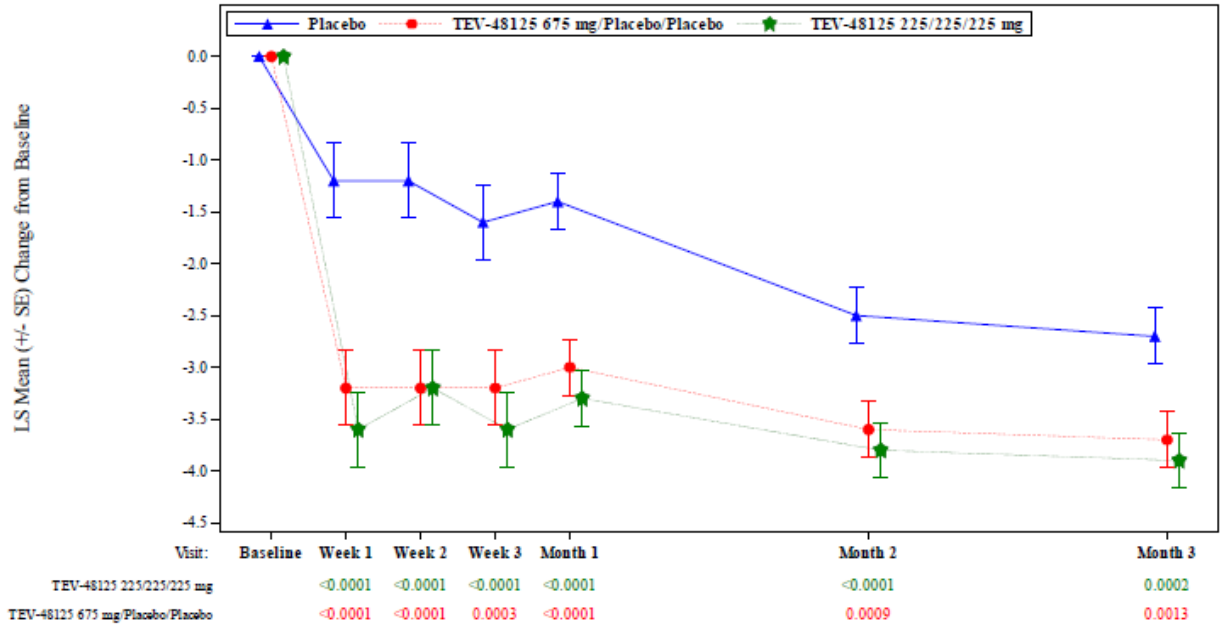


Figure 9

FAS=full analysis set; LS=least squares; MMRM=mixed-effects model for repeated measures; SE=standard error; TEV-48125=fremanezumab.

Note: P-values for Week 1, 2, and 3 and Month 2 are nominal.

Key secondary variables

Table 9 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 (FAS)

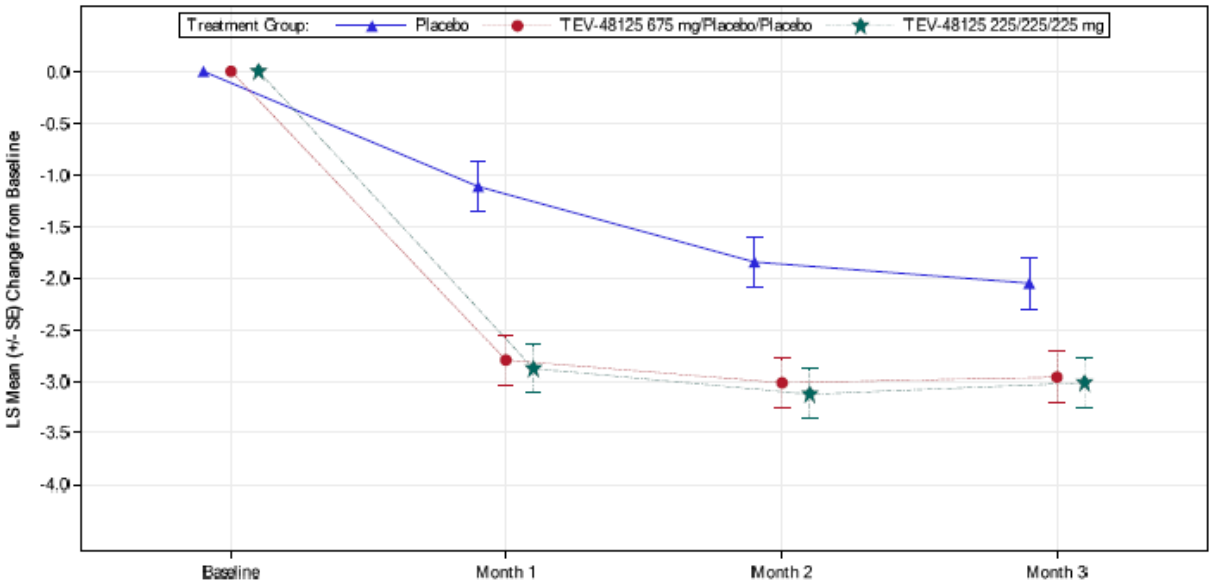
Time point statistic	Placebo (N=290) n (%)	Fremanezumab 675 mg/placebo/ placebo (N=288) n (%)	p-value fremanezumab 675 mg/placebo/ placebo vs placebo	Fremanezumab 225/225/225 mg (N=287) n (%)	p-value fremanezumab 225/225/225 mg vs placebo
Month 1, n	290	288	—	287	—
Yes	73 (25.2)	127 (44.1)	—	135 (47.0)	—
No	217 (74.8)	161 (55.9)	<0.0001	152 (53.0)	<0.0001
Month 2, n	274	274	—	274	—
Yes	101 (34.8)	135 (46.9)	—	139 (48.4)	—
No	173 (59.7)	139 (48.3)	0.0032	135 (47.0)	0.0010
Month 3, n	268	269	—	263	—
Yes	108 (37.2)	141 (49.0)	—	147 (51.2)	—
No	160 (55.2)	128 (44.4)	0.0048	116 (40.4)	0.0003
Overall, n	290	288	—	287	—
Yes	81 (27.9)	128 (44.4)	—	137 (47.7)	—
No	209 (72.1)	160 (55.6)	<0.0001	150 (52.3)	<0.0001

Table 10 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 1st dose of study drug – ANCOVA Results and Wilcoxon Rank-Sum Test (FAS)

	Placebo (N=290)	Fremanezumab 675 mg/placebo/placebo (N=288)	Fremanezumab 225/225/225 mg (N=287)
LS mean (SE)	-1.6 (0.21)	-2.9 (0.22)	-3.0 (0.22)
95% confidence interval	(-2.04, -1.20)	(-3.34, -2.48)	(-3.41, -2.56)
Comparison with placebo			
LS mean (SE)	—	-1.3 (0.24)	-1.4 (0.24)
95% confidence interval	—	(-1.76, -0.82)	(-1.84, -0.89)
p-value	—	<0.0001	<0.0001
Comparison with 675 mg/placebo/placebo			
LS mean (SE)	—	—	-0.1 (0.24)
95% confidence interval	—	—	(-0.55, 0.40)
Non-parametric analysis			
25% percentile	-4.0	-5.6	-5.2
Median	-1.7	-3.0	-3.2
75% percentile	0.0	-0.8	-1.2
Wilcoxon rank-sum test p-value (vs. placebo)	—	<0.0001	<0.0001

ANCOVA=analysis of covariance; FAS=full analysis set; LS=least squares; N=number of patients; n=number of patients with observations; SE=standard error.

Figure 10 Change from baseline in the monthly number of days of use of any acute headache medications by months and treatment group using MMRM (FAS)



FAS=full analysis set; LS=least squares; MMRM=mixed-effects model for repeated measures; SE=standard error.

Note: Nominal p≤0.0023 for all comparisons vs placebo at all time points

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11

Title: **A multicentre, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of 2 dose regimens of subcutaneous administration of fremanezumab (TEV-48125) versus placebo for the preventive treatment of chronic migraine**			
Study identifier	**TV48125-CNS-30049**		
Design	16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the safety, tolerability, and efficacy of 2 dose regimens of sc fremanezumab and placebo in adults with CM. The study consisted of a screening visit, a 28-day run-in period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose of study drug).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks (84 days) 28 days not applicable
Hypothesis	Superiority		
Treatments groups	Fremanezumab 675/225/225 mg sc once monthly		N = 379
	Fremanezumab 675 mg/ placebo/placebo sc once monthly		N = 376
	Placebo		N = 375
Endpoints and definitions	Primary endpoint	Headache days of at least moderate severity	Change in monthly average number of headache days of at least moderate severity during the 12-week treatment period
	Secondary endpoint	Migraine days of at least moderate severity	Change in monthly average number of migraine days of at least moderate severity during the 12-week treatment period
	Secondary Endpoint	>50% reduction rates	Proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity
	Secondary Endpoint	Acute headache medication	Reduction in the monthly average number of days of use of acute headache medication
Database lock	Undisclosed		

Results and Analysis

Primary Endpoint				
Analysis population and time point description	FAS			
Monthly average number of headache days of at least moderate severity during the 12-week treatment period	Treatment group	**PBO**	**Fremanezumab 675/225/225**	**Fremanezumab 675 mg/ placebo/placebo**
	Number of subject	371	375	375
	LS mean (SE)	-2.5 (0.31)	-4.6 (0.30)	-4.3 (0.31)
	95% confidence interval	-3.06, -1.85	-5.16, -3.97	-4.87, -3.66
	LS mean vs. placebo		-2.1 (0.33)	-1.8 (0.33)
	95% confidence interval vs. placebo		-2.76, -1.45	-2.46, -1.15
	p-value vs placebo		<0.0001	<0.0001
Key secondary endpoints				
Monthly average number of migraine days during the 12-week treatment period		**PBO**	**Fremanezumab 675/225/225**	**Fremanezumab 675 mg/ placebo/placebo**
	LS mean (SE)	-3.2 (0.35)	-5.0 (0.35)	-4.9 (0.35)
	95% confidence interval	-3.86, -2.47	-5.70, -4.33	-5.59, -4.20
	LS mean vs. placebo		-1.8 (0.39)	-1.7 (0.39)
	95% confidence interval vs. placebo		-2.61, -1.09	-2.48, -0.97
	p-value vs placebo		<0.0001	<0.0001
Proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least				
	Month 1, n (%)	80 (21.6)	155 (41.3)	150 (40.0)
	Month 2, n (%)	90 (24.3)	149 (39.7)	157 (41.9)
	Month 3, n (%)	98 (26.4)	152 (40.5)	167 (44.5)

moderate severity	Overall	67 (18.1)	141 (37.6)	153 (40.8)
	p-value vs placebo		<0.0001	<0.0001
Reduction in the monthly average number of days of use of acute headache medication				
	LS mean (SE)	-1.9 (0.30)	-3.7 (0.30)	-4.2 (0.30)
	95% confidence interval	-2.48, -1.28	-4.25, -3.06	-4.79, -3.61
	LS mean vs. placebo		-1.8 (0.33)	-2.3 (0.33)
	95% confidence interval vs. placebo		-2.43, -1.12	-2.97, -1.67
	p-value vs placebo		<0.0001	<0.0001

Title:

A multicentre, randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of 2 dose regimens of subcutaneous administration of fremanezumab (TEV-48125) versus placebo for the preventive treatment of episodic migraine

Study identifier	**TV48125-CNS-30050**		
Design	16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy, safety, and tolerability of 2 dose regimens of sc fremanezumab and placebo in adults with EM. The study consisted of a screening visit, a 28-day run-in period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose of study drug).		
	Duration of main phase:		12 weeks (84 days)
	Duration of Run-in phase:		28 days
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Fremanezumab 225/225/225 mg sc once monthly		N = 290
	Fremanezumab 675 mg/ placebo/placebo sc once monthly		N = 291
	Placebo		N = 294
Endpoints and definitions	Primary endpoints	Migraine days	Change in monthly average number of migraine days during the 12-week treatment period
		Safety	Safety and tolerability of 2 dose regimens of fremanezumab in the preventive treatment of EM

	Secondary Endpoint	>50% reduction rates	Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week treatment period
	Secondary Endpoint	Acute headache medication	Reduction in the monthly average number of days of use of acute headache medication
Database lock	Undisclosed		

Results and Analysis

Primary Endpoint

Analysis population and time point description	FAS			
Monthly average number of migraine days during the 12-week treatment period		**PBO**	**Fremanezumab 225/225/225**	**Fremanezumab 675 mg/ placebo/placebo**
	Number of subject	290	287	288
	LS mean (SE)	-2.2 (0.24)	-3.7 (0.25)	-3.4 (0.25)
	95% confidence interval	-2.68, -1.71	- 4.15, -3.18	-3.94, -2.96
	LS mean vs. placebo		-1.5 (0.28)	-1.3 (0.27)
	95% confidence interval vs. placebo		-2.01, -0.93	-1.79, -0.72
	p-value vs placebo		<0.0001	<0.0001

Key secondary endpoints

Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period				
	Month 1, n (%)	73 (25.2)	135 (47.0)	127 (44.1)
	Month 2, n (%)	101 (34.8)	139 (48.4)	135 (46.9)
	Month 3, n (%)	108 (37.2)	147 (51.2)	141 (49.0)
	Overall	81 (27.9)	137 (47.7)	128 (44.4)
Reduction in the monthly average number of days of use of acute headache medication				
	LS mean (SE)	-1.6 (0.21)	-3.0 (0.22)	-2.9 (0.22)
	95% confidence interval	-2.04, -1.20	-3.41, -2.56	-3.34, -2.48

	LS mean vs. placebo		-1.4 (0.24)	-1.3 (0.24)
	95% confidence interval vs. placebo		-1.84, -0.89	-1.76, -0.82
	p-value vs placebo		<0.0001	<0.0001

Title:

A multicentre, randomized, double-blind, parallel-group study evaluating the long-term safety, tolerability, and efficacy of subcutaneous administration of fremanezumab (TEV-48125) for the preventive treatment of migraine

Study identifier	**TV48125-CNS-30051**		
Design	Approximately 19-month, multicenter, randomized, double-blind, parallel-group study to evaluate the long-term safety, tolerability, and efficacy of sc fremanezumab in adult patients with migraine.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks (84 days) 28 days not applicable
Hypothesis	Superiority		
Treatments groups	Fremanezumab 225 mg sc once monthly with 675 mg loading dose		N = 945, hereof 554 with CM and 382 with EM in the FAS
	Fremanezumab 675 mg sc every three month		N = 944, hereof 548 with CM and 392 with EM in the FAS
Endpoints and definitions	Primary endpoint	Long-term safety and tolerability	To evaluate the long-term safety and tolerability of sc fremanezumab in the preventive treatment of migraine
	Secondary endpoint	none	n.a.
	Exploratory endpoint	Reduction of migraine days	To evaluate the reduction of the number of migraine days
	Exploratory endpoint	Reduction of headache days (moderate severity)	To evaluate the reduction of the number of headache days of at least moderate severity
Database lock	This study is ongoing and the current clinical study report is based on the data cut-off date of 31 May 2017.		

Results and Analysis				
Exploratory Endpoints				
Analysis population and time point description	FAS; study ongoing; based on data cut-off date of 31 May 2017;			
Change from baseline in monthly average number of migraine days by month	**CM**		**Fremanezumab 225mg monthly (675 mg loading dose)**	**Fremanezumab 675 mg quarterly**
Month 1	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	248 10.4/-6.7 7.95 / 6.15 0.50/ 0.39	241 11.0/ -5.9 7.98/ 6.23 0.51/ 0.40
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	305 9.5/ -6.4 7.3/ 5.98 0.42/ 0.34	304 9.9/ -6.2 7.63/ 6.67 0.44/ 0.38
Month 2	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	247 10.0/ -7.0 7.93/ 6.24 0.50/0.40	234 10.9/ -6.0 7.87/ 6.23 0.51/ 0.41
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	295 9.1/-6.8 7.21/ 6.26 0.41/ 0.36	290 10.1/ -6.0 7.69/ 6.63 0.45/0.39
Month 3	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	230 10.2/ - 6.7 8.05/ 6.56 0.53/ 0.43	220 11.0/ -5.8 8.01/ 5.84 0.54/ 0.39
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	265 9.1/ -6.8 7.37/ 6.79 0.45/ 0.42	265 9.9/ -6.0 7.76/ 6.80 0.48/ 0.42

Month 6	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	143 9.1/ -7.9 8.10/ 6.36 0.68/ 0.53	141 11.4/ -5.7 7.99/ 5.92 0.67/ 0.50
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	111 7.1/ -7.8 5.62/ 5.58 0.53/ 0.53	108 8.5/ -7.3 7.53/ 6.66 0.72/ 0.64
Month 12	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	71 10.9/ -6.9 9.12/ 6.98 1.08/ 0.83	66 11.0/ -6.7 8.39/ 6.25 1.03/ 0.77
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	1 13.4/ -9.8	6 5.5/ -9.4 8.09/ 8.70 3.30/ 3.55
Change from baseline in monthly average number of migraine days by month **Month 1**	**EM**		**Fremanezumab225mg monthly (675 mg loading dose)**	**Fremanezumab 675 mg quarterly**
	New/placebo rollover patients	N Mean/ Change SD/ Change SE/ Change	167 4.5/ -4.7 3.80/ 3.41 0.29/ 0.26	175 3.9/ -5.3 3.67/ 3.79 0.28/ 0.29
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	212 4.6/ -4.5 3.96/ 3.74 0.27/ 0.26	214 4.7/ -4.6 4.46/ 4.06 0.31/ 0.28

Month 2	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	158 4.5/ -4.8 4.04/ 3.5 0.32/ 0.28	171 4.3/ -4.9 3.93/ 3.92 0.30/ 0.30
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	210 4.4/ -4.6 4.08/ 3.75 0.28/ 0.26	207 4.2/ - 5.0 4.10/ 3.97 0.28/ 0.28
Month 3	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	148 4.7/ -4.6 4.61/ 3.72 0.38/ 0.31	164 4.6/ -4.6 4.51/ 4.28 0.35/ 0.33
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	200 3.9/ -5.0 4.08/ 3.81 0.29/ 0.27	191 4.3/ -4.8 4.05/ 3.99 0.29/ 0.29
Month 6	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	94 4.6/ -4.7 4.43/ 3.48 0.46/ 0.36	93 4.3/ -4.8 3.98/ 4.22 0.41/ 0.44
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	84 3.5/-5.4 4.13/ 4.10 0.45/ 0.45	85 3.5/ -5.5 3.99/ 3.83 0.43/ 0.42

Month 12	**New/placebo rollover patients**	N Mean/ Change SD/ Change SE/ Change	41 4.9/ -4.6 4.52/ 4.23 0.71/ 0.66	47 3.8/ -6.0 3.50/ 3.60 0.51/ 0.52
	Active rollover patients	N Mean/ Change SD/ Change SE/ Change	2 1.4/ -7.4 0.64/ 0.86 0.45/0.61	2 7.4/ -2.7 5.08/ 2.64 3.59/ 1.87

Analysis performed across trials (pooled analyses and meta-analysis)

No true across trials analyses have been performed.

