28 February 2019
EMA/CHMP/199629/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aimovig

International non-proprietary name: erenumab

Procedure No. EMEA/H/C/004447/X/0001

Note

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

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List of abbreviations

ADCC	antibody dependent cell-mediated cytotoxicity
AEX	anion exchange
AI	autoinjector
AML	Amgen Manufacturing Limited
ATF	alternating tangential flow filtration
ATO	Amgen Thousand Oaks
CDC	complement dependent cytotoxicity
CEX	cation exchange
CFU	*colony-forming unit*
cGMP	current good manufacturing practices
CGRP	calcitonin gene-related peptide
CHO	chinese hamster ovary
CPP	critical process parameter
CPV	continued process verification
CQA	critical quality attribute
dFBS	dialyzed fetal bovine serum
DNA	deoxyribonucleic acid
DOE	design of experiments
DP	drug product
DS	drug substance
DSC	differential scanning calorimetry
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESI-TOF-MS	electrospray ionization time-of-flight mass spectrometry
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration (US)
FVIP	filtered viral inactivation pool
HC	heavy chain
HCCF	harvested cell culture fluid
HCP	host cell protein
HIC	hydrophobic interaction chromatography
HMW	high molecular weight
HPLC	high-performance liquid chromatography
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IPC	in-process control
JP	Japanese Pharmacopoeia
LAL	limulus amebocyte lysate
LC	light chain
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
LIVCA	end of production cells at the limit of in vitro cell age
MCB	master cell bank

MFI	microflow imaging
MMV	mouse minute virus
N/A	not applicable
NF	National Formulary
NGHC	non-glycosylated heavy chain
PFS	prefilled syringe
Ph Eur	European Pharmacopoeia
PK	pharmacokinetic
PQRA	product quality risk assessment
PrV	Pseudo Rabies Virus
PV	process validation
rCE	reduced capillary electrophoresis
Reo-3	reovirus-3
RLP	retrovirus-like particles
RP-HPLC	reverse-phase high performance liquid chromatography
RTRT	real time release testing
RW	regular wall
Sc	subcutaneous
SDS	sodium dodecyl sulfate
SE-UHPLC	size exclusion ultra-high performance liquid chromatography
SmPC	Summary of Product Characteristics
SOP	standard operating procedures
SPR	surface plasmon resonance
SPTFF	single-pass ultrafiltration
STW	special thin wall
SV-AUC	sedimentation velocity-analytical ultracentrifugation
TCID50	50%Tissue Culture Infectious Dose endpoint
TEM	transmission electron microscopy
TSE	transmissible spongiform encephalopathy
UFDF	ultrafiltration/diafiltration
USP	United States Pharmacopeia
WCB	working cell bank
WHO	world Health Organization
xMuLV	xenotropic murine leukemia virus

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Limited submitted on 30 July 2018 an extension of the marketing authorisation.

Extension application to add a new strength of 140 mg.

The MAH applied for addition of a new strength.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) - Extensions of marketing authorisations

Information on Paediatric requirements

Not applicable

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder

The application was received by the EMA on	30 July 2018
The procedure started on	16 August 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	5 November 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	13 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	4 February 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 November 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Aimovig on	28 February 2019

2. Scientific discussion

2.1. Problem statement

Migraines are headaches that can involve significant pain and may be preceded by sensory warning symptoms or signs (auras). Migraine is seen as a spectrum disorder, although it has been arbitrarily classified as either episodic migraine (EM), characterized by fewer than 15 headache days per month, or chronic migraine (CM), characterized by 15 or more headache days per month with at least 8 days being migraine days (International Classification of Headache Disorders [ICHD 3], 2013).

Erenumab (also named Erenumab-aooe, Aimovig, AMG 334) is a human monoclonal antibody that binds to the calcitonin gene related peptide (CGRP) receptor. The CGRP receptor is located at sites that are relevant to migraine pathophysiology, such as the trigeminal ganglion. Erenumab potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor, and has no significant activity against other calcitonin family of receptors.

About the product

Erenumab-aooe (Erenumab/AMG 334) is indicated for the preventative treatment of migraine in adults with 2 dose options of 70 mg and 140 mg monthly (every 4 weeks), delivered subcutaneously (SC) as either 1 or 2 injections, respectively, of 70 mg/mL autoinjector pen (AI/pen) or prefilled syringe (PFS).

The 140 mg dose administered as two 1 mL injections of 70 mg/mL in the 2 pivotal migraine studies were included in the original submission (Studies 20120295 and 20120296).

The proposed commercial formulation is AI/pen or PFS with 1-mL injection of 140 mg/mL which supports one subcutaneous injection of 1ml for the 140mg dose in addition to two subcutaneous injections of 1ml 70-mg/mL (AI/pen or PFS) for140 mg dose or single injection of 1ml 70-mg/mL (AI/pen or PFS) for 70 mg dose treatment.

Type of Application and aspects on development

This application concerns a line extension to register an addition of a new strength of 140 mg, to Aimovig 70 mg for which marketing authorisation was obtained in July 2018.

The new solution for injection will be presented in both a pre-filled syringe and a prefilled pen:

- Aimovig 140mg solution for injection in pre-filled syringe
- Aimovig 140mg solution for injection in pre-filled pen

The new strength, Aimovig 140mg solution for injection, is also an aqueous solution for subcutaneous injection with same pharmaceutical excipients as the approved product, Aimovig 70 mg solution for injection.

Two type IB variations to reflect the data for drug substance manufacturing site transfer will be submitted for 70 mg/ml strength during the review period of this line extension procedure and for 140 mg/ml strength after approval of the line extension.

The development program regard for new 140mg strength has been informed by regulatory interactions during the discussion with United States FDA, the Swedish Medicinal Products Agency (MPA) and the French National Agency for the Safety of Medicine and Health Products (ANSM).

During the pre-submission meeting on Feb 2017 with the MPA (Rapporteur) and the ANSM (co-Rapporteur) for the EU MAA of Aimovig, the proposed bioequivalence study design (study 20140477 synopsis) to support the registration of the 140 mg/mL formulation was agreed. In line with this agreement, study 20160349 was conducted. The evaluation of the local tolerability with this new formulation as part of this bioequivalence study were also discussed and agreed that additional local tolerability testing will not be required since the local injection site tolerability has been evaluated in a phase I study (20150149) in which a 140 mg/mL formulation (PFS) was compared against a single 2 mL syringe injection and two 1 mL injections (PFS) of the 70 mg/mL formulation.

Study 20160442 was initiated at risk prior to knowing regulatory bioequivalence requirements. The study was terminated before planned study completion following United States FDA confirmation that this study was not required to support registration of the erenumab-aooe 140-mg/mL PFS or AI/pen drug product.

