



**Australian Government**

**Department of Health**

Therapeutic Goods Administration

# Australian Public Assessment Report for Erenumab

Proprietary Product Name: Aimovig

Sponsor: Novartis Australia Pty Ltd

**September 2019**

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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## Common abbreviations

Abbreviation	Meaning
~	Approximately
ADA	Anti-drug antibodies
ADME	Absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMG 334	Erenumab
AMQ	Amgen MedDRA query
aPTT	Activated partial thromboplastin time
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CEC	Cardiovascular Events Committee
CGRP	Calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use (EU)
CHO	Chinese hamster ovary
CHU	Clinical Home Use
CI	Confidence interval
CK	Creatinine kinase

Abbreviation	Meaning
CM	Chronic migraine
C <sub>max</sub>	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CMI	Consumer Medicines Information
C <sub>min</sub>	Trough serum concentrations
CNS	Central nervous system
CPD	Certified Product Details
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
CYP450	Cytochrome P450
DDI	Drug-drug interactions
EC <sub>90</sub>	90% effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EM	Episodic migraine
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
FTIR	Fourier transform infrared spectroscopy
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practice
HIT-6	Headache Impact Test
HLT	High level term
ICH	International Conference on Harmonisation

Abbreviation	Meaning
IgG2	Immunoglobulin G2
IHS	International Headache Society
IMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
IV	Intravenous
$K_D$	Dissociation constant
$K_i$	Inhibitory constant
LHH	Likelihood of being helped or harmed
LLOQ	Lower limit of quantification
LSM	Least squares mean
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment Questionnaire
MMD	Monthly migraine days
MPFID	Migraine Physical Function Impact Diary
MS/MS	Tandem mass spectrometry
MSQ	Migraine-specific quality of life
NEC	Not elsewhere classified
NNH	Number needed to harm
NNT	Number needed to treat
NSAID	Non-steroidal anti-inflammatory drug
P1NP	Procollagen type 1 N propeptide
PD	Pharmacodynamic(s)
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PMDA	Pharmaceutical and Medical Devices Agency (Japan)

Abbreviation	Meaning
PRO	Patient reported outcomes
PT	Prothrombin time
QoL	Quality of life
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous(ly)
sCTX	Serum C-telopeptide cross-link of type 1 collagen
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System Organ Class
SoC	Standard of care
SY	Subject years
TEAEs	Treatment emergent adverse events
T <sub>max</sub>	Time taken to reach the maximum concentration
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
UV	Ultraviolet
V <sub>d</sub>	Volume of distribution



## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	28 June 2018
<i>Date of entry onto ARTG:</i>	2 July 2018
<i>ARTG numbers:</i>	289959, 289960
<b>▼</b> <i>Black Triangle Scheme</i>	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
<i>Active ingredient:</i>	Erenumab
<i>Product name:</i>	Aimovig
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Ltd PO Box 101, North Ryde, NSW, 1670
<i>Dose form:</i>	Solution for injection (1 mL)
<i>Strength:</i>	70 mg/mL
<i>Containers:</i>	Prefilled syringe Prefilled pen
<i>Pack sizes:</i>	Prefilled syringe: 2 Prefilled pen: 6 (multipack of 2 times 3), 2 and 1
<i>Approved therapeutic use:</i>	<i>Aimovig is indicated for prophylaxis of migraine in adults</i>
<i>Route of administration:</i>	Subcutaneous
<i>Dosage:</i>	70 mg injected subcutaneously once every 4 weeks. Some patients may benefit from a dosage of 140 mg injected subcutaneously every 4 weeks. For further details please refer to the Product Information (PI).

## Product background

This AusPAR describes the application by Novartis Australia Pty Ltd (the sponsor) to register a new biological entity, Aimovig (erenumab) 70 mg/mL solution for injection, for the proposed indication:

*Aimovig is indicated for prophylaxis of migraine in adults.*

Migraine is the second most common cause of headache, and the most common headache-related, and indeed neurologic, cause of disability in the world. It afflicts approximately 15% of women and 6% of men over a 1 year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. The sensory sensitivity that is characteristic of migraine is probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and hypothalamus. Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene-related peptide (CGRP), at vascular terminations of the trigeminal nerve and within the trigeminal nucleus.<sup>1</sup> Patients with episodes of migraine that occur daily or near-daily are considered to have chronic migraine. Migraine is a highly debilitating disease in both its episodic and chronic forms, with the latter imposing more substantial individual and socioeconomic burden.

Migraine is treated with agent(s) for the acute headache attacks, typically involving non-specific (symptomatic) agents such as non-steroidal anti-inflammatory drugs (NSAIDs) or migraine-specific abortive medications such as triptans or ergotamine derivatives. Patients experiencing more frequent migraines and/or more severe functional impact, despite the use of acute medications, often require prophylaxis. The main goal of a prophylactic treatment is to reduce the frequency of migraine days. In Australia, beta-blockers (propranolol, metoprolol), topiramate, methysergide and botulinum toxin are approved for migraine prophylaxis; other drugs which may be used but are not officially approved for this indication include the anti-depressant, amitriptyline and the antiepileptic, sodium valproate.

Erenumab has been proposed as a prophylaxis for migraine. It is a potent and selective fully human immunoglobulin G2 (IgG2) monoclonal antibody (mAb) against the CGRP receptor. CGRP is a 37 amino acid peptide widely expressed in both the central and peripheral nervous systems and has been implicated as a key mediator in the initiation and progression of migraine pain. Erenumab binds to the CGRP receptor, blocking the interaction of CGRP ligand to its receptor and functionally inhibiting the CGRP signalling pathway. Despite the presence of CGRP receptors in the central nervous system (CNS), the likely site of action for erenumab is the trigeminal ganglion and as a mAb is expected to have minimal if any CNS penetration.

## Regulatory status

At the time the TGA considered this application erenumab had not been approved in any regulatory jurisdiction. As of 9 May 2018, submissions had been made in the European Union (EU; 23 May 2017), United States of America (USA; 17 May 2017), Switzerland (23 June 2017), Singapore (19 June 2017), Canada (18 August 2017) and Indonesia (22 June 2017).

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<sup>1</sup> Goadsby, P.J. and Raskin, N.H. (2014). Migraine and Other Primary Headache Disorders, Harrison's Principles of Internal Medicine, 19e Eds. Kasper, D. et al. New York, McGraw-Hill.

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Registration time line

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

**Table 1: Timeline for Submission PM-2017-02174-1-1**

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2017
First round evaluation completed	22 December 2017
Sponsor provides responses on questions raised in first round evaluation	6 March 2018
Second round evaluation completed	6 April 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	12 April 2018
Sponsor's pre-Advisory Committee response	9 May 2018
Advisory Committee meeting	31 May to 1 June 2018
Registration decision (Outcome)	28 June 2018
Completion of administrative activities and registration on ARTG	2 July 2018
Number of working days from submission dossier acceptance to registration decision*	178

\*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

TGA guidance at pre-submission meetings is nonbinding and without prejudice.

## III. Quality findings

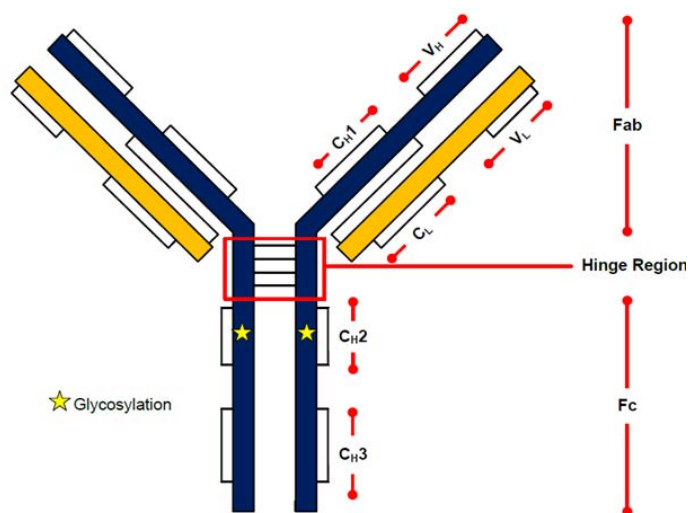
### Drug substance (active ingredient)

Erenumab is a fully humanised mAb of the immunoglobulin G2 (IgG2) subclass consisting of 2 heavy chains and 2 light chains of the lambda subclass generated using recombinant

DNA technology in Chinese hamster ovary (CHO) cells with specificity for an epitope within the CGRP-receptor. It contains a total of 36 cysteine residues involved in both intra-chain and inter-chain disulfide bonds. Each heavy chain contains 456 amino acids with 4 intra-chain disulfide bonds while each light chain contains 216 amino acids with 2 intra-chain disulfide bonds. Erenumab has 6 inter-chain disulfide bonds with 12 intra-chain disulfide bonds. Each heavy chain contains an N-linked glycan at a consensus glycosylation site on asparagine 306.

The structure of erenumab is shown schematically in Figure 1.

**Figure 1: Structural features of erenumab**



Heavy chains are shown in blue and light chains are shown in orange  
 Disulfide linkages are indicated by solid black lines  
 V<sub>H</sub> is the variable domain of the heavy chain  
 C<sub>H1</sub>, C<sub>H2</sub>, and C<sub>H3</sub> are the constant domains of the heavy chain  
 V<sub>L</sub> is the variable domain of the light chain  
 C<sub>L</sub> is the constant domain of the light chain

The amino acid sequence deduced from the DNA sequence of the heavy and light chains were later confirmed by tandem mass spectrometry (MS/MS) sequence analysis

Secondary structure was analysed by Fourier transform infrared spectroscopy (FTIR). The second derivative FTIR spectrum of erenumab exhibits a strong  $\beta$ -sheet band at  $1637\text{ cm}^{-1}$ , together with a  $\beta$ -turn and bend band at  $1689\text{ cm}^{-1}$ , consistent with the structure of an IgG2 antibody.

Tertiary structure was assessed by near ultraviolet (UV) circular dichroism spectroscopy. The spectrum is characterized by features at 296 nm attributable to tryptophan, at 289 nm attributable to tryptophan and tyrosine, at 270 to 285 nm attributable to tyrosine and tryptophan, and 250 to 275 nm attributable to phenylalanine, superimposed over the broad disulfide signal from 250 to 280 nm. These results are typical of IgG2 antibodies and suggest erenumab is folded in an appropriate tertiary structure.

Analysis of erenumab using multiple orthogonal assays showed it had features consistent with those of an IgG2 antibody.

The following steps are used in the manufacturing process of erenumab. The working cell bank vial undergoes thawing and expansion, followed by expansion in single-use bioreactors, then harvest collection to produce the bulk harvest drug substance. The bulk harvest is purified using chromatography, viral inactivation and filtration steps.

Overall, supplied data is satisfactory and there are no further quality related concerns pertaining to this issue.

## Drug product

There are no issues pertaining to manufacture or manufacturers of the product. All analytical procedures are validated. There are no issues pertaining to specifications.

The proposed shelf life is 2 years when stored at 5°C. This is applied to both the prefilled syringe and auto injector/pen presentations.

Storage of Aimovig prefilled syringe or auto-injector/pen for 14 days at 30°C is acceptable, providing that the material is used within that 14 days otherwise it must be discarded even if returned to the refrigerator.

Stability studies have been conducted in accordance with relevant International Conference on Harmonisation (ICH) guidelines.

## Quality summary and conclusions

There are no objections to the registration of this product from sterility; endotoxin, container safety and viral safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Aimovig have been controlled to an acceptable level.

## IV. Nonclinical findings

### Introduction

The sponsor has applied to register a new chemical entity, erenumab (Aimovig). Aimovig is proposed to be used for the prophylactic treatment of migraine in adults. The proposed dosing regimen is two 70 mg injections by the subcutaneous (SC) route once a month. Treatment duration is expected to be chronic.

The overall quality of the nonclinical dossier was good and in general accord with the ICH guideline.<sup>2</sup> All pivotal toxicity studies were conducted according to Good Laboratory Practice (GLP) standards. Erenumab is a human IgG2 mAb against CGRP-receptor and has no affinity for rodent CGRP receptor; thus all toxicity studies were conducted in cynomolgus monkeys, which are responsive to erenumab. The sponsor did not conduct any genotoxicity or carcinogenicity studies, which is acceptable for this biological product (according to ICH S6).

Erenumab is the first mAb developed as an antagonist of the CGRP receptor. A number of other monoclonal antibodies that target the CGRP pathway are currently under Phase III clinical trials for a similar indication as that sought for Aimovig.

### Pharmacology

Erenumab binds to the extracellular domain of the CGRP receptor. CGRP is widely expressed in the peripheral and central nervous systems, including the trigeminal ganglion;<sup>3</sup> and has been implicated in the pathophysiology of migraine.<sup>4</sup>

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<sup>2</sup> ICHS6 (R1) Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals, 2011.

<sup>3</sup> Karsan, N. and Goadsby, P.J. (2015) CGRP mechanism antagonists and migraine management. *Curr Neurol Neurosci Rep.*, 15: 25.

<sup>4</sup> Hay, D.L. and Poyner, D. (2009) Calcitonin gene-related peptide, adrenomedullin and flushing. *Maturitas*, 64: 104-108.

Pharmacology studies on erenumab examined its binding affinity and selectivity for the human CGRP receptor *in vitro*. Demonstration of erenumab-mediated inhibition of capsaicin induced increased dermal blood flow in monkeys was also provided.

### Primary pharmacology

Binding studies confirmed the affinity of erenumab for the human CGRP receptor (dissociation constant ( $K_D$ ) 56 pM). Erenumab potently inhibits binding of CGRP to the human CGRP receptor with an inhibitory constant ( $K_i$ ) of  $20 \pm 10$  pM. Erenumab inhibited CGRP-induced cyclic adenosine monophosphate (cAMP) accumulation with a half maximal inhibitory concentration ( $IC_{50}$ ) of  $2.3 \pm 0.9$  nM *in vitro*. Erenumab inhibited the CGRP receptor in monkeys with similar potency to that seen in humans ( $IC_{50}$   $5.7 \pm 2.8$ ). No binding of erenumab was observed to rat CGRP receptors, with modest binding affinity for rabbit and dog CGRP receptor ( $K_i$  230 to 260 nM).

*In vivo*, erenumab was shown to inhibit the capsaicin induced increased in dermal blood flow in cynomolgus monkeys in a dose dependent manner (up to 30 mg/kg intravenous (IV)) and did not induce contraction of the isolated human coronary artery (up to 1  $\mu$ M erenumab). In addition, erenumab blocked CGRP mediated vasodilation in a competitive manner.

### Secondary pharmacodynamics and safety pharmacology

*In vitro* studies demonstrated that erenumab is functionally inactive at the adrenomedullin, calcitonin, and amylin receptors, all members of the calcitonin receptor family.

Studies on tissue cross reactivity in samples from humans and cynomolgus monkeys (brain and spinal cord only) were conducted using erenumab. Staining specificity for erenumab was observed in the cerebellum and spinal cord of both humans and monkeys and in human pituitary tissue. Monoclonal antibodies are not known to cross the blood brain barrier, therefore the staining observed in the cerebellum and spinal cord of both species is unlikely to have any toxicological consequence. The observed staining in human pituitary tissue was cytoplasmic in nature and it is unlikely that cytoplasm and cytoplasmic structures would be accessible to the test article *in vivo*. Furthermore, repeat dose studies with erenumab showed no treatment related histopathological changes in these tissues.

Safety pharmacology studies on erenumab were conducted in cynomolgus monkeys. No notable changes to CNS (neurological, behaviour and body temperature) or respiratory parameters were reported. Electrocardiogram (ECG) examination showed long PR interval at a dose of 225 mg/kg (2 to 4.8%) over a persistent duration (block 1 to block 9). This observation was considered to be treatment-related but given the magnitude of the effect, it is not considered to be biologically relevant.

Safety pharmacology parameters were also integrated into the protocols of GLP repeat dose toxicity studies (1, 3 and 6 months) in cynomolgus monkeys. No notable changes to ECG (heart rate, QT interval duration and corrected QT interval duration) or respiratory parameters were reported. Thus overall, no effect on functions of CNS, cardiovascular and respiratory systems is predicted with fortnightly dosing of erenumab.

### Pharmacokinetics

Pharmacokinetic (PK) and toxicokinetic characteristics of erenumab were assessed in Cynomolgus monkeys. Single dose assessments were conducted following IV doses of 0.1

to 100 mg/kg. Repeat dose assessments were determined from repeat dose toxicity studies in monkeys that used twice-weekly SC doses of erenumab at 25, 75, 150 or 225 mg/kg.

SC administered erenumab showed slow systemic distribution, reaching maximum serum levels between 1 to 5 days post dose. Bioavailability of erenumab in monkeys was approximately 60%. Repeat dosing did not uncover differences in exposures of erenumab (as area under the curve (AUC)) between male and female animals. Erenumab exhibits nonlinear PK at lower doses (0.1 to 3 mg/kg) and linear PK at higher doses (> 70 mg/kg), which is typical for monoclonal antibodies with target mediated drug disposition. The estimated volume of distribution was 184 mL and clearance was 10.9 L/day. The concentration of erenumab in the cerebral spinal fluid of monkeys was less than 0.1% of serum concentrations at 24 hours following the last dose.

In human population PK studies following SC administration, peak serum concentration was reached between 4 and 11 days post dose, and bioavailability is approximately 82% at a dose of 140 mg every 4 weeks and the half-life is approximately 28 days. The pharmacokinetic of erenumab was similar for healthy patients and patients with migraine.

Distribution of erenumab to the fetus during gestation was demonstrated in Cynomolgus monkeys, with an infant:maternal serum ratio ranging from 2 to 20 at a dose of 50 mg/kg SC measured between post-partum Days 14 to 91. Erenumab was undetectable in infant serum on post-partum Day 180.

No specific studies on metabolism or excretion were conducted. This is acceptable given the protein nature of the drug in accordance with ICH S6 (R1).<sup>2</sup>

Blood samples were collected in the repeat dose studies to monitor the development of anti-drug antibodies (ADA), with a low incidence of ADAs noted across the 1 and 6 month repeat dose toxicity studies at low doses (25 mg/kg) during the dosing or recovery phase. When observed during the dosing phase, this was associated with a decrease in systemic drug exposure. Circulating immune complexes were noted in several animals. One animal dosed at 25 mg/kg had detectable circulating immune complexes in the serum on Day 22 and was euthanised on Day 29 displaying bilaterally enlarged inguinal lymph nodes consistent with ADA-related immune complex formation at these sites.

Overall, the PK studies showed that the cynomolgus monkey is an appropriate animal model for toxicity testing.

### **Pharmacokinetic drug interactions**

No specific studies on drug interaction potential of erenumab were conducted.

## **Toxicity**

### **Acute toxicity**

Single dose toxicity following IV administration was examined in the 4 week repeat-dose toxicity study (Study 113724) and observations on acute toxicity were made after the first dose in all repeat-dose toxicity studies. No acute treatment-related findings were noted in the repeat-dose studies in cynomolgus monkeys when either the intravenous or the subcutaneous routes were used with doses of up to 100 and 225 mg/kg/week, respectively.

## Repeat-dose toxicity

The sponsor submitted three repeat dose toxicity studies that were conducted in a responsive species: cynomolgus monkeys. The studies utilised twice weekly dosing and erenumab was administered using the SC route at doses of 25 to 225 mg/kg. The two pivotal studies were GLP-compliant. Dosing frequency was higher than the clinical dosing regimen (twice weekly compared with once a month in patients). Duration of studies was acceptable according to ICH guideline recommendations for non-rodent toxicity tests (ICH S4).<sup>5</sup>

### Relative exposure

Exposure ratios have been calculated based on animal: human plasma AUC from time zero to Day 7 (AUC<sub>0 to 7days</sub>) values. The clinical AUC values predicted by 2 compartment population PK modelling are used for exposure comparison. The AUC data used for animals is the mean of male and female values on the last sampling occasion.

Relative exposures in repeat dose toxicity studies based on AUC were moderate ( $\geq 10$  fold) to very high ( $> 100$  fold).

**Table 2: Relative exposure in repeat-dose toxicity study findings in cynomolgus monkeys**

Study details	Dose (mg/kg)	AUC <sub>0 to 7days</sub> ( $\mu\text{g}\cdot\text{day}/\text{mL}$ )	Exposure ratio#
<b>Study 114005</b> Repeat dose toxicity: 1 month Twice weekly dosing (day 28)	75	3345	26
	75*	3298	26
	225	9854	80
<b>Study 113732</b> Repeat dose toxicity: 3 or 6 months Twice weekly dosing (day 169)	25	2935	24
	150	15300	124
<b>Study 113724</b> Repeat dose toxicity: 1 month Twice weekly dosing (day 22)	25	2525	20
	75	8610	70
	225	16800	134
<b>Human: Population PK analysis</b> (2-compartment models)	(140 mg)	496	-

# = animal plasma AUC<sub>0 to 7 days</sub> (multiplied by 4 to match human AUC<sub>0 to 28 days</sub>); human plasma AUC<sub>0 to 28 days</sub>; ^ = data are for the sexes combined at the last sampling occasion; \*treatment 3 times per week.

### Major toxicities

Erenumab was well tolerated in repeat-dose toxicity studies following SC doses up to 225 mg/kg/fortnight for 6 months. One female treated with 25 mg/kg erenumab was euthanised during the four week study (on Day 29) due to the development of immune complex-associated pathology (pyogranulomatous inflammation of the lymph nodes). Circulating immune complexes were not observed in any other animal at any dose level.

<sup>5</sup> ICH, Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing), S4, 1998



No other erenumab-related mortality or morbidity was observed. There were no erenumab related clinical signs.