Comparing within each study (i.e. by treatment group) and across the studies, the patient populations were consistent with an adult migraine population and were generally similar with respect to age, weight, racial composition, and ethnic composition. The majority of patients in both studies were women, consistent with the observed gender distribution within the global adult migraine population.

Within each study, the treatment groups were similar in regard to the time since initial migraine diagnosis. The time since initial migraine diagnosis in patients was approximately 20 years in both Study 30049 and Study 30050.

In Study 30049 and Study 30050, the number of patients using preventive medications at baseline (21% overall in each study) was comparable across the treatment groups. In Study 30049, the most frequently reported preventive medications were topiramate, amitriptyline, and valproate. In Study 30050, topiramate was reported most frequently.

Supportive study(ies)

LBR-101-022

The primary and secondary objectives of this study were to evaluate the number of monthly treated with TEV-48125 for 12 weeks (2 dose regimens: monthly 675 mg or monthly 225 mg) in comparison with placebo. Exploratory objectives were to evaluate the number of headache hours and headache days of different severity levels, the number of days with nausea or vomiting, the number of days with photophobia and phonophobia, as well as consumption of headache acute medications and migraine-related disability with TEV-48125 treatment.

A statistically significant difference in favor of TEV-48125 was observed for both the high and low TEV-48125 dose regimens in comparison with placebo for the primary endpoint, that is, change from baseline in monthly migraine days at month 3. Improvements were evident as early as 1 month after administration of the first dose of TEV-48125.

At month 3, statistically significant differences in favor of TEV-48125 were also observed in regard to the number of days with headache of any severity (ie, secondary objective); fewer headache days were reported with both the high and low TEV-48125 dose regimens than with placebo.

Analyses of the exploratory endpoints showed similar improvements: reductions were observed in the number of headache days with headache of at least moderate severity, the number of hours with headache of moderate or severe intensity, the number of hours with headache of any severity, the number of days with photophobia and phonophobia, and the number of days using acute headache medication in patients treated with both the high and low dose regimen of TEV-48125 in comparison with placebo throughout the study. Initial improvement in comparison with placebo was observed in the 675-mg treatment group in regard to the number of days with nausea or vomiting, whereas treatment with 225 mg resulted in improvement compared to placebo throughout the study. Migraine-related disability, as assessed by the MIDAS questionnaire, showed that high and low dose TEV-48125 decreased migraine-related disability in comparison with placebo.

Ad hoc analysis of the primary efficacy variable showed that more patients reported at least 50% reduction in monthly migraine days in the TEV-48125 treatment groups than in the placebo group during the study.

Ad hoc analysis based on preventive migraine medication use demonstrated that TEV-48125 treatment is efficacious with and without the use of preventive migraine medication. Ad hoc analysis of patients using triptans at baseline showed similar results; decreases in the number of days using triptans to treat headaches in the TEV-48125 treatment groups in comparison with the placebo group were observed throughout the study.

PK analysis of trough plasma concentrations of TEV-48125 indicated that steady state levels were not achieved following 3 months of monthly TEV-48125 dosing at 675-mg and 225-mg dose levels. Comparison of the trough concentrations on Days 29, 57, and 85 relative to dose indicated that exposure increased with increasing dose in a manner that appears to be proportional.

In conclusion, patients in this study treated with TEV-48125 showed clinical improvement in HFEM, which was maintained throughout the 3-month duration of the study.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Design and conduct of clinical studies

Study 30049 (Chronic Migraine)

The study design, study endpoints/objectives and doses tested are considered acceptable. However, the extremely short study duration with a treatment phase of only 16 weeks (which equates only 1 to 3 study drug administrations) is considered not optimal. Fremanezumab is intended for migraine prophylaxis and hence is thought to be used as a chronic treatment for months or even years. In order to gain such long-term data on safety and efficacy the Applicant decided to conduct a separate, long-term safety and efficacy study, study 30051. However, this long-term trial did not include a placebo-control which to some extend limits the validity of efficacy evaluations.

The inclusion criteria are considered acceptable to define a typical migraine population and are overall supported. However, the Applicant's initial intention to claim for the broad indication "prevention of episodic and chronic migraine in adults", which would have included all stages of severity of the disease and all age groups,

was critically reviewed and discussed during the authorisation process, and as a result the Applicant chose to restrict the target indication to patients with at least 4 migraine days per month. In addition a statement on the limited data in patients > 60 years of age was included in Section 5.1 of the SmPC.

Study 30050 (Episodic Migraine)

The study design, study endpoints/objectives and doses tested are considered acceptable.

However, as for study 30049 the extremely short study duration with a treatment phase of only 16 weeks (which equates only 1 to 3 study drug administrations) is considered not optimal. Moreover, the same shortcomings as for study 30049 had also been raised for study 30050 during the authorisation process, namely the exclusion of patients > 65 years and of patients with significant cardiovascular or cerebrovascular disease. In addition, patient with EM were only eligible if the number of headache days at baseline was in the range of ≥6 and ≤14 days, with hereof ≥4 migraine days, fulfilling the diagnostic criteria for migraine or probable migraine. As has been discussed above, the Applicant opted to restrict the indication to patients with at least 4 migraine days per month and to include statements on the limited data in patients > 60 years of age, both of which were considered acceptable by CHMP.

Study 30051 (Long-term study in EM and CM)

The study included female and male patients 18 through 70 years of age with CM and EM who completed the pivotal efficacy studies (Studies TV48125-CNS-30049 and TV48125-CNS-30050) and approximately 300 patients (approximately half of whom had a diagnosis of CM and half of whom had a diagnosis of EM) who had not participated in the pivotal efficacy studies. In addition, patients who had not completed the pivotal efficacy studies and patients who completed the pivotal efficacy studies but did not wish to continue treatment during this long-term safety, tolerability, and efficacy study could attend a follow-up visit during this study for the purpose of ADA assessment approximately 7.5 months after their last dose of study drug during the pivotal efficacy study.

Patients rolling over from the pivotal efficacy studies who were randomized to the active treatment groups were to be continued receiving the same treatment throughout the study. Patients rolling over from the pivotal efficacy studies who received placebo and patients not rolling over were to be randomly assigned in a 1:1 ratio to receive quarterly TEV-48125 at 675 mg or monthly TEV-48125 at 225 mg (with CM patients receiving a 675-mg loading dosing at visit 2 and TEV-48125 at 225 mg at each subsequent visit.)

The study design, study endpoints/objectives and doses tested are considered acceptable. Due to the concept of this study as a long-term extension trial for patients of the parental studies 30049 and 30050 the same objections with regard to study population as have been discussed for these studies apply.

In addition, given the extremely short study duration of only 3 months of the pivotal studies (30049 and 30050), and given that fremanezumab is intended as a chronic migraine preventive treatment to be administered over months or even years, it would have been expected that an efficacy measure be evaluated as co-primary or at least secondary endpoint**.** This is not the case and the lack of a placebo control in this study might be the reason that efficacy was only assessed in the context of exploratory endpoints. This is a clear missed opportunity for this LTS.

The primary and key secondary endpoints are in accordance to previous scientific advices and international guidelines on migraine research. For both pivotal phase 3 studies the CHMP recommended the inclusion of an active comparator arm in scientific advices. The Applicant has opted not to follow up this advice, arguing that the choice of active comparator would be difficult as not all drugs for migraine prophylaxis were available in all EU

countries. The side-effect profiles of currently approved drugs (such as topiramate) and differences in routes of administration (for example botox) would further impact blinding. As no active comparator arm was included in the studies, the Applicant was requested to perform an exercise in comparative efficacy of versus existing therapies. This exercise was not included in the submitted dossier. The Applicant was therefore requested to perform such exercise to allow the placing of fremanezumab in the therapeutic window of currently approved migraine prophylaxis treatment. The Applicant provided an indirect comparison of the efficacy/safety profiles of fremanezumab, onabotulinumtoxinA (Botox®) and topiramate as requested. Taken together, the effect size of fremanezumab is comparable to that of these products while the safety profile of fremanezumab appeared even more favourable.

Efficacy data and additional analyses

Study 30049 (Chronic Migraine)

Of the 1130 subjects in the ITT population (i.e., who were randomized and received at least 1 dose of IP), 1121 patients (>99%) were evaluable for efficacy. 1034 patients (92%) completed the study. Baseline characteristics regarding sex and age were rather typical for a migraine population with a mean age of the patients of 41.3 years (range 18 to 71 years) and the majority being women (88%).

The primary endpoint was met and statistical significance for the mean reduction of monthly average number of headache days of at least moderate severity was demonstrated for both doses of fremanezumab compared to placebo. This superiority in treatment effect was demonstrated as early as 1 month after administration of the 1st dose, and this difference was maintained at month 2 and month 3 for both active treatment groups.

ANCOVA results showed an LS mean difference from placebo of -1.8 days for 675 mg/placebo/placebo and -2.1 days for 675/225/225 mg.

Results of the MMRM analysis of the mean change from baseline in headache days of at least moderate severity for the PP analysis were similar, showing that fremanezumab treatment resulted in a larger reduction from baseline in the average number of headache days of at least moderate severity compared with placebo during the complete treatment period.

Significant differences from placebo were also found for all secondary endpoint comparisons in favor of fremanzumab.

The statistical methods planned in the protocol are considered overall acceptable. A display of missing eDiary data per patient was lacking at time of the initial MAA and was therefore requested to be submitted. Based on the data subsequently submitted the rate of missing diary entries was relatively low (5.94 to 7.41 days were missing over the whole 12 week period in study 30049; 7.11 to 7.69 in study 30050). So, although in certain patients up to 100% missing diary entries was recognized and compliance steeply dropped the longer the duration of the study, the overall rate of missing data seemed to not have impacted study results substantially. The hierarchical approach to control for multiplicity is in general endorsed. Although the sequence of endpoints (especially when compared for monthly and quarterly dosing) was found to be rather erratic, this did not impact study results.

TV48125-CNS-30050 (Episodic Migraine)

Of the 874 subjects in the ITT population (i.e., who were randomized and received at least 1 dose of IP), 865 patients (99%) were evaluable for efficacy. 791 patients (90%) completed the study and 686 patients (78%) rolled into the long-term safety study 30051. The mean age of the patients was 41.8 years (range 18 to 70 years). The majority of patients were White (80%) and women (85%).

The primary endpoint was met and statistical significance for 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, demonstrated for both doses of fremanezumab compared to placebo.

Albeit statistically significant, the absolute difference over placebo treatment was only modest. With fremanezumab the mean reduction was 3.9 and 4.0 migraine days for the 675-mg/placebo/placebo and 225/225/225-mg treatment groups, respectively; in the placebo treatment group, a mean reduction of 2.6 migraine days was observed, which equates a LS mean difference versus placebo of only -1.3 migraine days for 675 mg/placebo/placebo and -1.5 migraine days for 225/225/225 mg (ANCOVA results). Although this reflects an only modest superiority over placebo, the beneficial treatment effect was consistently shown across all patient subgroups.

Only modest superiority versus placebo was also found with regard to secondary efficacy analysis.

The statistical methods planned in the protocol are considered acceptable. As was discussed for study 30049 the rate of missing diary entries was relatively low and therefore seemed not to have substantially impacted study results. In the same manner, the hierarchical sequence of endpoints was rather erratic than well-founded.

Study 30051 (Long-term study in EM and CM)

Of the 1889 subjects in the ITT population (i.e., who were randomized and received at least 1 dose of IP), 1887 patients (>99%) were evaluable for safety. The mean age of the patients was 43.1 years (range 18 to 71 years) with the majority of patients being women (88%). At the time of the initial MAA data for only 16 patients (<1%), hereof 8 with CM and 8 with EM, who had completed the study had been presented.

With the additional data long-term data submitted with their responses, the Applicant could demonstrate that the treatment effect observed during the first three treatment months was sustained over the whole study duration of up to 15 months. For CM patients treated with 225 mg monthly, the mean change in monthly number of migraine days from baseline to month 1 was -6.7 days for new/placebo rollover patients and -6.4 days for active rollover patients. For CM patients treated with 675 mg quarterly, the mean change in monthly number of migraine days from baseline to month 1 was -5.9 days for new/placebo rollover patients and -6.2 days for active rollover patients. For EM patients treated with 225 mg monthly, the mean change in monthly number of migraine days from baseline to month 1 was -4.7 days for new/placebo rollover patients and -4.5 days for active rollover patients. For EM patients treated with 675 mg quarterly, the mean change in monthly number of migraine days from baseline to month 1 was -5.3 days for new/placebo rollover patients and -4.6 days for active rollover patients.

As the effect of baseline severity on efficacy was not completely clear with the initially submitted analyses, the Sponsor was requested to assess the effect of baseline migraine frequency on efficacy. The Applicant provided most of the requested analyses which show that no relevant effect modification based on baseline disease severity exists. It is noted that according to the displayed data patients with less than 8 migraine days at baseline showed a higher improvement than patients with more than 8 days. The lowest treatment benefit in patients with EM was observed in the intermediate group (> 8 to 12 migraine days at baseline) in both dosing

groups. For episodic migraine, patients with lower baseline disease severity in tendency also showed a higher benefit, although not to the same extend and not in all groups.

Clinical implications of the primary endpoints

In the main studies 7 patient reported outcomes (PRO's) were evaluated as secondary (MIDAS and HIT-6) and exploratory (MSQoL, PGIC, EQ-5D-5L, PHQ-9, WPAI). Most of the questionnaires evaluated disease disability and some quality of life.

The Applicant states that the differences between the EM and CM studies are likely to be explained by the baseline severity between the 2 conditions, as well as how broad or specific the PRO measure is.

Some of the questionnaires only provide a very general score that is not migraine specific, which may lead to a more variable outcome and are difficult to interpret.

The reported baseline values for the PRO's are displayed in table 2. It can be seen that patients with CM have an overall worse score at baseline (indicating more disability) than patients with EM. This is an indication that patients with CM rate their disease as more severe than patients EM. This will have likely translated in more improvement when treatment with fremanezumab is initiated, compared to patients with EM which will be less sensitive to a change as they were not worse off at baseline.

Different dose regimens (675-225-225 mg, 675 mg-placebo-placebo, 225-225-225 mg) have demonstrated highly similar efficacy results. However, the decision to recommend two alternative dosing options (675 mg quarterly or 225 mg monthly) for the same indication and treatment group was to be critically reflected with regard to accidental overdose. The Aplicant argued that the likelihood for accidental overdose would have been highest for patients on the 225-mg once monthly dosing regimen, with a starting dose of 675 mg for the first month. Based on the Applicant's decision to remove the starting dose from the monthly dosing scheme in patients with chronic migraine, this risk of continued monthly administration of the 675 mg dose is substantially mitigated. Moreover, the information and guidance on the dosing and administration of fremanzumab provided with the SmPC and patient information leaflet is considered appropriate. Based on these considerations and given that the monthly administration of higher Fremanezumab doses (up to 900 mg) did not reveal an altered safety profile, CHMP agrees that there is currently no need to include "accidental overdose" to the list of important potential risks.