2.2. Quality aspects

2.2.1. Introduction

Novartis submitted an application for extension of marketing authorisation for the addition of a new finished product presentation. The currently approved commercial presentations for the erenumab finished product include a pre-filled syringe (PFS) and pre-filled auto-injector/pen (AI/Pen) containing a 1 mL deliverable volume of 70 mg/mL erenumab solution for subcutaneous injection. The purpose of this application is to add a new finished product presentation as a 140 mg/mL PFS or AI/Pen supplied as a sterile, single-use, preservative-free solution for subcutaneous injection.

The qualitative composition in excipients in the proposed 140 mg/mL presentation remains unchanged: sucrose, polysorbate 80, sodium hydroxide (for pH adjustment), glacial acetic acid and water for injections.

The 140 mg/mL was developed to reduce the number of injections required from two injections to a single injection for a 140 mg dose.

The nature and contents of the container for 70 mg/mL and 140 mg/mL is as follows:

- Pre-filled syringe:

Aimovig is supplied in a pre-filled syringe (1 ml, Type 1 glass) with a stainless steel needle and a needle cover (rubber containing latex). Aimovig is available in packs containing 1 pre-filled syringe.

- Pre-filled pen:

Aimovig is supplied in a pre-filled pen (1 ml, Type 1 glass) with a stainless steel needle and a needle cover (rubber containing latex).

Aimovig is available in packs containing 1 pre-filled pen and in multipacks containing 3 (3x1) pre-filled pens.

Not all pack sizes may be marketed.

2.2.2. Active Substance

Erenumab is a human monoclonal immunoglobulin G2 (IgG2) antibody expressed in a Chinese hamster ovary (CHO) cell line. Erenumab specifically binds to the extracellular domain of the calcitonin gene-related peptide receptor (CGRP-R) and prevents its interaction with the neuropeptide CGRP.

Module 3.2.S remains unchanged compared to the initial erenumab marketing authorisation application for the 70 mg/mL presentation (EMEA/H/C/4447, EU/1/18/1293/001-003).

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is supplied as a sterile, single-use, preservative-free solution for subcutaneous injection in either a PFS or a pre-filled AI/Pen. The AI/Pen is a disposable, handheld, mechanical (spring -based) delivery device that is provided ready-to-use, pre-assembled with the PFS. The primary container closure system for the PFS and AI/Pen is the same, except the PFS uses a regular wall (RW) needle and the AI/Pen uses a special thin wall (STW) needle.

The quantitative and qualitative composition of the finished product is provided.

Pharmaceutical development

The finished product contains a target concentration of 140 mg/mL erenumab, formulated in an aqueous solution with acetate, sucrose and polysorbate 80, pH 5.2.

The applicant has previously developed an Aimovig finished product formulation which contains a 70 mg presentation (70 mg/ml) for subcutaneous administration in either a pre-filled syringe (PFS) or a pre-filled pen/auto-injector (AI) (EMEA/H/C/4447). This line extension application concerns a 140 mg presentation (140 mg/ml) of Aimovig including both PFS and pen/AI. The 140 mg presentation includes the same excipients as the 70 mg presentation but with slightly different quantities.

Formulation development

The 140 mg/mL formulation was designed to support the target product profile, focusing on development of a liquid formulation with a high protein concentration, stable at 2°C to 8°C, and compatible with injection.

A formulation robustness study has been conducted to investigate the relationship between several formulation variables and finished product stability. The data presented demonstrate robustness of the 140 mg/ml finished product formulation with an acceptable stability. The section on formulation development describes and justifies the chosen formulation and is sufficiently comprehensive.

Manufacturing process development

The commercial manufacturing process of erenumab finished product has been characterised through development studies. Process characterization studies have been performed for all process steps from active substance thaw to filling and stoppering. Process characterization details have been provided. The process characterization studies demonstrated that the finished product process is robust and can deliver the required product quality and process consistency when manufacturing is conducted within the prescribed operating ranges. The section on manufacturing process development has been sufficiently described and justifies the commercial manufacturing process.

Product comparability

Comparability was performed in accordance with ICH Q5E and has been sufficiently demonstrated in the comparison of 140 mg/mL pre-filled syringe and pre-filled pen/AI finished product with 70 mg/ml finished product manufactured at the commercial manufacturing site.

This is found acceptable.

Container closure system

The development of the container closure system is sufficiently presented and demonstrated safety and suitability for use to deliver the erenumab 140 mg/ml finished product. Detailed information has been provided for the primary container closure system as well as for the pre-filled pen/auto-injector (AI).

The primary container closure consists of a 1 mL Type I glass syringe with a stainless steel staked needle closed with an elastomeric needle shield and a bromobutyl elastomeric plunger-stopper laminated with a fluoropolymer film on the product contact surface and is the same for the 140 mg/mL presentation as for the already approved 70 mg presentation of Aimovig (EMEA/H/C/4447).

The erenumab 140 mg/ml pre-filled pen (auto-injector) contains a Type 1 glass pre-filled syringe (PFS). There is a slight difference in the auto-injector spring force required for the 140 mg/ml presentation compared to the already approved 70 mg/ml presentation. However, the pre-filled pen/AI for erenumab 140 mg/ml is the same as the SureClick pre-filled pen/AI that is marketed in another centrally authorised medicinal product.

Data has been presented on compatibility, Protection of Finished product Integrity, Performance/Functionality, Deliverable volume and hold-up volume. In addition, protection of the finished product by the container closure system is demonstrated by container closure integrity, stability of finished product and transport qualification. Protection of the finished product from light by the secondary packaging has also been demonstrated as well.

All container closure components meet the appropriate specifications in the Ph. Eur.

Manufacture of the product and process controls

Manufacture

The description of manufacturing process and process controls and control of critical steps and intermediates of the finished product is sufficiently described.

Process controls

The critical IPCs for the manufacturing process of the 140 mg/ml finished product have been presented.

Process validation

The manufacturing process is well described and documented.

The validation data presented demonstrate that the process is robust and performs as intended, giving a finished product which meets the quality requirements when conducted within the defined ranges.

Product specification

Specifications include control of identity, purity and impurities, potency and other general tests.

The specifications are found acceptable. Batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for Aimovig.

Stability of the product

The stability studies were performed as per the ICH Q5C and Q1A guidelines. The acceptable shelf-life is 24 months (2°C-8°C). The pre-filled syringe and pre-filled pen should be kept in the outer carton in order to protect from light. After removal from the refrigerator, Aimovig must be used within 14 days when stored at room temperature (up to 25°C), or discarded. If it is stored at a higher temperature or for a longer period it must be discarded.