No remarkable adverse effects on body weight, food consumption, body temperature or clinical pathology parameters were observed following erenumab administration. There were also no erenumab-related findings in ophthalmoscopic and physical examinations. Post-mortem examinations revealed no erenumab-related macroscopic observations. Histopathological changes consisted of minimal-mild focal mononuclear cell infiltrates at the SC injection site in all treated animals and three control animals in the 3 and 6 month study. These findings are considered to be a nonspecific response to the injection of a foreign protein and not a direct effect of erenumab.

Serum chemistry analyses did not show clear treatment-related effects, although there were small fluctuations that were not statistically significant (increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (statistically significant in females at 90 days)) in the high dose group, decreased ALT in males at the high dose, decreased ALT in females at the mid and high dose, increased gamma-glutamyl transferase (GGT) in males at the high dose, increased triglycerides at the high dose, decreased glucose at the high dose). Histological correlates were not observed for any of these observations and therefore they are unlikely to be toxicologically significant. In the 1 month study, non-significant decreases in ALT at all doses and GGT at the high dose (225 mg/kg) were noted in females, with changes being reversible following the recovery period.

Full haematological assessments did not reveal notable treatment-related changes in either male or female treated animals. Coagulation parameters (prothrombin time (PT), activated partial thromboplastin time (aPTT) and platelet counts) were not affected by treatment. Slight but non-significant decreases in white blood cell parameters were noted in treated females, and a decrease in neutrophils and lymphocytes were also noted in high dose males in the 6 month study. Similar changes were observed in males in the 1 month study, reversible following the recovery period.

A number of organ weight changes (relative to bodyweight) were noted following repeat-dose treatment for 6 months. Observations include, reduced thymus weight in both sexes at the low and high dose (11 to 28%), increased pituitary weights in both sexes at the high dose, increased prostate weight in males, and increased ovary weight in females at the high dose. These organ weight changes were not statistically significant, were reversed following the recovery period and had no histological correlate and were therefore not considered toxicologically relevant. A number of other changes in organ weights including fluctuations in the thyroid, spleen and adrenal weights were not considered to be treatment-related on the basis that they had no histological correlates, were not always observed in both sexes and had no dose relationship.

### **Genotoxicity**

The genotoxic potential of erenumab was not examined in dedicated nonclinical studies, which is acceptable for a biotechnology-derived pharmaceutical as per the ICH guideline S6 (R1).<sup>2</sup>

### **Carcinogenicity**

The carcinogenic potential of erenumab was not examined in dedicated nonclinical studies, which is acceptable under ICH S6 (R1).<sup>2</sup> Conventional carcinogenicity bioassays in rodents are not appropriate since rodents are not responsive to erenumab and are also likely to develop antibodies to erenumab over time. Life time carcinogenicity studies in primates are not ethically feasible.

## Reproductive toxicity

Reproductive toxicity was evaluated in a pre-/postnatal development study in cynomolgus monkeys. Animals received fortnightly subcutaneous doses of erenumab of 50 mg/kg/fortnight. In the pre-/postnatal development study dosing started from gestation Day 50 and ceased dosing at parturition. This study also included measurement of erenumab in maternal and infant serum and toxicokinetic parameters were determined. The study designs were generally acceptable in view of the limitations associated with relying on primate animal models. Timing and duration of dosing was also acceptable and appropriate for primate models.

### Relative exposure

**Table 3: Relative exposure in reproductive toxicity studies**

Species	Study (Study no.)	Dose (mg/kg)	AUC <sub>0 to 14 day</sub> (µg·day/mL)	Exposure ratio#
<b>Monkey</b> (cynomolgus)	Pre/postnatal development (Study 113734) Sampling: GD 133	50	4280	17
<b>Human</b>	Population PK analysis (2-compartment model)	140 mg	496	–

# = animal AUC<sub>0 to 14 days</sub> (multiplied by 2 to match human AUC<sub>0 to 28 days</sub>): human AUC<sub>0 to 28 days</sub> plasma

The relative exposure achieved in the reproductive toxicity studies based on AUC was moderate (> 10 fold).

Placental transfer was demonstrated in cynomolgus monkeys, with erenumab detected in infant serum. Infant to maternal serum ratios ranged from 2 to 20 following a dose of 50 mg/kg for up to 91 days post-natal, suggesting that rate of transfer is high. In addition, given the slow elimination half-life, the likelihood of erenumab levels persisting in the infant circulation is high. These results suggest that the placental transfer of erenumab and its long elimination half-life explain the high infant serum levels of erenumab. Excretion into milk was not investigated.

In a pre-/postnatal development study, pregnant female monkeys received fortnightly erenumab injections at a dose of 50 mg/kg via the SC route from the period of organogenesis to parturition. No adverse effects on maternal health were reported and rates of fetal and infant loss were comparable between the treated and vehicle control groups. The length of gestation was not affected by treatment and total number of infants delivered was similar between groups. External assessments found no overall difference in morphometric measurements (crown-rump length, chest circumference, femur length, anogenital distance, biparietal diameter, et cetera) of infants from treatment groups compared with vehicle group. There were no treatment-related effects on neurobehavioural parameters (various reflexes, general behaviour, proprioceptive positioning, eye reactions, et cetera), heart and respiration rates, haematology or clinical chemistry evaluations. Infant immune function was not evaluated which is considered acceptable given the absence of effect of antibody formation observed in repeat dose studies.

### ***Pregnancy classification***

The sponsor proposed Pregnancy Category B1;<sup>6</sup> for erenumab. A B1 category is considered appropriate for this product in the absence of any maternal or fetal effects in adequately conducted postnatal development studies in female monkeys.

### **Local tolerance**

Erenumab was well tolerated in repeat-dose toxicity studies in cynomolgus monkey following SC administration, with histopathology at the injection site consisting of mild to minimal mononuclear cell infiltration observed in the dermis in all treated animals and some control animals. These changes are considered to be non-adverse reactions to the injection of foreign protein.

### **Phototoxicity**

Phototoxicity studies were not conducted using erenumab. This is acceptable in accordance with ICH guideline S10.<sup>7</sup>

### **Paediatric use**

Erenumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

### **Comments on the Nonclinical Safety Specification of the Risk Management Plan**

Results and conclusions drawn from the nonclinical program for erenumab detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

### **Nonclinical summary and conclusions**

- The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines (ICH S6).<sup>2</sup> The overall quality of the nonclinical studies was generally high. All safety-related studies were GLP compliant.
- Erenumab has high affinity for the human CGRP receptor ( $K_D$  56 pM) and effectively competed with CGRP to bind to human CGRP receptors *in vitro* ( $K_i$  20 pM). Erenumab inhibited CGRP-induced cAMP accumulation with an  $IC_{50}$  of  $2.3 \pm 0.9$  nM *in vitro*. Erenumab is a potent functional CGRP antagonist in monkeys ( $IC_{50}$  5.7 nM). Erenumab inhibits the capsaicin induced increase in dermal blood flow in cynomolgus monkeys *in vivo*.
- Erenumab is functionally inactive at the adrenomedullin, calcitonin, and amylin receptors, all members of the calcitonin receptor family. Erenumab staining was generally comparably between the tested panel of humans and monkey tissues, with staining observed in the cerebellum and spinal cord of both humans and monkeys and in human pituitary tissue.

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<sup>6</sup> Pregnancy category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

<sup>7</sup> ICH, Guidelines on photosafety evaluation of pharmaceuticals, ICH S10, 13 November 2013

- Safety pharmacology parameters were assessed in cynomolgus monkeys with no biologically significant changes to CNS (neurological, behaviour and body temperature), ECG (heart rate, QT interval duration and corrected QT interval duration) or respiratory parameters reported.
- The pharmacokinetic profile in monkeys was qualitatively similar to that of humans. Erenumab was slowly absorbed in both humans and monkeys, with a time taken to reach the maximum concentration ( $T_{max}$ ) of 1 to 5 days in monkeys and 4 to 11 days in humans. The estimated volume of distribution was 184 mL and clearance was 10.9 L/day in monkeys. The bioavailability was 60% in monkeys and 82% in humans. Erenumab exhibits nonlinear PK at lower doses (0.1 to 0.3 mg/kg) and linear PK at higher doses (> 70 mg/kg).
- Erenumab had a low order of acute oral toxicity in monkeys.
- Three repeat dose toxicity studies with erenumab (25, 75, 150 and 225 mg/kg twice per week) by the clinical (SC; 1 and 3 to 6 months) route were conducted in monkeys. Treatment-related effects were minimal. Injection site reactions were the main effect.
- No genotoxicity or carcinogenicity studies were conducted, which is acceptable for a biotechnology derived pharmaceutical.
- A pre/postnatal development study reported no adverse effects on maternal health, no effect to length of gestation, infant morphometric measurements, neurobehavioural parameters, heart rate assessments. The incidence of fetal/infant loss was similar between control and treated animals and was within the historical control ranges. Erenumab was found to cross the placenta (infant: maternal serum ratio 2 to 20) in monkeys. The no observed effect level for maternal and pup development was > 50 mg/kg/fortnight, corresponding to an exposure margin of approximately 17.

### Conclusions and recommendation

The submitted data were in general accordance with the ICH guideline on the non-clinical evaluation of biotechnology-derived pharmaceuticals.<sup>2</sup> All pivotal repeat-dose toxicity and reproductive toxicity studies were GLP-compliant.

- Primary pharmacology studies provided sufficient evidence of erenumab affinity and selectivity for the human and monkey CGRP receptor.
- Treatment-related effects associated with twice weekly injections were minimal and limited to injection site reactions.
- Pregnancy Category B1 is considered appropriate.<sup>6</sup>
- Overall, there are no nonclinical objections to the registration of erenumab.

## V. Clinical findings

### Information on the condition being treated

Migraine is a common disabling primary headache disorder characterised by moderate-to severe headache and is often accompanied by nausea, vomiting, photophobia and phonophobia, which can have a detrimental effect on daily activities. Epidemiological studies have documented its high prevalence and high socio-economic and personal impacts. It was ranked as the third most prevalent disorder and seventh highest specific

cause of disability worldwide.<sup>8,9</sup> Migraine is more common in women of prime working and childbearing age, with the highest prevalence being reported for women aged 30 to 39 years.<sup>10</sup> It is estimated that there are up to 3 million migraine sufferers in Australia. Given the high prevalence and substantial disability, migraine causes large socioeconomic burden in terms of reduced work productivity, absenteeism and significant indirect patient costs.<sup>11,12</sup>

Migraine is considered a spectrum disorder and is typically characterised by the frequency of migraine days per month. Episodic migraine (EM) is defined as < 15 migraine days per month,<sup>13</sup> although in clinical prophylactic trials, a lower threshold of 4 migraine days are often chosen to reflect typical patients in need of a prophylactic treatment. Chronic migraine (CM) is defined as  $\geq$  15 headache days per month, at least 8 of which have to be typical migraine days.<sup>14</sup> The distinction between EM and CM is somewhat arbitrary based on migraine headache frequency and numerous lines of evidence support that they are a continuum of the same disorder. Migraine is a highly debilitating disease in both its episodic and chronic forms, with the latter imposing more substantial individual and socioeconomic burden.

### Current treatment options

Across the spectrum, migraine is treated with agent(s) for the acute headache attacks, typically involving non-specific (symptomatic) agents such as non-steroidal anti-inflammatory drugs (NSAIDs) or migraine-specific abortive medications such as triptans or ergotamine derivatives. Non-pharmacological interventions and lifestyle modifications may also play a role in the multidisciplinary management of migraine for individual patients. Acute therapies and non-pharmacological interventions, although helpful for many patients, are not adequate treatment for all. Patients experiencing more frequent migraines and/or more severe functional impact, despite the use of acute medications, often require prophylaxis. The main goal of a prophylactic treatment is to reduce the frequency of migraine days.<sup>15,16</sup> Additional benefits of prophylactic treatment include reduced use of acute treatments, improvement of a patient's ability to function and reduction of disability.<sup>17</sup>

Several therapeutic options are available for migraine prophylaxis. Approved prophylactic treatments in the EU include the beta-blockers (propranolol and metoprolol), topiramate and amitriptyline (an antidepressant recently approved for migraine prophylaxis across the EU), and in some countries flunarizine (a calcium channel blocker). In the US, approved prophylactic treatments for migraine include the beta blockers (propranolol and

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<sup>8</sup> Steiner, T.J. et al. (2015). Headache disorders are third cause of disability worldwide. *The Journal of Headache and Pain*, 2015; 16: 58.

<sup>9</sup> Global Burden of Disease 2015 Disease and Injury Incidence and Prevalence Collaborators (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015, *Lancet*, 2016; 388: 1545-1602.

<sup>10</sup> Lipton, R.B. et al (2007). Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*, 2007; 68: 343-349.

<sup>11</sup> Munakata, J. et al. (2009). Economic Burden of Transformed Migraine: Results From the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*, 2009; 49: 498-508.

<sup>12</sup> Linde, M. et al. (2012). The cost of headache disorders in Europe: the Eurolight project, 2012; 19: 703-715.

<sup>13</sup> Katsarava, Z. et al. (2012). Defining the Differences Between Episodic Migraine and Chronic Migraine, *Curr Pain Headache Rep*, 2012; 16: 86-92.

<sup>14</sup> Headache Classification Committee of the International Headache Society (IHS) (2013). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*, 2013; 33: 629-808.

<sup>15</sup> Evers, S. et al (2009). EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force, *European Journal of Neurology*, 2009; 16: 968-981.

<sup>16</sup> Silberstein, S.D. et al (2012). Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*, 2012; 78: 1337-1345.

<sup>17</sup> Silberstein, S.D. (2015). Preventive Migraine Treatment. *Continuum (Minneapolis)*, 2015; 21: 973-989.

timolol) and the anti-epileptics (divalproex and topiramate). Other compounds have shown some degree of efficacy in the prophylaxis of migraine but are not approved in the US and most EU countries, such as venlafaxine (antidepressants), lisinopril (angiotensin converting enzyme inhibitor) and candesartan (angiotensin receptor blocker).

In Australia,<sup>18</sup> beta-blockers (propranolol, metoprolol), topiramate (Epiramax, Tamate), methysergide (Deseril) and botulinum toxin (Botox) are approved for migraine prophylaxis; other drugs which may be used (but are not officially approved for this indication) include the anti-depressant, amitriptyline and the antiepileptic, sodium valproate (Epilim, Valpro). Given the different types of therapies available, the standard of care (SoC) beyond propranolol/ metoprolol and topiramate is highly variable across countries and this is also reflected in the large range of recommendations in national treatment guidelines.

### Clinical rationale

Across several classes of existing prophylactic therapies, the main reasons for discontinuation in both EM and CM patients are lack of efficacy and poor tolerability;<sup>19</sup> which underscores the urgent need for novel therapeutic options. Many of the existing treatments, including approved therapies were not originally developed for migraine prophylaxis and do not target the underlying pathophysiology of the migraine disorder. For many older therapies, such as beta-blockers, there is a lack of robust efficacy data because much of the available evidence is based on studies conducted decades ago that would not meet current regulatory and clinical trial quality standards. Few products approved or recommended for migraine prophylaxis have demonstrated efficacy across the full spectrum of migraine encompassing both CM and EM. Poor tolerability and adverse events (AE) necessitating discontinuation of treatment are commonly associated with all existing therapies (for example, topiramate is associated with paraesthesia and cognitive dysfunction).<sup>20,21</sup> Due to limited treatment options, CM patients commonly overuse acute medications leading to medication overuse in an attempt to manage their symptoms and allow them to perform their daily activities.<sup>22,23</sup> Prophylactic treatments that reduce acute medication use may therefore reduce the risk of medication overuse.

Patient opposition to receiving prophylactic treatment and a preference for acute treatments, adherence concerns and poor tolerability are some of the prescribing barriers for physicians. Thus, there remains a significant medical need for new prophylaxis therapeutics in migraine, in particular approaches that target specific pathophysiologic pathways of migraine, that are safe and well tolerated when administered chronically. One such target is CGRP based mechanisms. CGRP is a 37 amino acid peptide widely expressed in both the central and peripheral nervous systems and has been implicated as a key mediator in the initiation and progression of migraine pain. The CGRP receptor is part of a pathway that is pathophysiologically relevant in migraine.<sup>24,25,26,27</sup> CGRP is found within

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<sup>18</sup> 'Managing migraines'. Accessed from the National Prescribing Service (NPS) Medicinewise website 18 July 2019.

<sup>19</sup> Blumenfeld, A.M. (2013). Patterns of Use and Reasons for Discontinuation of Prophylactic Medications for Episodic Migraine and Chronic Migraine: Results From the Second International Burden of Migraine Study (IBMS-II). *Headache*, 2013; 53: 644-655.

<sup>20</sup> Lainez, M.J. et al. (2007). Time course of adverse events most commonly associated with topiramate for migraine prevention. *European Journal of Neurology*, 2007; 14: 900-906.

<sup>21</sup> Adelman, J. et al (2008). Analysis of Safety and Tolerability Data Obtained from Over 1,500 Patients Receiving Topiramate for Migraine Prevention in Controlled Trials. *Pain Medicine*, 2008; 9: 175-185.

<sup>22</sup> Bussone, G. (2010). Clinical considerations on chronic migraine, pharmacoresistance and refractoriness. *Neurol Sci*, 2010; 31: S83-S85.

<sup>23</sup> Diener, H-C. et al. (2016). Medication-overuse headache: risk factors, pathophysiology and management. *Nat Rev Neurol*, 2016; 12: 575-583.

<sup>24</sup> Goadsby, P.J. et al. (1990). Vasoactive Peptide Release in the Extracerebral Circulation of Humans During Migraine Headache. *Ann Neurol*, 1990; 28: 183-187.

the trigeminovascular nociceptive system widely from the trigeminal ganglion to second-order and third-order neurons and in regulatory areas in the brainstem. CGRP is released during severe migraine attacks and the reversal of the attack with treatment normalises those levels.

There is strong scientific and clinical rationale for targeting the CGRP receptor in the prophylactic treatment of migraine. Erenumab is a potent and selective fully human IgG2 mAb against the CGRP receptor, blocking the interaction of CGRP ligand to its receptor and functionally inhibiting the CGRP signalling pathway. Despite the presence of CGRP receptors in the CNS, the likely site of action for erenumab is the trigeminal ganglion and as a mAb is expected to have minimal if any CNS penetration.

## Guidance

A pre-submission meeting was held on 8 March 2017 to discuss erenumab. The main issues raised by the TGA included justification in regards to safety/ efficacy comparing the two doses (70 mg and 140 mg SC once monthly), justification of choice of the 140 mg dose, duration of treatment, lack of active comparators;<sup>28</sup> in studies, lack of long-term safety data regarding cardiovascular (CV) and cerebral risks due to potential vasoconstriction and evaluation of risk of potential effect on cerebral vessels. The action items from the meeting are addressed in the submission dossier.

In August 2015, the sponsor officially entered into a global collaboration with Amgen in co-development and commercial rights of erenumab for the European Union and all countries outside the USA, Canada and Japan. In April 2017 the collaboration between the companies was expanded in North America. The sponsor along with Amgen will co-commercialise Aimovig in the USA (the marketing authorisation holder in the USA will be Amgen) and will be the future marketing authorisation holder and commercialise Aimovig in Canada and the European Union.

For all four Phase II and III studies, the designs and patient populations were planned taking into consideration the recommendations provided in the:

- European Medicines Agency (EMA) Guidelines on the clinical investigation of medicinal products for treatment of migraine (2007).<sup>29</sup>
- International Headache Society (IHS) Guidelines for controlled trials of drugs in migraine (2012).<sup>30</sup>

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<sup>25</sup> Cernuda-Morollon, E. (2013). Interictal increase of CGRP levels in peripheral blood as a biomarker for chronic migraine. *Neurology*, 2013; 81: 1191-1196.

<sup>26</sup> Lassen, L.H. et al. (2002). CGRP may play a causative role in migraine. *Cephalalgia*, 2002; 22: 54-61.

<sup>27</sup> Petersen, K.A. et al. (2005). BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. *Clin Pharmacol Ther*, 2005; 77: 202-213.

<sup>28</sup> TGA indicated that EU guidelines recommended the use of an active comparator (AC) and a placebo in the clinical trials. TGA questioned the reasons why no active comparator was included at this stage. Novartis indicated that advice was sought with several different Health Authorities and although opinions slightly varied, the general consensus was that a placebo controlled trial was acceptable. While AC is recommended to control variable placebo response, no one comparator that is suitable worldwide was identified. There are also several issues with the study blinding as topiramate and beta-blockers have noticeable side effects such as cognitive dysfunction and paraesthesia with topiramate and CV effects with beta-blockers. Novartis is planning to contextualise the benefit risk versus standard of care via a qualitative and quantitative approach. TGA concluded that a justification for not including an active comparator in the studies should be included in the dossier.

<sup>29</sup> European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), Guidelines for the clinical investigation of medicinal products for treatment of migraine, 24 January 2007, CPMP/EWP/788/2001 Rev. 1.

<sup>30</sup> International Headache Society Clinical Trials Subcommittee (2012). Guidelines for controlled trials of drugs in migraine: Third edition. A guide for investigators, *Cephalalgia*, 2012; 32: 6-38.

- Consultations involving the US Food and Drug Administration (FDA) and National Scientific Advice procedures in Europe (Germany, Netherlands, United Kingdom (UK)), as well as with Health Canada and Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

## **Contents of the clinical dossier**

### ***Clinical pharmacology***

- Seven Phase I studies:
  - Five studies evaluated healthy subject and/or patient PK, pharmacodynamics (PD), immunogenicity, tolerability and drug-drug interactions (DDIs); (Studies 20101267 20120130, 20101268, 20150334 and 20140255).
  - Two biopharmaceutic studies evaluated bioequivalence of various formulations of erenumab (Studies 20140477 and 20150149).
- Population PK modelling report (123319).
- Population PK-PD report (123320).