A third dosing recommendation had initially been proposed by the Sponsor: a 675 mg loading dose for CM patients. Following CHMP request with respect to the results of the phase 2 and 3 studies the Applicant decided to change dosing recommendations in order to have the same dosing options (225 mg monthly and 675 mg quarterly) available for patients with EM and CM. The two dosing regimens that will now be available are 225 mg once monthly and 675 mg quarterly and have demonstrated comparable efficacy and safety in the phase 3 study program. Based on these phase 3 data the 225 mg monthly regimen appears to be equally effective in the CM population compared to the 225 mg monthly regimen with a 675 mg starting dose. The Applicant provided thorough analyses on this issue, including analyses of efficacy in patients with high-frequency episodic migraine (as chronic migraine surrogate), PK/PD modelling and simulations. This approach was considered adequate.

With the initial assessment CHMP raised concerns regarding the broad indication "prevention of episodic and chronic migraine in adults". The Applicant acknowledged these concerns and decided to change the indication wording in order to limit the indication to patients with at least 4 migraine days per month. This restriction adequately reflects the population in the phase 3 program. Moreover, the more restricted indication statement takes into account that patients with less severe disease may be "overtreated" with prophylactic migraine

treatment. The distinction of episodic and chronic migraine in the indication wording was not considered necessary, as these are spectrum of the same condition and not considered separate entities.

Another concern was related to the treatment of older patients, since only few patients >65 years had been included in clinical studies. The Applicant therefore submitted additional analyses on the efficacy and safety of fremanzumab stratified by age. Based on these data no additional risks were identified for older patients. With regard to efficacy, the treatment effect was more pronounced in middle-aged patients. However, it was confirmed that patients of all age groups benefitted from fremanezumab treatment and that the (average) treatment effect of Fremanezumab in patients > 60 was in line with other age groups. Based on these data an indication wording without additional limitations in terms of age was agreed. However, statements on the limited data in elderly patients (> 60 years) were included in the SmPC.

With regard to evaluating when a person is a non-responder and should cease treatment, the Applicant initially stated that it would be worthwhile to allow each patient sufficient time for fremanezumab to reach its full efficacy potential, given the favourable safety profile. No deadline was suggested as to when this "sufficient time" is reached. This was not agreed by CHMP. The Applicant was requested to provide clear guidance in the SmPC on when to evaluate whether a patient is a (non)responder in order to inform prescribers. Given that steady state of fremanezumab is reached by 3 months of dosing, a cut-off point of 3 months was considered long enough to evaluate if fremanezumab is working for the patient. Therefore, the following recommendation was included in section 4.2 of the SmPC:

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

Efficacy across subgroups

Gender. Subgroup analysis on the effects of gender (male/female) was performed on mean headache days of at least moderate severity and migraine days for both pivotal studies. These analyses revealed a significant effect of all fremanezumab dosing regimens on both endpoints for women, but not for men.

The Applicant stated in their responses that the observed differences in efficacy between men and women were likely caused by the small sample size in the male subgroup (< 50 men per study arm). In addition, the analyses performed in the main studies were not statistically powered to examine efficacy in patient subgroups.

Region. The Applicant has not performed separate studies evaluating the efficacy/safety in the EU setting. European study centres were included in studies 30049 and 30050; however the majority of data was from North America. The Applicant was therefore requested to demonstrate that result from the global phase 3 studies can be extrapolated to the EU setting.

The Applicant explained that extrapolation to the EU setting is possible due to use of diagnostic criteria recognized worldwide, similarities of therapeutic guidelines, and the majority of the US patients were Caucasian which is representative of the EU general population. In addition it was also not expected that the prevalence of known CGRP polymorphisms to be ethnically disproportionate.

The Applicant also stated that the subgroup analysis for the primary endpoint based on region showed substantial improvement after fremanezumab treatment across the geographical regions.

Overall it can be seen that regardless of region, patients benefit from fremanezumab treatment compared to placebo. The observed differences in treatment response between the EU and US populations seem to be driven by the differences in treatment response in the placebo groups. Though the European population is small compared to the North American population, there is still a notion of effect modification.

Taken together the Applicant has sufficiently justified that the study data can be extrapolated to the EU setting.

Concomitant preventative medication use

In the pivotal studies approximately 30% of the participants were allowed to use one concomitant preventative migraine treatment method, provided they were stable on a regime prior to study onset. In study 30049 it was shown that use of concomitant preventative treatment does not affect the effect size. The mean reduction in number of days was similar between the concomitant and the non-concomitant subgroups. In study 30050, the subgroup analysis on average number of migraine days showed that in both subgroups all fremanezumab treatments had a statistical significant effect. When comparing this subgroup with the subgroup that did not receive any concomitant treatment, there seems to be a slight numerical greater reduction in migraine days for concomitant users (-1.7 and -1.9 for the active treatment groups) than for the non-concomitant users (-1.1 and -1.3 for the active treatment groups). This is somewhat in contrast to the findings of the subgroup analysis in the CM study. The applicant was therefore requested to explain the possibility of a clinical benefit of combining fremanezumab treatment with other prophylactic medication.

During the clinical development program it was shown that there was no additional benefit of add-on fremanezumab compared to fremanezumab monotherapy. The Applicant argued that patients who have more severe migraine and/or have a suboptimal response to their current prophylactic medication would benefit from add-on fremanezumab. It is also stated by the Applicant that fremanezumab could be an add-on therapy until the patient will have adequate migraine relief and wean off the existing prophylactic medication. Considering the safety profiles of existing migraine prophylaxis medication, it would be better for the patient to consider switching to fremanezumab altogether. Thus, this notion is supported.

Initially there was no recommendation with regard to concomitant use of multiple migraine prophylaxis medication in the SmPC. The Applicant agreed to develop a rule on concomitant use of Ajovy with other migraine prophylaxis treatments and to which situations it applies. Additional text was included in the SmPC.

Past use of preventative treatment

The applicant performed a subgroup analysis on participants who have used topiramate or botox for migraine prophylaxis in the past. In both studies participants who previously used topiramate benefitted from fremanezumab treatment, as reflected by a significant reduction in the number of headache days of at least moderate severity or migraine days. However, this effect is not as apparent in the subgroup that previously used botox. In the CM study only the participants in the fremanezumab 675/225 mg group had a significant reduction whereas the 675 mg Q12W regimen did not. In the EM study, the analysis had no clear conclusion the efficacy of fremanezumab in participants who received treatment with Botox before. The applicant argued that this is due to the small sample size of participants who had previous exposure to botox.

The Applicant has provided a pooled analysis on age, sex, region, and use of concomitant preventive treatment, exposure to previous treatment with topiramate or Botox across studies. Overall the plots support the previous findings that fremanezumab treatment has a beneficial effect across the subgroups.

2.5.4. Conclusions on the clinical efficacy

The efficacy of fremanezumab in prevention of migraine is considered to be sufficiently demonstrated.

2.6. Clinical safety

Patient exposure

The fremanezumab clinical program comprises 13 studies with healthy subjects and patients with migraine: 8 Phase 1 studies, 2 Phase 2b studies (double-blind, placebo-controlled), and 3 Phase 3 studies (2 double-blind, placebo-controlled studies and 1 long-term, double-blind extension study). With the exception of the long-term, double-blind extension study and a Phase 1 bioequivalence study, all studies were completed at the time of data cut-off date (31 May 2017 for all safety data except for immunogenicity [immunogenicity data cut-off date: 02 May 2017]). A total of 2768 patients and subjects have been exposed to at least 1 dose of fremanezumab in the migraine clinical development program. Considering all fremanezumab studies in the migraine clinical development program, 2229 patients received at least 3 months of fremanezumab treatment, 1343 patients received at least 6 months of fremanezumab treatment, and 260 patients received at least 12 months of fremanezumab treatment as time of the initial MAA (data cut-off 31 May 2017). These data were completed with updated numbers and analyses provided with the Days 121 Responses (cut-off 30 May 2018).The integrated safety analysis for this MAA encompasses all completed and ongoing studies. Data from 2 Phase 2b studies and 3 Phase 3 studies in patients with EM and CM (Studies 021, 022, 30049, 30050, and 30051 [not competed] were integrated into 7 cohorts. With the exception of Study 30051, all integrated studies were completed by the data cut-off date. For Study 30051: 16 of these patients in the safety population had completed the study, 120 patients had discontinued from the study, and 1751 patients were ongoing in the study as of the data cut-off date. Data from patients in Study 30051 available in the clinical database as of 31 May 2017 (or 02 May 2017 for immunogenicity data) are summarized in this SCS. Therefore, throughout this SCS, the summaries that include these data are footnoted as "preliminary."

- 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 migraine: 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.

Patient exposure

Patient disposition for all patients in the placebo-controlled studies (cohort 1)

A total of 2566 patients were randomized (862 in the placebo treatment group, 386 in the 225 mg monthly treatment group, 667 in the 675 mg quarterly treatment group, 467 in the 225 mg monthly with 675 mg starting dose treatment group, 97 in the 675 mg monthly treatment group, and 87 in the 900 mg monthly treatment group), and all but 3 of these patients (>99%) received at least 1 dose of study drug and were evaluable for safety. Most patients (90% and 91% of patients who received fremanezumab and placebo, respectively) completed the study. The most common reasons for discontinuation in the fremanezumab and placebo treatment groups were withdrawn consent (3% and 2% of patients, respectively), lost to follow-up (2% and 3% of patients, respectively), and adverse events (2% in each group). The frequency of study discontinuations due to adverse events was similar across the proposed dosing regimens of 225 mg monthly, 675 mg quarterly, and 225 mg monthly with a 675 mg starting dose (1% to 2% of patients in each treatment group).

Two patients in the 675 mg quarterly treatment group died: 1 patient (Study 30050) died 110 days after study drug exposure from an intentional overdose of diphenhydramine per the autopsy report after withdrawing consent due to a family emergency, and 1 patient (Study 30049) died 69 days after study drug exposure from chronic obstructive pulmonary disease (COPD) per the autopsy report. A third fatal case was reported with the Day 121 Responses.

Patient disposition for all fremanezumab treated patients with migraine (cohort 4):

A total of 2830 patients were randomized across Studies 021, 022, 30049, 30050, and 30051; 2515 patients were randomized to receive fremanezumab, and 862 patients were randomized to receive placebo. All but 3 of these patients (>99%) received at least 1 dose of study drug and were evaluable for safety. This cohort also included data from patients in Study 30051. A total of 1890 patients, 1578 patients from Study 30049 (N=916) and Study 30050 (N=661) and 312 new patients (ie, new patients and patients who completed the Phase 2b studies), were enrolled in Study 30051. All but 2 of these patients received at least 1 dose of study drug and were evaluable for safety. As of the last data cut-off date (30 May 2018), all but 2 patients completed the study, 120 patients had discontinued from the study, and 1751 patients were ongoing in the study. The most frequent reasons for discontinuation from the study were withdrawn consent, adverse event, and lack of efficacy. The frequency of study discontinuations due to adverse events was similar across the proposed dosing regimens of 225 mg monthly, 675 mg quarterly, and 225 mg monthly with a starting dose of 675 mg (<1% to 1% of patients in each treatment group).

Table 12 Study Drug Exposure by Treatment Group for All Patients in the Placebo-Controlled Studies—Cohort 1 (Safety Population)

Variable Statistic	Placebo	Fremanezumab					
	Monthly (N=861)	225 mg monthly (N=386)	675 mg quarterly[a] (N=667)	675/225 mg monthly[b] (N=467)	675 mg monthly (N=96)	900 mg monthly (N=86)	Total (N=1702)
Duration of treatment (days)							
Mean	83.6	83.0	84.2	83.7	84.0	83.8	83.8
SD	14.34	14.58	12.21	14.09	16.06	13.78	13.60
25th percentile	84.0	84.0	84.0	84.0	84.0	84.0	84.0
Median	85.0	85.0	85.0	85.0	85.0	85.0	85.0
75th percentile	88.0	87.0	87.0	88.0	87.0	88.0	87.0
Min, max	1, 154	1, 169	4, 181	1, 147	1, 134	22, 127	1, 181
Duration of treatment, n (%)[c]							
>0 month	861 (100)	386 (100)	667 (100)	467 (100)	96 (100)	86 (100)	1702 (100)
≥1 month	852 (99)	382 (99)	660 (99)	464 (>99)	94 (98)	85 (99)	1685 (>99)
≥2 months	816 (95)	369 (96)	648 (97)	450 (96)	92 (96)	82 (95)	1641 (96)
≥3 months	705 (82)	294 (76)	524 (79)	364 (78)	77 (80)	71 (83)	1330 (78)
Patient-years	197.10	87.74	153.82	106.99	22.09	19.73	390.38

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

c 1 month=28 days.

ISS=Integrated Summary of Safety; max=maximum; min=minimum; N=number of patients; SD=standard deviation.

Table 13 Study Drug Exposure by Age Group and Sex for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population)

Age group	Patients (N=2512) n (%)		Patient-years	
	M	F	M	F
Children (0 to 11 years)	0	0	0	0
Adolescents 12 to 17 years)	0	0	0	0
Adults (18 to 64 years)	319 (13)	2132 (85)	155.49	1087.06
Elderly people				
65-69 years	12 (<1)	40 (2)	8.22	24.62
70-74 years	0	9 (<1)	0	3.94
≥75 years	0	0	0	0

Table 14 Study Drug Exposure by Special Populations for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population)

Special populations	**Patients (N=2512) n (%)**	**Patient-years**
Pregnant women	**7 (<1)**	**3.31**
Breastfeeding women	**0**	**0**
Patients with cardiovascular medical history (patients with at least 1 finding)	**314 (13)**	**167.70**
Cardiac disorders SOCa	38 (2)	20.52
Investigations SOCb	29 (1)	18.03
Surgical and medical procedures SOCc	8 (<1)	4.07
Vascular disorders SOCd	259 (10)	135.16
Patients receiving cardiovascular medications at	**358 (14)**	**192.23**
Agents acting on the renin-angiotensin system	108 (4)	NC
Antihypertensives	9 (<1)	NC
Beta blocking agents	161 (6)	NC
Calcium channel blockers	58 (2)	NC
Cardiac therapy	13 (<1)	NC

Table 15 Study Drug Exposure by Special Populations for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population) (Continued)

Special populations	Patients (N=2512) n (%)	Patient-years
Diuretics	75 (3)	NC
Peripheral vasodilators	1 (<1)	NC
Patients with cardiovascular or cerebrovascular risk factor (patients with at least 1 risk factor)	**1398 (56)**	**734.41**
Patients using hormonal birth control pillsf	450 (18)	228.87
Patients who are smokersg	14 (<1)	7.26
Patients with abnormal ECGh	4 (<1)	1.83
Patients with albuminuriai	1 (<1)	0.24
Patients with atrial fibrillationj	5 (<1)	2.00
Patients with diabetes mellitusg	43 (2)	21.25
Patients with hypertensiong	259 (10)	135.16
Patients with impaired glucose toleranceg	14 (<1)	7.16
Patients with lipid metabolism disordersg	225 (9)	126.59
Patients with medical history for cardiovascular disease	439 (17)	233.37
Patients with obesity (BMI ≥30)k	689 (27)	358.82
Patients with sleep apnoea syndromel	58 (2)	36.46
Patients with tachycardiah	17 (<1)	9.44
Patients using triptans	1304 (52)	749.83

Adverse events

Common Adverse Events (AE) for all patients in the placebo-controlled studies (cohort 1)

A common AE was defined as an event occurring in ≥2% of patients. A total of 1109 patients (65%; 981.10 events/100 patient-years) who received fremanezumab experienced at least 1 adverse event compared with 505 patients (59%; 833.61 events/100 patient-years) who received placebo. For the proposed dose regimens, 236 patients (61%; 910.62 events/100 patient-years) in the 225 mg monthly treatment group, 458 patients (69%; 1112.31 events/100 patient-years) in the 675 mg quarterly treatment group, and 317 patients (68%; 1026.24 events/100 patient-years) in the 225 mg monthly with 675 mg starting dose treatment group had at least 1 adverse event.

Among patients treated with fremanezumab, adverse events were most frequently reported in the SOCs of general disorders and administration site conditions (41%) and infections and infestations (20%). Adverse events in the SOCs of general disorders and administration site conditions (33%) and infections and infestations (19%) were also the most frequently reported among patients who received placebo. Adverse events occurred with similar frequency across active treatment groups with the exception of general disorders and

administration site conditions, which occurred at a slightly higher frequency in the fremanezumab treatment groups that include patients in the Phase 3 studies (225 mg monthly, 675 mg quarterly, and 225 mg monthly with a starting dose of 675 mg).

The adverse event profile for all patients with CM in the placebo-controlled studies (cohort 2) and all patients with EM in the placebo-controlled studies (cohort 3) also showed the same trends as for all patients in the placebo-controlled studies (cohort 1). The adverse event profile of fremanezumab for all patients in the pivotal studies (cohort 7) was similar to that of all patients in the placebo-controlled studies (cohort 1).

Common Adverse Events for all fremanezumab-treated patients (cohort 4)

A total of 1895 patients (75%; 998.34 events/100 patient-years) who received fremanezumab experienced at least 1 adverse event. The incidences of adverse events (event rates) for patients in the 225 mg monthly, 675 mg quarterly, and 225 mg monthly with 675 mg starting dose treatment groups were 71% (986.48 events/100 patient-years), 79% (998.53 events/100 patient-years), and 79% (1059.42 events/100 patient-years), respectively.