Adventitious agents

The active substance used for the 140 mg/mL presentation is the same as the active substance used for the already approved 70 mg/mL presentation (EMEA/H/C/4447, EU/1/18/1293/001-003). Therefore, the quality information in 3.2.A remains unchanged.

This is found acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Module 3.2.S is not affected by this application.

The dossier is of good quality. No major objections were identified. Very few issues were raised and were mainly related to information on the finished product manufacturing process description and validation data for the pre-filled pen assembly process at the commercial manufacturing site. Following the applicant's responses, the issues are considered resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the extension of marketing authorisation for Aimovig is approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

No new non-clinical data was submitted in this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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.

- Tabular overview of clinical studies

Table 1 - Tabular overview of clinical studies

Type of Study	Study Identifier Protocol Number	Objectives of the Study	Study Design and Type of Control	Treatment(s) Administered	No. of Subjects Enrolled/ Completed Study[a]	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Duration of Study[b]	Study Status; Type of Report/ Location
Module 5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports								
BE	20160349	Bioequivalence, PK, safety, tolerability, and immunogenicity	Phase 1, randomized, open-label	AMG 334 as single 1-mL (140 mg/mL) PFS injection or two 1-mL (70 mg/mL) PFS injections	211/201	Healthy subjects Age: 18 to 55 years BMI: 19.2 to 30.4 kg/m^2	Up to 120 days	Complete; full CSR/ 5.3.1.2
BE	20160442	Bioequivalence, PK, safety, tolerability, and immunogenicity	Phase 1, randomized, open-label	AMG 334 as single 1-mL (140 mg/mL) Prefilled AI/Pen injection or two 1-mL (70 mg/mL) Prefilled AI/Pen injections	104/60[a]	Healthy subjects Age: 18 to 55 years BMI: 18.4 to 30.4 kg/m^2	Up to 120 days	Complete; full CSR/ 5.3.1.2

Study 20160442 was terminated before planned study completion based on Food and Drug Administration (FDA) feedback that this study was not necessary to support approval of the 140-mg single-injection delivery system (AI/pen or PFS). In Europe, the Swedish Medical Products Agency (MPA) and the French National Agency for the Safety of Medicine and Health Products (ANSM); Rapporteur and co-Rapporteur for the EU MAA, respectively, agreed that Study 20160349 was appropriate on its own to bridge the new 140-mg/mL formulation with currently approved product presentations. Safety data for Study 20160442 were summarized but the PK and anti-erenumab-aooe antibody samples collected were not tested and analyses were not conducted.

2.4.2. Pharmacokinetics

Study 20160349

Study design

This was a multicenter, open-label, randomized, single-dose, parallel group study conducted in healthy volunteers to assess the bioequivalence, pharmacokinetics, safety, tolerability, and immunogenicity profile of a single dose of AMG 334 administered by 1x140 mg or 2x70 mg prefilled syringe subcutaneous (SC) injections, administered by a healthcare provider in the abdomen. Blood samples for pharmacokinetic analysis were taken pre-dose and up to 98 days post-dose.

Test and reference products

- Treatment A (test): AMG 334 140 mg (1 x 1 mL 140 mg/mL) prefilled syringe.
- Treatment B (reference): AMG 334 140 mg (2 x 1 mL 70 mg/mL) prefilled syringe.

Population studied

A total of 211 healthy male and female volunteers were enrolled and randomized to receive either the test or the reference product. Of these, 201 subjects completed the study. Ten subjects discontinued the study and the primary reason was lost to follow-up.

Analytical methods

AMG 334 concentration in human serum was determined using a validated ELISA method.

Anti-AMG 334 binding antibodies and neutralising antibodies were determined according to validated analytical procedures.

Pharmacokinetic variables and statistical methods

Standard non-compartmental methods were used. Primary endpoints were C_{max}, AUC_{last} and AUC_{inf}. Analysis of variance (ANOVA) was performed in order to compare PK parameters between treatments.

Results

The results from the comparative bioavailability study are presented below.

Table 2 - Pharmacokinetic parameters for erenumab (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	Arithmetic	SD
$AUC_{(0\text{-}t)}$ (day*µg/mL)	361	121	382	106
$AUC_{(0\text{-}\infty)}$ (day*µg/mL)	358	126	381	108
C_{max} (µg/mL)	13.2	4.30	13.6	3.57
T_{max}* (days)	6.0	1.9-11	6.0	0.98-11

$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (* median, range)

Table 3 – Statistical analysis for erenumab (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals
$AUC_{(0-t)}$	0.93	0.86-1.10
C_{max}	0.95	0.88-1.03

Bioequivalence was demonstrated for the primary parameters AUC0-t and Cmax.

2.4.3. Pharmacodynamics

Primary pharmacology

Immunogenicity

Study 20160349

Development of binding antibodies against erenumab-aooe was observed in 35 subjects (16.9%) post-baseline in the total erenumab-aooe group, including 16 subjects (15.8%) in the erenumab-aooe 1 x 1 mL 140-mg/mL PFS (test) group and 19 subjects (17.9%) in the erenumab-aooe 2 x 1 mL 70-mg/mL PFS (reference) group. Of the 35 subjects that tested positive for binding antibodies, 4 were transient (ie, negative result at the last time point tested).

Neutralizing antibodies against erenumab-aooe developed in 1 subject (0.5%) after administration of erenumab-aooe 2 x 1 mL 70-mg/mL PFS; the subject was positive for anti-erenumab-aooe neutralizing antibodies at the end of study visit, but reverted to neutralizing antibody negative at the 3-month antibody follow-up.

No notable differences in the development of anti-erenumab-aooe antibodies between the1 x 1 mL 140-mg/mL PFS (test) group and 2 x 1 mL 70-mg/mL PFS (reference) group. The applicant claimed that the presence of anti-erenumab-aooe antibodies was not associated with immune disorder-related adverse events.

The presence of ADA did not influence the exposure of AMG334. This is in accordance with results from the original application. The incidence of ADAs was 16.9% in the total erenumab 140mg treated group which is somewhat higher compared to that in the studies in the original MAA. It is noted that the same immunoassays as in the original application were used.

Study 20160442: Blood samples were collected, but analysis of ADAs was not performed.

2.4.4. Discussion on clinical pharmacology

This line extension concerns a new strength of Aimovig, 140 mg to be administered as a single monthly injection. The drug product consists of a solution of injection filled in either a pre-filled syringe (PFS) or an autoinjector pen (AI/pen). Study 20160349, in which the bioavailability of the new 140 mg PFS was compared to the already approved PFS given as 2x70 mg, is pivotal for the application.

Study 20160442 in which the bioavailability of the AI/pen was evaluated was terminated early and only safety results were reported. The PK samples were not analysed and thus bioequivalence not evaluated. The PFS and the AI/pen are both filled with the same solution for injection. It is therefore considered sufficient to establish bioequivalence with the PFS only. In the original application bioequivalence was demonstrated between the 70 mg PFS and AI/pen, which further supports that a study with the PFS is sufficient.