### ***Efficacy/safety studies***

- Two pivotal studies (both evaluated the 70 mg and 140 mg SC monthly doses):
  - Phase IIb Study 20120295 in CM.
  - Phase III Study 20120296 in EM.
- Other supportive studies (both in EM which evaluated only the 70 mg dose, which is not proposed dose in submission):
  - Phase III Study 20120297.
  - Phase II Study 20120178.
- One ongoing Phase II CV safety: Study 20140254 (stable angina patients)

### ***Analysis of results from more than one study***

- Integrated Immunogenicity report.
- Integrated Summary of Efficacy and Safety.
- Migraine Physical Function Impact Diary (MPFID: v2.0) Dossier.
- Supplemental Clinical Study Report: 20120178/20130255 clinical home use (CHU) sub study.

A Phase I study of erenumab in women with hot flashes associated with menopause was conducted (Study 20120180), but as the hot flash indication is not being pursued at this time, the clinical study report for Study 20120180 was not provided in the submitted dossier. However, safety and immunogenicity data from this study were described in the clinical dossier.

## **Paediatric data**

No paediatric data was submitted. The sponsors have an agreed Paediatric Investigation Plan (PIP) in the EU; a preclinical study was submitted on 30 January 2017 and compliance with PIP confirmed for this study by the EMA. The sponsors also have an agreed Paediatric Plan under the *Paediatric Research Equity Act* in the USA with partial waiver for pre-term infants to 23 months paediatric subjects as well as for children < 6 years of age. Deferral for the initiation and completion of the Phase III studies in children (6 to < 12 years of age) and adolescents (12 to < 18 years of age) was also



requested and it was considered appropriate to obtain sufficient efficacy and safety data in adults with migraine before initiating studies in the paediatric population (6 to < 18 years of age). Phase III paediatric studies were deferred until: a) full Phase III data in adults is available, which will allow the establishment of the benefit-risk in migraine as well as a decision on dosing before starting the paediatric program, and b) completion of study design discussions with the FDA during a special protocol assessment.

Paediatric investigation plans for Australia have not been specified.

### Good clinical practice

All the studies in the erenumab clinical development program were conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

## Pharmacokinetics

### Studies providing pharmacokinetic information

Serum erenumab concentrations were determined using a validated enzyme-linked immunosorbent assay method with a lower limit of quantification (LLOQ) of 1 ng/mL (range of 1.0 to 100 ng/mL). Intensive PK sampling was used for the healthy subject and patient PK, PD and initial tolerability Studies 20101267, 20101268 and 20120130 as well as the 2 biopharmaceutic Studies 20140477 and 20150149. Limited PK sampling strategy was used for the PK/PD Studies 20140255 and 20150334 as well as the Phase II/III efficacy/safety Studies 20120178 and 20120295. Sparse PK sampling strategy as used for Studies 20120296, 20120297 and 20130255. Details regarding sampling times are summarised in synopses of study reports. Individual serum erenumab concentration-time data collected with intensive sampling were analysed by non-compartmental PK analysis methods. The primary PK parameters estimated included area under the curve (AUC), maximum observed concentration ( $C_{max}$ ) and time of maximum observed concentration ( $t_{max}$ ). Additionally, population PK (Report 123319) and PK/PD analyses (Report 123320) in healthy subjects and subjects with EM or CM were performed using the non-linear mixed effects modelling method.

Table 4 shows a summary of the submitted pharmacokinetic studies.

**Table 4: Submitted pharmacokinetic studies**

PK topic	Subtopic *	Study ID
PK in healthy adults	General PK, single dose	20101267 20120130
	General PK, multi-dose	20101268
	Bioequivalence †- single dose	20140477 20150149
	Bioequivalence multi-dose	None
	Food effect	NA

PK topic	Subtopic *	Study ID
PK in special populations	Target population § Limited PK sampling in 5 Phase II/III efficacy/safety studies	201201178, 20120295, 20120296, 20120297 and 20130255.
	Hepatic impairment	None
	Renal impairment	None
	Neonates/infants/children/adolescents	None
	Elderly	None
Genetic/gender related PK	None	
PK interactions	Oral contraceptive pills (ethinyl estradiol/norgesterone)	20150334
	Sumatriptan	20140255
Population PK analyses	Population PK modelling report	123319
	Population PK/PD report	123320

\* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

### Evaluator's conclusions on pharmacokinetics

The current submission contains 6 Phase I studies that examined the PKs of erenumab as well as 2 population PK and PK/PD analyses. Overall, the conduct of the studies was satisfactory and was compliant with existing TGA guidelines, validated analytical methods were employed and the data analyses undertaken were appropriate. Furthermore, PK data was also available from the Phase II/III efficacy/safety studies and was included in the population PK and PK/PD analyses.

- Absorption, distribution, metabolism, excretion (ADME) profile:
  - Following a single subcutaneous dose of 140 mg Aimovig administered to healthy adults, median peak serum concentrations were attained in 4 to 6 days, and estimated absolute bioavailability was 82%.
  - Erenumab exhibits non-linear kinetics as a result of binding to CGRP receptor. SC administration of a 140 mg dose in healthy volunteers resulted in a  $C_{max}$  mean (standard deviation (SD)) of 15.8 (4.8)  $\mu\text{g/mL}$  and AUC last mean (SD) of 505 (139) day  $\mu\text{g/mL}$ .
  - Consistent with the nonlinear PK displayed after a single dose of erenumab, PK after multiple SC doses of erenumab were nonlinear from 21 mg to 70 mg and approximately linear from 70 mg to 140 mg. Less than 2 fold accumulation was observed in trough serum concentrations ( $C_{min}$  (SD) 12.8 (6.53) and 14.9 (6.45)  $\mu\text{g/mL}$  for EM and CM subjects, respectively) following 140 mg doses administered subcutaneously every 4 weeks and serum trough concentrations

approached steady state by 12 weeks of dosing. The effective half-life of erenumab is 28 days.

- The mean (SD) steady state volume of distribution was estimated to be 3.86 (0.77) L.

Two elimination phases were observed for Aimovig. At low concentrations, the elimination is predominantly through saturable binding to target (CGRP receptor), while at higher concentrations the elimination of Aimovig is largely through a non-specific, non-saturable proteolytic pathway. Total clearance is predominantly linear (that is, nonlinear clearance is negligible) at the clinical dose regimen and the terminal half-life can be approximated using clearances and volumes of distribution, which is approximately 28 days for a typical subject.

- Bioequivalence
  - The proposed marketing formulation is a prefilled syringe or a prefilled syringe loaded into a SureClick auto-injector containing 1.0 mL of 70 mg/mL erenumab (2 injections for the 140 mg dose). Study 20140477 demonstrates that the treatments used in pivotal studies (70 mg vial (Process 1), 70 mg prefilled syringe (Process 2) and 70 mg prefilled syringe loaded in a SureClick auto-injector (Process 2) are bioequivalent.
  - Results of Study 20150149 suggested that a 140 mg dose of erenumab administered as a single 2.0 mL (70 mg/mL) injection or a single 1.0 mL (140 mg/mL) injection did not lead to PK differences or any differences in treatment emergent adverse events (TEAEs) when compared with the proposed two 1.0 mL (70 mg/mL) injections.
- Population PK modelling results
  - A 2 compartment PK model with linear distribution to the peripheral compartment, parallel linear and non-linear elimination and first order SC absorption process described the PK of erenumab after IV and SC administration of various dose regimens. Similar to other therapeutic monoclonal antibodies, absorption of erenumab after SC administration is slow, with an absorption half-life of 2.3 days. The absorption half-life suggested that the absorption phase is complete in approximately 12 days. The estimated SC bioavailability for erenumab is 81.8% which is consistent with the reported values for mAbs.
  - The inter-individual variability for erenumab was 42% for central volume of distribution, 27.6% for clearance and 79.5% for absorption rate.
  - The pharmacokinetics of erenumab were not affected by age, gender, race, migraine subtype (EM or CM), or creatinine clearance, across all approved populations based on population PK analysis.
- PK interactions:
  - A single dose of 140 mg erenumab administered SC did not affect the PKs of a combined oral contraceptive containing ethinyl estradiol and norgesterone in an open label study involving healthy females.
  - In a double blind, randomised, placebo controlled study in healthy subjects, concomitant administration of erenumab (140 mg IV) with sumatriptan had no effect on resting blood pressure (BP) or PKs of sumatriptan.
  - Interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely as erenumab is not metabolised by cytochrome P450 enzymes. However, DDIs of erenumab with other prophylactic treatments for migraine were not evaluated.

- PKs in special patient populations:

No specific studies were conducted in patients with hepatic or renal impairment. However, population PK analysis of integrated data from the erenumab clinical studies showed similar erenumab PKs in subjects with mild to moderate renal impairment compared to those with normal renal function. Subjects with severe renal impairment were excluded from the erenumab clinical studies.

The PK sections of the proposed PI are satisfactory.

- Limitations of PK data:
  - Despite demonstration of bioequivalence between the 3 erenumab treatment groups in Study 20150149, it is not clear why the single injection (with either the 140 mg/mL prefilled syringe or a single 2 mL (70 mg/mL) injection) was not evaluated further. The proposed dosing regimen requires two 1.0 mL (70 mg/mL) injections while the other options would only require one injection. Clarification regarding this has been sought from sponsors.
  - Erenumab PKs in subjects with hepatic impairment were not evaluated.
  - Results of the population PK analysis suggesting lack of effect of moderate renal impairment on erenumab PKs should be interpreted with caution as number of subjects with moderate renal impairment was much smaller compared to those with mild renal impairment and normal renal function.

## Pharmacodynamics

### Studies providing pharmacodynamic data

Table 5 outlines the submitted pharmacodynamic studies.

**Table 5: Submitted pharmacodynamic studies**

PD Topic	Subtopic	Study ID
Primary Pharmacology	None	
Secondary Pharmacology	Effect on exercise time in patients with stable angina	20140254
PD Interactions	Sumatriptan	20140255
Population PK and PK-PD analyses	Healthy subjects	123319
	Target population	123320

### Evaluator's conclusions on pharmacodynamics

Evaluation of effect of erenumab on inhibition of capsaicin induced increase in dermal blood flow showed that the minimal effective dose was 21 mg, but results failed to show a dose dependent increase of percent inhibition of capsaicin induced increase in dermal blood flow in the erenumab group compared with the placebo group in both healthy subjects and migraine patients (Studies 20101267 and 20101268).

There was no significant difference between the erenumab groups and placebo group at all measured time points for change in bone biomarker (procollagen type 1 N propeptide (P1NP) and serum C-telopeptide cross-link of type 1 collagen (sCTX)) levels compared with Baseline in healthy subjects and migraine patients.

In a randomised, double-blind, placebo-controlled Study 20140254 to evaluate the effect of Aimovig (140 mg IV, single dose) in patients with stable angina, Aimovig did not decrease exercise duration during a treadmill test compared to placebo. However, safety results from this study were not provided in the submitted dossier and sponsor states that these will be submitted with the final study report.

Exposure-response models were developed to describe the relationship between concentration time course and daily migraine response in chronic and episodic migraine. Mixed effects modelling approach was implemented to estimate population response and inter-subject variability and identify potential explanatory factors.

In both patient populations, exposure response analysis suggests that benefit of erenumab is seen within days of treatment and increasing erenumab concentration decreases the probability of a migraine day. The exposure response relationship in daily migraine response correlates with higher monthly migraine day (MMD) reduction and responder rate with increasing trough concentrations at Week 12. The time to 50% of maximum placebo effect was shorter for EM than CM (32 days versus 50 days). After adjustment for baseline migraine rate, the maximum probability of migraine day with placebo group for CM is approximately double that for EM (approximately 49% versus 25% of subjects with a migraine day).

In both populations, there is a trend for better efficacy in subjects who previously failed prophylactic medications due to a smaller placebo effect in these subjects. Although the estimate is more precise with EM than CM. Erenumab concentration effect is significant in explaining the migraine day probability. Whereas CM data showed a shallow decrease in migraine day probability with increased concentration, episodic migraine data showed an asymptotic decrease in migraine day probability that plateaued at approximately 8.15 µg/mL. The analyses suggest that although the net concentration effect (above placebo) is larger in CM than EM, the range of concentration effect is smaller than that in EM. At Week 12, the incremental improvement was 0.76 days for subjects with EM (Studies 20120178, 20120296 and 20120297) and 0.38 days for subjects with CM (Study 20120295). The observed efficacy increment with higher exposure was generally consistent across studies and visits. Overall, a 140 mg regimen may provide a more robust maintenance of therapeutic concentrations than a 70 mg regimen.

The clinical evaluator also made comments with regards to the PD sections of the proposed PI; however these are beyond the scope of this AusPAR.

## **Dosage selection for the pivotal studies**

### **Pharmacokinetics and pharmacodynamics: dose finding studies**

Phase I studies explored inhibition of capsaicin induced dermal blood flow after administration of a wide range of SC doses to healthy subjects and subjects with migraine (Studies 20101267 and 20101268). Erenumab treatment resulted in inhibition of the capsaicin induced increase in dermal blood flow, although the effects were not dose dependent. These data were analysed using a model based approach for the exposure response relationship and were used for selecting the Phase II doses, assuming the inhibition of capsaicin induced dermal blood flow was predictive of the clinical efficacy. Three dose levels of erenumab (that is, 7 mg, 21 mg and 70 mg) were chosen for testing in the Phase II Study 20120178 to enable dose selection for the Phase III program. The low

dose of 7 mg was anticipated to be minimally effective and transiently (for approximately 2 weeks) achieve 50% of the maximum inhibition of the capsaicin induced increase in dermal blood flow after the second monthly dose. The middle dose of 21 mg was predicted to achieve trough serum concentrations approximately equivalent to the 90% effective concentration ( $EC_{90}$ ) from the dermal blood flow model at steady state (that is, after the third monthly dose). The high dose of 70 mg was chosen because it resulted in nearly complete inhibition of the peripheral CGRP receptor from the first dose, based on inhibition of the capsaicin induced increase in dermal blood flow. The trough serum concentration achieved at 70 mg was predicted to be approximately 10 fold higher than the  $EC_{90}$  from the dermal blood flow model.

### **Phase II dose finding studies**

Results from the Phase II Study 20120178 in subjects with EM showed that higher doses and systemic exposures than that suggested by dermal blood flow results are required for migraine efficacy. Only the 70 mg dose resulted in reductions in monthly migraine days compared with placebo while the 7 mg and 21 mg doses were ineffective. Exposure response analyses over a large range of PK exposures indicated that 70 mg monthly is the lowest dose that results in efficacious concentrations and maximal efficacy may require an even greater dose. As the results from the Phase II study were inconsistent with the doses expected to result in complete inhibition, based on the dermal blood flow model, and to ensure optimal efficacy is achieved with erenumab, a higher dose of 140 mg SC monthly was also studied in the open label extension phase of Study 20120178. Additionally, both the 70 mg monthly and 140 mg monthly doses were evaluated in the pivotal studies for CM (Study 20120295) and EM (Study 20120296).

### **Phase III pivotal studies investigating more than one dose regimen**

Erenumab 70 mg and 140 mg SC monthly doses were evaluated in both the pivotal studies (the Phase IIb Study 20120295 in CM, and the Phase III Study 20120296 in EM). Other supportive studies were the Phase III Study 20120297 and Phase II Study 20120178, both in EM only evaluated the 70 mg dose.

### **Evaluator's conclusions on dose finding for the pivotal studies**

Higher doses and systemic exposures than that suggested by dermal blood flow results (Studies 20101267 and 20101268) were required for migraine efficacy in the Phase II dose ranging Study 20120178. As the results from the Phase II dose ranging study were inconsistent with the doses expected to result in complete inhibition, based on the dermal blood flow model, and to ensure optimal efficacy is achieved with erenumab, a higher dose of 140 mg SC monthly was also studied in the open label extension phase of Study 20120178. Additionally, both the 70 mg monthly and 140 mg monthly doses were evaluated in the pivotal studies for CM (Study 20120295) and EM (Study 20120296).

The above rationale for dose selection for the pivotal efficacy studies in patients with migraine was acceptable.

## **Efficacy**

### **Studies providing efficacy data**

Two pivotal studies, the Phase IIb Study 20120295 in CM and the Phase III Study 20120296 in EM (both evaluated the 70 mg and 140 mg SC monthly doses). Other supportive studies: Phase III Study 20120297 and Phase II Study 20120178, both in EM which only evaluated the 70 mg dose.

### Evaluator's conclusions on efficacy

Two pivotal studies evaluated efficacy of erenumab in 1,612 adults with migraine; 660 with CM in Phase IIb Study 20120295 and 952 with EM in Phase III Study 20120296. Both studies were randomised, multicentre, double blind, placebo controlled, parallel group with double blind treatment periods of 12 to 24 weeks. The studies included a prospective run-in period of least 1 month to determine the baseline characteristics and frequency of attacks per month.

The inclusion and exclusion criteria were well defined to enable evaluation in a population representative of the target patient population for erenumab treatment. Diagnosis of migraine was confirmed by IHS International Classification of Headache Disorders (ICHD-III 2013);<sup>31</sup> based on medical records and/or patient self-report. Definition of CM and EM was based on the frequency of migraine headache days per month, that is  $\geq 15$  headache days of which  $\geq 8$  headache days meet criteria as migraine days during the Baseline phase for diagnosis of CM in Study 20120295 and migraine frequency  $\geq 4$  and  $< 15$  migraine days per month and headache (that is migraine and non-migraine headache) frequency:  $< 15$  headache days per month on average across the 3 months prior to screening for diagnosis of EM in Study 20120296. Patients were required to discontinue other prophylactic therapies prior to study enrolment (with the exception of a small number of patients in Study 20120296). Two doses of erenumab (70 mg and 140 mg) were chosen for the 2 pivotal studies with the intent to aid in dose selection for the marketing application. The dose selection for these 2 studies was based on preclinical, Phase I and Phase II safety data, as well as PD data obtained in humans with the capsaicin induced dermal blood flow model.

The efficacy endpoints were appropriate and were designed to evaluate all aspects of migraine disorder. The primary endpoint was change from Baseline in mean migraine days during last month of treatment in the 12 week Study 20120295 in CM while it was the averaged over last 3 months of the 24 week double blind period in Study 20120296 in EM patients. Agreement on this proposed primary endpoint was reached during prior interactions with the US FDA and EU national health authorities. The current IHS guidelines recommend either the number of migraine attacks or the number of migraine days, without preference, as the primary endpoint in controlled migraine prophylaxis studies.<sup>30</sup> By contrast, the 2007 EMA guideline,<sup>29</sup> which is currently under revision, recommends the number of migraine attacks as the primary endpoint. Migraine days are a more commonly used, sensitive and reliable measure compared with migraine attacks which are influenced by acute treatment and by any recurrence of the migraine pain, neither of which is typically standardised in migraine prophylaxis studies. In CM, individual attacks are often difficult to differentiate and therefore do not provide adequate sensitivity. Overall, selection of reduction in MMD as the primary efficacy endpoint was acceptable as it is a clinically relevant and is also being used in ongoing pivotal trials with other CGRP targeted therapies. Furthermore, migraine attacks were assessed as a secondary or exploratory endpoint in erenumab studies.

The 2007 EMA guidelines;<sup>29</sup> recommend analysis of efficacy for the entire treatment period, as well as for the specified treatment period. The primary endpoint was assessed in the last month of the double blind treatment period in Studies 20120178, 20120295 and 2012097, while average values over the last three months were assessed in Study 20120296. However, monthly assessments of efficacy were performed in all pivotal and supportive studies.

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<sup>31</sup> Headache Classification Committee of the International Headache Society (IHS) (2013) The International Classification of Headache Disorders, 3rd edition (beta version) *Cephalgia*, 2013; 33: 629-808.

The 2007 EMA guidelines also recommend a 3 arm trial with active comparator and placebo, with the active comparator for internal validation on the basis of the 'large and highly variable placebo effect' seen in early migraine studies. While the erenumab Phase II/III studies all included a placebo arm, an active comparator arm was not included. The reasons for not including an active comparator were 2 fold:

- Due to the wide range of existing therapies across regions, it was also not possible to identify a single active comparator arm meeting all regional needs in a global development program.
- The typical side effect profile associated with existing treatments had the potential to functionally un-blind treatment assignments which may have confounded interpretation of study results especially due to fact that there are no objective endpoints in migraine and the clinical assessments of efficacy are self-reported.

Five recently reported placebo controlled studies have shown robust results within the class of CGRP targeted mAb therapies with some variability in placebo response, which did not preclude the detection of clinically relevant treatment effects in both EM and CM.

Overall, the lack of active comparator did not appear to confound interpretation of results in the erenumab especially since the placebo response was consistent across studies. Furthermore, the sponsors have provided a benefit-risk assessment of erenumab versus standards of care in migraine prophylaxis using qualitative and quantitative approaches. This has been evaluated and discussed in this report.

As migraine causes significant disability and functional impairment, all Phase II/III studies also included several patient reported outcome (PRO) assessments on the impact of treatment on patients' health-related quality of life (QoL) commonly used in both clinical trials and in clinical practice, including Headache Impact Test (HIT-6) assessing overall headache impact, Migraine Disability Assessment (MIDAS) questionnaire addressing migraine-specific disability and Migraine-Specific Quality of Life (MSQ) questionnaire for migraine-specific QoL. Based on patient input, physical impact was identified as an important additional aspect that is not adequately covered by these established PRO scales. The MPFID was developed as a complementary PRO scale addressing aspects relevant for migraine patients, including physical impact and impact on everyday activities, with a daily recall period. Following FDA guidance/agreement, the MPFID was included in Studies 20120296 and 20120297 as a secondary endpoint.