As with all patients in the placebo-controlled studies (cohort 1), the most frequently reported adverse events among all fremanezumab-treated patients (cohort 4) were in the SOCs of general disorders and administration site conditions (52%) and infections and infestations (34%). Adverse events occurred with similar frequency across the doses evaluated in Phase 3 (ie, 225 mg monthly, 675 mg quarterly, and 225 mg monthly with a starting dose of 675 mg).

The adverse event profile for all fremanezumab-treated patients with CM (cohort 5) and all fremanezumab-treated patients with EM (cohort 6) showed the same trends as for all fremanezumab-treated patients (cohort 4).

Treatment-related Adverse Events in all patients in the placebo-controlled studies (cohort 1)

A total of 758 patients (45%; 681.13 events/100 patient-years) who received fremanezumab experienced at least 1 adverse event considered related to the study drug by the investigator compared with 307 patients (36%; 528.17 events/100 patient-years) who received placebo. For the proposed dose regimens, 164 patients (42%; 642.79 events/100 patient-years) in the 225 mg monthly, 323 patients (48%; 803.52 events/100 patient-years) in the 675 mg quarterly, and 219 (47%; 704.72 events/100 patient-years) in the 225 mg monthly with 675 mg starting dose treatment groups had at least 1 adverse events considered related to the study drug.

The most frequently occurring events in patients treated with fremanezumab were in the SOCs of general disorders and administration site conditions (39%), nervous system disorders (3%), and gastrointestinal disorders (2%), and the most frequently occurring events in patients treated with placebo were in these same SOCs (31%, 2%, and 2%, respectively).

The most frequently occurring adverse events considered related to the study drug by the investigator were injection site reactions with a slight preponderance in patients who received fremanezumab.

Treatment-related Adverse Events in all fremanezumab-treated patients (cohort 4)

A total of 1355 patients (54%) who received fremanezumab experienced at least 1 treatment-related adverse event. The incidence of treatment-related adverse events and the event rates were similar for patients in the 225 mg monthly (53%; 737.54 events/100 patient-years), 675 mg quarterly (56%; 704.63 events/100 patient-years), and 225 mg monthly with 675 mg starting dose (58%; 753.06 events/100 patient-years) treatment groups.

Consistent with all patients in the placebo-controlled studies (cohort 1), the most frequently reported treatment-related adverse events among all fremanezumab-treated patients (cohort 4) were in the SOC of general disorders and administration site conditions (49%), nervous system disorders (4%), investigations (3%), gastrointestinal disorders (2%), and skin and subcutaneous tissue disorders (2%); all other SOCs reported treatment-related adverse events from ≤1% of the patients in cohort 4. Treatment-related adverse events occurred with similar frequency across the doses evaluated in Phase 3 (ie, 225 mg monthly, 675 mg quarterly, and 225 mg monthly with a starting dose of 675 mg).

As with all patients in the placebo-controlled studies (cohort 1), the most frequently occurring adverse events considered related to the study drug by the investigator in all fremanezumab-treated patients (cohort 4) were injection site pain (in 29% of patients [288.43 events/100 patient-years]), injection site induration (in 27% of patients [197.06 events/100 patient-years]), and injection site erythema (in 23% of patients [127.80 events/100 patient-years]). Each of these treatment-related adverse events occurred with similar incidence and event rates across the 225 mg monthly, 675 mg quarterly, and 225 mg monthly with 675 mg starting dose treatment groups.

Table 16 Adverse events by age group for all fremanezumab-treated patients (cohort 4)

MedDRA Terms	**Age <65 2451 (98)**	**Age >65 61 (2)**
Patients with at least 1 AEs	1846 (75)	49 (80)
Fatal	2 (<1)	--
Psychiatric disorders	115 (5)	7 (11)
Nervous system disorders	213 (9)	9 (15)
Accidents and injuries	175 (7)	6 (10)
Cardiac disorders	24 (<1)	1 (2)
Vascular disorders	58 (2)	5 (8)
Cerebrovascular disorders	1 (<1)	
Infections and infestations	840 (34)	24 (39)
Eye disorders	49 (2)	2 (3)
Skin disorders	127 (5)	2 (3)

Adverse events by sex

Table 17 Adverse events occurring in at least 2% of women or men treated with fremanezumab for all patients in placebo-controlled studies – cohort 1 (safety population)

MedDRA PT	Number of patients (%)			
	Women		Men	
	Placebo (N=745)	Fremanezumab (N=1473)	Placebo (N=116)	Fremanezumab (N=229)
Number of patients with at least 1 AE	**444 (60)**	**985 (67)**	**61 (53)**	**124 (54)**
Injection site pain	177 (24)	377 (26)	12 (10)	36 (16)
Injection site induration	98 (13)	252 (17)	15 (13)	40 (17)
Injection site erythema	95 (13)	247 (17)	9 (8)	26 (11)
Upper respiratory tract infection	30 (4)	65 (4)	5 (4)	3 (1)
Nasopharyngitis	31 (4)	51 (3)	4 (3)	11 (5)
Urinary tract infection	15 (2)	35 (2)	0	0
Dizziness	8 (1)	29 (2)	1 (<1)	2 (<1)
Injection site pruritus	2 (<1)	29 (2)	0	1 (<1)
Sinusitis	21 (3)	28 (2)	1 (<1)	1 (<1)
Back pain	8 (1)	23 (2)	4 (3)	6 (3)
Injection site hemorrhage	15 (2)	27 (2)	1 (<1)	1 (<1)
Bronchitis	6 (<1)	24 (2)	0	2 (<1)
Nausea	20 (3)	23 (2)	1 (<1)	1 (<1)
Influenza	8 (1)	16 (1)	0	5 (2)

Adverse Events by Baseline Migraine Medication Use

Table 18 Adverse Events Occurring in at Least 2% of Total Patients Treated with Fremanezumab by Preferred Term, Treatment Group, and Baseline Preventive Migraine Medication Use for All Patients in the Placebo- Controlled Studies—Cohort 1 (Safety Population)

MedDRA PT	Number of patients (%)			
	Not using preventive migraine medication		Using preventive migraine medication	
	Placebo (N=656)	Fremanezumab (N=1295)	Placebo (N=205)	Fremanezumab (N=407)
Number of patients with at least 1 AE	**393 (60)**	**849 (66)**	**112 (55)**	**260 (64)**
Injection site pain	148 (23)	332 (26)	41 (20)	81 (20)
Injection site induration	97 (15)	230 (18)	16 (8)	62 (15)
Injection site erythema	84 (13)	218 (17)	20 (10)	55 (14)
Upper respiratory tract infection	30 (5)	55 (4)	5 (2)	13 (3)
Nasopharyngitis	26 (4)	40 (3)	9 (4)	22 (5)
Urinary tract infection	12 (2)	30 (2)	3 (1)	5 (1)
Dizziness	7 (1)	23 (2)	2 (<1)	8 (2)
Injection site pruritus	2 (<1)	22 (2)	0	8 (2)
Back pain	11 (2)	21 (2)	1 (<1)	8 (2)
Sinusitis	18 (3)	24 (2)	4 (2)	5 (1)
Injection site hemorrhage	15 (2)	20 (2)	1 (<1)	8 (2)
Bronchitis	5 (<1)	17 (1)	1 (<1)	9 (2)
Nausea	17 (3)	17 (1)	4 (2)	7 (2)
Migraine	12 (2)	7 (<1)	1 (<1)	8 (2)

Serious adverse event/deaths/other significant events

Deaths

Three deaths occurred in the fremanezumab migraine clinical development program. Additional details follow:

- A 59-year-old patient in the 675 mg quarterly treatment group (Study 30049) died 69 days after study drug exposure. The cause of death as indicated in the autopsy report was COPD, and the manner of death was reported to be natural. The event was assessed by the investigator as unrelated to the study drug.
- A 21-year-old woman with EM in the 675 mg quarterly treatment group (Study 30050) died 110 days after study drug exposure. According to autopsy, the patient died due to an intentional

diphenhydramine overdose, and the manner of death was suicide. The investigator assessed the death as unrelated to the study drug at the time of notification.

- A third fatal case was a patient with an arterial brain aneurysm and multiple strokes approximately 300 days after the last dose of fremanezumab.

Other serious adverse events

Analysis of serious adverse events by MedDRA SOC and PT in all patients in the placebo-controlled studies revealed no clinically relevant trends. Serious adverse events were infrequent and occurred with similar incidences across the treatment groups. No event by PT occurred in ≥1% of patients, and the majority of serious adverse events (by PT) occurred in 1 patient each. Furthermore, no new safety signals were identified with long-term exposure to fremanezumab.

Serious Adverse Events in all patients in the placebo-controlled studies (Cohort 1) Serious adverse events occurred in 21 patients (1%) who received fremanezumab and in 14 patients (2%) who received placebo in the placebo-controlled studies (cohort 1). No event by PT occurred in ≥1% of patients. By PT, serious adverse events that occurred in more than 1 patient in an individual treatment group were drug hypersensitivity and nephrolithiasis in 2 patients each in the placebo treatment group. Other serious adverse events that occurred in more than 1 patient included pneumonia (in 1 patient each in 675 mg quarterly and 225 mg monthly with 675 mg starting dose treatment groups), fall (in 1 patient each in the placebo and 225 mg monthly with 675 mg starting dose treatment groups), road traffic accident (in 1 patient each in the placebo and 675 mg quarterly treatment groups), wrist fracture (in 1 patient each in the placebo and 675 mg quarterly treatment groups), migraine (in 1 patient each in the placebo and 225 mg monthly treatment groups), and hypertensive crisis (in 1 patient each in the 225 mg monthly and 225 mg monthly with 675 mg starting dose treatment groups). The most frequently occurring serious adverse events among all patients in the placebo-controlled studies occurred in 2 patients each, which included drug hypersensitivity, nephrolithiasis, pneumonia, fall, road traffic accident, wrist fracture, migraine, and hypertensive crisis. One of the hypertensive crisis occurred in a patient with hypertension history. On the day of the event, the patient had a migraine attack and took ibuprofen, rizatriptan, and tramadol. The other event occurred in a 70-year-old woman in the 225 mg monthly with 675 mg starting dose treatment group with a history of myocardial infarction and hypertension who experienced multiple similar events before entering the study and was diagnosed with labile hypertension on discharge from the emergency room.

Table 19 Serious Adverse Events Occurring in at Least 2 Patients by System Organ Class, Preferred Term, and Treatment Group for All Patients in the Placebo-Controlled Studies—Cohort 1 (Safety Population)

SOC MedDRA PT	Number of patients (%)				
	Placebo	Fremanezumab			
	Monthly (N=861)	225 mg monthly (N=386)	675 mg quarterly (N=667)	675/225 mg monthly[a] (N=467)	Total[b] (N=1702)
Patients with at least 1 SAE	**14 (2)**	**5 (1)**	**6 (<1)**	**6 (1)**	**21 (1)**
Immune system disorders	2 (<1)	0	0	0	0
Drug hypersensitivity	2 (<1)	0	0	0	0
Infections and infestations	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Pneumonia	0	0	1 (<1)	1 (<1)	2 (<1)
Injury, poisoning and procedural complications	3 (<1)	1 (<1)	2 (<1)	1 (<1)	4 (<1)
Fall	1 (<1)	0	0	1 (<1)	1 (<1)
Road traffic accident	1 (<1)	0	1 (<1)	0	1 (<1)
Wrist fracture	1 (<1)	0	1 (<1)	0	1 (<1)
Nervous system disorders	3 (<1)	2 (<1)	0	0	3 (<1)
Migraine	1 (<1)	1 (<1)	0	0	1 (<1)
Renal and urinary disorders	2 (<1)	0	0	1 (<1)	1 (<1)
Nephrolithiasis	2 (<1)	0	0	0	0
Vascular disorders	0	1 (<1)	0	1 (<1)	2 (<1)
Hypertensive crisis	0	1 (<1)	0	1 (<1)	2 (<1)

a Patients received fremanezumab at 225 mg monthly with a starting dose of 675 mg.
b Adverse events that occurred in patients in all fremanezumab treatment groups, including the 675 mg monthly and 900 mg monthly treatment groups, are included in this total group. Refer to Module 5.3.5.3, ISS Section 4.1.8.1, Study 022 CSR, and Study 021 CSR for additional details regarding adverse events in each of these treatment groups.
ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; PT=preferred term; SAE=serious adverse event; SOC=System Organ Class.
Note: Adverse events summarized in this table are those events that started on or after starting study drug (ie, treatment-emergent adverse events).
Note: Patients are counted only once in each SOC and PT category.

Serious adverse events considered related to the study drug by the investigator occurred in 3 patients: 1 patient in the 225 mg monthly treatment group (PT: generalized tonic-clonic seizure) and 2 patients in the placebo treatment group (PTs: diplopia, drug hypersensitivity, dyspnea, and peripheral edema in 1 patient and lentigo maligna in another patient). The event of generalized tonic-clonic seizure occurred in a 23-year-old patient who was taking nortriptyline for migraine headaches. The patient had a previous (at approximately age 5) and recent (occurred 2 weeks prior to the event) history of concussion and was diagnosed with bilateral ankle clonus approximately 6 months before receiving the 1st dose of study drug. With the exception of the event of generalized tonic-clonic seizure, each of the serious adverse events considered related to the study drug by the investigator led to discontinuation from the study drug. Other serious adverse events (all considered unrelated to the study drug by the investigator) that led to discontinuation from the study drug included migraine and hypertensive crisis in a 70-year-old woman in the 225 mg monthly treatment group with a history of myocardial

infarction and hypertension who experienced multiple similar events before entering the study and diagnosed with labile hypertension on discharge from the emergency room, pneumonia and suicidal ideation in 1 patient each in the 225 mg monthly with 675 mg starting dose treatment group, tremor in a patient in the 675 mg monthly treatment group, suicide attempt in a patient in the 900 mg monthly treatment group, and drug hypersensitivity in a patient in the placebo treatment group.

All serious adverse events resolved or were resolving by the end of study participation with the exception of an event of intestinal hemorrhage (unknown outcome) in a patient with Munchausen syndrome, short bowel syndrome, and multiple intestinal surgeries who was lost to follow up, and events of antiphospholipid syndrome (not resolved/resolving), COPD leading to death, and death from an intentional overdose of diphenhydramine.

Table 20 Treatment-Related Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group for All Patients in the Placebo- Controlled Studies—Cohort 1 (Safety Population)

SOC MedDRA PT	Number of patients (%)				
	Placebo	Fremanezumab			
	Monthly (N=861)	225 mg monthly (N=386)	675 mg quarterly (N=667)	675/225 mg monthly[a] (N=467)	Total[b] (N=1702)
Patients with at least 1 treatment-related SAE[c]	**2 (<1)**	**1 (<1)**	**0**	**0**	**1 (<1)**
Eye disorders	1 (<1)	0	0	0	0
Diplopia	1 (<1)	0	0	0	0
General disorders and administration site conditions	1 (<1)	0	0	0	0
Edema peripheral	1 (<1)	0	0	0	0
Immune system disorders	1 (<1)	0	0	0	0
Drug hypersensitivity	1 (<1)	0	0	0	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (<1)	0	0	0	0
Lentigo maligna	1 (<1)	0	0	0	0
Nervous system disorders	0	1 (<1)	0	0	1 (<1)
Generalised tonic-clonic seizure	0	1 (<1)	0	0	1 (<1)
Respiratory, thoracic, and mediastinal disorders	1 (<1)	0	0	0	0
Dyspnea	1 (<1)	0	0	0	0

a Patients received fremanezumab at 225 mg monthly with a starting dose of 675 mg.
b Adverse events that occurred in patients in all fremanezumab treatment groups, including the 675 mg monthly and 900 mg monthly treatment groups, are included in this total group.

c Treatment-related adverse events are those events considered related (or possibly related) to the study drug according to the investigator and those events with unknown relationship to the study drug.
AE=adverse event; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; PT=preferred term; SAE=serious adverse event; SOC=System Organ Class.
Note: Patients are counted only once in each SOC and PT category.
Note: AEs summarized in this table are those events that started on or after starting study drug (ie, treatment-emergent AEs).