The pivotal study 20160349 and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated. The 90% CI of the test/reference ratio for both AUClast and Cmax was within the conventional acceptance range for bioequivalence, 80.00-125.00%. Hence, the new 140 mg prefilled syringe is considered bioequivalent to 2x70 mg of the already approved prefilled syringe.

Development of binding antibodies against erenumab-aooe and neutralizing antibodies against erenumab-aooe were similar between the 1 x 1 mL 140-mg/mL PFS (test) group and 2 x 1 mL 70-mg/mL PFS (reference) group. The presence of ADA did not influence the exposure of AMG334. This is in accordance with results from the original application. The incidence of ADAs was 17.9% in study 20160349 which is somewhat higher compared to that in the original application. The incidence of ADAs during the double-blind treatment phase of the clinical studies is 6.3% (56/884) among subjects receiving a 70mg dose of erenumab and 2.6% (13/504) among subjects receiving a 140mg of erenumab. In the day 120 AR, the applicant was asked to discuss the discrepancy of the ADA data**.**

In the response, the applicant briefly discusses the causes of the discrepancy of the ADA data in clinical trials such as inclusion of different clinical trial scenarios, dosing regimens and ADA assessment schedules, arguing that the occurrence of ADAs is often associated with a substantial inter-study variability.

2.4.5. Conclusions on clinical pharmacology

Based on the presented comparative bioavailability study (20160349) the new 140 mg prefilled syringe was bioequivalent to 2x70 mg of the already approved prefilled syringe. The results of study 20160349 can be extrapolated to the 140 mg autoinjector pen.

The incidence of ADAs was 17.9% in study 20160349 which is somewhat higher compared to that in the original application. No new safety concern of immunogenicity was identified based on the ADA data submitted in this application.

2.5. Clinical efficacy

No new clinical efficacy studies of erenumab administered as a single 140-mg/mL dose by PFS or AI/pen delivery system were conducted for this line extension application. The 140 mg dose administered as two 1 mL injections of 70 mg/mL in the 2 pivotal migraine studies were included in the original submission (Studies 20120295 and 20120296). Since the posology for Aimovig will not be changed, a new efficacy study is not required.

2.6. Clinical safety

Patient exposure

Study 20160349:

In total, 211 subjects were enrolled in the study in which 105 subjects received 1 SC injection of 140 mg (ie, 1 x 1 mL 140 mg/mL PFS [test] and 106 subjects received 2 SC injections of 70 mg (ie, 2 x 1 mL 70 mg/mL PFS [reference] (Table 9-1 of Study 20160349 CSR).

201 of the 211 enrolled subjects (95.3%) completed the study; 10 subjects (4.7%) discontinued the study for the following reasons: loss to follow-up (7 subjects [3.3%]), withdrawal of consent from study (2 subjects [0.9%]), and decision by sponsor (1 subject [0.5%])

Study 20160442 (terminated early as previous described):

In total, 104 subjecs were enrolled in the study in which 52 subjects received 1 SC injection of 140 mg (ie, 1 x 1 mL 140 mg/mL PFS [test] and 52 subjects received 2 SC injections of 70 mg (ie, 2 x 1 mL 70 mg/mL PFS [reference] (Table 14-1.1 of Study 20160442 CSR).

60 of the 104 enrolled subjects (57.7%) completed the study and 44 subjects (42.3%) discontinued the study. The most frequently reported reason for study discontinuation was withdrawal of consent from study (41 subjects). All of these subjects withdrew consent within 1 to 2 months of study termination notification (these subjects were followed for a mean of 38 days [range, 22 to 68 days] after receiving investigational product. In addition, 3 subjects were lost to follow-up.

For both studies, no subjects discontinued the study due to AEs. In study 20160442, the majority of the subjects discontinued in the study by withdrawal of consent which is likely due to early study termination.

Demographics and baseline characteristics were similar across treatment groups.

Adverse events

The overall incidence of treatment-emergent AEs collected in the single dose bioequivalent studies 20160349 and 20160442 is summarized in Table 4:

Table 4 – Summary of Subject Incidence of adverse Events in Studies 20160349 and 20160442 (Safety Analysis Set)

	Study 20160349 Erenumab-aooe 140 mg PFS SC			Study 20160442[a] Erenumab-aooe 140 mg AI/pen SC		
	2 x 1 mL 70 mg/mL (N = 106) n (%)	1 x 1 mL 140 mg/mL (N = 105) n (%)	Total (N = 211) n (%)	2 x 1 mL 70 mg/mL (N = 52) n (%)	1 x 1 mL 140 mg/mL (N = 52) n (%)	Total (N = 104) n (%)
All treatment-emergent adverse events - n (%)	35 (33.0)	31 (29.5)	66 (31.3)	17 (32.7)	12 (23.1)	29 (27.9)
Grade ≥ 2 adverse events	8 (7.5)	8 (7.6)	16 (7.6)	7 (13.5)	2 (3.8)	9 (8.7)
Grade ≥ 3 adverse events	0 (0.0)	1 (1.0)	1 (0.5)	1 (1.9)	0 (0.0)	1 (1.0)
Grade ≥ 4 adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.0)
Serious adverse events	1 (0.9)	2 (1.9)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Device-related treatment-emergent adverse events - n (%)	1 (0.9)	1 (1.0)	2 (0.9)	4 (7.7)	4 (7.7)	8 (7.7)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AI/pen = autoinjector pen; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects reporting at least 1 occurrence of an adverse event; N = number of subjects in the analysis set; PFS = prefilled syringe, SC = subcutaneous
For both studies, the safety analysis set consisted of all randomized subjects who received investigational product.
Coded using MedDRA version 20.0 (Study 20160349) and MedDRA version 20.1 (Study 20160442).
Graded using CTCAE version 4.0.
[a] Study 20160442 was terminated early following confirmation that the data was not required to support approval of the 140-mg/mL PFS or AI/pen drug product presentation (refer to Section 1.1.1 for details).
Source: Table 12-1 and Table 14-6.2.3 of Study 20160349 CSR; Table 14-6.1.1 and Table 14-6.4.1 of Study 20160442 CSR

Treatment-emergent adverse events by System Organ Class and Preferred Term are summarized in Table 5 below:

Table 5 – Treatment-emergent Adverse Events by Preferred Term Occurring in ≥ 2 Subjects in the Total Erenumab-aooe Group of Study 20160349 and Study 20160442 (Safety Analysis Set)