Overall, both pivotal studies (Study 20120295 in subjects with CM and Study 20120296 in subjects with EM) were well controlled, adequately designed and powered to achieve their objectives. Subject retention was high in both studies, with over 95% completing study treatment during the 12 week double blind phase of the study in CM subjects and over 90% of subjects completing the study treatment during the 24 week double blind phase of the study in EM subjects. These high retention rates minimise concerns over the impact of missing data on the results and suggest that erenumab may offer an advantage for migraine prophylaxis, as enhanced compliance with the treatment regimen is necessary for sustained treatment benefit.

Subjects enrolled in the 2 pivotal studies were generally representative of the target population. The majority of subjects were female (> 80%) and white (> 89%) with mean age across treatment groups in both studies of approximately 40 to 43 years. It is important to note that the highest prevalence of migraine is reported for women aged 30 to 39 years;<sup>32</sup> and so the mean age (41 to 42 years) in the pivotal erenumab studies was a bit higher. Furthermore, there were more patients > median age of 42 to 43 years in both pivotal studies. Subjects in both studies had long histories of migraine (about 20 years or

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<sup>32</sup> Lipton, R.B. et al (2007) Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*, 2007; 68: 343-349.



longer). Over 96% of subjects reported using acute headache medication during the baseline phase; 78% of CM subjects and 59% of EM subjects used acute migraine-specific medications during the baseline phase. Other baseline disease characteristics that differed between the CM and EM subjects largely reflect the different eligibility requirements, in particular migraine/headache frequency. Approximately 40% of EM subjects and over 70% of CM subjects had previously used a migraine prophylactic medication, the vast majority of whom failed this previous treatment for intolerance or lack of efficacy.

Dose selection: Exposure-response analyses supported the choice of the 140 mg SC once monthly regimen for subjects with CM and EM on the basis that when compared to 70 mg SC once monthly, 140 mg once monthly provided the highest systemic exposure that resulted in the greater monthly migraine days percent reduction from Baseline at Week 12 (Population PK-PD analysis report 123320). In the CM study, the placebo adjusted least squares mean (LSM) differences for erenumab 140 mg and 70 mg were similar (approximately -2.5 days for both doses). In the EM study, slight numerical additional benefit was seen for the erenumab 140 mg dose compared with the erenumab 70 mg dose; at Week 24 (which was the average of changes from Baseline in Months 4, 5 and 6), the LSM differences were -1.4 and -1.9 days for erenumab 70 mg and 140 mg, respectively. However, subgroup analysis in both studies showed that the higher proposed 140 mg dose did show greater benefits in patients who had failed prior prophylaxis treatment. The pivotal studies were not powered to evaluate differences between the 70 mg and 140 mg erenumab doses and that there were no formal dose comparisons. Since the 140 mg dose does not offer significant benefits over the 70 mg dose for most other subgroups of patients, it may be prudent to offer the lower dose which requires only 1 injection for other migraine patients who have not failed prior prophylactic therapy.

The secondary efficacy endpoints common to the 2 pivotal studies showed similar patterns of results; that is, statistically significant and clinically meaningful differences favouring erenumab 140 mg and erenumab 70 mg over placebo, with erenumab 140 mg showing additional benefit (numerical) over erenumab 70 mg. The proportions of placebo subjects who achieved at least a 50% reduction in monthly migraine days were similar in the 2 studies (23.5% in CM Study 20120295 and 26.6% in EM Study 20120296). Achievement of at least a 50% reduction from Baseline in monthly migraine days is a highly clinically relevant endpoint for both patients and clinicians and is less susceptible to the numerical differences in Baseline monthly migraine days seen in subjects with CM compared to subjects with EM. A statistically significantly higher proportion of 50% responders were seen in both erenumab dose groups at Week 12 in CM Study 20120295 and at Week 24 in EM Study 20120296 compared to the proportions seen in the respective placebo groups. Notably, 41.2% of erenumab 140 mg subjects with CM and 50.0% of erenumab 140 mg subjects with EM had at least a 50% reduction in monthly migraine days at the end of the double blind treatment phases (Week 12 and Week 24 (averaged over months 4, 5 and 6), respectively) in the pivotal studies.

Analyses using response rates of at least a 75% reduction and a 100% reduction from Baseline in monthly migraine days (post hoc in Study 20120295, exploratory in Study 20120296) were conducted to determine whether a subset of subjects had dramatic, or even complete, response over the time period assessed. At the end of the 12 week double blind phase in CM Study 20120295, the proportions of subjects who achieved at least a 75% reduction from Baseline in monthly migraine days were 7.8%, 17.0% and 20.9% in the placebo, erenumab 70 mg and 140 mg groups, respectively. Similar results were observed in the EM Study 20120296 with 75% responder rate of 7.9%, 20.8% and 22.0%, respectively at the end of the 24 week double blind treatment phase. Small proportions of subjects in each study reported a complete absence of migraines (that is 100% reduction from Baseline in monthly migraine days): 2.4%, 4.3% and 2.7% in placebo, erenumab 70 mg and 140 mg groups, respectively in CM Study 20120295; 2.8%, 3.2% and 5.0%, respectively in EM Study 20120296. These proportions

were numerically larger in the erenumab treatment groups than in the placebo group in both studies. Although exploratory and post hoc, these results are of considerable clinical interest, as responses of this magnitude are rarely seen with currently available prophylactic treatments, particularly in subjects with CM.

For the change from Baseline in monthly acute migraine-specific medication treatment days, a secondary efficacy endpoint in both pivotal studies, the pattern of results was similar to that seen for the primary efficacy endpoint; that is, a statistically significantly larger reduction in mean monthly acute migraine-specific medication treatment days in the erenumab treatment groups compared with placebo, with additional benefit (numerical) for erenumab 140 mg over erenumab 70 mg.

Results from the PROs utilised in the pivotal studies, including the HIT-6 (overall impact of headache), the MSQ and the MIDAS (migraine related disability) show patterns of results that were generally similar to those seen for the primary and secondary efficacy endpoints; that is, all showed larger improvements from Baseline for the erenumab treatment groups compared with the placebo group, with additional benefit (numerical) seen for erenumab 140 mg over erenumab 70 mg.

In CM Study 20120295, numerically greater reductions from Baseline to Week 12 in cumulative headache hours (a secondary endpoint) were seen in the erenumab dose groups, but these differences were not statistically significant compared with placebo. Difficulties in reliably measuring the duration of migraine headaches have been noted in the IHS guidelines. However, the change from Baseline in monthly headache days and in monthly moderate and severe headache days (migraine and non-migraine) showed nominally statistically significant differences favouring the erenumab groups over the placebo group.

The mean change from Baseline in MPFID impact on everyday activities and physical impairment domain scores were secondary efficacy endpoints in EM Study 20120296 and showed statistically significant greater mean reductions in the erenumab treatment groups compared with placebo, with additional benefit (numerical) seen for erenumab 140 mg over erenumab 70 mg. A similar pattern of results was seen when the proportions of subjects with at least 5 point reductions in these 2 MPFID domain scores (exploratory endpoints) were compared. However, the mean MPFID scores at Baseline were in the 12 to 13 point range (measured from 0 to 100 range with higher scores indicating higher disease burden). Hence, effects on MPFID should be interpreted with caution as patients did not have much impairment at Baseline.

Supportive Studies 20120297 and 20120278 used only the 70 mg dose of erenumab and also evaluated efficacy only in EM patients. Although, these studies did show benefits in primary, secondary and exploratory endpoints with the lower 70 mg dose compared with placebo, they did not provide any evidence to support proposed dosing regimen of 140 mg once monthly.

The data submitted to support use of erenumab 140 mg SC once monthly for proposed indication of prophylaxis treatment of adults with migraine had the following limitations:

1. Lack of adequate evidence to support long term maintenance of efficacy especially in patients with CM. Evidence for efficacy of erenumab up to 6 months was provided by pivotal Study 20120296 in EM patients. However, it is accepted that this deficiency should be addressed by the longer-term efficacy data from the open label extension study of the pivotal CM Study 20120295 (extension Study 20130255) and the active treatment phase of the pivotal EM Study 20120296 and these results should be provided for evaluation when available.
2. There is no specific information regarding proposed duration of treatment with erenumab. However, the sponsors have mentioned the following: '6 month data' from

the double blind treatment phase of pivotal EM Study 20120296 and the open label extension phase of the supportive EM Study 20120178 provide evidence for the persistence of efficacy beyond the minimum trial duration of 3 months recommended in IHS guidelines with the latter study assessing efficacy up to 64 weeks. There was no indication of the development of tolerance or loss of effect with longer term treatment. The consistency of results seen across the migraine continuum for the prophylactic treatment with erenumab in the double blind treatment phases also suggest sustained efficacy beyond 3 months for CM. There was no evidence of rebound after treatment discontinuation based on review of migraine AEs. The sponsor considers that the decision on how long a patient is going to be treated needs to be made by the treating physician for each individual patient. It is standard practice for prophylactic treatment of migraine that treatment continuation needs to be re-evaluated in intervals of 3 to 6 months as per Australian Therapeutic Guideline, Neurology.<sup>33</sup>

The above clarification regarding duration of treatment is justified, but a statement should be added to the proposed PI and Consumer Medicines Information (CMI).

3. There is lack of adequate follow-up after discontinuation of treatment and withdrawal/rebound effects cannot be ruled out.
4. The efficacy sections of the proposed PI are quite inadequate and fail to provide an accurate and clear representation of data submitted in the dossier.

## Safety

### Studies providing safety data

#### *Pivotal and/or main efficacy studies*

Evidence of safety of erenumab in treatment of migraine was based primarily on the integrated analyses of data from the following studies:-

- One Phase II EM Study 20120178 (including its open label phase).
- One Phase II CM Study 20120295 and its open label extension Study 20130255.
- Two Phase III EM Studies 20120296 and 20120297 (including their open label/active treatment phases).

The double blind phases of the studies were placebo controlled and did not include an active comparator arm. For all of the above mentioned integrated studies, data from the 12 week, double blind, placebo controlled periods were included in the integrated analysis. The open label extension phases from Studies 20120178 and 20120297 are ongoing, as is the active treatment phase of Study 20120296. Study 20120295 is completed; however, Study 20130255, its open label extension, is ongoing. Data from the ongoing phases are included in the integrated analysis based on data cut off dates.

The rationale for integrating the safety data from studies in EM and CM is that although EM and CM are somewhat arbitrarily distinguished based on migraine headache frequency (migraine/headache day frequency  $\geq 4$  to  $14 < 15$  and  $\geq 8 > 15$ , respectively), numerous lines of evidence support that they are a continuum of the same disorder. Not only are clinical symptomology and functional impairments very similar, but functional imaging results demonstrating that similar areas of the brain are involved support a common

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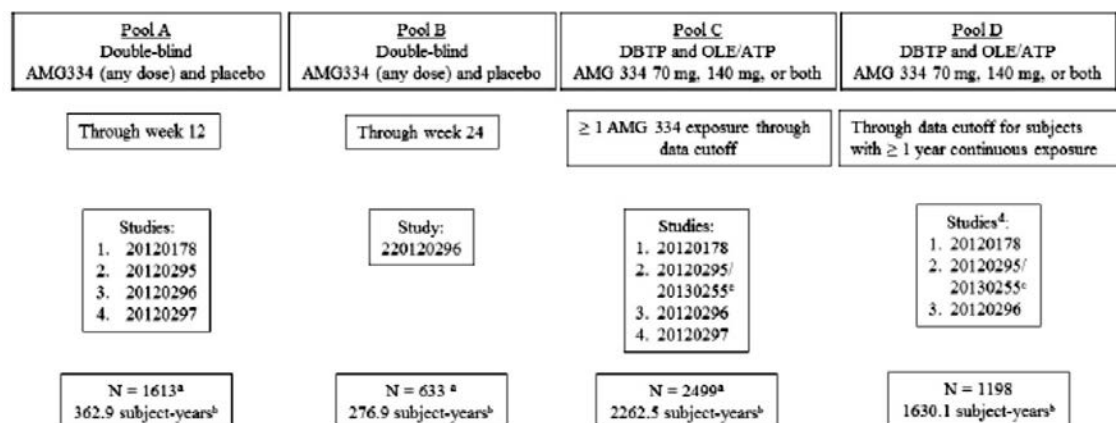
<sup>33</sup> Australian Therapeutic Guideline, Neurology as per <https://www.racgp.org.au/membership/therapeutic-guidelines> (accessed July 2019)

underlying pathophysiology.<sup>34,35,36,37</sup> From a safety perspective, demographics and baseline characteristics in episodic migraine and chronic migraine studies are similar and it is appropriate to assess the safety of erenumab on the totality of data from both the episodic and chronic migraine studies.

The above justification provided by sponsors for integrating safety data is acceptable.

The integrated safety analysis set is defined as all subjects in a data pool or in a study, who have received at least 1 dose of investigational product.<sup>38</sup> Four analysis pools were defined (shown in Figure 2, below).

**Figure 2: Migraine analysis pools**



ATP = active treatment period; DBTP = double-blind treatment period; OLE = open-label extension

<sup>a</sup> For Pools A and B, N represents number of subjects who received ≥ 1 dose of investigational product. For Pool C, N represents the number of subjects as of the data cut-off date who received at least 1 dose of AMG 334 (70 mg/140 mg).

<sup>b</sup> Represents subject-years of exposure.

<sup>c</sup> Study 20130255 is the long-term extension of Study 20120295.

<sup>d</sup> Study 20120297 is not included in the long-term pool because the maximum exposure is 40 weeks.

AMG 334 = erenumab

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. For Pools A and B, AEs were summarised by subject incidence, with select summaries additionally being presented using exposure adjusted subject incidence rates (per 100 subject years (SY)) to allow for direct comparison of short-term safety to longer-term safety.

For Pools C and D, data were summarised by exposure adjusted subject incidence rates (per 100 SY), defined as the number of subjects with at least 1 reported occurrence of the event in a given time period divided by total subject-years at risk during that phase. For subjects who had an AE, the time (days) at risk for reporting the AE at the respective dose level = time (days) at the respective dose level before the occurrence of the AE.<sup>39</sup>

During the course of erenumab clinical development, a number of events of interest were identified and were based either on risks that could theoretically be associated with CGRP

<sup>34</sup> Aurora, S.K. and Wilkinson, F. (2007). The Brain is Hyperexcitable in Migraine. *Cephalalgia*, 2007; 27: 1442-1453.

<sup>35</sup> Afridi, S.K. et al. (2005). A Positron Emission Tomographic Study in Spontaneous Migraine, *Arch Neurol*, 2005; 128: 932-939.

<sup>36</sup> Aurora, S.K. et al. (2005). Cortical Inhibition Is Reduced in Chronic and Episodic Migraine and Demonstrates a Spectrum of Illness, *Headache*, 2005; 45: 546-552.

<sup>37</sup> Welch, K.M.A. et al. (2001). Periaqueductal Gray Matter Dysfunction in Migraine: Cause or Burden of Illness?, *Headache*, 2001; 41: 629-637.

<sup>38</sup> Subjects are grouped within a study by the actual treatment group as defined by the individual study statistical analysis plans, otherwise the randomised treatment group was used.

<sup>39</sup> A subject could have been at the respective dose level for non-consecutive time periods before the occurrence of the AEs.

inhibition (cardio and cerebrovascular effects, gastrointestinal effects), safety concerns associated with small molecule CGRP inhibitors (hepatic effects) and safety concerns associated with an injectable protein therapy (immunogenicity, hypersensitivity and injection site reactions). For each event of interest, a search strategy using Standardised MedDRA Queries (SMQs) or Amgen MedDRA Queries (AMQ) was used to identify AEs.

Absolute values and change from Baseline were summarised for haematology and clinical chemistry parameters. All haematology and clinical chemistry parameters with toxicity Grade 3 or 4 were also summarised. Vital signs and ECG changes were also summarised at each visit and subject incidences for clinically relevant changes from Baseline were also summarised. Subject incidence was also summarised for maximum severity changes in Columbia-Suicide Severity Rating Scale (C-SSRS) from Baseline to post-Baseline at any time. Subject incidence was summarised for anti-erenumab (binding and neutralising) antibody formation and select AEs were summarised for subjects who developed anti-erenumab antibodies.

Although each of the individual studies within pool A was randomised, the treatment group comparisons may no longer be protected by randomisation when the data are integrated across studies and hence results should be interpreted with caution.

Differences in rates between doses should be interpreted with caution in Pool C as subjects could have switched between 2 different dose levels in different sequences. Pool D is a subset of Pool C, the same limitations regarding comparison of safety data between the 70 mg and 140 mg doses apply as in Pool C. In addition, interpretation of between dose comparisons in Pool D are further limited by the imbalance in exposure as substantially more subjects were exposed to the 70 mg dose than the 140 mg dose.

Furthermore, the pooled safety analysis predominantly includes patients with EM with only Study 20120295 providing data in CM patients. Hence, the safety results of the 2 pivotal studies (Study 20120295 in CM, and Study 20120296 in EM) were also briefly summarised in the clinical evaluation report.

### **Other studies**

#### *Other efficacy studies*

The seven Phase I studies and the single-dose Phase IIa safety study in subjects with stable angina (Study 20140254) were not included in the integrated analyses because of different study designs, populations and limited exposures. In addition, an ongoing Phase II Japanese study (Study 20120309) is not included because it remains blinded at the time of this submission.

#### *Studies with evaluable safety data: dose finding and pharmacology*

Safety results of all clinical pharmacology studies are provided in the study synopses in the clinical evaluation report.

### **Patient exposure**

Overall, 3150 subjects were exposed to at least 1 dose of erenumab and of these subjects, a total of at least 2537 were subjects with migraine (included in the integrated analysis) and 613 were healthy subjects. An additional 50 subjects with hot flashes associated with menopause from Study 20120180 and 44 subjects with stable angina from the treadmill Study 20140254 were exposed to at least 1 dose of erenumab.

In the integrated safety analysis, 2537 subjects (2310.3 SY of exposure) were exposed to at least 1 dose of erenumab: 2128 subjects were exposed to 70 mg (1673.1 SY of exposure) at any time and 1198 subjects were exposed to 140 mg (589.4 SY of exposure) at any time. The mean (SD) duration of exposure was 47.5 (33.0) weeks for subjects exposed to any dose of erenumab. Overall, 2392 subjects (94.3%) were exposed to

erenumab for  $\geq 3$  months, 2066 subjects (81.4%) were exposed to erenumab for  $\geq 6$  months and 1213 subjects (47.8%) were exposed to erenumab for  $\geq 12$  months. For subjects with continuous exposure, 1598 (63.0%) received 70 mg and 768 (30.3%) received 140 mg for  $\geq 6$  months; 682 (26.9%) and 134 (5.3%) received 70 mg and 140 mg for  $\geq 12$  months, respectively. The majority of subjects completed the prescribed number of doses for the treatment period. Of the subjects completing 3, 6 and 12 months of treatment, 2330 (98.8%), 2007 (97.6%) and 1132 (94.5%) did not miss any of their doses, respectively.

In the double blind period, 2656 of 2682 randomised subjects (99.0%) received at least 1 dose of investigational product (1043 subjects received placebo and 1613 subjects received erenumab). A total of 2497 of 2682 subjects (93.1%) completed investigational product and 159 subjects (5.9%) discontinued treatment prematurely with subject request most common reason for discontinuation in both treatment groups (placebo versus erenumab: 3.9%; 41 out of 1056 versus 2.6%; 42 out of 1626). A total of 36 out of 2682 subjects (1.3%) discontinued treatment because of AEs. A total of 2375 subjects (88.6%) (924 subjects who received placebo and 1451 subjects who received erenumab during the placebo controlled double blind period) entered the open label phase/active treatment and received either 70 mg or 140 mg once monthly SC or both. A total of 383 subjects (14.3%) discontinued open label/active treatment phases prematurely; 6.9% (186 out of 2682) discontinued due to subject request and 2.2% (60 out of 2682) due to AEs. Overall, 632 subjects (23.6%) completed their respective studies, including subjects who completed Study 20120295 through the double blind, placebo controlled phase including the safety follow up, but did not enrol in Study 20130255. As of the data cut offs for this integrated analysis, 1449 of the originally randomised subjects (54.0%) are continuing in their respective studies (either continuing treatment or have entered the safety follow up period).

The majority of subjects in the Integrated safety analysis set were female (83.8%) and White (91.0%) with mean (SD) age of 41.5 (11.2) years. Almost all subjects used acute headache medications (2601 subjects, 97.9%); 1746 subjects (65.7%) used acute migraine specific medications during the baseline period and 1391 subjects (52.4%) had previously or concurrently been treated with a prophylactic migraine medication and almost half of subjects reported prior migraine prophylactic treatment failure due to lack of efficacy and/or poor tolerability (1216 subjects, 45.8%). Migraine disease characteristics were similar across the treatment groups. Overall, most subjects had 1 or more baseline cardiovascular risk factor(s) (1891 subjects, 71.2%). The most frequent individual cardiac risk factors (not mutually exclusive) were high cholesterol at screening (1271 subjects, 47.9%), high lipid level at screening (648 subjects, 24.4%) and body mass index (BMI)  $> 30$  kg/m<sup>2</sup> (665 subjects, 25%). Overall,  $> 80\%$  of subjects reported a history of  $\geq 1$  medical or surgical condition. Frequently reported ( $\geq 6\%$ ) medical conditions included seasonal allergy, depression, anxiety, drug hypersensitivity, insomnia, asthma, back pain, hypothyroidism, hysterectomy, gastroesophageal reflux disease and tension headache. Some studies had a dedicated cardiovascular medical history electronic case report form (eCRF) page (Studies 20120296 and 20120297). A total of 13 subjects (0.5%) reported a vascular medical history: 3 of the 13 subjects (0.1%) had coronary artery disease and 11 (0.4%) had cerebrovascular or peripheral arterial disease.