Table 21 Serious Adverse Events Occurring in at Least 2 Patients by System Organ Class, Preferred Term, and Treatment Group for All Fremanezumab-Treated Patients—Cohort 4 (Safety Population)

SOC MedDRA PT	Fremanezumab							
	225 mg monthly (N=551; PY=269.5)		675 mg quarterly (N=1086; PY=597.5)		675/225 mg monthly[a] (N=712; PY=370.5)		Total[b] (N=2512; PY=1279.3)	
	n (%)	ER per 100 yrs	n (%)	ER per 100 yrs	n (%)	ER per 100 yrs	n (%)	ER per 100 yrs
Patients with at least 1 SAE	**14 (3)**	**5.94**	**26 (2)**	**5.69**	**16 (2)**	**6.21**	**60 (2)**	**6.10**
Infections and infestations	2 (<1)	0.74	5 (<1)	0.84	4 (<1)	1.08	11 (<1)	0.86
Appendicitis	1 (<1)	0.37	0	0	2 (<1)	0.54	3 (<1)	0.23
Pneumonia	0	0	1 (<1)	0.17	2 (<1)	0.54	3 (<1)	0.23
Musculoskeletal and connective tissue disorders	1 (<1)	0.37	1 (<1)	0.17	2 (<1)	0.54	4 (<1)	0.31
Osteoarthritis	1 (<1)	0.37	0	0	1 (<1)	0.27	2 (<1)	0.16
Psychiatric disorders	1 (<1)	0.37	4 (<1)	0.84	1 (<1)	0.27	7 (<1)	0.70
Suicidal ideation	1 (<1)	0.37	1 (<1)	0.17	1 (<1)	0.27	3 (<1)	0.23
Depression	0	0	1 (<1)	0.17	0	0	2 (<1)	0.16
Suicide attempt	0	0	1 (<1)	0.17	0	0	2 (<1)	0.16
Vascular disorders	1 (<1)	0.37	2 (<1)	0.33	3 (<1)	0.81	6 (<1)	0.47
Deep vein thrombosis	0	0	1 (<1)	0.17	1 (<1)	0.27	2 (<1)	0.16
Hypertensive crisis	1 (<1)	0.37	0	0	1 (<1)	0.27	2 (<1)	0.16

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.
b Adverse events that occurred in patients in all fremanezumab treatment groups, including the 675 mg monthly and 900 mg monthly treatment groups, are included in this total group.
ER=event rate; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients observed; PT=preferred term; PY=patient-year; SAE=serious adverse event; SOC=system organ class.
Note: Adverse events summarized in this table are those events that started on or after starting study drug (ie, treatment-emergent adverse events).
Note: Patients are counted only once in each SOC and PT category.

Adverse Events of special interest

Ophthalmic adverse events, events of possible drug-induced liver toxicity, and hypersensitivity reactions and anaphylaxis were identified as adverse events of special interest based on the potential risks of fremanezumab identified in unconfirmed preliminary preclinical studies, small molecule CGRP antagonist development programs, and intrinsic factors for any biological molecule. These adverse events of special interest were defined as follows in the protocols for the Phase 3 studies:

- ophthalmic adverse events of at least moderate intensity
- events of possible drug-induced liver injury (defined as any of the following: AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN, or INR >1.5) and Hy's law events
- events of suspected anaphylaxis and severe hypersensitivity reactions

Table 22 Adverse Events of Special Interest by System Organ Class, Preferred Term, and Treatment Group for All Patients in the Placebo-Controlled Studies— Cohort 1 (Safety Population)

SOC MedDRA PT	Number of patients (%)				
	Placebo	Fremanezumab			
	Monthly (N=861)	225 mg monthly (N=386)	675 mg quarterly (N=667)	675/225 mg monthly[a] (N=467)	Total[b] (N=1702)
Patients with at least 1 AESI	**5 (1)**	**3 (<1)**	**8 (1)**	**11 (2)**	**25 (1)**
Eye disorders	1 (<1)	0	0	5 (1)	8 (<1)
Diplopia	1 (<1)	0	0	1 (<1)	1 (<1)
Blepharitis	0	0	0	0	1 (<1)
Blindness unilateral	0	0	0	1 (<1)	1 (<1)
Conjunctivitis allergic	0	0	0	0	1 (<1)
Hypoaesthesia eye	0	0	0	1 (<1)	1 (<1)
Optic disc drusen	0	0	0	0	1 (<1)
Retinal detachment	0	0	0	1 (<1)	1 (<1)
Vision blurred	0	0	0	1 (<1)	1 (<1)
Visual acuity reduced	0	0	0	1 (<1)	1 (<1)
Vitreous detachment	0	0	0	0	1 (<1)
Infections and infestations	0	0	2 (<1)	1 (<1)	3 (<1)
Conjunctivitis	0	0	2 (<1)	0	2 (<1)
Hepatitis A	0	0	0	1 (<1)c,d	1 (<1)c,d
Investigations	4 (<1)	3 (<1)	6 (<1)	5 (1)	14 (<1)
Alanine aminotransferase increased	1 (<1)c	0	2 (<1)	3 (<1)	5 (<1)
Aspartate aminotransferase increased	0	0	3 (<1)	2 (<1)	5 (<1)
Blood bilirubin increased	1 (<1)	1 (<1)	2 (<1)c	0	3 (<1)c
Hepatic enzyme increased	0	2 (<1)c	1 (<1)	0	3 (<1)c
Liver function test abnormal	1 (<1)	0	0	2 (<1)c	2 (<1)c
International normalized ratio	1 (<1)	0	0	0	0

a Patients received fremanezumab at 225 mg monthly with a starting dose of 675 mg.
b Adverse events that occurred in patients in all fremanezumab treatment groups, including the 675 mg monthly and 900 mg monthly treatment groups, are included in this total group. Refer to Module 5.3.5.3, ISS Section 4.1.9.2, Study 022 CSR, and Study 021 CSR for additional details regarding adverse events in each of these treatment groups.
c One patient had an event that started before study drug administration (ie, the event was not treatment emergent) (Module 5.3.5.3, ISS Listing 6.5 and ISS Listing 7.2.1 through Listing 7.2.5).
d Hepatitis A was not an AESI.
AESI=adverse event of special interest; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; PT=preferred term; SOC=system organ class.
Note: Patients are counted only once in each SOC and PT category.
Note: Unless otherwise stated, adverse events summarized in this table are those events that started on or after starting study drug (ie, treatment-emergent adverse events).

Fourteen patients in the placebo-controlled studies (cohort 1; 2 of 861 patients who received placebo and 12 of 1702 patients who received fremanezumab) had at least 1 ophthalmic adverse event of at least moderate intensity. There was no pattern in the types of ophthalmic adverse events that occurred; diplopia in 2 patients (1 in the placebo treatment group and 1 in the 225 mg monthly with 675 mg starting dose treatment group) and conjunctivitis in 2 patients (both in the 675 mg quarterly treatment group) were the only events to occur in more than a single patient.

Other ophthalmic events of at least moderate intensity that occurred in patients in the placebo-controlled studies included eye injury in a patient in the placebo treatment group; vision blurred, retinal detachment, unilateral blindness (transient loss of vision on 2 occasions that resolved without treatment), eye hypoaesthesia and visual acuity reduced, and eye pain in 1 patient each in the 225 mg monthly with 675 mg starting dose treatment group; optic disc drusen, vitreous detachment, and blepharitis in 1 patient each in the 675 mg monthly treatment group; and allergic conjunctivitis and eye infection in 1 patient each in the 900 mg monthly treatment group.

Ophthalmic events of at least moderate intensity leading to discontinuation from the study drug in all patients in the placebo-controlled studies included a serious adverse event of diplopia considered related to the study drug in 1 patient in the placebo treatment group and a non-serious adverse event of retinal detachment considered unrelated to the study drug in 1 patient in the 225 mg monthly with 675 mg starting dose treatment group. The latter event was associated with acute stress-induced hypertension.

Events of possible drug-induced liver injury/ Hy's law events

No Hy's law events were reported in all patients in the placebo-controlled studies (cohort 1). Adverse events of liver enzyme elevations meeting adverse event of special interest criteria (defined per the Phase 3 protocols as any of the following: AST or ALT ≥3× the ULN, total bilirubin ≥2× the ULN, or INR >1.5) occurred infrequently among patients in the placebo-controlled studies, and there was no meaningful difference in the frequency of events across the treatment groups.

No adverse event of special interest related to liver enzyme elevations occurred ≥1% of patients who received fremanezumab. In addition, none of the adverse events of special interest related to liver enzyme elevations in all patients in the placebo-controlled studies were serious, and none led to discontinuation from the study. All the events resolved while on study drug, and none needed treatment.

A total of 13 patients from Study 30049 (3 patients in the placebo treatment group and 5 patients in each fremanezumab treatment group) had adverse events of special interest related to elevated liver enzymes, hereof 3 patients in the placebo treatment group,

Of the 10 patients from the active treatment group, 6 had elevation of ALT and/or AST at a single visit either during the study or at the end of the study. Five of these cases were 3 to 5× the ULN and 1 was 6× the ULN. No treatments were necessary for these events, and none led to discontinuation.

Of the remaining 4 patients on active treatment,

- One patient had 3 consecutive ALT increases (3 to 4.5× the ULN). The event resolved by the end of the study while on study drug. The patient used oxycodone/ acetaminophen as needed for migraine and fluoxetine for depression.
- One patient had elevated ALT at screening (6× the ULN) and visit 4 (>10× the ULN). The visit 4 elevation was concurrent with an upper respiratory tract infection, which was treated with

ethanol/paracetamol/dextromethorphan hydrobromide/ephedrine sulfate/doxylamine succinate. The elevated liver function test normalized after stopping the concomitant medication. This patient also had recent medical history of cholelithiasis and cholecystectomy (both in June 2015).

- One patient had elevated ALT and AST (3 to 5× the ULN) during 3 consecutive visits. This patient was confirmed during the study to have chronic cholelithiasis by ultrasound and moderate hepatitis B, moderate hepatitis C, and mild hepatitis A through serological tests.
- One patient had elevated total bilirubin at baseline (>1.5× the ULN) with 3 more consecutive elevations (1.1 to 2.3× the ULN). There were no concurrent ALT/AST increases. The elevated bilirubin value normalized by end of study. This patient used ibuprofen and acetaminophen/caffeine/ salicylamide as needed for migraine.

A total of 4 patients (1 patient in the placebo treatment group and 3 patients in the fremanezumab treatment groups) in Study 30050 had adverse events of special interest related to liver enzyme elevations:

- One patient each who received placebo and fremanezumab had mild elevation of total bilirubin at baseline and at several times during the study. Both patients have Gilbert's syndrome.
- One patient in the 225 mg monthly group had a single elevation of AST to 3× the ULN. The patient took acetaminophen/diphenhydramine approximately 5 days/week for insomnia and had wine at night 3 to 4 days a week.
- One patient had several ALT increase of 3 to 5× the ULN from 10 January 2017 to 13 February 2017. This patient had recent cholecystectomy (2015) and used venlafaxine hydrochloride, losartan potassium, and metamizole sodium for different medical conditions.
- A total of 3 patients from the Phase 2b studies had adverse events of special interest related to liver enzyme elevations:
- One patient had hepatitis C.
- One patient had an unrelated adverse event of cholelthiasis and coincident elevated liver function test results at 3 consecutive visits, which peaked at >10× the ULN.
- One patient had ALT approximately 6.5× the ULN and AST approximately 4× the ULN at 1 visit, which normalized the visit after. This patient's concomitant medications included valproate semisodium, ibuprofen, trazodone hydrochloride, pantoprazole sodium sesquihydrate, and macrogol.

Liver enzyme elevations that met adverse event of special interest criteria and led to discontinuation from the study drug in all treated patients included the following events in Study 30051:

- AST increased (maximum AST value reported = 134 U/L) assessed as moderate in intensity and unrelated to the study drug by the investigator in 1 patient in the 225 mg monthly treatment group
- ALT increased (maximum ALT value reported = 121 U/L) assessed as moderate in intensity and related to the study drug by the investigator in 1 patient in the 225 mg monthly treatment group (
- hepatic enzyme increased (maximum ALT value reported = 274 U/L, maximum ALP value reported = 168 U/L, and maximum AST value reported = 92 U/L) assessed as moderate in intensity and unrelated to the study drug by the investigator in 1 patient in the 675 mg quarterly treatment group

- transaminases increased (maximum ALT value=310 U/L, maximum AST value 172 U/L, and ALP and bilirubin within normal limits) in a patient in the 675 mg quarterly treatment group with a recent primary infection with Epstein-Barr virus also led to discontinuation from the study drug

Each of these events resolved.

Potential risks of calcitonin gene-related peptide inhibition

Cardiovascular effects

Because CGRP is a vasodilator, cardiovascular effects, including medication-induced hypertension, counterbalancing the effect of anti-hypertensive drugs that have vasodilatory properties, inhibition of stress- or ischemia-induced vasodilation, and impairment of cardioprotective mechanisms, are of potential concern with CGRP inhibition.

Animal data have not raised any issues regarding potential cardiovascular effects of fremanezumab. Nonetheless, a broad evaluation of all adverse events related to cardiovascular function was undertaken to determine if a cardiovascular signal is apparent. No pattern was observed in cardiovascular events. The following PTs were evaluated: palpitations, tachycardia, atrial fibrillation, angina pectoris, aortic valve incompetence, arrhythmia, bundle branch block left, mitral valve incompetence, sinus arrhythmia, tricuspid valve incompetence, ventricular extrasystoles, blood pressure increased, heart rate increased, blood pressure diastolic increased, ECG PR prolongation, ECG QT prolonged, ECG T wave amplitude decreased, transient ischemic attack, cerebrovascular accident, hypertension, hot flush, hypertensive crisis, flushing, deep vein thrombosis, pallor, peripheral coldness, Raynaud's phenomenon, hypotension, superficial vein prominence, peripheral venous disease, thrombophlebitis superficial, thrombosis, and venous thrombosis limb.

Despite the prevalence of hypertension (9% and 10% of patients who received fremanezumab and placebo, respectively) in the patient population per medical histories, cardiovascular adverse events occurred infrequently with similar incidence in all patients in the placebo-controlled studies (cohort 1) who received fremanezumab and in patients who received placebo. Hypertension in 15 patients (11 patients [<1%] who received fremanezumab and 4 patients [<1%] who received placebo); tachycardia in 6 patients (3 patients [<1%] who received fremanezumab and 3 patients [<1%] who received placebo); and palpitations, blood pressure increased, and heart rate increased in 5 patients each (each in 3 patients [<1%] who received fremanezumab and 2 patients [<1%] who received placebo) occurred most frequently. The only other cardiovascular adverse event that occurred in more than a single patient was hypertensive crisis in 2 patients who received fremanezumab (<1%).

Both patients had a medical history of hypertension, and both of these patients were taking antihypertensive medication at the time of onset of the event

Table 23 Cardiovascular Adverse Events in All Patients in the Placebo-Controlled Studies by System Organ Class and Preferred Term—Cohort 1 (Safety Population)

SOC MedDRA PT	Number of patients (%)				
	Placebo	Fremanezumab			
	Monthly (N=861)	225 mg monthly (N=386)	675 mg quarterly (N=667)	675/225 mg monthly[a] (N=467)	Total[b] (N=1702)
Cardiac disorders	6 (<1)	1 (<1)	1 (<1)	2 (<1)	6 (<1)
Palpitations	2 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Tachycardia	3 (<1)	0	0	1 (<1)	3 (<1)
Atrial fibrillation	1 (<1)	0	0	0	0
Investigations	38 (4)	25 (6)	33 (5)	23 (5)	91 (5)
Blood pressure increased	2 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Heart rate increased	2 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Electrocardiogram PR prolongation	0	0	1 (<1)	0	1 (<1)
Electrocardiogram QT prolonged	0	1 (<1)	0	0	1 (<1)
Electrocardiogram change	1 (<1)	0	0	0	0
Vascular disorders	4 (<1)	1 (<1)	7 (1)	8 (2)	20 (1)
Hypertension	4 (<1)	0	6 (<1)	2 (<1)	11 (<1)
Flushing	0	0	0	1 (<1)	2 (<1)
Hypertensive crisis	0	1 (<1)	0	1 (<1)	2 (<1)
Hypotension	0	0	0	1 (<1)	1 (<1)
Pallor	0	0	1 (<1)	0	1 (<1)
Peripheral coldness	0	0	0	1 (<1)	1 (<1)
Raynaud's phenomenon	0	0	0	1 (<1)	1 (<1)
Superficial vein prominence	0	0	0	1 (<1)	1 (<1)

a Patients received fremanezumab at 225 mg monthly with a starting dose of 675 mg.
b Adverse events that occurred in patients in all fremanezumab treatment groups, including the 675 mg monthly and 900 mg monthly treatment groups, are included in this total group.
ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients;
PT=preferred term; SOC=system organ class.
Note: Patients were counted only once in each PT category.
Note: Adverse events summarized in this table are those events that started on or after starting study drug (ie, treatment-emergent adverse events).

Serious cardiovascular adverse events that occurred in all fremanezumab-treated patients during participation in Study 30051 included deep vein thrombosis in 2 patients, and transient ischemic attack, hypertension, and limb venous thrombosis in 1 patient each. Each of these serious adverse events was considered unrelated to the study drug by the investigator and resolved. Among these serious adverse events, transient ischemic attack and atrial fibrillation led to discontinuation from the study drug. The event of transient ischemic attack, which resolved without sequelae, occurred in a 58-year-old white female with a medical history of hypertension and cervical cancer. The investigator suspected atrial fibrillation as the cause of the transient ischemic attack. Other cardiovascular adverse events that occurred in patients in Study 30051 and led to discontinuation from the study drug included unrelated events of aortic valve incompetence, mitral valve incompetence, and tricuspid

valve incompetence in the same patient in the 225 mg monthly treatment group and angina pectoris (verbatim term: cardiac chest pain) considered related to the study drug in a patient in the 225 mg monthly with 675 mg starting dose treatment group. The event of angina pectoris resolved within 3 hours without treatment. No similar events were reported before or after this event.

Hypersensitivity reactions and anaphylaxis

Type I hypersensitivity (allergic) reactions and type III hypersensitivity reactions are theoretically possible with any injected protein. Anaphylaxis and severe hypersensitivity reactions were analyzed as adverse events of special interest in the Phase 3 pivotal efficacy studies and in the Phase 3 long-term safety study, and the individual CSR listings for the Phase 2b studies were also searched for events of anaphylaxis and severe hypersensitivity reactions.