	Study 20160349 Erenumab-aooe 140 mg PFS SC			Study 20160442[a] Erenumab-aooe 140 mg AI/pen SC		
	2 x 1 mL 70 mg/mL (N = 106) n (%)	1 x 1 mL 140 mg/mL (N = 105) n (%)	Total (N = 211) n (%)	2 x 1 mL 70 mg/mL (N = 52) n (%)	1 x 1 mL 140 mg/mL (N = 52) n (%)	Total (N = 104) n (%)
Number of subjects reporting treatment-emergent adverse events	35 (33.0)	31 (29.5)	66 (31.3)	17 (32.7)	12 (23.1)	29 (27.9)
Headache	6 (5.7)	10 (9.5)	16 (7.6)	5 (9.6)	3 (5.8)	8 (7.7)
Upper respiratory tract infection	7 (6.6)	8 (7.6)	15 (7.1)	2 (3.8)	0 (0.0)	2 (1.9)
Pain in extremity	3 (2.8)	1 (1.0)	4 (1.9)	- (-)	- (-)	- (-)
Dizziness	2 (1.9)	1 (1.0)	3 (1.4)	- (-)	- (-)	- (-)
Nasal congestion	2 (1.9)	1 (1.0)	3 (1.4)	- (-)	- (-)	- (-)
Nausea	2 (1.9)	1 (1.0)	3 (1.4)	1 (1.9)	1 (1.9)	2 (1.9)
Skin abrasion	2 (1.9)	1 (1.0)	3 (1.4)	- (-)	- (-)	- (-)
Toothache	2 (1.9)	1 (1.0)	3 (1.4)	1 (1.9)	0 (0.0)	1 (1.0)
Anxiety	0 (0.0)	2 (1.9)	2 (0.9)	- (-)	- (-)	- (-)
Back pain	0 (0.0)	2 (1.9)	2 (0.9)	0 (0.0)	1 (1.9)	1 (1.0)
Blood creatine phosphokinase increased	0 (0.0)	2 (1.9)	2 (0.9)	1 (1.9)	0 (0.0)	1 (1.0)
Constipation	0 (0.0)	2 (1.9)	2 (0.9)	- (-)	- (-)	- (-)
Injection site hemorrhage	1 (0.9)	1 (1.0)	2 (0.9)	1 (1.9)	4 (7.7)	5 (4.8)
Injection site pain	0 (0.0)	2 (1.9)	2 (0.9)	3 (5.8)	0 (0.0)	3 (2.9)
Laceration	2 (1.9)	0 (0.0)	2 (0.9)	1 (1.9)	1 (1.9)	2 (1.9)
Viral upper respiratory tract infection	2 (1.9)	0 (0.0)	2 (0.9)	- (-)	- (-)	- (-)
Vessel puncture site haemorrhage	- (-)	- (-)	- (-)	1 (1.9)	2 (3.8)	3 (2.9)
Cough	- (-)	- (-)	- (-)	1 (1.9)	1 (1.9)	2 (1.9)
Neutropenia	- (-)	- (-)	- (-)	2 (3.8)	0 (0.0)	2 (1.9)
Rhinitis allergic	0 (0.0)	1 (1.0)	1 (0.5)	2 (3.8)	0 (0.0)	2 (1.9)

In general, treatment-emergent adverse events and the frequency of these AEs were similar across treatment groups in study 20160349. Among the treatment-emergent Adverse Events reported by Preferred Term Occurring in ≥ 2 Subjects (Study 20160349 and Study 20160442), constipation and injection site reactions has already been identified as ADR and is listed in SmPC 4.8. Device-related Adverse Events/Injection site reactions are described in the section below.

Serious adverse event / deaths / other significant events

Study 20160349

No fatal adverse events were reported. Serious adverse events were reported by 3 subjects (1.4%), including 2 subjects (1.9%) in the 1 x 1 mL 140 mg/mL PFS (test) group and 1 subject (0.9%) in the 2 x 1 mL 70 mg/mL PFS (reference) group. These events are further discussed below.

Study 20160442

No serious or fatal adverse events were reported.

Table 6 – Serious Treatment-emergent Adverse Events by Preferred Term (Safety Analysis Set)

	Study 20160349 Erenumab-aooe 140 mg PFS SC			Study 20160442[a] Erenumab-aooe 140 mg AI/pen SC		
	2 x 1 mL 70 mg/mL (N = 106) n (%)	1 x 1 mL 140 mg/mL (N = 105) n (%)	Total (N = 211) n (%)	2 x 1 mL 70 mg/mL (N = 52) n (%)	1 x 1 mL 140 mg/mL (N = 52) n (%)	Total (N = 104) n (%)
Number of subjects reporting serious treatment-emergent adverse events	1 (0.9)	2 (1.9)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Arthritis bacterial	0 (0.0)	1 (1.0)	1 (0.5)	- (-)	- (-)	- (-)
Cellulitis	0 (0.0)	1 (1.0)	1 (0.5)	- (-)	- (-)	- (-)
Deafness unilateral	1 (0.9)	0 (0.0)	1 (0.5)	- (-)	- (-)	- (-)
Drug-induced liver injury	0 (0.0)	1 (1.0)	1 (0.5)	- (-)	- (-)	- (-)
Laceration	1 (0.9)	0 (0.0)	1 (0.5)	- (-)	- (-)	- (-)

AI/pen = autoinjector pen; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects reporting at least 1 occurrence of an adverse event; N = number of subjects in the analysis set; PFS = prefilled syringe, SC = subcutaneous
- Event not reported in the study
For both studies, the safety analysis set consisted of all randomized subjects who received investigational product.
Coded using MedDRA version 20.0 (Study 20160349) and MedDRA version 20.1 (Study 20160442).
[a] Study 20160442 was terminated early following confirmation that the data was not required to support approval of the 140-mg/mL PFS or AI/pen drug product presentation (refer to Section 1.1.1 for details).
Source: Table 12-4 of Study 20160349 CSR; Table 14-6.1.1 and Table 14-6.3.2 of Study 20160442 CSR

Serious adverse event (DILI):

A case of drug-induced liver injury concerning a 51 year old Hispanic female was reported from study 20160349. In brief, 10 days after single administration of AMG334 (1x1 140 mg/mL), the subject was noted to have elevated liver tests with AST 1713 U/L, ALT 1626 U/L, total bilirubin (TBL) 1.3 mg/dL and direct bilirubin 0.5 mg/dL. At day 12, repeat liver function tests were AST 2065 U/L, ALT 6025 U/L, TBL 4.9 mg/dL and direct bilirubin 3.1 mg/dL. The subject reported nausea and decreased appetite and was hospitalized for elevated liver tests and discharged 4 days later by which time liver test results were decreasing: AST 162 U/L, ALT 1528 U/L, TBL 3.3 mg/d, direct bilirubin 2.24 mg/dL. The liver tests returned to normal on study day 43. Medical history included cholelithiasis and cholecystectomy and a positive urine screen for benzodiazepines. Additional laboratory testing showed a normal hepatitis panel, furthermore, an EBV panel performed on study day 29 was suggestive of a past EBV infection. The subject did not meet the criteria for Hy's Law.