## Safety issues with the potential for major regulatory impact

### *Liver function and liver toxicity*

#### *Integrated safety analyses*

##### Pool A

The incidence of ALT or AST elevations > 3 times the upper limit of normal (ULN) post-Baseline was low and similar across the placebo (0.5%; 5 out of 1029), erenumab 70 mg (0.5%; 4 out of 885) and 140 mg (0.4%; 2 out of 504) treatment groups. Of these subjects, 3 (0.3%) in the placebo group, 1 (0.1%) in the 70 mg group and 2 (0.4%) in the 140 mg group had baseline values within the normal range. One subject in the placebo group and 1 subject in the erenumab 140 mg group had ALT or AST elevations > 5 times ULN post Baseline; however, the values returned to normal for both subjects during the study despite continued study treatment. There were no elevations in AST or ALT > 10 times or > 20 times ULN. The incidence of total bilirubin elevations > 1.5 times the ULN post Baseline was low and similar across the placebo (0.6%; 6 out of 1029), erenumab 70 mg (0.3%; 3 out of 885) and 140 mg (0.6%; 3 out of 504) treatment groups. Of these subjects, 3 (0.3%) in the placebo group, 1 (0.1%) in the 70 mg group and 2 (0.4%) in the 140 mg group had baseline values within normal range. One subject in the 70 mg group had total bilirubin elevations > 2 times ULN post Baseline; this subject's bilirubin was within normal limits at Baseline. The subject's AST and ALT were normal at the time of this bilirubin elevation and no associated AEs were reported. A total of 2 subjects (0.2%) in the placebo group, 1 subject (0.1%) in the 70 mg group and 2 subjects (0.4%) in the 140 mg group had alkaline phosphatase (ALP) elevations > 1.5 times ULN post-Baseline; all subjects had baseline levels ≤ 1 times ULN. There were no shifts in any LFT to Grade 3 or Grade 4 for any subjects in the erenumab treatment groups. No subject met the criteria for Hy's Law.<sup>40</sup>

##### Pool B

In the placebo, 70 mg and 140 mg treatment groups, there were few post-Baseline elevations in ALT > 3 times ULN, total bilirubin > 1.5 times ULN, or ALP > 1.5 times ULN (there were no elevations for AST > 3 times or > 5 times ULN). In most instances, the baseline values for these subjects were also elevated, although to a lesser degree. The greatest elevations post-Baseline included an ALT value in 1 subject in the 70 mg group that was > 5 times ULN (this subject's baseline ALT was elevated between 1 and 3 times ULN) and a total bilirubin value in 1 subject in the 70 mg group that was > 2 times ULN (this subject's baseline total bilirubin was ≤ 1 times ULN). There were no shifts from Baseline to Grade 3 or Grade 4 values post-Baseline (only 1 subject in the 70 mg group demonstrated a shift in ALT from Grade 1 at Baseline to Grade 3 post Baseline). No subject in Pool B met the Hy's Law criteria.

##### Pool C

Few subjects with normal baseline LFTs increased to > 3 times ULN or > 5 times ULN during the 12 month period. During months 1 to 3, incidence of subjects with normal or slightly elevated baseline AST or ALT levels that had post Baseline levels of > 3 times ULN was 0.7% (13 out of 1785) and 0.4% (3 out of 677) in the 70 mg and 140 mg groups, respectively. The incidence was lower between > 3 months and 6 months as only 3 subjects receiving 70 mg and no subjects receiving 140 mg group had AST or ALT levels > 3 times ULN post Baseline; 2 subjects receiving 70 mg and 1 subject receiving 140 mg had post Baseline levels > 5 times ULN by Month 12. There were no elevations in AST or ALT > 10 times or > 20 times ULN. In subjects with AST or ALT levels > 5 times ULN, these were all single elevations of > 5 times ULN and all had normal bilirubin values at the time of the elevation. Elevations of total bilirubin from Baseline to post-Baseline remained

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<sup>40</sup> Hy's law: ALT > 3 times ULN and total bilirubin > 2 times ULN.

consistent in subjects receiving 70 mg (1.7% to 1.9%). Elevations in total bilirubin from Baseline to post Baseline in subjects receiving 140 mg occurred in 2.5% of subjects during months 1 to 3, 1.8% of subjects during months > 3 to 6 and 3.3% of subjects during months > 6 to 12. Few subjects had shifts to grade 3 LFTs; 1 subject receiving 70 mg shifted from normal baseline ALT/AST levels to grade 4 during the > 12 month time period. No subject met the criteria for Hy's Law.

#### Pool D

Few subjects receiving either erenumab dose who had normal baseline LFTs increased to > 3 times ULN or > 5 times ULN during the 12 month period. The results for Pool D were consistent with those observed in Pool C.

### **Renal function and renal toxicity**

#### *Integrated safety analyses*

No differences in mean changes or clinically significant changes from Baseline were observed in renal function laboratory parameters between placebo and erenumab treatment groups at any time point in Pools A and B with similar results observed in the long term safety Pools C and D.

### **Other clinical chemistry**

#### *Integrated safety analyses*

In Pool A, < 1% of subjects across all treatment groups had Grade  $\geq$  3 or Grade  $\geq$  4 laboratory toxicities post-Baseline. Creatine kinase (CK) levels were the most frequently reported Grade  $\geq$  3 laboratory toxicity while on study and were balanced across the treatment groups: 4 subjects (0.4%), 7 subjects (0.9%) and 3 subjects (0.6%) in the placebo, 70 mg and 140 mg groups, respectively; Grade  $\geq$  4 post Baseline CK levels were reported for 1 subject (0.1%), 3 subjects (0.4%) and 2 subjects (0.4%), respectively.

Pool B also showed similar results with Grade  $\geq$  3 post baseline levels of CK reported in 1 subject (0.3%), 4 subjects (1.3%) and 5 subjects (1.6%) in the placebo, 70 mg and 140 mg groups, respectively; grade  $\geq$  4 levels were reported in and 0%, 0.6% (2 subjects) and 0.9% (3 subjects), respectively. Grade  $\geq$  3 post baseline levels of triglycerides were reported in 3 subjects (1.0%), 2 subjects (0.6%) and 4 subjects (1.3%), respectively. There were no grade  $\geq$  4 post baseline values reported.

Grade  $\geq$  3 CK levels were the most frequently reported laboratory toxicity while on study in Pool C with similar incidence during Months 1 to 3 (70 mg = 15, 1.0%; 140 mg = 4, 0.6%), Months > 3 to 6 (70 mg = 6, 0.6%; 140 mg = 2, 0.5%) and Months > 6 to 12 (70 mg = 10, 1.0%; 140 mg = 2, 0.4%). Grade  $\geq$  4 CK levels were reported for 5 subjects (0.3%) receiving 70 mg and 3 subjects (0.4%) receiving 140 mg during Months 1 to 3, 0.3% each during Months 3 to 6 and ) 0.3% (with 70 mg only) during Months 6 to 12. There were no notable differences observed during the > 12 month period. Similar results were observed in Pool D.

### **Haematology and haematological toxicity**

#### *Integrated safety analyses*

No differences in mean changes or clinically significant changes from Baseline were observed in haematology parameters between placebo and erenumab treatment groups at any time point in Pools A and B with similar results observed in the long term safety pools C and D.

### **Other safety assessments Analysis of Adverse Events by Organ System or Syndrome**

The organ systems and syndromes presented in this section were considered important for the complete characterisation of the erenumab safety profile. There were effects on



hepatic function, cardiovascular effects, immunological AEs and skin and subcutaneous tissue AEs. The effect of erenumab on other organ systems and syndromes is discussed in the following section.

#### *General disorders and administration site conditions*

In Pool A, subject incidence rates for AEs in the 'General disorders and administrative site conditions' System Organ Class (SOC) were similar across the treatment groups (8.1%, 10.3% and 7.9% in the placebo, 70 mg and 140 mg groups, respectively) with injection site pain (1.7%, 3.7% and 1.6%, respectively) and fatigue (1.7%, 2.2% and 2.0%, respectively) reported most frequently. The only serious adverse event (SAE) was non-cardiac chest pain in 1 subject in the 70 mg group. Similar results were observed in Pool B (9.1%, 11.1% and 6.9% in the placebo, 70 mg and 140 mg groups, respectively). In Pool C, the exposure-adjusted subject incidence rates (per 100 SY) were 15.6 and 18.4 for the 70 mg and 140 mg doses, respectively; injection site (4.5 and 2.7, respectively) and fatigue (3.2 and 5.9, respectively) were reported most frequently. Non-cardiac chest pain was the only event reported as serious in 3 subjects receiving 70 mg and 1 subject receiving 140 mg. Similar results were observed in Pool D (11.6 and 15.6 per 100 SY for the 70 mg and 140 mg doses, respectively).

Injection site reaction was identified as an event of interest. In Pool A, incidence rates of injection site reactions were 3.2%, 5.6% and 4.5% in placebo, erenumab 70 mg and 140 mg groups, respectively; the most frequently reported Preferred Term mapping to the injection site reactions AMQ were injection site pain (1.7%, 3.7% and 1.6%, respectively) and injection site erythema (0.2%, 1.0% and 2.0%, respectively). There were no SAEs and only one AE of injection site rash led to study treatment discontinuation in a subject in the 70 mg group. Similar results were observed in Pool B with incidence rates for AEs mapping to injection site reactions AMQ of 1.9%, 6.1% and 3.4% in placebo, erenumab 70 mg and 140 mg groups, respectively; the most frequently reported Preferred Term mapping to the injection site reactions AMQ were injection site pain (0.3%, 3.2% and 0.6%, respectively) and injection site erythema (0.3%, 1.9% and 1.6%, respectively). In Pool C, exposure-adjusted subject incidence rates of adverse events (per 100 SY) mapping to the Injection Site Reaction AMQ were 7.5 and 7.7 for the 70 mg and 140 mg doses, respectively and they were 5.3 and 7.3 in Pool D.

#### *Gastrointestinal disorders*

Preclinical data suggest that  $\alpha$ CGRP is gastroprotective;<sup>41</sup> in mammals. It is contained in the afferent nerve fibres and is believed to exert a trophic role in gastric mucosal integrity. Hence, inhibition of CGRP may potentially increase the risk of gastrointestinal inflammation and/or ulcer. However, there were no gastrointestinal-mediated clinical signs or lesions in the repeat-dose toxicology studies of up to 6 months in duration with erenumab. Assessment of the gastrointestinal effect of erenumab was performed via review of the 'Gastric disorder' SOC and a dedicated search strategy using Gastrointestinal nonspecific inflammation and dysfunctional conditions SMQ (narrow and broad) and Gastrointestinal perforation, ulceration, haemorrhage or obstruction SMQ (narrow and broad).

In Pool A, subject incidence rates of AEs in the 'Gastrointestinal disorders' SOC were similar across treatment groups (9.1%, 8.1% and 8.9% in the placebo, 70 mg and 140 mg groups, respectively) and most common AEs were nausea (2.6%, 2.4% and 2.0%, respectively) and constipation (1.1%, 1.3% and 3.2%, respectively). Gastrointestinal disorder SAEs were reported in 2 subjects in the placebo group (pancreatitis and

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<sup>41</sup> Several mechanisms for its protective effects against gastric injury have been postulated, including inhibition of gastric secretion of somatostatin, stimulation of gastric mucin synthesis, and mucosal hyperaemia via direct vasodilation (Evangelista, A. (2009). Role of Calcitonin Gene-Related Peptide in Gastric Mucosal Defence and Healing. *Current Pharmaceutical Design*, 2009; 15: 3571-3576).

vomiting) and 1 subject in the 140 mg dose group (abdominal adhesions and abdominal pain). Similar results were observed in Pool B with AE incidence of 8.2%, 9.2% and 10.7% in the placebo, 70 mg and 140 mg groups, respectively; constipation (1.3%, 1.9% and 3.8%, respectively) and nausea (1.9%, 2.2% and 1.9%, respectively) were reported most frequently. In Pool C, the exposure-adjusted subject incidence rates (per 100 SY) were 17.8 and 21.9 for the 70 mg and 140 mg doses, respectively; the most frequently reported AEs (per 100 SY) were nausea (3.7 and 6.0 for the 70 mg and 140 mg doses, respectively) and constipation (1.8 and 4.5, respectively). SAEs;<sup>42</sup> were reported by 9 subjects (0.5 per 100 SY) receiving 70 mg and 2 subjects (0.3 per 100 SY) receiving 140 mg. Similar results were observed in Pool D with the exposure-adjusted subject incidence rates (per 100 SY) of 15.5 and 20.4 for the 70 mg and 140 mg doses, respectively with nausea (2.4 and 5.8, respectively) and constipation (1.5 and 3.8, respectively).

Constipation is the only AE that was reported at a higher rate in subjects receiving erenumab. The events of constipation were all non-serious and Grade 1 or Grade 2 severity. Only 1 subject receiving 140 mg discontinued because of constipation (Day 2) and had several concurrent AEs including flatulence, dyspepsia, diarrhoea and abdominal pain (all occurring on Day 2 as well). The majority of constipation events were transient and were not recurrent with continued treatment. The time to onset for constipation ranged from 1 to 954 days, with more subjects reporting a time to onset within a few days of the first dose.

In Pool A, subject incidence rates for AEs mapping to Gastrointestinal perforation, ulceration, haemorrhage or obstruction SMQ was low and similar across groups (0.2%, 0.4% and 0.2% in the placebo, 70 mg and 140 mg groups, respectively) with similar results in Pool B (0.0%, 0.3% and 0.3%, respectively). In Pool C, the exposure-adjusted subject incidence rates (per 100 SY) were 1.2 and 0.6 for the 70 mg and 140 mg doses, respectively with similar results were observed in Pool D.

#### *Nervous system disorders*

In Pool A, subject incidence rates of AEs in the 'Nervous system disorder' SOC were similar across treatment groups (6.8%, 7.1% and 6.7% in subjects receiving placebo, 70 mg and 140 mg, respectively); the most frequently reported AEs ( $\geq 1\%$ ) in all treatment groups were migraine (2.0%, 1.6% and 1.0%, respectively) and dizziness (1.1%, 1.0% and 1.4%, respectively). Three subjects reported SAEs: migraine for 2 subjects (0.2%) in the placebo group and 2 subjects (0.2%) in the 70 mg group and cerebral venous thrombosis for 1 subject in the 140 mg group. Similar results were observed in Pool B with incidence rates of 10.3%, 7.0% and 7.8% in subjects receiving placebo, 70 mg and 140 mg, respectively. In Pool C, the exposure-adjusted subject incidence rates (per 100 SY) of AEs in the 'Nervous System Disorder' SOC were 13.9 and 16.9 for the 70 mg and 140 mg doses, respectively; the most frequently reported AEs (per 100 SY) were migraine (2.9 and 4.2 for 70 mg and 140 mg respectively), dizziness (2.8 and 2.7, respectively) and headache (1.5 and 2.4, respectively). SAEs were reported by 15 subjects (0.8 per 100 SY) receiving 70 mg and 5 subjects (0.7 per 100 SY) receiving 140 mg.<sup>43</sup> Similar results were observed in Pool D with exposure-adjusted subject incidence rates (per 100 SY) of AEs of 11.4 and 16.6 for the 70 mg and 140 mg doses, respectively with most frequently reported AEs (per 100 SY) being migraine (2.2 and 3.8 for 70 mg and 140 mg, respectively), dizziness (2.1 and 1.7, respectively) and headache (1.3 and 2.8, respectively).

The exposure-adjusted subject incidence of migraine and headache was numerically greater with the higher proposed dose of 140 mg compared with the lower 70 mg dose in

<sup>42</sup> Abdominal pain and abdominal adhesions were reported as serious by 2 subjects and all other events were reported by 1 subject.

<sup>43</sup> Migraine for 5 subjects (0.3 per 100 SY) receiving 70 mg and 1 subject receiving 140 mg and syncope for 4 subjects (0.2 per 100 SY) receiving 70 mg and no subjects receiving 140 mg

the long-term safety Pools (C and D) although interpretation was limited by small number of events.

#### *Neoplasms benign, malignant and unspecified*

Nonclinical findings in the cynomolgus monkey do not suggest increased carcinogenic risk following treatment with erenumab. At exposures as high as 123 fold over the clinical exposure, there was no evidence of histopathological risk factors of neoplasia including, cellular hypertrophy, cellular hyperplasia, tissue injury and/or inflammation, pre-neoplastic changes.

In Pool A, subject incidence rates of AEs in the 'Neoplasms benign, malignant and unspecified' SOC were low and similar across treatment groups (0.5%, 0.3% and 0.2% in placebo, 70 mg and 140 mg groups, respectively);<sup>44</sup> with similar results observed in Pool B (0.9%, 1.3% and 0.3%, respectively). In Pool C, the exposure-adjusted subject incidence rates (per 100 SY) of AEs were 1.7 and 1.2 for the 70 mg and 140 mg doses, respectively. A limited number of malignancies;<sup>45</sup> were reported in Pool C. Similar results were observed in Pool D with exposure adjusted subject incidence rates (per 100 SY) of 1.5 and 0.8 for the 70 mg and 140 mg doses, respectively.

#### *Musculoskeletal and connective tissue SOC*

In the repeat dose chronic toxicology study in cynomolgus monkeys, biomarkers of bone formation and resorption were not affected by erenumab and there were no histopathological changes in the bone. In a Phase I study, there were no clinically relevant differences between the erenumab groups and the placebo group in healthy subjects and migraine subjects in the change from Baseline in bone turnover biomarkers P1NP and sCTX.

In Pool A, subject incidence rates of AEs in the 'Musculoskeletal and connective tissue disorders' SOC were similar across the treatment groups (7.9%, 7.2% and 9.3% in subjects receiving placebo, 70 mg and 140 mg, respectively) and most frequently reported AEs were back pain (1.7%, 1.3% and 1.0%, respectively), arthralgia (1.4%, 1.3% and 1.0%) and musculoskeletal pain (1.1%, 1.0% and < 1.0%). With the exception of muscle spasms, all other events were balanced across the treatment groups. The incidence of high level terms (HLTs) of joint related signs and symptoms, arthropathies, musculoskeletal and connective tissue pain and discomfort were balanced across treatment groups. Few SAEs were reported in Pool A (0.3%, 0.4% and 0.0%, respectively); in the 70 mg group, intervertebral disc protrusion (2 subjects, 0.2%), back pain (1 subject, 0.1%) and costochondritis (1 subject, 0.1%) were reported as serious. Similar results were observed in Pool B with AE incidence of 12.2%, 11.1% and 12.2% in subjects receiving placebo, 70 mg and 140 mg, respectively. In Pool C, the exposure adjusted subject incidence rates (per 100 SY) of AEs were 19.4 and 22.7 for the 70 mg and 140 mg doses, respectively with arthralgia (4.2 and 4.0 for 70 mg and 140 mg, respectively) and back pain (3.9 and 4.3, respectively) reported most frequently. SAEs were reported by 9 subjects (0.5 per 100 SY) receiving 70 mg and 3 subjects (0.4 per 100 SY) receiving 140 mg. Intervertebral disc protrusion (4 subjects) and costochondritis (2 subjects) were the only events reported by > 1 subject. Similar results were observed in Pool D with exposure adjusted subject incidence rates (per 100 SY) of 18.4 and 20.5 for the 70 mg and 140 mg doses, respectively; the most frequently (per 100 SY) occurring AEs were back pain (4.6 and 2.5, respectively) and arthralgia (3.9 and 3.0) and muscle spasms (< 2.0 and 2.3).

<sup>44</sup> In the placebo group, uterine leiomyoma was reported for 2 subjects (0.2%) and basal cell carcinoma, melanocytic naevus, and thyroid neoplasm were reported for 1 subject each. In the 70 mg group, fibroadenoma of the breast, fibroma, and fibrous histiocytoma were reported for 1 subject each. In the 140 mg group, leiomyoma was reported for 1 subject.

<sup>45</sup> Included breast cancer (2 subjects, < 0.1 per 100 SY), papillary thyroid cancer (2 subjects, < 0.1 per 100 SY), fibrous histiocytoma (malignancy unconfirmed) (2 subjects, < 0.1 per 100 SY), malignant sweat gland neoplasm (1 subject, < 0.1 per 100 SY) and lung adenocarcinoma Stage III (1 subjects, < 0.1 per 100 SY).

### *Psychiatric disorders*

In Pool A, subject incidence rates of AEs in the 'Psychiatric disorder' SOC were similar across treatment groups (2.5%, 3.1% and 3.6% in placebo, 70 mg and 140 mg groups, respectively). The most frequently occurring AE in all treatment groups was insomnia (0.8%, 0.7% and 1.2%, respectively), none of which were serious. There was one non-serious, Grade 1 AE of suicidal ideation, which occurred in a subject;<sup>46</sup> 2.5 months after the subject's last dose of 70 mg at Week 4. No SAEs were reported in Pool A. Similar results were observed in Pool B with AE incidence of 4.1%, 2.5% and 4.1%, respectively.