No events of anaphylaxis or severe hypersensitivity to the study drug were observed in the studies in patients with migraine

A review of events of drug hypersensitivity regardless of intensity in all patients in the placebo-controlled studies (cohort 1) demonstrates that drug hypersensitivity occurred in 2 patients (<1%) who received placebo and 2 patients (<1%) who received fremanezumab. For patients in the placebo treatment group, drug hypersensitivity was assessed by the investigator as related to the study drug in 1 patient and attributed to a concomitant medication (ceftriaxone) in 1 patient. Both events in patients in the placebo treatment group were serious. For patients who received fremanezumab, drug hypersensitivity was assessed by the investigator as related to the study drug in 1 patient (900 mg monthly) and attributed to a concomitant medication (sulfa drugs) in 1 patient (225 mg monthly with a 675 mg starting dose). Neither event in patients who received fremanezumab was serious. All events resolved with steroid treatment (oral and/or topical) and/or antihistamine treatment, and all but 1 led to discontinuation from the study drug. The event of drug hypersensitivity that was attributed to ceftriaxone also required epinephrine.

A review of events of drug hypersensitivity among all fremanezumab-treated patients (cohort 4) demonstrates that 3 additional patients who received fremanezumab had drug hypersensitivity events (for a total of 5 patients [<1%; 0.39 events/100 patient-years]). Each of these events resolved with steroid treatment (oral and/or topical application) and/or antihistamine treatment, and all but 1 event led to discontinuation from the study drug. Drug hypersensitivity events that occurred in Study 30051 included 2 events, assessed as mild and moderate in intensity (1 of each intensity) and considered related to the study drug by the investigator. The third event was attributed to a concomitant medication (ciprofloxacin).

In order to further characterize the safety of fremanzumab in patients with cardiovascular risk factors/ cardiovascular medication use the Applicant provides updated graphs and tabular overviews following analyses of long-term data from study 30051. Overall, these data do not reveal specific patterns of Fremanzumab's safety profile in patients with cardiovascular risk factors.
Nonetheless, with regard to changes in blood pressure, there seems to be a trend for patients with poorly controlled hypertension (defined as systolic BP ≥ 140 mm HG or diastolic BP ≥ 90 mm Hg) to develop blood pressure (BP) increases with higher doses (675 mg, 675/225 mg) of fremanezumab.

Laboratory findings

Laboratory tests

Clinical laboratory tests were performed at each visit in the placebo-controlled studies and at screening for "new" patients and at baseline and every other visit thereafter in the long-term safety study. Evaluation of changes from baseline in serum chemistry, hematology, coagulation, and urinalysis parameters over time, shifts from baseline, and programmatically identified PCS values demonstrated no clinically meaningful trends in all patients in the placebo-controlled studies (cohort 1), and no safety signals based on laboratory test results were identified in all fremanezumab-treated patients (cohort 4), the majority of whom were treated for 6 months or more with fremanezumab.

There were no clinically meaningful trends in mean changes from baseline for any serum chemistry, hematology, coagulation, and urinalysis variables. Mean serum/ urine values for patients who received fremanezumab were generally similar to mean values for patients who received placebo.

Results in all patients with CM in the placebo-controlled studies (cohort 2) and all patients with EM in the placebo-controlled studies (cohort 3) were similar to those seen in all patients in the placebo-controlled studies (cohort 1).

Vital signs

Vital signs measurements were performed at every visit through the EOT visit for all studies included in the integrated safety cohorts. Evaluation of changes from baseline in vital signs parameters over time and programmatically identified PCS values demonstrated no clinically meaningful trends in all patients in the placebo-controlled studies (cohort 1), and no safety signals based on vital signs data were identified in all fremanezumab-treated patients (cohort 4), the majority of whom were treated for 6 months or more with fremanezumab.

There were no clinically meaningful trends in changes from baseline in heart rate, systolic and diastolic blood pressure, respiratory rate, and weight, and there were no notable differences between the placebo and fremanezumab treatment groups in vital signs measurements over time.

Immunogenicity

Immunogenicity was assessed for patients receiving fremanezumab in the placebo-controlled studies (cohort 1). In total, 1702 patients received fremanezumab in Studies 021, 022, 30049, and 30050, and 1701 patients had samples for immunogenicity assessment. ADA samples were collected at predose and at day 28, day 56 (in the Phase 2b studies only), and day 84 prior to fremanezumab administration/end of study (Study 021 CSR, Study 022 CSR, Study 30049 CSR, and Study 30050 CSR). Six of 1701 patients (0.4%) had treatment-emergent anti-fremanezumab antibody responses: 2 patients in Study 30049 and 4 patients in Study 30050. Five of the 6 patients had ADA occurring at day 84, and the remaining patient was ADA-positive at day 28 but became negative at day 84.

ADA-positive patients were randomly distributed across the monthly and quarterly fremanezumab dosing schemes. The ADA titers were relatively low, varying from 0.306 to 1.13 in log10 scale. One of the 6 patients developed anti-fremanezumab NAb at day 84 in Study 30050. None of the 6 ADA-positive patients had significant safety consequences of ADA development.

Immunogenicity is also being assessed in the long-term safety study (Study 30051). As of the data cut-off date for immunogenicity (02 May 2017), the immunogenicity response from 1140 patients (312 new patients and

828 patients who rolled over from the pivotal studies [Studies 30049 and 30050]) had been monitored. In these interim results, ADA samples were collected at predose (new patients) and at day 84 (visit 5), day 168 (visit 8), and day 336 (visit 14) posttreatment. Treatment-emergent anti-fremanezumab antibody response was detected in a low proportion of fremanezumab-treated patients (18 patients [1.6%], 1 of whom had positive ADA in the pivotal study and remained positive in Study 30051), who were distributed across the monthly and quarterly treatment groups. Five of these patients were new patients, and 13 were rollover patients. The majority of the ADA positive samples occurred at day 84, ie, after 3 months of exposure (new patients or rollover placebo patients) or 6 months of exposure (rollover active patients) to fremanezumab.

The ADA titers were relatively low, ranging from 0.239 to 1.14 in log10 scale. Out of 18 ADA-positive patients, 11 had a neutralizing activity in their post-dose samples. Two of the ADA-positive patients showed decreased fremanezumab concentration at the time point coinciding with ADA occurrence. This observation may suggest that the drop in fremanezumab concentration could be due to the presence of ADA. There were no significant adverse events related to ADA development in patients with treatment-emergent ADAs, and no lack of efficacy was observed.

With submission of the Day 121 Responses the Applicant provided an update on the immunogenicity results from study TV48125-CNS-30051. The results for treatment-emergent ADA (2%) were comparable to the previous results provided with the initial report (1.6%). The rate of neutralizing antibodies to fremanezumab was also unchanged (approx. 1%).

47 of the 52 ADA-positive patients reported adverse events and none of these reported events were potentially related to type I or type III hypersensitivity. The other 5 ADA positive patients had no reported adverse events at the time of the data cut-off date.

Therefore, the Applicant concludes that there is no evidence for a correlation between ADA development and hypersensitive reactions. No increase in the incidence of hypersensitivity reactions has been observed in ADA-positive patients.

Immunological events

Six of 1701 patients (0.4%) had treatment-emergent anti-fremanezumab antibody responses: 2 patients in Study 30049 and 4 patients in Study 30050. Five of the 6 patients had ADA occurring at day 84, and the remaining patient was ADA-positive at day 28 but became negative at day 84.

ADA-positive patients were randomly distributed across the monthly and quarterly fremanezumab dosing schemes. The ADA titers were relatively low, varying from 0.306 to 1.13 in log10 scale. One of the 6 patients developed anti-fremanezumab NAb at day 84 in Study 30050. None of the 6 ADA-positive patients had significant safety consequences of ADA development.

Among all fremanezumab-treated patients (cohort 4), no events of anaphylaxis occurred, and only 3 patients had adverse events of drug hypersensitivity. Each of these events was not serious and resolved with steroid and/or antihistamine treatment.

The incidence of ADA formation as of the data cut-off date was low, and there were no significant adverse event related to ADA or Nab development..

This finding was confirmed by the updated analyses submitted with the Day 121 Responses.

Safety related to drug-drug interactions and other interactions

Fremanezumab is a fully humanized immunoglobulin G2 (IgG2). As such it is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous immunoglobulins. Drug interactions are not expected, therefore, no drug-interaction studies have been conducted. There are no known interactions of fremanezumab with other medications, and there are no other forms of interactions currently known for fremanezumab.

Discontinuation due to AES

The most common reasons for discontinuation in the fremanezumab and placebo treatment groups were withdrawn consent (3% and 2% of patients, respectively), lost to follow-up (2% and 3% of patients, respectively), and adverse events (2% in each group). The frequency of study discontinuations due to adverse events was similar across the proposed dosing regimens of 225 mg monthly, 675 mg quarterly, and 225 mg monthly with a 675 mg starting dose (1% to 2% of patients in each treatment group).

2.6.1. Discussion on clinical safety

A total of 2566 patients were randomized (862 in the placebo treatment group, 386 in the 225 mg monthly treatment group, 667 in the 675 mg quarterly treatment group, 467 in the 225 mg monthly with 675 mg starting dose treatment group, 97 in the 675 mg monthly treatment group, and 87 in the 900 mg monthly treatment group), and all but 3 of these patients (>99%) received at least 1 dose of study drug and were evaluable for safety. Thus, the extent of exposure in the dose regimens intended for MAA (225 mg sc monthly, 225 mg sc quarterly with a 675 mg starting dose, and 675 mg sc quarterly) meets the exposure requirements of the International Conference of Harmonisation (ICH) guidance.

The median exposure for cohort 1 was 85.0 days (range 84.0; 87.00) for patients treated with fremanezumab and 85.0 days (range 84.0; 88.0) for patients treated with placebo. Duration of exposure corresponds to the 12-week treatment duration that was employed in the phase 2 and phase 3 placebo-controlled studies. For cohort 4, as of the data cut-off date (May 2017), the median duration of exposure was 175.0 days (range 89.0; 259.5) A total of 260 participants have had fremanezumab treatment for over a year. This is in line with the ICH E1 guideline on the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions.

The subjects integrated in the safety cohorts are considered representative for the migraine patient population with regards to demographics, disease characteristics, gender distribution, and concomitant medication. Patients with a history of or with currently suffering from clinically significant cardiac/cardiovascular disease as well as patients >70 years of age had been excluded from trial participation. Only few patients >65 years were enrolled. The interpretation of results for older patients is hence limited due to the low number of patients > 65 years of age. Results may indicate that the risk for psychiatric disorders, neurologic disorders, accidents and injuries, and vascular disorders was increased in the higher age groups. Such finding would not be completely unexpected for an overall older population.

Adverse events

For both cohorts approximately 65-75% of the subjects experienced at least one adverse event. Most of these were mild to moderate in nature. Most common reported adverse events under fremanezumab were injection site pain (24% and 30%, cohorts 1 and 4 respectively), injection site induration (17% and 27% cohorts 1 and 4 respectively) and injection site erythema (16% and 24% cohorts 1 and 4 respectively). The incidences were similar in both cohorts. There was no difference between the treatment groups.

The Applicant presented the incidence of adverse events over time. The most frequent occurring adverse events up to 24hr were injection site reactions. Adverse events seem to decline over months of exposure. The increase in months 3 to < 6 months is likely to be due to the start of the long term extension study. The emergence of adverse events over time was not further specified at time of initial MAA and it was therefore considered that the presented data only show that there is a general decrease. As it was considered unclear when exactly the adverse events emerged and how long they persisted over time, the Applicant was requested to provide data on when injection site reactions occurred and how long they persisted . The Applicant clarified that most injection site reactions after administration of fremanezumab were of short duration and mild severity. Most injection site reactions occurring with fremanezumab were seen with frequency similar to that of placebo-induced injection site reactions. All reactions resolved. Reactions that were seen with increased frequency in fremanezumab compared with placebo were erythema, pruritus, induration, and rash.

There was no clear dose-response relationship seen in either duration or onset by the median times to the onset and the duration of the reactions in all patients in the double-blind studies (Cohort 1). The onset of reactions varies significantly. Injection site erythema and induration onset were seen within 1 minute in the 225-mg monthly, 675-mg quarterly, and 675/225/225-mg groups. Injection site pruritus had significant variations within these same groups, with the higher dose, 675 mg quarterly, having a later onset than the 225-mg dose. Injection site rash also had no clear dose-response relationship, with both the 675/225/225-mg and 675-mg quarterly dosing regimens having a later onset than the 225-mg dosing regimen. Variation is also seen in the durations of the reactions. Injection site pruritus and injection site rash both had a longer duration with the 225-mg monthly dose than with the 675-mg quarterly dose. The Applicant concluded that this finding was likely due to the overall low numbers of patients with these reactions. (There were only 30 cases of injection site pruritus and 13 cases of injection site rash in all the fremanezumab groups together.) As a result, the minimum-maximum range in both duration and onset was very large. In conclusion, the injection site reactions in all treatment groups were of relatively short duration. All of the reactions resolved, and no significant differences were seen in the 225-mg monthly and 675-mg quarterly dosing regimens. The Applicant's argumentation on this issue is considered plausible and the issue is therefore considered resolved.

The percentage of injection site reactions is higher for the active treatment groups as compared to placebo. However in both cohorts, the 675mg Q12W treatment group has a higher incidence of injection site reactions when compared to the 225 mg Q4W group. Based on the lower time interval between active injections, it would be expected that the 225 Q4W group show a higher incidence of the injection site reactions. The applicant was therefore asked to clarify. The Applicant responded that the small differences in the incidence of injections site reactions between the active treatment groups are considered to be normal variability since there is no clear evidence of a greater incidence in patients who received the highest number of active injections. This argumentation is not completely agreed. Injection site erythema was found most frequently in the 675 mg quarterly group, although this dosing regimen was the one with the less frequent active injections. This might indicate that local tolerability of higher single doses of fremanezumab is reduced. However, the difference in the incidence of injection site reactions is relatively slow and data do not indicate a prolongation of symptoms with the administration of higher single doses. Moreover, overall safety and efficacy have demonstrated to be

comparable. Therefore, the Applicants argumentation that having two alternative dosing regimens, monthly and quarterly dosing, may offer viable options for patients with migraine is considered acceptable.

Abnormalities in laboratory values occurred at similar incidences among all treatment groups (all fremanzumab dosing regimens and placebo). No patterns could be found.

Changes in vital sign occurred at similar incidences among all treatment groups (all fremanzumab dosing regimens and placebo). However, cases of hypertensive crisis occurred more often with fremanezumab. Based on fremanezumab's mechanism of action, it can be assumed that patients with pre-existing hypertension may be at risk for aggravation of hypertensive disease with CGRP antagonists. The Applicant was therefore requested to present blood pressure data for all patients with a history of hypertension, patients with hypertensive blood pressure values at baseline, and patients using antihypertensive medications concomitantly and to discuss these data. It appears that the mean blood pressure remained unchanged over the course of months. The Applicant has provided a time to event analysis where an event was defined as consecutive visits with increase in diastolic blood pressure ≥10 mm Hg or increase in systolic blood pressure ≥20 mm Hg or started new hypertensive treatment.

In cohort 1 it appears that more patients with diastolic blood pressure ≤ 90 mm Hg/ systolic blood pressure ≤ 140 mmHg in the higher dose fremanezumab groups (675mg monthly and 900mg monthly) experience this event over time (~15% at month 3). For the dosing regimes as proposed in the current SmPC this is around 5% at month 3. This dose-response is much less visible in patients with diastolic blood pressure > 90 mm Hg / systolic blood pressure > 140 mm Hg.

In cohort 4 it is shown that more patients with diastolic blood pressure ≤ 90 mm Hg experience this event over time i.e. 25% at 15 months. No dose response effect is observed. For patients with blood pressure > 90 mm Hg, around 25% of patients also experienced an event at 15 months. It does appear that approximately 30% of patients in the 675mg quarterly dosing group experience this event at month 15, suggesting a dose dependent effect. For the systolic blood pressure, similar incidences are reported for both ≤ 140 mm Hg and > 140 mm Hg groups. No clear dose response relationship is observed.

The Applicant also provided a relative risk analysis of blood pressure increased in patients without and patients with high blood pressure at baseline. From this, it appears that patients treated with higher doses of fremanezumab have a higher risk of experiencing blood pressure increases, in particular for the high dosing regimes. It is acknowledged that the patient groups for the 675mg monthly and 900mg monthly dosing regimes are small and that these regimes are also not proposed in the current SmPC by the Applicant. Nevertheless there dose dependent increase in relative risk. This effect is more apparent in patients who already had a high blood pressure at baseline. This may indicate a dose-dependent effect of fremanezumab on blood pressure in subjects with elevated blood pressure at baseline. However, patient numbers were rather small.