This event was initially reported as an SAE of acute liver failure and later was updated by the investigator to drug induced liver injury due to investigator's concern related to concomitant medications (namely Augmentin, taken for 10 days, approximately 6 weeks prior to liver enzyme elevations;the subject had also taken chlordiazepoxide). The investigator's final causality assessment was not related to AMG 334. The subject completed the study.

Based on the review of the information provided for this case report, a conclusive causality assessment could not be established due to multiple confounding factors.

Other SAEs

In addition, two serious adverse events from study 20160349 were reported which included a 35 year old male experienced left side hearing loss and laceration left axilla after a motor vehicle accident while driving. The events resolved after treatment. The investigator considered the SAEs was not related to both AMG 334 and the device and the subject completed the study. One subject, a 24 year old male experienced left hand septic arthritis, metacarpophalangeal joint and cellulitis following an infection secondary to a spider bite. The events resolved after treatment. The investigator considered the SAEs was not related to both AMG 334 and the device and the subject completed the study.

Laboratory findings

Data from serum chemistry, haematology laboratory values in general were consistent with the original marketing application dossier. The subject with abnormal lab values at or above CTCAE grade 3 and one SAE were reviewed in detail:

Study 20160349 (N= 211 subjects):

A total of 7 subjects had laboratory values at or above CTCAE grade 3, one of which occurred during screening.

Six subjects following erenumab treatment include: 2 subjects with creatine kinase elevation (Grade 4,), 1 subject with creatine kinase elevation + decrease in magnesium (Grade 4,) and 1 subject with decrease in neutrophils (Grade 3) in the 1 x 1 mL 140 mg/mL PFS (test) group; 1 subject (Subject 34966007090, see SAE section) reported as drug-induced liver injury in the 2 x 1 mL 70 mg/mL PFS (reference) group. One additional subject in study 20160349 had transient AST (Grade 1, <2ULN) and ALT (<3 ULN) increase at day 10-day 23 after erenumab 140 mg treatment, the subject had evaluated ALT (<2 ULN) at baseline. Very limited information was provided.

Study 20160442 (N=104 subjects):

A total of 4 subjects had laboratory values at or above CTCAE grade 3 ,4 subjects including sodium elevation (Grade 3, 1 subject) and elevation in creatine kinase (grade 3, 1 subject) in the erenumab 1 x 1 mL 140 mg/mL AI/pen (test) group; magnesium elevation(Grade 3, 1 subject) and elevation in creatine kinase (Grade 4, 1 subject) in the erenumab 2 x 1 mL 70 mg/mL AI/pen (reference) group.

Vital signs

Based on the review of the Vital signs data for systolic and diastolic blood pressure, heart and respiratory rates, and temperature provided in the CSR, no new safety concerns were identified.

Adverse events of special interest

Device-related Adverse Events / Injection site reactions

Device-related treatment-emergent adverse events defined as any adverse event related to the use of a medical device were reviewed and discussed by the applicant.

Study 20160349

Adverse events mapping to the injection site reaction Amgen Medical Query (AMQ) occurred in 5 subjects (2.4%) including 3 subjects (2.9%) in the erenumab 1 x 1 mL 140-mg/mL PFS (test) group and 2 subjects (1.9%) in the erenumab 2 x 1 mL 70-mg/mL PFS (reference) group. Injection site reaction events included injection site hemorrhage, injection site pain (2 subjects [0.9%] each); and injection site swelling (1 subject [0.5%]). None of these events were considered serious and all were mild in severity (CTCAE grade 1).

Study 20160442

Adverse events mapping to the injection site reaction AMQ occurred in 12 subjects (11.5%), 6 subjects in each group.

Injection site reaction events included injection site hemorrhage in 5 subjects (4.8%, 4 subjects in 1 x 1 mL 140 mg/mL AI/pen group and 1 subject in 2 x 1 mL 70 mg/mL AI/pen group); injection site pain in 3 subjects (2.9%, all in 2 x 1 mL 70 mg/mL AI/pen group); vessel puncture site hemorrhage in 3 subjects

(2.9%, 2 subjects in the 1 x 1 mL 140 mg/mL AI/pen group and 1 subject in the 2 x 1 mL 70 mg/mL AI/pen group); and injection site bruising, injection site rash, and injection site reaction (1 subject [1.0%] each). None of these events were considered serious and all were mild in severity (CTCAE grade 1). The overall incidence of injection site reactions was the same for each formulation

Safety in special populations

Safety data relative to the following special groups and situations were not evaluated aspart of the erenumab 140-mg dose single-injection delivery system clinical studies: intrinsic factors, extrinsic factors, drug interactions, overdose, drug abuse, withdrawal and rebound, and effects on ability to drive or operate machinery or impairment of mental ability.

Use in Pregnancy and Lactation

As of 31 January 2018 across the clinical development program, a total of 34 pregnancies have been reported in which subjects or their partners were exposed to erenumab or blinded investigational product before or during pregnancy.

Table 7 – Cumulative Birth outcomes for Pregnancies in the Erenumab-aooe Clinical Program Through 31 January 2018

Birth Outcomes	Maternal Exposures	Paternal Exposures
Full-term birth without complications	7	0
Live birth, normal	3	2
Delivered NOS	0	1
Full-term birth with complications	1[a]	0
Preterm birth without complications	1	1
Elective termination NOS	3	0
Spontaneous abortion NOS	2	0
Unknown	3	0
Lost to follow-up	8	2
Total	28	6

NOS = not otherwise specified
Pregnancies in subjects who were unblinded as having received placebo are not included in cumulative tabulations.
[a]Subject XXXXXXXXXX: the baby had no reported birth complications or congenital anomalies but was admitted to the neonatal intensive care unit for 4 days. The reason for admission was not provided.

The pregnancy outcomes are listed in Table 7 above. There have been no reports of infants receiving breast milk from mothers who were being treated with erenumab.

In Study 20160349, there were 4 pregnancies reported in 3 subjects. One subject had 2 pregnancies: the first pregnancy was electively terminated, and the outcome of the subsequent pregnancy was lost to follow-up. For the remaining 2 subjects, 1 pregnancy was lost to follow-up (last contact indicated elective termination was planned), and the remaining pregnancy outcome was unknown with an anticipated date of delivery in March 2018. Narratives for pregnancies from Study 20160349 are also provided.

In Study 20160442, no pregnancies were reported.