In Pool C, the exposure adjusted subject incidence rates (per 100 SY) of AEs were 7.3 and 6.8 for the 70 mg and 140 mg doses, respectively; the most frequently occurring AEs (per 100 SY) were insomnia (1.8 and 1.8 for 70 mg and 140 mg, respectively) and anxiety (1.9 and 1.6, respectively). SAEs were reported by 6 subjects (0.3 per 100 SY) receiving 70 mg and no subjects receiving 140 mg. Depression (4 subjects) was the only event reported in >1 subject. Similar results were observed in Pool D with exposure adjusted subject incidence rates (per 100 SY) of 6.4 and 6.9 for the 70 mg and 140 mg doses, respectively; the most frequently occurring AE was insomnia (1.7 per 100 SY) and anxiety (1.9 per 100 SY) for the 70 mg and 140 mg doses, respectively.

In Pool A, subject incidence rates of AEs mapping to the Depression (excluding suicide and self-injury) SMQ were low and similar across treatment groups (1.1%, 1.8% and 1.4% in placebo, 70 mg and 140 mg groups, respectively) with similar results observed in Pool B (1.9% in each treatment group). Similar results were observed in Pool C (3.1 and 2.8 for the 70 mg and 140 mg doses, respectively) and Pool D (2.3 and 3.4 for the 70 mg and 140 mg doses, respectively). Review of C-SSRS data did not identify an increased risk of suicidality.

### ***Electrocardiograph findings and cardiovascular safety***

#### *ECG<sup>47</sup> findings*

Pool A: ECG abnormalities were reported infrequently ( $\leq 2\%$  of subjects in all treatment groups) and were balanced across the treatment groups. The most frequent ECG abnormality finding was first degree atrioventricular block, which was overall observed in 5.2% of subjects receiving erenumab, and was similar to the placebo group (4.9%). In subjects with a normal baseline ECG, first degree atrioventricular block was observed in 2.6%, 3.3% and 2.7% of subjects receiving placebo, 70 mg and 140 mg, respectively. Abnormal flat T waves were observed for 4.7% of subjects in the erenumab groups, and lower than the occurrence in the placebo group (7.1%). ECG abnormalities were generally balanced across treatment groups with the exception of ectopic supraventricular rhythm which was observed in numerically more patients treated with erenumab 140 mg (0.3%, 0.7% and 1.8% in placebo, 70 mg and 140 mg groups, respectively). ECG tracings of all subjects with a diagnosis of ectopic supraventricular rhythm were reviewed by a blinded cardiologist and it was concluded that the majority of these ECGs were normal with a finding of bradycardia and/or right bundle branch block for a few subjects. Overall, this finding is not considered clinically relevant. Review of the PR interval, QRS complex and corrected QT interval (QTc) did not identify any safety concerns. Dizziness was reported for 3 subjects; however, none of these events coincided with the ECG diagnosis, none were

<sup>46</sup> The subject had previously discontinued investigational product because of an increase in migraine and non-migraine headaches, and cold intolerance. The event was not considered related to treatment by the investigator.

<sup>47</sup> For Pool A (12 weeks) and Pool B (24 weeks), summary statistics for corrected QT Interval (Fridericia) (QTcF), PR interval and QRS complex were summarised along with a subject's maximum post-Baseline and maximum increase from Baseline in QTcF. In addition, for each of the 4 pools, the number and percentage of subjects with Baseline and at least 1 post-Baseline measurement meeting any of the following criteria were summarised: • QTcF at Baseline:  $\leq 450$  ms,  $> 450$  to  $480$  ms,  $> 480$  to  $500$  ms,  $> 500$  ms • Maximum post-Baseline QTcF:  $\leq 450$  ms,  $> 450$  to  $480$  ms,  $> 480$  to  $500$  ms,  $> 500$  ms • Maximum QTcF increase from Baseline:  $\leq 30$  ms,  $> 30$  to  $60$  ms,  $> 60$  ms • PR interval  $< 120$  ms during treatment and a normal Baseline value • PR interval  $> 210$  ms during treatment and a normal Baseline value • QRS complex  $> 110$  ms during treatment and a normal Baseline value.

reported as serious, and the investigators considered them to be unrelated to treatment. One subject also reported a medical history of dizziness.

Pool B: The incidence of abnormal ECG findings was similar to those observed in Pool A; ectopic supraventricular rhythm occurred in 0.3%, 1.3% and 2.2% of subjects receiving placebo, 70 mg and 140 mg, respectively. Review of the PR interval, QRS complex and QTc did not identify any safety concerns.

Pool C and D: In Pool C, the incidence of abnormal ECG findings over time were similar to those observed in Pool A; there were no new emergent abnormalities noted in either Pool C or in Pool D.

### *Cardiovascular safety results*

An independent Cardiovascular Events Committee (CEC);<sup>48</sup> was established to adjudicate select cardiovascular, cerebrovascular and peripheral vascular AEs in the integrated studies, as well as Study 20140254. The select clinical events for adjudication were: death; acute myocardial infarction/hospitalisation for unstable angina event; non-fatal stroke/transient ischemic event; coronary revascularisation procedure; hospitalisation for hypertension; hospitalisation for peripheral artery disease event; revascularisation procedure for peripheral artery disease.

Study 20140254, which evaluated the effect of erenumab compared to placebo on exercise capacity in 88 subjects with stable angina as measured by total exercise time during an exercise treadmill test. The lower limit of the 90% CI of the difference in total exercise time did not reach the non-inferiority margin of -90 seconds (adjusted least squares mean (90% CI) of -9.4 (-43.6, 24.8)) which showed that erenumab does not decrease exercise capacity compared to placebo in subjects at risk of myocardial ischemia.

The final report will contain final safety data, including all safety data over the 12 week safety follow up period for all subjects who completed end of study visits after the primary analysis. The final safety report was not provided in the submitted dossier.

The number of subjects with pre-existing major cardiovascular disease enrolled in the integrated erenumab studies was 0.5%. At least 1 pre-existing cardiovascular risk factor, such as diabetes, high cholesterol, high lipid levels, or high BMI was reported for 71.2% of subjects and  $\geq 2$  risk factors were reported for 29.9% of subjects. The most frequently reported cardiovascular risk factor was high cholesterol;<sup>49</sup> (47.9% of subjects) and high BMI (25% of subjects) (defined as BMI > 30 kg/m<sup>2</sup>).

In Pool A, subject incidence of AEs in the 'Cardiac disorders' SOC was low and similar across treatment groups (1.2%, 0.7% and 1.4% in the placebo, 70 mg and 140 mg groups, respectively) with palpitations being most common and all AEs were Grade 1 or 2. There were no reports of any serious cardiac AE. Similar results were reported in Pool B with incidence of 1.6%, 1.3% and 1.3% in the placebo, 70 mg and 140 mg groups, respectively; palpitations and atrioventricular block first degree were the only events to occur in > 1 subject;<sup>50</sup> (all erenumab group) but none of these events were serious. In Pool A, subject incidence rates were low for AEs mapping to the 'Ischemic central nervous system vascular conditions' SMQ (0.0%, 0.0% and 0.2% for the placebo, 70 mg and 140 mg groups, respectively) and the 'Ischemic heart disease' SMQ (< 0.1%, 0.1% and 0.2%, respectively). No subject reported AEs mapping to the 'Peripheral arterial disease' AMQ. Similar results were observed in Pool B.

<sup>48</sup> The CEC was charged with providing an adjudication of all potential clinical events according to established event definitions, regardless of causality. All adjudicators are vascular experts in cardiology and/or neurology. Members of the CEC adjudicated each potential event based on pre-specified definitions. The members of the CEC were blinded to treatment assignment throughout the adjudication process and the duration of the studies.

<sup>49</sup> Defined as a total cholesterol of > 11.1mmol/L or LDL > 7.2 or HDL < 2.2mmol/L.

<sup>50</sup> Palpitations were reported for 2 subjects (0.6%) in the 70 mg group and 2 subjects (0.6%) in the 140 mg group; atrioventricular block first degree was reported for 1 subject (0.3%) each in the placebo, 70mg and 140 mg groups.

In Pool C the exposure adjusted subject incidence rates (per 100 SY) of AEs in the 'Cardiac disorders' SOC were 1.6 and 2.2 for the 70 mg and 140 mg doses (palpitations most frequently reported). There were 4 subjects who reported SAEs: myocardial ischemia (2 subjects receiving 70 mg); atrial fibrillation (1 subject receiving 70 mg), pericarditis (1 subject receiving 140 mg) and hypertensive heart disease (1 subject receiving 70 mg). In Pool D, the exposure adjusted subject incidence rates (per 100 SY) were 1.5 and 1.9 for the 70 mg and 140 mg doses, respectively with palpitations being most common at the 70mg dose ((0.7 per 100 SY). AEs at the 140 mg dose were palpitations (0.4 per 100 SY), atrioventricular block first degree (0.6 per 100 SY), cardiac flutter (0.2 per 100 SY), extrasystoles (0.2 per 100 SY) and supraventricular extrasystoles (0.2 per 100 SY). There were no new SAEs over those reported in Pool C. In Pool C, exposure adjusted subject incidence rates of AEs mapping to 1 or more cardio and cerebrovascular disorder SMQ/AMQ were similar between treatments: 1.0 and 1.3 per 100 SY for the 70 mg and 140 mg doses, respectively. Reported Preferred Terms included: cerebral venous thrombosis (2 subjects (0.3 per 100 SY) receiving 140 mg); cerebrovascular disorder (1 subject (0.1 per 100 SY) receiving 140 mg); transient ischemic attack (1 subject (0.1 per 100 SY) receiving 140 mg); myocardial ischemia (2 subjects (0.1 per 100 SY) receiving 70 mg); arteriosclerosis coronary artery (1 subject (< 0.1 per 100 SY) receiving 70 mg); blood creatine phosphokinase increased (13 subjects (0.7 per 100 SY) receiving 70 mg and 4 subjects (0.6 per 100 SY) receiving 140 mg); blood creatine phosphokinase muscle/brain increased (1 subject (< 0.1 per 100 SY) receiving 70 mg); ECG T wave inversion (1 subject (< 0.1 per 100 SY) receiving 70 mg); Raynaud's phenomenon (1 subject (< 0.1 per 100 SY) receiving 70 mg and 1 subject (0.1 per 100 SY) receiving 140 mg).

In Pool D, the exposure adjusted subject incidence rates (per 100 SY) of events mapping to 1 or more cardio and cerebrovascular disorder SMQ/AMQ were 0.8 and 0.4 for the 70 mg and 140 mg doses, respectively. A total of 18 subjects (0.7%) had events that were submitted to the CEC for adjudication. Of these, 4 subjects (0.2%) had positively adjudicated clinical events following their first dose of 70 mg and/or 140 mg (Pool C).

Overall, the number of subjects who were receiving CV medication at Baseline was low. For the placebo controlled pools, there were no imbalances between the erenumab treatment groups and placebo group in the proportion of subjects who started a new CV medication during the study, in the number of subjects who had increased their CV medication dose, or any other evidence to suggest that subjects treated with erenumab require the use of more CV medications relative to placebo.

### ***Vital signs and clinical examination findings***

#### ***Integrated safety analyses***

Vital signs (BP, heart rate, respiratory rate and oral temperature) were measured at predefined time points according to each study's schedule of assessments.<sup>51</sup> Notable changes were not observed in vital signs in the erenumab studies as of the data cut-off. In Pool A, changes from Baseline in systolic BP and diastolic BP at all time points were small and not clinically meaningful.

Study 20101268, evaluated the effect of erenumab on the change in blood pressure that was collected through 24 hour ambulatory BP monitoring in healthy subjects and

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<sup>51</sup> Absolute values and change from Baseline were summarised for systolic BP, diastolic BP and heart rate at each visit. Subject incidence was summarised for the following categories: • Change from Baseline:  $\geq 10$  mmHg in diastolic BP or  $\geq 20$  mmHg in systolic BP and analysed for: – systolic BP ( $\leq 140$  mmHg,  $> 140$  mmHg) and – diastolic BP ( $\leq 90$  mmHg,  $> 90$  mmHg) • Systolic BP:  $< 90$  mmHg,  $> 140$  mmHg,  $> 160$  mmHg • Diastolic BP:  $< 50$  mmHg,  $> 90$  mmHg,  $> 100$  mmHg • Change from Baseline in heart rate of  $\geq 15$  beats per minute (bpm) (that is, an increase of at least 15 bpm) or  $\geq 120$  bpm post-Baseline • Change from Baseline in heart rate  $\leq -15$  bpm (that is, a decrease of at least 15 bpm) or  $\leq 50$  bpm post-Baseline.

migraine patients. There was no statistically significant difference in LSM 24 hour blood pressure and nocturnal blood pressure between healthy or migraine subjects in the erenumab groups and the placebo group. Study 20140255, which assessed the effects of SC sumatriptan (Imitrex) alone and the effects of a single IV dose of erenumab and SC sumatriptan concomitant therapy on resting blood pressure in healthy subjects. No clinically meaningful differences in time weighted averages of mean arterial pressure, systolic and diastolic BP were observed between subjects who received sumatriptan alone and those who received concomitant sumatriptan and erenumab.

### ***Immunogenicity and immunological events***

#### ***Immunogenicity***

The incidence of ADA was low being detected in 2.6% of patients treated with erenumab 140 mg during the double blind treatment phase of the two pivotal placebo controlled migraine Studies (20120295 and 20120296). Neutralising antibodies were not detected in any patient receiving 140 mg SC once monthly (every 4 weeks) in these studies. The potential clinical impact of anti erenumab antibodies on PK, clinical efficacy, and clinical safety of erenumab was evaluated using data pooled from 4 placebo controlled migraine Studies (20120178, 20120295, 20120296 and 20120297) and the open label extension Study 20130255, and included patients treated with doses of erenumab other than 140 mg and long term data up to 6 months pooled from Studies 20120296 and 20120178 as well as data through Week 64 of the open label phase of Study 20120178. The main findings are summarised below:

- Mean trough levels of erenumab (Week 12) among patients developing anti erenumab antibodies were 40% (for 140 mg dose group) and 35% (for 70 mg dose group) lower than antibody negative patients. Despite moderately lower exposure, the concentration values in patients who developed anti erenumab antibodies were within the range of patients in whom no anti erenumab antibodies were detected, indicating that the development of anti erenumab antibodies had minimal impact on erenumab concentrations. Additionally, post hoc analysis showed that the presence of anti erenumab antibodies had minimal impact on the variance of the population PK model of erenumab.
- The mean change from Baseline in MMD, the primary efficacy endpoint, was similar for anti erenumab antibody positive patients compared with those who remained antibody negative. While the number of patients with anti erenumab neutralising antibodies is limited, their reduction in MMD is within the range of those for the ADA negative patients. Overall, the limited data suggest that efficacy of erenumab may not be impacted by the presence of ADA despite a modest reduction in exposure among ADA positive patients.
- There was no impact of anti-erenumab antibody development on safety ('Injection site reactions' AMQ, 'Hypersensitivity' SMQ, or 'Immune related disorder' SOC (also see below)).

#### ***Immune system disorders***

In Pool A, subject incidence of AEs in the 'Immune system disorders' SOC was low and similar across treatment groups: 0.7%, 1.0% and 0.4% in the placebo, 70 mg and 140 mg groups, respectively with seasonal allergy reported most frequently in all treatment groups (0.3%, 0.4% and 0.2%, respectively). One case of a non-serious event of anaphylactic reaction (allergy to penicillin) was reported in a subject receiving 140 mg and the AE was not considered treatment related. There were no events of immune complexes disorders (Type III hypersensitivity). The only event reported as serious was hypersensitivity, which was reported in 2 subjects in the placebo group. Similar results

were observed in Pool B with subject incidence of AEs in the 'Immune system disorders' SOC of 3.1%, 3.5% and 2.8% in the in the placebo, 70 mg and 140 mg groups, respectively.

In Pool C, the exposure adjusted subject incidence rate (per 100 SY) of adverse Immune system disorders was 1.9 and 1.6 for the 70 mg and 140 mg doses, respectively. Seasonal allergy was the most frequently reported AE at both doses (0.8 and 1.2 per 100 SY for the 70 mg and 140 mg doses, respectively). There were 3 events of anaphylactic reactions reported (discussed below). There were no events of immune complexes disorders (Type III hypersensitivity). In Pool D, the exposure adjusted subject incidence rate (per 100 SY) of Immune system disorders was 1.9 and 1.7 for the 70 mg and 140 mg doses, respectively. Seasonal allergy was the most frequently reported AE at both doses (0.8 and 1.3 per 100 SY, respectively). There were no events of immune complexes disorders (Type III hypersensitivity). There were no events reported as serious.

#### *Hypersensitivity/anaphylactic reactions*

For events of hypersensitivity, a search strategy using SMQs ('Hypersensitivity' and 'Anaphylactic reactions') and AMQs ('Rash' and 'Urticaria') were used to identify relevant AEs. The skin and subcutaneous tissue disorders SOC was also reviewed. In Pool A, subject incidence rates for AEs mapping to the 'Hypersensitivity' SMQ were 1.9%, 2.0% and 2.2% in subjects receiving placebo, 70 mg and 140 mg, respectively with rash, rash maculopapular and eczema reported most frequently (> 2 subjects All erenumab). Similar results were observed in Pool B with AE incidence of 3.1%, 3.5% and 2.8% in subjects receiving placebo, 70 mg and 140 mg, respectively.

In Pool C, exposure adjusted subject incidence rates (per 100 SY) for AEs mapping to the 'Hypersensitivity' SMQ were 5.7 and 5.1 for the 70 mg and 140 mg doses, respectively; rash was the most frequently reported Preferred Term mapping to the 'Hypersensitivity' SMQ (0.7 and 0.9 per 100 SY for the 70 mg and 140 mg doses, respectively) and none of the events were reported as serious. At the 70 mg dose, there was 1 SAE of urticaria.<sup>52</sup> In Pool D, exposure adjusted subject incidence rates (per 100 SY) were 4.6 and 5.4 for the 70 mg and 140 mg doses, respectively; eczema was reported most frequently (0.9 and 1.0 per 100 SY at the 70 mg and 140 mg doses, respectively) and none of the events were reported as serious.

Overall, there was no notable imbalance in the rates of AEs mapping to 'Hypersensitivity' SMQ with an onset within 1 day of erenumab treatment or onset any time after treatment with erenumab. There were no serious hypersensitivity reactions associated with erenumab.

Anaphylactic reactions were reported in 11 subjects: 3 subjects reported an anaphylactic reaction AE all with an alternative aetiology (allergy to penicillin (140 mg dose group); due to insect stinging (70 mg dose group); due to unknown food allergy (70 mg dose group). Review of the remaining subjects did not identify a probable anaphylactic reaction.

#### *Serious skin reactions*

##### *Integrated safety analyses*

In Pool A, subject incidence rates through Week 12 of AEs in the 'Skin and subcutaneous tissue disorder' SOC were slightly higher in the 140 mg group (3.6%, 3.1% and 4.7% in the placebo, 70 mg and 140 mg groups, respectively) with pruritus reported most frequently (0.5%, 0.7% and 1.8%, respectively). None of these events was considered serious or led to discontinuation of study treatment and for majority of subjects this event was not accompanied by rash. One subject in the 140 mg dose group had rash maculopapular that led to discontinuation of investigational product. Similar results were observed for in

<sup>52</sup> A 64 year old female, developed urticaria, eyelid edema, and pruritus on Day 184. The event was considered not related to treatment, but related to lansoprazole and sun exposure.



Pool B with incidence rates through Week 24 of 6.9%, 5.1% and 5.0% in the % in the placebo, 70 mg and 140 mg groups, respectively; pruritus was reported most frequently (1.6%, 1.6% and 2.2%, respectively); rash maculopapular led to discontinuation of study treatment in 2 subjects (1 each in placebo and 140 mg group). In Pool C, the exposure adjusted subject incidence rate (per 100 SY) of AEs in the skin and subcutaneous disorders SOC was 8.5 and 8.1 for the 70 mg and 140 mg doses, respectively with pruritus most common (1.3 and 1.5 per 100 SY, respectively). Similar results were observed in Pool D (7.5 and 6.7 per 100 SY for the 70 mg and 140 mg doses, respectively).

There were no notable imbalances for majority of AEs in the 'Skin and subcutaneous tissue disorder' SOC, with the exception of pruritus (generalised), which showed a trend towards increased incidence in the erenumab group and a causal association between pruritus and erenumab cannot be ruled out.

### ***Other safety parameters***

#### ***Use in pregnancy/lactation***

Pregnant and/or lactating women were excluded from participation in clinical studies and thus there is limited human data in this patient population. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were administered erenumab SC from organogenesis through parturition at exposures up to 16 fold the exposure at the maximum recommended human dose of 140 mg once monthly. Measurable erenumab serum concentrations were observed in the infant monkeys at birth, confirming that erenumab, like other immunoglobulin antibodies, crosses the placental barrier. There are no data on the effects of erenumab on the breastfed child or the effects of erenumab on milk production. Furthermore, increased risk of adverse fetal outcomes have also been observed in patients exposed to select migraine medications, including NSAIDs and anti-epileptics.

As of 31 January 2017 across the clinical development program including Phase I, II and III studies, a total of 29 pregnancies were reported, including 24 maternal exposures and 5 paternal exposures. Of these, 5 maternal exposures occurred while the subjects were receiving placebo. The birth outcomes of the placebo exposed subjects included 2 full term births without complications and 3 lost to follow up. A summary of outcomes of the 19 maternal exposures and 5 paternal exposures while on erenumab was provided. For pregnancy outcomes noted as unknown, either safety follow up is pending or the pregnancy is ongoing. With regard to the single case of full term birth with complications, it should be noted that the baby had no reported birth complications or congenital anomalies but was admitted to the neonatal intensive care unit for 4 days (reason for admission not known). Two spontaneous abortions were reported: one in a subject for whom pregnancy was not viable due to prior uterine ablation and another in a healthy subject who received a single dose of 140 mg and experienced a miscarriage approximately 3 months after her dose. Overall, the numbers of pregnancies and outcomes reported are too limited to enable definitive conclusions regarding effects of erenumab on pregnancies. Hence, the proposed PI includes precaution stating that erenumab should be used in pregnancy/lactation only if benefits outweigh the potential risks to the fetus/child.