The adverse event profile of fremanezumab in patients on preventive migraine medication at baseline (24% of fremanezumab-treated patients and 24% of placebo-treated patients in the placebo-controlled studies) is similar to that of the overall population and does not raise concerns. However, nervous system disorders including dizziness, headache and migraine seemed to occurr more often in fremanezumab treated patients using baseline migraine medications compared to those not using baseline migraine medications (in this respect the ISS differs slightly from the number presented in the table above). The Applicant was requested to discuss this finding, including results from study 30051 which had not been included in the current data set. Based on the analyses submitted the incidence of neurologic AEs was not increased in patients treated concomitantly with standard migraine prophylactic therapies.

Adverse events leading to discontinuation were infrequent (overall < 4%). Discontinuation rates did not differ between the study arms and there was no pattern for the active treatment groups. The most common reason for study discontinuation was withdrawal of consent by the participant (5% in cohort 1, 4% in cohort 4). Time to withdrawal was not presented with the initial MAA and was therefore requested. The Applicant provided analyses on time-to-withdrawal for the long-term extension study. There appears to be no differences between treatment arms in drop outs for whatever reason. This may indicate that patients in the long term extension study benefit from fremanezumab treatment regardless of the treatment regime they have been randomized to.

In order to improve the comparability of safety results, the Applicant was requested to provide a tabular overview of AEs/SAES which have been found to have occurred more often in older patients. This summary of AEs should be tabulated by age strata and treatment group (fremanezumab total vs. placebo) and should also include those data from study 30051 which had not been included in the initial dossier. Based on the updated safety data submitted in response to the D120 LoQ no new safety risks were found, neither for the whole study population nor for the group of patients > 65 years of age. Compared to other age strata, there was no increase in frequency of adverse events in the central nervous system, cardiovascular system, or any other system organ class (SOC). These analyses are considered supportive for the Applicants intention that a restriction of the indication in terms of age is not required.

Clinical withdrawal or rebound effects have not been observed in clinical studies conducted in subjects and patients receiving fremanezumab up to 2000 mg iv. Therefore, no concerns have been raised in this regard.

Cardiovascular Safety

56% of patients had at least 1 cardiovascular or cerebrovascular risk factor at baseline; 13% had a cardiovascular medical history including myocardial ischemia, arrhythmia, and other, and 14% were receiving cardiovascular medications at baseline (patients on cardiovascular medications" used for migraine prevention were excluded). 65% percent of patients were using triptans that are known for potential cardiovascular effects, such as cardiac arrhythmias and myocardial infarction. Vascular disorders were found more frequently in patients treated with fremanezumab. Vascular events reported more frequently included cases of hypertensive crisis, peripheral coldness, and Raynaud's phenomenon. It is recognized that the incidences of these events were rather small. Drugs frequently used to treat migraine, such as triptans, and which are known to potentially adversely affect the cardiovascular system were included in the studies. No signal was identified in this patient population. Concomitant use of anti CGRP mAbs with medications that have potential cardiovascular effect, such as birth control pills, triptans, and ergots, did also not show to have negative cardiovascular effects in the assessed patient population. However, the population included in the phase 3 program was not entirely representative for the migraine population. It is known that migraine patients have an increased risk for vascular events, including stroke and myocardial infarction. Patients with significant cardiovascular risk factors and > 70 years of age had been excluded from trial participation. This may have led to a bias in safety signal detection. Consequently, even the only slightly increased number of vascular events observed should be handled as safety signal. The Sponsor was therefore requested to discuss this potential safety risk and to propose safety measures to mitigate this risk in clinical practice.

Based on the data on cardiovascular safety presented in response to this question, the safety profile of Fremanezumab is comparable across age groups without specific safety signals for patients with cardiovascular risk factors (with exemption of the possible risk of blood pressure increase in patients with preexisting hypertension). Hence, the Applicant's proposal for including a statement that safety data for patients with major cardiovascular diseases are lacking in section 4.4 of the SmPC ("*Patients with certain major cardiovascular*

diseases were excluded from clinical studies (see section 5.1). No safety data are available in these patients.") is agreed.

Based on the updated analyses, there seemed to be a trend for patients with poorly controlled hypertension to develop blood pressure increases with higher doses (675 mg, 675/225 mg) of Fremanezumab. This finding was based on rather small sample sizes, and the dosing regimen of 675/225 mg which seemed to have the strongest impact on BP increase is no more intended for MAA. Moreover, of the 11 patients in the analysis, in actuality only one patient (13560012) in the 675mg study arm experienced 2 consecutive increases in BP. This patient had a history of hypertension which was not controlled, and was not on any study medication at the time of enrolment.

The other ten cases described patients which initiated new anti-hypertensive treatment. In most of these cases there was also a prior diagnosis of hypertension and after initiation of a new antihypertensive treatment blood pressure returned to normal or improved.

Thus, considering the above, it is agreed with the Applicant that a warning regarding monitoring of BP in patients with hypertension is not warranted.

Two deaths occurred during the clinical program: one in study 30049 and one in study 30050. In the first case the cause of death was COPD as the report revealed evidence of COPD as well as hypertensive atherosclerotic cardiovascular disease. There are theoretical concerns of potential cardiovascular risks associated with CGRP inhibition, thus a potential aggravating role of fremanezumab cannot completely be excluded. The second death concerned a suicide due to an intentional diphenhydramine overdose. Both deaths were considered to be unrelated to the study drug by the investigator. The Applicant was requested to further justify this labelling, in particular for the assumed COPD death. In response to this question the Applicant provided a discussion of the relationship between fremanezumab use and the two deaths that occurred during the clinical development program.

For the COPD death, the Applicant provided a discussion on the association between COPD/sudden death and left ventricular hypertrophy/sudden cardiac death. In the autopsy report, evidence of concentric left ventricular hypertrophy of the heart with perivascular fibrosis was found. The patient had a long medical history of hypertension, which was likely the cause of the fibrosis. In addition, the patient also recently had suffered from a respiratory infection, for which the patient was noncompliant to the prescribed medication. Taken together, it appears that the underlying medical conditions the patient had contributed to death, and not fremanezumab treatment.

A third fatal case was reported with the Day 121 Responses. This case was a patient who experienced a brain aneurysm and multiple strokes approximately 300 days after the last dose of fremanezumab. He was hospitalized and died approximately a month later. The fatal event was assessed as not related to the study drug by the investigator and the sponsor. Detailed information on this case was provided. Based on these data, a relationship with fremanezumab use appears unlikely.

Adverse events of special interest

Eye disorders occurred most frequently in the fremanezumab 675/225/225 mg group. Ophthalmic AE by preferred term that occurred with higher frequencies in the fremanezumab 677/225/225 mg group included blurred vision, dry eye, visual acuity reduced, blindness unilateral, eye pruritus, hypoaesthesia eye, retinal detachment, and scleral detachment. There was no increased incidence for eye disorders found in the fremanezumab 225 mg monthly and the fremanezumab 675 mg quarterly group compared with placebo. However, based on preclinical findings of periciliar inflammation in some animals and given the lack of long-term

safety data at the time of MAA submission, the Applicant was requested to provide and thoroughly analyse updated data on ophthalmic events including final study data from study 30051.

In response, the Applicant provided detailed analyses of all eye-related adverse events. The types of these events varied, and were analysed as being of different pathophysiologic mechanisms. Special attention was paid on the 6 cases of retinal events. There were two cases of retinal hole, one case and retinal tear and three cases of retinal detachment, which were classified as rhegmatogenous retinal detachment (RRD) which would point to a mechanistic origin. This assumption is supported by the case reports which reveal that all patients with RRD had specific risk factors for this disease. Overall, the Applicant concluded that a relationship of the reported ophthalmic AEs and Fremanezumab is unlikely and that analyses do not reveal a specific pattern with regard to time to onset or type of ophthalmic AE. This argumentation can be followed and the issue is considered resolved.

Overall, the incidence of hypersensitivity reactions has been low (<1%) and events have been of mild to moderate intensity. No cases of anaphylaxis or severe hypersensitivity occurred. Two hypersensitivity events occurred during the long term extension study. The investigator assessed that these were related to the study drug. The Applicant was therefore requested to provide data on what time points these events occur and how long participants were exposed to fremanezumab treatment as well as further substantiate the relationship between fremanezumab treatment and the observed hypersensitivity events. In the first case, the hypersensitivity reaction occurred a few hours after fremanezumab injection. In the second case the reaction occurred a two weeks after the first treatment session, which was reported as resolved at the next visit. After the second injection with fremanezumab the patient developed a reaction the following day. Both patients discontinued due to these adverse events.

No conclusions with regard to a timeline of hypersensitivity reactions can be drawn based on these narratives as one occurred within a few hours whereas the other after a few days. Hypersensitivity to fremanezumab is currently addressed in the RMP and in the SmPC as a contraindication. The issue is therefore considered resolved.

Elevation of hepatic enzymes was observed with a low incidence across fremanezumab treatment groups (< 1%) and no association was found with lower or higher fremanezumab doses. For most cases of elevated liver enzyme test concurrent factors could be attributed (eg, co-medications with known hepatotoxicity, infections). In the long term extension a single case was identified with two events of increased ALT. These were assessed by the investigator as related to the study drug. It was unclear if there was any potential confounding of underlying diseases or concomitant medication use in these cases. The Applicant was therefore requested to clarify the relation between the elevated liver enzymes and fremanezumab. Eighteen cases were identified of patients with protocol-defined adverse event of possible drug-induced liver injury deemed by the Investigator as related to the study drug. Protocol-defined adverse events of special interest of possible drug induced liver injury include AST or ALT $\geq 3 \times$ the ULN, total bilirubin $\geq 2 \times$ the ULN, or international normalized ratio >1.5.

A total of 18 cases of increased liver function measures as predefined were identified. Of these 18 patients, 4 discontinued from the study due to the liver adverse event. Most of the adverse events seemed to have resolved within a month. All cases were assessed to be unrelated to fremanezumab. Two cases were considered unresolved due to completion of the study or withdrawal from the study. Overall, elevated liver enzymes were sporadic reported and no clear pattern could be distinguished. Most cases were confounded by concomitant medication use by the patient. As fremanezumab is a monoclonal antibody and is not metabolized by the liver, the risk of liver toxicity is considered low. Considering all this, a relationship between fremanezumab injection and the observed liver injury is considered unlikely.

Suicidality was measured by the ec-CSSRS. No obvious pattern that is related to a dosing regime could be identified. However, there seemed to be more adverse events of suicidal ideation/behaviour occurring in the

active treatment groups, which has not been picked up by the eC-SSRS scores. There have also been 5 cases where a treatment-emergent positive score occurred on a single visit. It is unclear if there were confounding factors that lead to these positive scores and suicidality adverse events. The Applicant was therefore requested discuss how the positive scores are considered to be treatment related and provide and discuss narratives of the suicidality adverse events . Based on the information provided with the Day 121 Responses it was confirmed that the overall incidence of positive eC-SSRS scores post baseline and adverse events related to suicidal ideation/behaviour are low across the treatment groups. Most cases appear to be confounded by pre-existing psychiatric illness, such as depression or anxiety, for which they received concomitant treatment. It is agreed that the cases reported appear to be unrelated to fremanezumab treatment.

The effects of fremanezumab on human foetal development are not known. The Applicant was therefore requested to discuss the pregnancy cases in more detail. The number of pregnancies reported on fremanezumab was 15. The complication rate under fremanezumab was 33%, compared to 60% in the placebo arm. Based on the updated data, no association of use of fremanezumab with an increase in pregnancy complications or with a specific pattern of pregnancy complications can be drawn. The Applicant agreed to further study the safety of fremanezumab in pregnancy with a Post-Authorization Safety Study (PASS) as an additional pharmacovigilance activity to collect additional data on the use of fremanezumab in pregnancy in the post-approval period. Based on the data on use of fremanezumab available today this approach is considered adequate.

Immunogenicity

Treatment-emergent anti fremanezumab antibody (ADAs) responses were low across the clinical studies and in the long-term extension study. In the randomized-control studies, 1 participant developed anti-fremanezumab neutralizing antibodies (NABs). Based on the updated immunogenicity results from study TV48125-CNS-30051 provided, the results for treatment-emergent ADA (2%) were comparable to those provided with the initial report (1.6%). The rate of neutralizing antibodies to fremanezumab was also unchanged (approx. 1%). In conclusion, it was confirmed that the development of ADA in response to the treatment with fremanezumab was rather low and that the occurrence of ADA was not associated with specific safety issues, i.e. hypersensitivity, or with a reduced efficacy.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Fremanezumab at all doses tested was generally well tolerated in migraine patients. The long term safety, in particular with regards to cardiovascular outcomes and pregnancy will be closely monitored post-approval as these patients were not studied in the clinical trials.

2.7. Risk Management Plan

Safety concerns

Table 24 Summary table of the Safety Concerns

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 pregnant women (including those at risk of pre-eclampsia)

Pharmacovigilance plan

Table 25 Ongoing and Planned Additional Pharmacovigilance Activities in the PV Plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine (Study number TV48125-CNS-30051) **Status: Ongoing**	The primary objective of the study is to evaluate the long-term safety and tolerability of subcutaneous (sc) fremanezumab in the preventive treatment of migraine.	• Severe hypersensitivity reactions • Long-term safety	Final study report	30 September 2019
A post authorization safety study for assessment of pregnancy outcomes in patients treated with fremanezumab **Status: Planned**	The objectives of this study are to examine pregnant women exposed to fremanezumab during pregnancy and to evaluate: Primary objective: • pregnancy outcomes of major birth defects Secondary objectives: • pre-eclampsia/ eclampsia during pregnancy • maternal and fetal outcomes, including pre-term birth, spontaneous abortions, and stillbirth	• 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 Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice. **Status: Planned**	The study is intended to investigate the long-term safety profile (including cardiovascular safety) of fremanezumab in patients with migraine in a real-world clinical practice setting. The primary objectives of this study are the following: • To evaluate the long-term safety of fremanezumab in all patients with migraine (Cohort 1) • To evaluate the safety of fremanezumab in the subset of cardiovascular-compromised patients (both patients with a history of major cardiovascular disease and/or hypertension, as well as those who currently have major cardiovascular disease and/or hypertension) with migraine with regard to cardiovascular events, including development or worsening of hypertension, major adverse cardiovascular events (MACE; including myocardial infarction [MI], stroke, sudden cardiac death, and unstable angina), and heart failure (Cohort 2)	• Unfavourable cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable, and hypertension • Long-term safety	Submission of protocol to PRAC	9 months after MAA approval
			Final report of study results	12 months after end of data collection

Risk minimisation measures

Table 26 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		
Severe hypersensitivity reactions	**Routine risk minimisation measures:** • SmPC sections 4.3 and 4.4 • PL section 2 • Medicinal product subject to restricted medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific hypersensitivity follow-up questionnaire.
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 Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice. Final study report due date: 12 months after end of data collection
MISSING INFORMATION		
Long-term safety	**Routine risk minimisation measures:** • Medicinal product subject to restricted medical prescription	**Additional pharmacovigilance activities:** • A Multicenter, Randomized, Double-Blind, Parallel-Group Study Evaluating the Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine (Study number TV48125-CNS-30051). Final study report due date: 30 September 2019 • A Long-Term Observational Study to Evaluate the Safety, Including Cardiovascular Safety, of Fremanezumab in Patients with Migraine in Routine Clinical Practice. Final study report due date: 12 months after end of data collection
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:** • A post authorization safety study for assessment of pregnancy outcomes in patients treated with fremanezumab. Final study report due date: 12 months after end of data collection

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 (dated 29 January 2019) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14 September 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that fremanezumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers fremanezumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, AJOVY (fremanezumab) is included in the additional monitoring list as it contains a new active substance and is a biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Migraine is a neurological disorder, characterized by recurrent episodes of headaches, accompanied by associated symptoms such as nausea, vomiting, photophobia and phonophobia. The headache is often unilateral, of moderate to severe intensity, throbbing and aggravated by physical activity. An attack can be preceded by sensory warning symptoms or signs (aura), and may last for 4-72 hours. The attacks are often disabling and associated with missed activities at work, school or at home.

Migraine prophylaxis is recommended if the subject has more than 2 - 4 attacks per month. The main goal of prophylactic treatment in migraine is to reduce the number of migraine attacks or number of migraine days.

Migraine is considered a spectrum disorder, including episodic migraine (EM) and chronic migraine (CM). EM is defined as having fewer than 15 headache days per month. CM is defined by more than 15 headache days per month, with at least 8 days being migraine days thus having intercurrent headache days. The differential diagnosis between CM and medication overuse headache and tension headache can be difficult.

3.1.2. Available therapies and unmet medical need

The majority of patients with low-frequency episodic migraine treat individual attacks by taking medication for acute treatment on an as needed basis. These medications include triptans, nonsteroidal anti-inflammatory drugs, simple and combination analgesics, opioids, and ergots.

Patients with more frequent migraine attacks may need migraine prophylactic treatments. Several migraine prophylactic treatments are available in the European Union. Beta-blockers (metoprolol and propranolol), calcium channel blockers (flunarizine) or anticonvulsants (topiramate and valproic acid) are recommended in prophylactic treatment of migraine in order of preference. Botulinumtoxin A is currently the only treatment approved in some member states for migraine prophylaxis in CM.

Patients often switch between prophylactic medications. This is likely due to the combination of factors complicated titration schedules, requirement of daily dosing, side effects, delayed onset of efficacy affecting long-term compliance and/or insufficient long term efficacy.