Overall, the numbers of pregnancies, information and outcomes reported are too limited to evaluate and conclude on the effects of erenumab on pregnancies.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials <and post-marketing> have been included in the Summary of Product Characteristics.

The new safety data were derived from the Phase 1 Study 20160349 evaluating the safety, tolerability, immunogenicity profile, and PK of a single SC dose of 140 mg erenumab-aooe delivered by PFS as either 1 injection of 140 mg (test) or 2 injections of 70 mg (reference) to healthy volunteers. The safety population included 211 subjects. In addition, safety data from a terminated phase 1 study (Study 20160442) were included in the submission. This study was similar to 20160349 except that erenumab-aooe 140 mg was delivered by prefilled AI/pen. The safety population included 104 subjects.

In study 20160349, treatment-emergent adverse events were similar across treatment groups and were reported in 33.0% and 29.5% of subjects in the AMG 334 140 mg (2 x 1 mL 70 mg/mL) and AMG 334 140 mg (1 x 1 mL 140 mg/mL) groups respectively. The most common treatment-emergent AEs were headache, upper respiratory tract infection, and pain in extremity. Most AEs were mild or moderate in intensity. SAEs were reported in 1 (0.9%) and 2 (1.9%) subjects in the respective groups.

One subject in the AMG 334 140 mg (1 x 1 mL 140 mg/mL) group with normal baseline aminotransferase experienced an SAE of drug-induced liver injury. The subject developed grade 4 ALT and AST elevations at day 10 after a single dose of AMG 140mg. The subject did not meet the criteria for Hy's Law. This case was reviewed in detail given the close temporal relationship between the administration of Aimovig and the onset of the events. However, confounding factors were identified including concomitant medications (such as coamoxicillin/clavulanate and chlordiazepoxide) and medical history which precluded drawing conclusions on causality.

In the original MAA for AMG334, a small number of subjects with normal baseline LFTs showed elevations to > 3 times ULN or > 5 times ULN during the 12-month AMG 334 treatment period. It was recommended that the risk of increased hepatic enzymes should be further monitored in the future PSUR. Based on the current DILI case, it is considered that this recommendation is still adequate, to which the applicant has agreed. In this response, the applicant also agreed to continue to collect the necessary information on reported suspected adverse liver reactions with established PV practices which include written or verbal follow-up. This is considered acceptable at the current stage and this issue will be further monitored. The applicant should ensure an adequate analysis of reports of increased hepatic enzymes and suspected adverse liver reactions cases for assessment in future PSURs.

In study 20160442, treatment-emergent AEs were reported in 32.7% and 23.1% of subjects in the AMG 334 140 mg (2 x 1 mL 70 mg/mL) and AMG 334 140 mg (1 x 1 mL 140 mg/mL) groups, respectively. Overall, treatment-emergent adverse events were similar between treatment groups. The most frequently reported AEs were headache (5 subjects [4.8%] overall) and nausea (2 subjects [1.9%]). No SAEs were reported.

In both studies, there were subjects who reported increased blood creatinine phosphokinase after receiving 140mg treatment (1 x 1 mL 140 mg/mL AI/pen or 2 x 1 mL 70 mg/mL AI/pen). In total, 5 of the 315 subjects treated with erenumab reported Grade 3 (4 subjects) or Grade 4 (1) elevations. This should be further monitored in the future PSUR in line with the recommendation of the original MAA.

Device-related AEs and injection site reactions were generally similar between the erenumab-aooe (2 x 1-mL 70 mg/mL) and the erenumab-aooe (1 x 1-mL 140 mg/mL) groups.

The results of the comparative study (20160349) demonstrated that development of binding antibodies against erenumab-aooe and neutralizing antibodies against erenumab-aooe were similar between the 1 x 1 mL 140-mg/mL PFS (test) group and 2 x 1 mL 70-mg/mL PFS (reference) group. The presence of ADA did not influence the exposure of AMG334. This is in accordance with results from the original application. However, the incidence of ADAs was 17.9% in the present study which is somewhat higher compared to 6.7% (56/884) among the subjects receiving a 70mg dose of erenumab and 2.6% (13/504) among subjects receiving a 140mg dose of erenumab in the original application although the same immunoassay was used. No new safety concern of immunogenicity was identified based on the ADA data submitted in this application. It is considered that the overall incidence of ADAs for Aimovig specified in the Current SmPC does not evoke new safety concerns. See also Discussion in PD section 3.3.5.

2.6.2. Conclusions on the clinical safety

Studies 20160349 and 20160442 were submitted to support a line extension for the addition of a new strength of 140 mg, to Aimovig 70 mg. The safety data from these studies is consistent with the original application and no new concerns have been identified. The application may be approvable from a safety point of view.

2.7. Risk Management Plan

Safety concerns

Summary Table of the Safety Concerns

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

Pharmacovigilance plan

Summary Table of Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
NIS - A Non-Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries Study status: Planned	The following will be estimated: • Number of migraine patients prescribed with a migraine prophylactic drug (with and without CV history) • Number of pregnant migraine patients prescribed with erenumab and other prophylactic treatments • Pattern of utilization (prescriber, length of treatment, switching); • General characteristics and clinical features of migraine patients prescribed prophylactic drug • Exploratory: rates of CV events.	Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension Use in pregnant women (including those at risk of pre-eclampsia)	Protocol Submission	9 months after approval
			Final report submission	End of data collection + 1 year
20120178 - A Phase II, Randomized, Double-blind, Placebo controlled Study to Evaluate the Efficacy and Safety of AMG334 in Migraine Prevention This study includes a 5-year extension for long-term safety data collection. Study status: Ongoing	To collect long-term safety data for safety of erenumab in Migraine Prevention	Long-term safety	First patient first visit:	06-Aug-2013 for initiation of the double-blind phase
			Last patient last visit:	Q4-2019 of extension phase
			Final report submission:	Q4-2020

Risk minimisation measures

Summary Table of Pharmacovigilance and Risk Minimization Activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	Routine risk minimization measures: SmPC Section 5.1 (Pharmacodynamic properties) SmPC Section 4.4 (Special warnings and precautions for use) Additional risk minimization measures: None	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: None Additional pharmacovigilance activities: NIS - A Non-Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries.
Use in pregnant women (including those at risk of pre-eclampsia)	Routine risk minimization measures: SmPC Section 4.6 (Fertility, pregnancy and lactation) Additional risk minimization measures: None	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: Intensive monitoring of pregnancy outcomes Additional pharmacovigilance activities: NIS - A Non-Interventional Study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in the Nordic registries.
Long-term safety	No risk minimization measures	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: None Additional pharmacovigilance activities: 20120178 – A Phase 2, Randomized, Double-blind, Placebo controlled Study to Evaluate the Efficacy and Safety of AMG334 in Migraine Prevention This study includes a 5-year extension for long-term safety data collection.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 (dated 27 July 2018) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH 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 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Erenumab (AMG 334), Aimovig, is indicated for the preventative treatment of migraine in adults who have at least 4 migraine days per month. There are 2 dose options of 70 mg and 140 mg monthly (every 4 weeks), delivered subcutaneously (SC) as either 1 or 2 injections, respectively, of 70-mg/mL autoinjector.