#### ***Overdose, drug abuse***

There were no cases of overdose reported in clinical studies. The highest dose of erenumab administered in clinical trials was a mixed dosing regimen of a single SC dose of 280 mg followed by 2 monthly SC doses at 210 mg to healthy volunteers during the multiple dose portion of the Phase I. No SAEs or dose limiting toxicities were observed at this dose.

Erenumab is not expected to have any potential for abuse or dependence based on the mechanism of action and the lack of meaningful exposure within the central nervous

system.<sup>53,54</sup> No dependence nonclinical studies were performed. Like other antibodies, a small fraction of erenumab may cross the blood-brain barrier, although central concentrations (0.2% or less of blood concentrations) and activity is expected to be low. In addition, a comprehensive review of the literature (including primary and secondary pharmacology) shows that CGRP and its receptors have no positive psychoactive effects identified as leading to abuse potential, including sedation, euphoria, perceptual and other cognitive distortions, hallucinations and mood changes. In the erenumab clinical studies, there was no evidence of increased risk of abuse potential based on nature and frequency of AEs reported (no evidence of an imbalance in the HLT emotional and mood disturbances not elsewhere classified (NEC) and no other HLTs that would suggest abuse potential).

#### *Withdrawal and rebound*

Withdrawal and rebound effects were not formally examined in erenumab clinical studies. Although Phase II/III studies included 8 or 12 week follow up periods, data from these periods are limited for the assessment of withdrawal and rebound because of the small number subjects who have entered these periods to date (the majority of subjects enrolled in Study 20120295 and thus did not participate in the parent study safety follow up visit). Additionally, during the safety follow up periods subjects were not required to report information regarding their migraine and non-migraine headaches via the eDiary used during the double blind and open label/active treatment phases, thereby limiting the information available. Of the 2499 subjects who received erenumab, 83 subjects (3.3%) reported a total of 103 migraine AEs (includes migraine, migraine with aura, migraine without aura and vestibular migraine Preferred Terms) after starting erenumab treatment: 97 (94.2%) events occurred while on treatment and 6 (5.8%) events occurred in the safety follow up period following the treatment. Of 582 out of 2499 subjects who completed the study, 24 (1.0%) reported a total of 27 (26.2%) migraine events with 4 (3.9%) events occurring in the safety follow-up period. Overall, of the majority of migraine events were Grade 1 and 2 in severity and a total of 17 events were Grade 3 migraine AEs. Of the 6 migraine events occurring in the safety follow up period, 5 were Grade 2 in severity and 1 event was a Grade 3.

Although, there is no evidence of withdrawal/ rebound effects based on review of migraine AEs, there is inadequate data for a comprehensive assessment of withdrawal and rebound effects and this issue should be included in the missing information for safety concerns in the RMP.

*Effects on ability to drive or operate machinery or impairment of mental ability:* erenumab is not expected to have any potential effects on the ability to drive or operate machinery or impairment of mental ability. No relevant adverse CNS, coordination or eye effects were observed in nonclinical studies. In determining the potential risk of erenumab on driving, operating machinery or impairment of mental ability the following were evaluated: HLTs and Preferred Terms related to coordination-related events and vertigo, mental impairment events, visual impairment events and accident-related events. Overall there were no differences observed across treatment groups

#### **Post-marketing data**

Not applicable as erenumab has not received marketing approval in any country to date.

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<sup>53</sup> Boado, R. J. et al. (2010). Pharmacokinetics and Brain Uptake of a Genetically Engineered Bi-functional Fusion Antibody Targeting the Mouse Transferrin Receptor. *Mol Pharm*, 2010; 7: 237-244.

<sup>54</sup> Pardridge, W. M. (2007). Drug Targeting to the Brain, *Pharmaceutical Research*, 2007; 24: 1733-1744.

### Evaluator's conclusions on safety

Safety of erenumab has been evaluated based on data from a total of 2537 patients with migraine exposed to at least 1 dose of erenumab, representing 2310.3 SY of exposure. Among migraine patients with continuous exposure to erenumab, 1598 and 768 patients have received 70 mg and 140 mg, respectively, for  $\geq 6$  months, and 682 and 134 patients have received 70 mg and 140 mg, respectively for  $\geq 12$  months. This exposure meets or exceeds the ICH E1 safety exposure requirements;<sup>55</sup> of  $> 1500$  patients exposed, 300 to 600 for 6 months and  $> 100$  for 1 year.

The incidence of AEs was comparable across all treatment groups in Pool A (47.4% for all erenumab group, 49.0% for placebo). The majority of AEs in all treatment groups were mild or moderate in severity (Grade 1 or Grade 2). The rates of specific AEs were low; with the exception of nasopharyngitis (6.0% for All erenumab group, 7.3% for placebo), all AEs occurred at a frequency of  $< 5\%$ . The incidence of SAEs and AEs leading to discontinuation in Pool A for erenumab was low ( $\leq 2\%$ ) and similar between the 140 mg and 70 mg dose groups and also comparable to placebo. Two deaths were reported; both occurred in the open label treatment phase and had confounding features, and both were considered by the investigator as unrelated to study treatment.

Adverse drug reactions (ADRs) were identified as injection site reactions, constipation, pruritus and muscle spasm. There were no additional safety concerns with self-administration using prefilled syringes or auto-injector/pens.

The safety profile was comparable for erenumab 140 mg and 70 mg, with no dose dependent effects across AEs, SAEs and AEs leading to discontinuation. The only AEs showing numerically higher rates for 140 mg are injection site erythema, constipation, muscle spasm and generalised pruritus, although the overall incidences in Pool A were low ( $< 4\%$ ), the events were mild or moderate in severity (except for a single case of Grade 3 muscle spasm), none was serious and none led to discontinuation (except for a single case of constipation).

The overall AE exposure adjusted incidence rates with longer exposure in Pools C and D were similar to or lower than those in the placebo controlled Pools A and B and no additional signals of concern were identified with long-term treatment. Ongoing open label extension phases of the pivotal and supportive studies will provide further long term data (up to 5 years in Study 20120178), especially for the proposed 140 mg dose.

No patterns of clinically relevant abnormalities were observed for clinical laboratory results, vital signs or ECGs. Review of both individual and aggregate AEs did not find any evidence of an association between erenumab treatment and cardiovascular, cerebrovascular or peripheral vascular events. While a limited number of cardiovascular AEs were reported, these cases occurred in the open label phases and interpretation of significance of these findings was confounded with plausible alternative aetiology in most cases.

Overall, there is no evidence that CGRP inhibition increases risk of gastrointestinal inflammation and/or ulcer. With the exception of constipation, all other Preferred Terms were generally balanced across the treatment groups. Evaluation of AEs related to neoplasms benign, malignant and nonspecific SOC did not suggest increased risk of malignancy beyond what is expected in this patient population. There is no evidence of hepatotoxicity or increased risk of musculoskeletal and connective tissue disorders. With the exception of muscle spasms all other AEs were balanced across the treatment groups.

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<sup>55</sup> European Medicines Agency (EMA) Committee for Proprietary Medicinal Products (CPMP), ICH E1 Guidelines on population exposure: the extent of population exposure to assess clinical safety, 1 June 1995, CPMP/ICH/375/95.

There was no evidence of increased risk of depression or suicidality in subjects receiving erenumab.

Although, there is no evidence of withdrawal/rebound effects based on review of migraine AEs, there is inadequate data for a comprehensive assessment of withdrawal and rebound effects.

The safety profile of erenumab was consistent across subgroups of age, race, sex, region, CM versus EM, baseline cardiovascular risk factors, and treatment failures versus non-failures. The incidence of anti-erenumab antibody development is low ( $\leq 3\%$ ). Despite a modest reduction in exposure among anti erenumab antibody positive patients, there was no clinically meaningful impact on drug efficacy and safety.

Overall, the safety profile of erenumab (erenumab) for migraine prophylaxis is favourable.

## First round benefit-risk assessment

### First round assessment of benefits

Table 6 shows the first round assessment of benefits.

**Table 6: First round assessment of benefits**

Benefits	Strengths and Uncertainties
Statistically significant reduction in MMD in both pivotal studies (at 12 weeks in CM Study 20120295 and at Week 24 in EM Study 20120296).	The placebo-subtracted LSM difference (-2.5 days) was similar for the 70 mg and 140 mg dose in the pivotal CM study; it was -1.4 and -1.9 days with 70 mg and 140 mg, respectively in the pivotal EM study. However, the pivotal studies were not powered to evaluate differences between the 70 mg and 140 mg doses and there were no formal dose comparisons.
Clinically and statistically significant greater proportion of subjects with > 50% reduction in MMD. The 50% responder rates were 23.5%, 39.9% and 41.2% in placebo, erenumab 70 mg and 140mg groups, respectively in the pivotal CM study; corresponding responder rates in the pivotal EM study were 26.6%, 43.3% and 50%, respectively.	The 50% responder rate is a highly clinically relevant endpoint for both patients and clinicians. Furthermore, 75% responder rates in CM study were 7.8%, 17.0% and 20.9% placebo, erenumab 70 mg and 140 mg groups, respectively; in EM study: 7.9%, 20.8% and 22.0%, respectively. Few patients also showed complete absence of migraine (100% reduction in MMD): 2.4%, 4.3% and 2.7%, respectively in CM study; 2.8%, 3.2% and 5.0%, respectively in EM study.
Statistically significant greater reduction in acute migraine specific medication days in both studies: the placebo-subtracted difference in LSM values were: CM study: -1.86 and -2.55 days with 70 mg and 140 mg, respectively. EM study: -0.94 and -1.42 days, respectively.	Interpretation of this endpoint in the EM study was confounded by fact that this endpoint was analysed for the total study population although a considerable proportion of subjects did not use migraine-specific medications during Baseline period.
Compared with placebo, erenumab showed larger improvements from Baseline in PROs utilised in the pivotal studies, including the HIT-6 (overall impact of headache), the MSQ (migraine-specific QOL) and the MIDAS	The new PRO assessment tool MPFID showed significant improvement in the physical impairment and everyday activities domain scores in the EM study (as a secondary endpoint), although interpretation was limited due to low scores (less

Benefits	Strengths and Uncertainties
(migraine related disability); the 140 mg dose showed additional benefit (numerical) over the 70 mg dose.	disability) at Baseline.
Rapid onset of effect with no need for dose titration.	Benefits observed within first week of treatment and effects were sustained over time.
High retention in both pivotal studies.	Low discontinuations rate (< 2%) and discontinuations rates did not worsen with time.
Requires only once monthly dosing (can be self-administered); No dose titration required.	With exception of onabotulinumtoxin A, other approved migraine prophylaxis treatments require daily dosing. Onabotulinumtoxin A is dosed every 3 months but requires > 30 injections every time (cannot be self-administered).
The safety profile was comparable for erenumab 140 mg and 70 mg, with no dose dependent effects across AEs, SAEs and AEs leading to discontinuation.	The only AEs showing numerically higher rates for 140 mg are injection site erythema, constipation, muscle spasm and generalised pruritus, although the overall incidences in Pool A were low (< 4%), the events were mild or moderate in severity (except for a single case of Grade 3 muscle spasm), none was serious and none led to discontinuation (except for a single case of constipation).
There was no evidence that CGRP inhibition increases risk of gastrointestinal inflammation and/or ulcer, neoplasms (benign, malignant and nonspecific SOC) or of musculoskeletal and connective tissue disorders.  No risk of drug interactions.	With the exception of constipation, all other Preferred Terms were generally balanced across the treatment groups.  With the exception of muscle spasms all other AEs were balanced across the treatment groups.
Erenumab is effective in patients who have failed prior prophylactic therapy.	Help address the unmet need in patients who have already failed prior migraine prophylaxis treatments.
Erenumab targets specific pathophysiologic pathways of migraine.	

## First round assessment of risks

Table 7 shows the first round assessment of risks.

**Table 7: First round assessment of risks**

Risks	Strengths and Uncertainties
Common ADRs associated with erenumab treatment were injection site reactions, constipation, pruritus and muscle spasm.	Majority of events were mild or moderate. There were no additional safety concerns with self-administration using prefilled syringes or auto-injector/pens.
Potential of increased risk of CV, cerebrovascular or peripheral vascular effects.	Review of both individual and aggregate AEs did not find any evidence of an association between erenumab treatment and CV, cerebrovascular or peripheral vascular events. Study in stable angina patients showed that erenumab did not affect exercise time, but detailed safety results not yet available for review.
Proposed dose of 140 mg requires 2 injections.	Although single injection of 140 mg was shown to be bioequivalent to 2 injections of 70 mg/mL, the 140 mg formulation was not pursued further.
Lack of adequate long term data on efficacy and safety in patients with CM.	The open label extension of the CM Study 20120295 should provide this information.
Risk of development of antibodies to erenumab which could potentially reduce efficacy.	The incidence of anti-erenumab antibody development is low (< 3%). Despite a modest reduction in exposure among anti-erenumab antibody-positive patients, there was no clinically meaningful impact on drug efficacy and safety although interpretation is limited by small number of subjects with positive antibodies.
The highest prevalence of migraine is reported for women aged 30-39 years, <sup>10</sup> but the median age of patients was higher in both pivotal studies (median of 42 to 43years.)	In the CM study, there were more patients > median age of 43 years compared to those < 43 years. Information on number of patients < and > median age not provided in the EM study and subgroup analysis in this study did not evaluated effect of age on efficacy of erenumab.
Lack of adequate data on withdrawal/rebound effects following discontinuation of erenumab.	

## First round assessment of benefit-risk balance

As no active comparators were included in the pivotal studies, the sponsors have provided a qualitative and quantitative benefit-risk assessment of erenumab versus the SoC therapies. The overall benefit risk assessment has been discussed below under the 2 headings:

- Comparison of erenumab with standards of care.
- Overall assessment of benefit-risk profile.

### ***Comparison of erenumab with standards of care***

For this comparative assessment, evidence for the efficacy and safety/tolerability of erenumab 140 mg is based on data from CM Study 20120295 and EM Study 20120296. SoC therapies selected for this comparison are topiramate, propranolol and onabotulinum toxin A, all of which are approved for migraine prophylaxis in Australia. The evidence considered for these studies included placebo controlled, parallel group trials in monotherapy of high quality clinical trial design (modified Jadad score  $\geq 6$ );<sup>56</sup> that evaluated efficacy and safety endpoints of interest. Clinical trial data for each SoC therapy selected based on these criteria included the following:

- Topiramate: a pooled analysis of 3 comparable placebo controlled clinical trials in EM at the recommended 100 mg dose; and 2 placebo controlled clinical trials in CM: a larger trial and a smaller trial.
- Propranolol: one placebo controlled study in EM with propranolol 160 mg.
- Onabotulinum toxin A: pooled analysis of 2 comparable placebo controlled trials in CM.

Key characteristics of the studies used for the comparative assessment of erenumab to SoC therapies in CM and EM were summarised in the clinical evaluation.

It is noted that all treatments selected for comparison with erenumab are currently approved in Australia for migraine prophylaxis.

#### *Qualitative comparison*

A qualitative approach for the systematic review and comparison of treatment outcomes in chronic pain trials was established by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT), which recommended a systematic framework for interpreting the clinical meaningfulness of group differences in clinical trial data.

Characteristics of erenumab and SoC therapies with respect to clinical trial outcomes relative to placebo and distinct aspects of each compound per IMMPACT criteria are presented. As onabotulinum toxin A did not demonstrate efficacy in EM and propranolol 160 mg was not formally studied in CM, so no comparisons to these compounds in the respective migraine condition were possible. Erenumab shows numerically greater benefits in the magnitude of improvement in the primary endpoint (mean change in MMD versus placebo) and in the responder analysis (difference in 50% responder rate versus placebo), as well as more favourable tolerability (discontinuation due to AE) and patient adherence (treatment completion rate) compared with SoC therapies in both CM and EM. The reduction in migraine days with erenumab was associated with fast onset of action and improvements in quality of life and functional outcomes (HIT-6, MIDAS and MSQ), whereas data are lacking for some SoC therapies in one or several of these patient reported outcomes. The numerically greater benefits and fast onset of action for erenumab coupled with its anticipated ease of use increase the likelihood that patients will adhere to treatment, which collectively will enhance the durability of treatment effect over the long term.

Indirect comparison of data from across individual clinical trials has its inherent limitations given the differences in study design, duration of treatment or observation, patient population studied and statistical methodologies. However, the overall evidence in accordance with IMMPACT criteria support a more favourable benefit-risk ratio for erenumab compared with topiramate and onabotulinumtoxin A in CM and with topiramate and propranolol in EM.

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<sup>56</sup> Jackson, J.L. et al. (2015). A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache, *PLoS One*, 2015; 10: e0130733.

### *Quantitative comparison*

The likelihood of being helped or harmed (LHH), a ratio of number needed to harm (NNH) to number needed to treat (NNT), is a useful metric to express the relative efficacy and safety of a therapy in a quantitative manner that allows for comparison across therapies.<sup>57,58,59</sup> A LHH value > 1 indicates a higher likelihood to help rather than harm, which in turn reflects a favourable benefit-risk ratio for the therapy over the comparator treatment. Values > 10 in general are considered as very favourable.

The results show more favourable LHH ratios for erenumab (41.7) relative to topiramate (1.6 and 3.3) and onabotulinum toxin A (4.3) in CM, and for erenumab (166.7) relative to topiramate (1.6) and propranolol (2.2) in EM, indicating a higher likelihood to experience favourable outcomes with erenumab treatment across the entire migraine spectrum. The higher LHH values for erenumab were predominantly driven by substantially higher NNH values for erenumab (250) versus topiramate (21 and 13) and onabotulinum toxin A (39) in CM, and for erenumab (1000) versus topiramate (8) and propranolol (11) in EM. Hence, using the NNH values for CM as an example, 250 CM patients can be treated with erenumab before one additional discontinuation due to an AE relative to placebo occurs, whereas this threshold is reached with 21 or 13 patients for topiramate and 39 patients for onabotulinum toxin A. The NNT values were numerically lower indicating higher benefit, for erenumab compared with topiramate and onabotulinum toxin A in CM (6 versus 13 and 9, respectively). Similar findings of more favourable LHH ratios driven by larger NNH values were also observed for EM.

The LHH method has certain inherent limitations due to requirement for dichotomous outcomes, the need for consistent definitions of responder rates across studies, and potential differences in baseline characteristics across trials. However, selection of the 50% responder rate and discontinuations due to AEs for NNT and NNH calculations is appropriate and clinically relevant for migraine prophylaxis due to increased drop-out rates usually associated with current prophylactic therapies. Furthermore, sensitivity analyses performed to evaluate the potential effects of different outcomes on NNT (for example, 75% and 100% responder rates) and on NNH (for example, total AE rate, SAE rate and frequency of pre-defined typical compound specific AEs) showed that despite residual variations, the overall magnitude of LHH consistently favoured erenumab relative to other therapies. Hence, the LHH results for erenumab were robust across different definitions underlying the NNH and NNT calculations.

### ***Overall assessment of benefit-risk profile***

It is estimated that there are up to 3 million migraine sufferers in Australia. The currently approved preventive treatments which are approved in Australia, such as beta-blockers (propranolol, metoprolol), topiramate (Epiramax, Tamate), methysergide (Deseril) and botulinum toxin (Botox) were not designed specifically for migraine and are frequently associated with variable efficacy and poor safety and tolerability, leading to low persistence and adherence rates.<sup>60,61</sup> In Australia, only 8.3% of migraine sufferers are

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<sup>57</sup> Straus, S. E. et al. (2002). Individualizing treatment decisions; the likelihood of being helped or harmed. *Eval Health Prof*, 2002; 25: 210-224.

<sup>58</sup> Citrome, L. and Ketter, T.A. (2013). When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract*, 2013; 67: 407-411.

<sup>59</sup> Citrome, L. et al. (2013). Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Journal of Affective Disorders*, 2014; 155: 20-27.

<sup>60</sup> Hepp, Z. et al. (2015). Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia*, 2015; 35: 478-488.

<sup>61</sup> Hepp, Z. et al. (2015). Systematic Review of Migraine Prophylaxis Adherence and Persistence, *J Manag Care Pharm*, 2014; 20: 22-33.



currently taking prophylactic medication, increasing reliance on acute medications and raising risks of medicine overuse for headache.

Aimovig is a fully human antibody, specifically targeting the CGRP receptor and is proposed for prevention of episodic and chronic migraine. Aimovig inhibits the binding of CGRP to the human CGRP receptor, effectively blocks the CGRP signalling pathway leading to its therapeutic effects in migraine. Patients who received Aimovig experienced statistically significant reductions in monthly migraine days, improvements in the 50% responder rates, reductions in days per month using acute migraine-specific medications and reduction in migraine impact on QoL (assessed by HIT-6, MSQ, MIDAS and the EA and PI domain scores of the MPFID). These effects were robust and consistent across both the pivotal EM and CM studies as well in subgroups of patient populations. Aimovig was especially effective in patients with a high unmet need, that is, those who had failed prior prophylactic treatments. Other characteristics of erenumab, such as the absence of a need for titration and less frequent dosing (SC injection once every 4 weeks) allow for greater convenience and the absence of DDIs support its utility in the prophylaxis of migraine.