3.1.3. Main clinical studies

The primary evaluation of efficacy was based on the data from 2 nearly identical Phase 3, 16-week, multicentre, double-blind, placebo-controlled, randomized, parallel-group studies (**Study 30049** in patients with CM and **Study 30050** in patients with EM), which tested the proposed dose regimen of 225 mg monthly or 675 mg every 3 months (quarterly). Patients with CM received a starting dose of 675 mg the first month, when initiating the monthly dose regimen. The studies included female and male patients, aged 18 to 70 years, with a history of migraine for at least 12 months.

The studies consisted of a screening visit, a 28-day run-in period, and a 12-week (84-day) treatment period, including a final evaluation at week 12 (end-of-treatment [EOT] visit, approximately 4 weeks [28 days] after the final dose of study drug).

Long-term efficacy data will be evaluated in Study 30051, which is an ongoing Phase 3 multicentre, randomized, double-blind, parallel-group study evaluating the long-term safety, tolerability, and efficacy of sc administration of fremanezumab for the preventive treatment of migraine. Study duration for patients who completed the pivotal efficacy studies of fremanezumab (Studies 30049 and 30050) consists of a 12-month treatment period and a 6.5-month follow-up period. Patients who received either of the 2 active fremanezumab dose regimens during the pivotal studies remained in their same treatment arm during the long-term study without switching between dose regimens at any time during the studies. Placebo-treated patients were randomized to receive active fremanezumab treatment (either monthly or quarterly). For patients who had not participated in a pivotal efficacy study, the study consists of a screening visit and 28-day run-in period, a 12-month treatment period, and a 6.5-month follow-up period (Figure 1 and Figure 2). There were approximately 300 new patients (not participants on pivotal trials 30049/30050) allowed to enter the study. Patients receive 1 of the following dose regimens in a treatment-blinded fashion:

- s.c. fremanezumab at 675 mg followed by 11 monthly s.c. doses of fremanezumab at 225 mg
- monthly s.c. fremanezumab at 225 mg for 12 months
- quarterly s.c. fremanezumab at 675 mg for 12 months for a total of 4 doses

3.2. Favourable effects

The Applicant demonstrated superiority of fremanezumab versus placebo in the reduction in the monthly average number of headache days of at least moderate severity (primary endpoint in study 30049), and in the monthly average number of migraine days (primary endpoint in study 30050). Key secondary endpoints have also been met, indicating the potential of fremanezumab to decrease the number, duration and burden of migraine symptoms.

The different dose regimens tested (675-225-225 mg, 675 mg quarterly, and 225-225-225 mg) have demonstrated similar efficacy results.

In the *chronic migraine study (30049),* subjects had a LS mean change from baseline (13.1) in monthly average number of headache days of at least moderate severity of -4.2 in the 675 mg Q12W group, -4.5 in the 675/225 mg group and -2.5 in the placebo group. Differences versus placebo were significant ($p<0.001$)

Change in monthly migraine days form baseline (16.2) were -4.9, -5.0 and –3.2 days for the 675mg Q12W group, 675/225 mg and placebo respectively. Difference versus placebo were significant ($p<0.001$)

The proportion of responders defined as a subjects with a 50% reduction in headache days was 37.6% of subjects in the 675 mg/placebo/placebo group, 40.8% of subjects in the 675/225/225mg group and 18.1% subjects in the placebo group. Differences versus placebo were significant ($p<0.001$).

Change in monthly days of acute headache medication use from baseline was –3.7, -4.2 and -1.9 days for the 675mg Q12W group, the 675/225 mg group and placebo respectively. Difference versus placebo was significant ($p<0.001$ for both groups).

The headache impact score, as measured by the HIT-6 questionnaire, also improved under fremanezumab treatment when compared to placebo. The change from baseline (64.3) in migraine-related disability score was -6.4, -6.8 and -4.5 for fremanezumab 675mg Q12W, fremanezumab 675/225mg and placebo respectively. For

the PGIC a similar effect was observed, participants in both active treatment groups were more likely to be responders (>= moderate improvement) than patients who received placebo (37% in placebo, 55% in fremanezumab Q12W, 54% in fremanezumab 675/225mg).

Efficacy over the subgroups (i.e. age, sex, concomitant prophylactic medication use, past use of botox, past use of topiramate) were consistent with the findings on the primary analysis with the exception of sex. Here, there was a lack of efficacy in the males. In the concomitant prophylactic treatment subgroup analysis, it was shown that subjects who did not use concomitant migraine prophylaxis medication also had a significant reduction in the number of headache days of at least moderate severity (nominal $p < 0.001$). Overall subjects had a mean difference of -4.6 days for the 675mg Q12W group, -4.8 for the 675/225 group and -2.6 for the placebo group. Subjects with concomitant prophylactic medication had a mean reduction in the number of headache days of -3.8 days for the 675mg Q12W group and -4.4 days for the 675/225 mg group ($p= 0.0549$ and 0.0031 respectively).

In the *episodic migraine study (30050),* subjects had a mean change from baseline (9.1) in migraine days of 3.4- in the 675 mg/placebo/placebo group, -3.7 in the 225/225/225 mg group and -2.2 in the placebo group. Differences versus placebo were significant ($p<0.001$)

Change in monthly days of acute headache medication use from baseline (7.8) was –3.4, -3.7 and –2.2 days for the 675mg Q12W group, the 225 mg Q4W group and placebo respectively. Difference versus placebo was significant ($p<0.001$ for both groups).

The proportion of responders defined as a subject with a 50% reduction in migraine days was 44.4% of subjects in the 675 mg Q12W group, 47.7% of subjects in the 225 mg Q4W group and 27.9% in the placebo group. Differences versus placebo were significant ($p<0.0001$ for both groups).

The Migraine Disability Assessment Score supported the primary endpoint. Improvement form baseline MIDAS score (39.0) was -23.0 for the 675mg Q12W group, -24.6 for the 225mg Q4W group and -17.5 points for the placebo group. Difference form placebo was statistically significant ($p=0.0023$ and $p=0.0021$). For the PGIC a similar effect was observed, participants in both active treatment groups were more likely to be responders than patients who received placebo (51% in placebo, 64% in fremanezumab Q12W, 72% in fremanezumab 225mg Q4W)

Efficacy over in subgroups (i.e. age, sex, concomitant prophylactic medication use, past use of topiramate or past use of botox) were consistent with the findings on the primary analysis with the exception of sex. Here, there was a lack of efficacy in males. For the concomitant prophylactic treatment subgroup analysis, it was shown that subjects who did not use concomitant migraine prophylaxis medication also had a significant reduction in the number of migraine days (nominal $p < 0.001$). Overall subjects had a mean difference of -3.5 days for the 675mg Q12W group, -3.7 days for the 225mg Q4W group and –2.4 days for the placebo group. Subjects who did use concomitant prophylactic medication also showed statistical significant reduction in the number of migraine days: -3.7 days for the 675mg Q12W group, -4.0 days for the 225mg Q4W group and -2.0 days for the placebo group (nominal $p=0.044$ and $p=0.0088$ respectively). Participants who used topiramate in the past for migraine prophylaxis also benefitted from prophylactic treatment.

Persistence of effect is likely based on the preliminary results of the ongoing long term extension study i.e. 30051. Overall, the results are consistent showing a positive effect of fremanezumab treatment with regard to the main and exploratory endpoints in both episodic and chronic migraine. The effect is present after the first week after the first dose. All three treatment regimens (675mg Q12W. 675/225 mg and 225mg Q4W) seem to have equal efficacy, thus allowing the migraine patient the choice to adopt the most convenient treatment regimen for them.

3.3. Uncertainties and limitations about favourable effects

It is still uncertain how long should treatment continue considering that migraine severity fluctuates over time. As requested, the Applicant agreed to add guidance on the evaluation of non-responder in section 4.2 of the SmPC (**"**The treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter.")

3.4. Unfavourable effects

Fremanezumab at all doses tested was generally well tolerated in migraine patients. Injection site reactions were the most common AEs and an increased incidence of local injection site reactions was found with higher fremanezumab doses, including injection site pain, injection site induration, injection site erythema, and injection site pruritus. With regard to the different fremanzumab dose groups, injection site reaction of each type occurred more frequently with the higher single dose of 675 mg quarterly.

There is a concern that treatment with GCRP antagonists may lead to an increased risk for vascular events, including but not limited to ischemic stroke and myocardial infarction. Indeed, vascular disorders were found more frequently in patients treated with fremanezumab (including cases of hypertensive crisis, peripheral coldness, and Raynaud's phenomenon). It is recognized that the overall incidence of these events were rather small. However, since it is known that migraine patients have an increased risk for vascular events and as the population included in the phase 3 program was not entirely representative for the migraine population (patients with cardiovascular risk factors and > 70 years of age had been excluded from trial participation which may have led to a bias in safety signal detection), even the only slightly increased number of vascular events observed should be handled as safety signal.

Changes in vital sign occurred at similar incidences among all treatment groups (all fremanzumab dosing regimens and placebo). However, cases of hypertensive crisis occurred more often with fremanezumab. Based on fremanezumab's mechanism of action and based on the data submitted, it can be assumed that patients with pre-existing hypertension may be at risk for aggravation of hypertensive disease with CGRP antagonists.

Overall, the incidence of hypersensitivity reactions has been low (<1%) and events have been of mild to moderate intensity. No cases of anaphylaxis or severe hypersensitivity occurred. However, hypersensitivity and injection site reactions are common risks of all monoclonal antibodies.

3.5. Uncertainties and limitations about unfavourable effects

Patients >70 years of age and patients with major cardiovascular disease have not been included in the efficacy trials. Whether the safety of fremanezumab as demonstrated in studies 30049 and 30050 can be extrapolated to an older population and to cardio-vascularl more severely compromised subjects remains subject for further monitoring.

The theoretical risk that CGRP blockade may aggravate ischemic events by lack of compensatory vasodilation still remains. In particular for patients with migraine, as they already have an increased risk for these events. However there is uncertainty whether chronic fremanezumab administration is safe in cardiovascular severly compromised subjects**.** The current exposure of fremanezumab in elderly patients is still very limited. In the clinical trial program only 2% of patients were >65 years. This population may be at higher risk of potential adverse vascular effects, but sufficient clinical data are currently not available.

The effects of fremanezumab on human foetal development are not known. There is some evidence that CGRP could be involved in feto-placental resistance and in blood pressure regulation during pregnancy. Low CGRP levels have found to be associated with pre-eclampsia. The data on pregnancies available today do not indicate a specific risk profile. However, the number of pregnancies reported is rather small which may limit the prognostic value of these data. "Use in pregnant women (including those at risk for pre-eclampsia)" will therefore be included as an area of "Missing Information" in the RMP. Teva in addition proposes to study the safety of Fremanezumab in pregnancy post-marketing with a Post-Authorization Safety Study as an additional pharmacovigilance activity (see also response to Question 164). This approach is endorsed.

3.6. Effects Table

Table 27 Effects Table for Fremanezumab in the prevention of chronic and episodic migraine in adults (data cut-off: 31 May 2017).

Effect	Short Description	Unit	Treatment	Results LSmean (SE)	Uncertainties/ Strength of evidence	References
Favourable Effects in Chronic Migraine						
Headache days of at least moderate severity	Change in monthly average number of headache days of at least moderate severity during the 12-week treatment period	Days	PBO 675/225/225 675/PBO/PBO	-2.5 (0.31) -4.6 (0.30) -4.3 (0.31)	 <0.0001 <0.0001	**TV48125-CNS-30049**
Migraine days	Change in monthly average number of migraine days of at least moderate severity during the 12-week treatment period	Days	PBO 675/225/225 675/PBO/PBO	-3.2 (0.35) -5.0 (0.35) -4.9 (0.35)	 <0.0001 <0.0001	
≥50% reduction	Proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity	%	PBO 675/225/225 675/PBO/PBO	18.1 37.6 40.8	 <0.0001 <0.0001	

Effect	Short Description	Unit	Treatment	Results LSmean (SE)	Uncertainties/ Strength of evidence	References
Acute headache medication	Reduction in the monthly average number of days of use of acute headache medication	Days	PBO 675/225/225 675/PBO/PBO	-1.9 (0.30) -3.7 (0.30) -4.2 (0.30)	<0.0001 <0.0001	
Favourable Effects in Episodic Migraine						
Migraine days	Change in monthly average number of migraine days during the 12-week treatment period	Days	PBO 225/225/225 675/PBO/PBO	-2.2 (0.24) -3.7 (0.25) -3.4 (0.25)	<0.0001 <0.0001	**TV48125-CNS-30050**
>50% reduction	Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week treatment period	%	PBO 225/225/225 675/PBO/PBO	27.9 47.7 44.4	<0.0001 <0.0001	
Acute headache medication	Reduction in the monthly average number of days of use of acute headache medication	Days	PBO 225/225/225 675/PBO/PBO	-1.6 (0.21) -3.0 (0.22) -2.9 (0.22)	<0.0001 <0.0001	
Unfavourable Effects						
Injection site reactions	Pain, induration, erythema, hemorrhage, and pruritus		PBO 225/225/225 675/PBO/PBO 675/225/225 Frem. total	22 % 25 % 30 % 22 % 24 %		**ISS, Cohort 1**

Effect	Short Description	Unit	Treatment	Results LSmean (SE)	Uncertainties/ Strength of evidence	References
Eye disorders	Blurred vision, dry eye, visual acuity reduced, blindness unilateral, eye pruritus, hypoaesthesia eye, retinal detachment, and scleral detachment		PBO 225/225/225 675/PBO/PBO 675/225/225 Frem. total	1 % <1 % <1 % 3 % 2 %		
Vascular events	Peripheral coldness, Raynaud's phenomenon, hypertension		PBO 225/225/225 675/PBO/PBO 675/225/225 Frem. total	<1 % <1 % 1 % 2 % 1 %		
Nervous system disorders			PBO 225/225/225 675/PBO/PBO 675/225/225 Frem. total	5 % 4 % 5 % 6 % 6 %		

Abbreviations: PBO = placebo, Frem. = Fremanezumab, ISS = integrated safety summary

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoints of the studies have been met and superiority of fremanezumab over placebo in reducing the number of headache days of at least moderate severity, and in reducing the number of migraine days in both CM and EM patients has been demonstrated. Key secondary endpoints have also been met, indicating the potential of fremanezumab of decreasing the number, duration and burden of migraine symptoms.

However, albeit demonstration of the statistical significance of the treatment effect, the absolute difference compared to placebo-control was relatively small due to a significant placebo effect. Especially in the treatment of EM the difference in treatment effect was small. This may limit the usefulness of fremanezumab in this group of patients and should be considered with regard to the benefit-risk-evaluation. Reduction of acute medications could be considered a clinical relevant additional benefit, but even for this endpoint the absolute difference to placebo was rather small. However, clinical benefit was consistently demonstrated for all patient subgroups over a treatment period of up to 15 months. The different dose regimens tested (675-225-225 mg, 675 mg quarterly, and 225-225-225 mg) have demonstrated highly similar efficacy results.

The overall LS mean reduction from baseline in the number of average monthly headache days of at least moderate severity during the double-blind treatment phase was -4.6 days for fremanezumab 675-225-225 mg and -4.3 days for fremanezumab 675 mg-placebo-placebo compared with -2.5 days for placebo (study 30049). The LS man change difference from placebo was -2.1 and -1.8; p<.0001 for each dose group versus placebo.

The overall LS mean reduction from baseline in the number of average monthly migraine days during the double-blind treatment phase was -3.7 days for fremanezumab 225-225-225 mg and -3.4 days for fremanezumab 675 mg-placebo-placebo compared with -2.2 days for placebo (study 30050). The LS mean change difference from placebo was -1.5 and -1.3; p<.0001 for each dose group versus placebo.

Based on current study data the safety profile of fremanezumab is considered acceptable. Fremanezumab at all doses tested was generally well tolerated in migraine patients. An slightly increased incidence of local injection site reactions was found with higher fremanezumab doses. Only few discontinuation due to AEs have been registered in clinical trials and most events have been judged as been manageable and being of mild to moderate intensity.

However, some AEs appeared to occur with higher frequency in fremanzumab-treated patients. Such imbalances have been found for vascular disorders (including cases of hypertensive crisis, peripheral coldness, and Raynaud's phenomenon). It is recognized that the overall incidence of these events were rather small. However, since it is known that migraine patients have an increased risk for vascular events and as the population included in the phase 3 program excluded patients with severe cardiovascular disease and patients > 70 years of age, this may have led to a bias in safety signal detection. Therefore even the only slightly increased number of vascular events observed should be handled as safety signal.

3.7.2. Balance of benefits and risks

The favourable effects of fremanezumab have been consistently demonstrated in two phase 2 and two phase 3 studies in patients with chronic or episodic migraine. These results were found to be clinically relevant and considered to outweigh the observed risks.

The indication has been restricted to patients who have at least 4 migraine days per month as this reflects the population in the phase 3 program. Moreover, the more restricted indication statement takes into account that patients with less severe disease may be "overtreated" with prophylactic migraine treatment.

3.8. Conclusions

The overall benefit risk balance of Ajovy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of AJOVY is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

N/A

Obligation to conduct post-authorisation measures

N/A

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that fremanezumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.