The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks.

To avoid 2 separate injections for the 140-mg erenumab-aooe dose, a single-injection delivery system (AI/pen or PFS) has been developed.

The proposed indication and recommended dose for Aimovig is the same as that already approved for Aimovig in EU.

3.1.2. Main clinical studies

Studies 20160349 and 20160442 were submitted to support a line extension for the addition of a new strength of 140 mg, to Aimovig 70 mg. These were phase 1, multicenter, open-label, randomized, parallel-group studies in healthy subjects studies comparing the new 140 mg strength with the already authorised 70 mg strength.

Study 20160349 was conducted to assess the bioequivalence, pharmacokinetics, safety, tolerability, and immunogenicity profile of a single dose of AMG 334 administered by 1x140 mg or 2x70 mg prefilled syringe subcutaneous (SC) injections, administered by a healthcare provider in the abdomen. Blood samples for pharmacokinetic analysis were taken pre-dose and up to 98 days post-dose.

Study 20160442 was designed to evaluate the safety, tolerability, immunogenicity profile, and PK of a single SC dose of 140 mg erenumab-aooe delivered by prefilled AI/pen as 1 injection (test) or 2 injections of 70 mg (reference). This study was initiated at risk prior to knowing regulatory bioequivalence requirements and was terminated before planned study completion. The results from Study 20160349 are aimed to bridge the new 140 mg/mL formulation with currently approved product presentations. Safety data for Study 20160442 were summarized but the PK and anti-erenumab antibody samples collected were not tested and analyses were not conducted. This is considered as acceptable.

3.2. Favourable effects

Based on the presented comparative bioavailability study (20160349), the new 140 mg prefilled syringe was bioequivalent to 2x70 mg of the already approved prefilled syringe. The results of study 20160349 can be extrapolated to the 140 mg autoinjector pen. The 140 mg dose administered as two 1 mL

injections of 70 mg/mL in the 2 pivotal migraine studies were included in the original submission (Studies 20120295 and 20120296).

No new efficacy studies were conducted. The efficacy profile of Aimovig remains unchanged.

3.3. Uncertainties and limitations about favourable effects

N/A

3.4. Unfavourable effects

Overall, the results from Study 20160349 and Study 20160442 are quite consistent with the safety demonstrated in the original application.

Study 20160349: injection site reaction events were reported in 5 subjects (2.4%) including 3 subjects (2.9%) in the erenumab 1 x 1 mL 140-mg/mL PFS (test) group and 2 subjects (1.9%) in the erenumab 2 x 1 mL 70-mg/mL PFS (reference) group, which included injection site hemorrhage, injection site pain (2 subjects [0.9%] each); and injection site swelling (1 subject [0.5%]). All were mild in severity.

Study 20160442: injection site reaction events were reported in 12 subjects (11.5%), 6 subjects in the 1 x 1 mL 140 mg/mL AI/pen group and/or the 2 x 1 mL 70 mg/mL AI/pen group, which included injection site hemorrhage in 5 subjects (4.8%); injection site pain in 3 subjects (2.9%); vessel puncture site hemorrhage in 3 subjects (2.9%); and injection site bruising, injection site rash, and injection site reaction (1.0%). All were mild in severity.

Among the treatment-emergent Adverse Events reported by Preferred Term Occurring in ≥ 2 Subjects (Study 20160349 and Study 20160442), constipation was reported in 2 subjects (1.9%) in the erenumab 1 x 1 mL 140-mg/mL PFS in Study 20160349.

3.5. Uncertainties and limitations about unfavourable effects

In this application, one subject in the AMG 334 140 mg (1 x 1 mL 140 mg/mL) group with normal baseline aminotransferase experienced an SAE of drug-induced liver injury. The subject developed grade 4 ALT and AST elevations at day 10 after a single dose of AMG 140mg. The subject did not meet the criteria for Hy's Law. This case was reviewed in detail given the close temporal relationship between the administration of Aimovig and the onset of the events. However, confounding factors were identified including concomitant medications (such as coamoxicillin/clavulanate and chlordiazepoxide) and medical history which precluded drawing conclusions on causality.

It was recommended that the risk of increased hepatic enzymes should be further monitored in the future PSUR. Based on the current DILI case, it is considered that this recommendation is still adequate. The applicant also agreed to continue to collect the necessary information on reported suspected adverse liver reactions with established PV practices which include written or verbal follow-up to ensure an adequate analysis of increased hepatic enzymes reports and suspected adverse liver reactions cases for assessment in future PSURs.

In both studies, there were subjects who reported increased blood creatinine phosphokinase after receiving 140mg treatment (1 x 1 mL 140 mg/mL AI/pen or 2 x 1 mL 70 mg/mL AI/pen). In total, 5 of the

315 subjects treated with erenumab reported Grade 3 (4 subjects) or Grade 4 (1) elevations. This should be further monitored in the future PSUR in line with the recommendation of the original MAA.

Overall, the results from Study 20160349 and Study 20160442 are quite consistent with the safety demonstrated in the original application. No new safety concerns were identified.

3.6. Benefit-risk assessment and discussion

3.6.1. Balance of benefits and risks

This line extension concerns a new strength of Aimovig, 140 mg to be administered as a single monthly injection. Based on the assessment of the pivotal study 20160349, it is concluded that the new 140 mg prefilled syringe is considered bioequivalent to 2x70 mg of the already approved prefilled syringe. The results of study 20160349 can be extrapolated to the 140 mg autoinjector pen.

No major objections were identified that would preclude this extension of marketing authorization from quality perspective and this line extension of Aimovig is approvable from the quality point of view.

The safety profile from Study 20160349 and Study 20160442 are quite consistent with the safety demonstrated in the original application. No new safety concerns were identified.

The proposed indication and recommended dose for Aimovig is the same as that already approved for Aimovig in EU. In principle, provided data are considered to support the approval of Aimovig 1ml 140mg/ml formulation in addition to the already approved Aimovig 1ml 70mg/ml.

3.6.2. Additional considerations on the benefit-risk balance

N/A

3.7. Conclusions

The overall B/R of Aimovig (Solution for injection in pre-filled syringe 140 mg and Solution for injection in pre-filled pen 140 mg) is positive.

4. Recommendations

Outcome

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

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Aimovig subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the marketing 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

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.