The evidence to support long term maintenance of efficacy especially in patients with CM is limited. Evidence for efficacy of erenumab up to 6 months was provided by pivotal Study 20120296 in EM patients. It is accepted that this deficiency should be addressed by the longer term efficacy data from the open label extension study of the pivotal CM Study 20120295 (extension Study 20130255) and the active treatment phase of the pivotal EM Study 20120296 and this should be provided for evaluation when available.

Safety of erenumab in migraine prophylaxis was assessed from integrated safety analyses of 2537 migraine patients exposed to at least one dose of erenumab, with a cumulative exposure of 2310.3 SY. No major safety concerns or important or potential risks were identified. The incidences of SAEs and AEs leading to discontinuation were low (< 3%) and comparable across the treatment groups. A limited number of ADRs were identified, all occurring at low frequencies (< 5%) that were mostly mild or moderate in severity and did not lead to discontinuation. There were no clinically meaningful differences in the AE profile between CM and EM populations. There were no new or unexpected trends with long-term exposure ( $\geq 1$  year). Although, the safety and tolerability profile of erenumab was similar between the 140 mg and 70 mg doses and also comparable to placebo, the following AEs did show a significantly higher incidence in the 140 mg dose group compared to both 70 mg and placebo: injection site erythema, constipation, pruritus and muscle spasm. However, it is felt that the use of the lower 70 mg dose as a starting dose could have been explored further (especially in subgroups other than those who have failed prior prophylactic therapies) considering dose related higher incidence of common AEs such as injection site erythema, pruritus, constipation and muscle spasm which could potentially affect long term compliance as well as risk of development of antibodies.

Supportive Studies 20120297 and 20120278 used only the 70 mg dose of erenumab and also evaluated efficacy only in EM patients. Although, these studies did show benefits in primary, secondary and exploratory endpoints with the lower 70 mg dose compared with placebo, they did not provide any evidence to support proposed dosing regimen of 140 mg once monthly.

Furthermore, clarification regarding use of the proposed 2 injections of 70 mg/mL rather than a single injection of 140 mg/mL or 2 mL injection of 70 mg/mL has been sought from the sponsors, especially since bioequivalence was established between the 3 formulations.

A qualitative and quantitative assessment for erenumab versus standard of care therapies showed a favourable benefit-risk ratio for erenumab compared with topiramate (100 mg) and onabotulinum toxin A in CM and with topiramate and propranolol (160 mg) in EM. The favourable LHH ratios for erenumab compared to other SoC therapies were mainly

driven by significantly higher NNH but the NNT values were also numerically lower for erenumab.

Hence, erenumab provides an effective, safe and well tolerated therapeutic option that targets specific pathophysiologic pathways of migraine and would especially help address the unmet need in patients who have already failed prior migraine prophylaxis treatments.

Overall, the benefit risk balance of erenumab 140 mg (administered SC every 4 weeks) is favourable for proposed usage (prophylaxis of migraine in adults).

## First round recommendation regarding authorisation

It is recommended that the submission for marketing authorisation of erenumab be approved for:

*prophylaxis of migraine in adults.*

However, the approval is subject to the following conditions:

- Satisfactory response to clinical questions.
- Incorporation of the recommended changes to the proposed PI, CMI and RMP.
- Submission of long term efficacy and safety data when available: open label extension study of the pivotal CM Study 20120295 (extension Study 20130255) and the active treatment phase of the pivotal EM Study 20120296.
- Submission of final study report of Phase II Study 20140254 in subjects with stable angina.

## Clinical questions and second round evaluation

The initial questions from the first round report are repeated below followed by summary of the sponsor's response and then the evaluator's comments on the sponsor's response.

### Pharmacokinetic and pharmacodynamics (PK-PD)

#### Question 1

***Results of Study 20150149 suggested that a 140 mg dose of erenumab administered as a single 2.0 mL (70 mg/mL) injection or a single 1.0 mL (140 mg/mL) injection would not increase injection site pain or lead to PK differences when compared with the proposed two 1.0 mL (70 mg/mL) injections. Despite demonstration of bioequivalence between the 3 erenumab treatment groups, it is not clear why the single injection (with either the 140 mg/mL prefilled syringe or a single 2 mL (70 mg/mL) injection) was not evaluated further. The proposed dosing regimen requires 2 injections while the other options would only require one injection. Could the sponsors provide clarification on why the proposed dose regimen which requires 2 injections was chosen over the other treatments which require a single injection?***

*Sponsor's response*

[Information redacted]

The sponsor provided details about the development process of the dosing schedules and comparison of tolerability and pharmacokinetics of a single 1mL 140 mg/mL dose, single 2 mL 70 mg/mL dose and two 1mL 70 mg/mL doses.

*Evaluation of response*

The sponsor's response is acceptable.

**Question 2**

***The following was mentioned in the PK/PD report: 'The probability model estimates were used to summarise MMD and responder rate for CM population at Week 12 ( $C_{min}$ ) (based on a 50-50 mix of 70 mg or 140 mg regimens. Consistent with the underlying probability model, increasing trough concentrations results in greater reduction in monthly migraine days.' There appears to be an error as the figure describes MMD and responder rate in the EM and not the CM population. Could the sponsors clarify above statement?***

*Sponsor's response*

[Information redacted]

The sponsor clarified that there was a typographical error and the figure shows the responder rate in EM.

*Evaluation of response*

The sponsor's response is satisfactory.

**Efficacy****Question 3**

***The highest prevalence of migraine is in women aged 30 to 39 years, but the median age of patients in both the pivotal studies was slightly higher than that (43 years in CM Study 20120295 and 42 years in EM Study 20120296). In the CM study, the number of patients > median age (n = 334) was greater than < median age (n = 312). In EM Study 20120296, the number of patients > and < median age of 42 years was not provided. The clinical study report only mentions age groups in terms of 18 to 64 years (99.6%) and 65 to 74 years (0.4%).***

***The sponsor has been asked to provide the numbers of patients < and > median age in the pivotal EM study. Furthermore, effect of age was not evaluated in the subgroup analysis in the EM study. Could the sponsor provide clarification on above issues in order to confirm that the age of patients involved in the pivotal studies was truly representative of the target patient population?***

*Sponsor's response*

[Information redacted]

The sponsor provided details of subgroup analyses by age across Studies 20120295 and 20120296, and stated that the enrolled population is considered to be representative for the target population.

*Evaluation of response*

The sponsor's response is satisfactory.

**Question 4**

***In the pivotal Study 20120295 in patients with CM, increased efficacy (only numerically better as statistical significance was not evaluated) with the proposed higher dose of 140 mg compared to the 70 mg dose (which is not proposed for marketing) was only evident in patients who had failed prior prophylactic treatment and had used prior topiramate.***

***The option of the proposed 140 mg dose (which requires 2 injections) could be reserved for patients who have failed prior prophylactic therapy, while the option of a lower 70 mg dose could be made available for most other subgroups of patients. Could the sponsors provide justification for why the 70 mg dose was not proposed for marketing?***

*Sponsor's response*

[Information redacted]

The sponsor provided rationale for 140 mg as the dose with the optimal benefit-risk across the spectrum of migraine, including through discussing:

1. Key findings from the pivotal studies.
2. Results from recently completed longer term studies that complement the available evidence, as well as additional exposure response modelling.
3. A summary of additional long-term safety data.
4. Additional exposure-response modelling in pooled EM/CM studies.

*Evaluation of response*

After submission of the initial Category 1 application to TGA, additional data from two extensions to the CM and EM pivotal studies have become available. A final clinical study report was provided for Study 20120296 and the full clinical study report for Study 20130255 has also been provided.

The final results from Study 20120296 confirmed that the additional numerical reductions during the blinded active treatment phase were consistently favouring the 140 mg dose in a magnitude ranging from -0.56 to -0.74 MMD irrespective of double blind treatment phase dose. Review of the final clinical study report for Study 20130255 provided more data on long term efficacy of the proposed dose of 140mg. A post hoc analysis was conducted in subjects who completed the 52 week open label extension treatment as they received the same open label extension dose (70 mg once monthly versus 140 mg once monthly) for at least 6 months at the Week 52 visit. This open label extension study was not designed to statistically compare efficacy between erenumab dose levels, the post hoc analysis results in these subjects based on the last open label extension dose received showed a numerically greater benefit for the 140 mg once monthly dose (mean (95% CI): -10.48 (-11.52, -9.43)) at Week 52, with an additional reduction of 2 migraine days compared with the 70 mg once monthly dose (mean (95% CI): -8.49 (-9.35, -7.63)). The group completing the 52 week treatment phase on the 140 mg once monthly dose had a greater proportion of subjects with  $\geq 50\%$  reduction in monthly migraine days from Study 20120295 Baseline (67.3) than those who finished the 52 week treatment phase on 70 mg once monthly (53.3%). Although interpretation was limited by the open label design and the lack of a formal dose comparison, the overall results showed that erenumab 140 mg provides greater longer term efficacy in CM compared with 70 mg with further clinically meaningful benefits of -1.95 MMD and 13.6% additional patients achieving the clinically relevant  $\geq 50\%$  reduction in MMD after 52 weeks.

The applicant has now confirmed the results in the episodic treatment failure group in a dedicated trial in EM in patients that have failed 2 to 4 prior therapies (Study CAMG334A2301, ClinicalTrials.gov Identifier NCT03096834) at the 140 mg dose reinforcing the safety and efficacy of erenumab across the spectrum of prophylaxis of migraine (not part of the original submission dossier). However, this study has not been provided for evaluation.

The additional exposure-response modelling in pooled EM/CM studies was reviewed and summarised in. Results suggested that greater % reduction in erenumab treated patients

with  $C_{min}$  above 4.12 $\mu$ g/mL and more patients at receiving 140 mg were likely to sustain  $C_{min}$  levels above 4.12 $\mu$ g/mL compared to those receiving 70 mg.

Overall, the data provide evidence for a higher treatment benefit with 140 mg and also confirm that there are no new safety findings with the 140 mg dose.

#### **Question 5**

***In the pivotal Study 20120295, it is difficult to interpret effect of disease duration (in the subgroup analysis) based on just values < or > median value of 21.7 years; analysis based on disease duration < 10years, 10 to 20 years and > 20 years may have been more useful. Was this done and if so, can the results be provided?***

*Sponsor's response*

[Information redacted]

The sponsor provided additional subgroup analysis, as requested.

*Evaluation of response*

The sponsor has provided efficacy subgroup analysis based on disease duration < 10years, 10 to 20 years and > 20 years which has shown consistent results. The sponsor's response is satisfactory.

#### **Question 6**

***In the supportive EM Study 20120278, the Baseline BMI was not mentioned which is important considering lack of or reduced efficacy shown in subjects with higher BMI in other EM Studies 21020296 and 20120297. Can the sponsors provide this information?***

*Sponsor's response*

[Information redacted]

The sponsor provided Baseline BMI in pooled studies in EM (Studies 20120296, 20120297 and 20120178) and argued that confounding factors, including treatment naivety and triptan use, make an interpretation of BMI with reduced efficacy difficult.

*Evaluation of response*

The sponsor's response is acceptable.

#### **Question 7**

***In both the pivotal studies, 2 injections have to be administered in order to deliver the proposed dose of 140mg and the clinical study report mentions that the same injection site was used for both injections.***

***The sponsors need to confirm that the 2 injections were given adjacent to each other on the same anatomical site.***

*Sponsor's response*

[Information redacted]

The sponsor provided information that although no specific instructions were given regarding the distance between the two injections, population PK analysis did not show differences in erenumab exposure, irrespective of injection site.

*Evaluation of response*

The sponsor's response is satisfactory.

## Safety

### Question 8

***In the Integrated safety analysis, treatment-related AEs were not provided for Pools B, C and D. The sponsors are requested to provide this data for evaluation.***

*Sponsor's response*

[Information redacted]

The sponsor provided tables of adverse events which met the numerical imbalance criteria for Pool A and for Pool B. Constipation, injection site reactions (for example injection site pain, injection site erythema), bronchitis, and generalised pruritus met the criteria in both Pool A and Pool B. Gastroenteritis viral, viral upper respiratory tract infection, ear infection, osteoarthritis, and neck pain was observed in Pool B but not Pool A.

Numerical imbalance criteria were not applied for Pool C or Pool D as there was no placebo comparison.

*Evaluation of response*

The sponsor's response is satisfactory.

### Question 9

***The median age in the placebo-controlled studies (Pool A) was 42 to 43 years. There were more subjects > median age (n = 857) compared to those < median age (n = 756) which is not an accurate representation of the target patient population as highest prevalence of migraine is observed in women aged 30 to 39 years. Can the sponsors provide clarification on this?***

*Sponsor's response*

[Information redacted]

The sponsor discussed the relationship between disease duration and age at inclusion and stated that the trial populations well reflect the anticipated use of erenumab in clinical practice and hence the data from the trials are considered appropriate and representative for the target population.

*Evaluation of response*

The sponsor's response is satisfactory.

### Question 10

***In the Phase II Study 20140254 involving 88 patients with chronic stable angina, PK, anti-erenumab antibody, biomarker or safety data were not presented in this submitted clinical study report. The final analysis report for this study should be presented for evaluation.***

*Sponsor's response*

[Information redacted]

The sponsor provided the final analysis report results, as requested. This included results for final safety data through end of study; and also results of the PK and anti-erenumab antibody assay are included.

*Evaluation of response*

This final study report has now been provided and reviewed. Overall, the safety profile observed in this study was similar to that observed with previous studies of erenumab and no new safety concerns were identified.

## Comments for RMP

In the first round report, it was recommended that:

‘The following should be added to the list of ‘missing information’:

- Hepatic impairment
- Incidence of withdrawal/rebound.’

### *Sponsor’s response*

[Information redacted]

The sponsor stated that the absence of data itself (for example exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile.

The sponsor stated that erenumab does not go through cytochrome P450-mediated metabolism, thus, the pharmacokinetics of erenumab are not expected to be affected by hepatic impairment. Hence, the sponsor does not consider to add ‘Hepatic impairment’ to the list of missing information.

The sponsor also stated that overall, the data does not speak to an elevated incidence or severity of migraine related adverse events. The sponsor, therefore, disagrees to include ‘Incidence of withdrawal/rebound’ to the list of missing information.

### *Evaluation of response*

The sponsor’s justification for not including ‘hepatic impairment’ to the list of missing information is acceptable. Following submission of the updated safety data, the justification provided for not including ‘incidence of withdrawal and rebound’ to the list of missing information is also acceptable.

The Australian Specific Annex (ASA) has not been updated as part of these responses to the TGA, as RMP recommendations and the sponsor’s response do not directly impact the ASA. The ASA will be updated per usual process when the next updated version of the EU RMP is available.

The sponsors have stated that a summary table showing comparison between the Summary of product characteristics (SmPC) and the Australian PI could be generated upon approval of the EU-SmPC.

The sponsor has also agreed to include the 5 year extension Study (20120178) as a revised pharmacovigilance activity for Missing Information ‘Long term safety’ in the RMP. The following milestones apply:

First patient first visit (FPFV): 6 August 2013 for initiation of the double blind phase.

Last patient last visit (LPLV): Fourth quarter 2019 of extension phase.

## Second round benefit-risk assessment

### **Second round assessment of benefits**

After consideration of the responses to clinical questions, the benefits of Aimovig in the proposed usage are unchanged from those identified in the first round evaluation report.

### **Second round assessment of risks**

After consideration of the responses to clinical questions, the risks of Aimovig in the proposed usage are shown in Table 8.

**Table 8: Aimovig risks versus strengths and uncertainties**

Risks	Strengths and Uncertainties
Common ADRs associated with erenumab treatment were injection site reactions, constipation, pruritus and muscle spasm.	Majority of events were mild or moderate. There were no additional safety concerns with self-administration using prefilled syringes or auto-injector/pens
Potential of increased risk of cardiovascular, cerebrovascular or peripheral vascular effects.	Review of both individual and aggregate AEs did not find any evidence of an association between erenumab treatment and CV, cerebrovascular or peripheral vascular events. Review of the final study report for Phase II Study 20140254 in stable angina showed a similar safety profile to that observed with previous studies of erenumab and no new safety concerns were identified.
Proposed dose of 140mg requires 2 injections.	However, sponsors have stated that the 140mg formulation was pursued further and will be submitted as part of a post approval change immediately after the initial approval.
Lack of adequate long-term data on efficacy and safety in patients with CM.	The open label extension of the CM Study 20120295 should provide this information.
Risk of development of antibodies to erenumab which could potentially reduce efficacy.	The incidence of anti-erenumab antibody development is low (< 3%). Despite a modest reduction in exposure among anti-erenumab antibody positive patients, there was no clinically meaningful impact on drug efficacy and safety although interpretation is limited by small number of subjects with positive antibodies.
The highest prevalence of migraine is reported for women aged 30-39 years <sup>10</sup> , but the median age of patients was higher in both pivotal studies (median of 42 to 43years.	In the CM study, there were more patients > median age of 43 years compared to those < 43 years. Information on number of patients < and > median age not provided in the EM study and subgroup analysis in this study did not evaluated effect of age on efficacy of erenumab.
Lack of adequate data on withdrawal/rebound effects following discontinuation of erenumab.	While the data are limited for a comprehensive assessment of withdrawal and rebound effects, there is no evidence of such an effect based on review of migraine adverse events.

### Second round assessment of benefit-risk balance

The benefit-risk balance of Aimovig, given the proposed usage is favourable.

### Second round recommendation regarding authorisation

Approval of Aimovig is recommended for the following indication:

*Aimovig is indicated for prophylaxis of migraine in adults. (Refer to 'Clinical trials' and 'Dosage and administration' for available data in chronic and episodic migraine).*



The sponsor has addressed all the clinical questions and incorporated all recommended changes to the draft PI and CMI and also provided long term efficacy and safety data (Study 20130255: open label extension study of the pivotal CM Study 20120295 and the active treatment phase of the pivotal EM Study 20120296). The final study report for Phase II Study 20140254 in subjects with stable angina was also provided.

## VI. Pharmacovigilance findings

### Risk management plan

#### Summary of RMP evaluation<sup>62</sup>

- The sponsor has submitted EU-RMP version 1.0 (dated 11 May 2017; data lock point 31 January 2017) and Australian Specific Annex (ASA) version 1.0 (dated 8 June 2017) in support of this application.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9.

**Table 9: Summary of safety concerns**

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None				
Important potential risks	None				
Missing information	Use in pregnant or breastfeeding patients	✓ <sup>^</sup>	–	✓	–
	Use in patients with major cardiovascular disease (MI, stroke, TIA, and unstable angina)	✓	–	–	–
	Long-term safety	✓	✓ <sup>*</sup>	–	–

<sup>^</sup>Routine pharmacovigilance includes a Pregnancy follow-up questionnaire. <sup>\*</sup>5-year extension Study 20120178 is an additional pharmacovigilance activity for Missing Information 'Long term safety'.

- No additional pharmacovigilance activities were proposed. However, the RMP evaluator requested that the 5 year extension Study 20120178 should be included in

<sup>62</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

the ASA as an additional pharmacovigilance activity for Missing Information 'Long term safety.' In response, the sponsor has agreed to include this study in the next update of the ASA.

- There are no additional risk minimisation activities which is acceptable as there are no Important Identified or Potential risks included in the Safety Specification at this stage.

### **New and outstanding recommendations from second round evaluation**

The recommendations made in the first round evaluation, along with consideration of the sponsor's response were detailed in the RMP evaluation report.

There were no outstanding issues post second round.

### **Proposed wording for conditions of registration**

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

1. The Aimovig EU-Risk Management Plan (RMP) (version 1.0, dated 11 May 2017, data lock point 31 January 2017), with Australian Specific Annex (version 1.0, dated 8 June 2017), included with submission PM-2017-02174-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

2. Aimovig (erenumab) is to be included in the Black Triangle Scheme. The PI and CMI for Aimovig must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

## **VII. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations.

## Background

Migraine, the second most common cause of headache, and the most common headache-related, and indeed neurologic, cause of disability in the world, afflicts approximately 15% of women and 6% of men over a 1 year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. The sensory sensitivity that is characteristic of migraine is probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and hypothalamus. Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly CGRP, at vascular terminations of the trigeminal nerve and within the trigeminal nucleus.<sup>1</sup>

Patients with episodes of migraine that occur daily or near daily are considered to have CM. Intractable migraine (status migrainosus) is defined as a migraine attack that persists for more than 72 hours.

Pharmacological treatments for acute episodes include non-specific (symptomatic) agents such as NSAIDs or migraine-specific abortive medications such as triptans or ergotamine derivatives. Patients experiencing more frequent migraines and/or more severe functional impact, despite the use of acute medications, often require prophylaxis. The main goal of a prophylactic treatment is to reduce the frequency of migraine days. In Australia, beta-blockers (propranolol, metoprolol), topiramate, methysergide and botulinum toxin are approved for migraine prophylaxis; other drugs which may be used but are not officially approved for this indication include the anti-depressant, amitriptyline and antiepileptic, sodium valproate.

Erenumab has been proposed as a prophylaxis for migraine. It is a potent and selective fully human IgG2 mAb against the CGRP receptor. CGRP is a 37 amino acid peptide widely expressed in both the central and peripheral nervous systems and has been implicated as a key mediator in the initiation and progression of migraine pain. Erenumab binds to the CGRP receptor, blocking the interaction of CGRP ligand to its receptor and functionally inhibiting the CGRP signalling pathway. Despite the presence of CGRP receptors in the CNS, the likely site of action for erenumab is the trigeminal ganglion and as a mAb is expected to have minimal if any CNS penetration.

The sponsor has advised that small molecule CGRP receptor antagonists have demonstrated clinical efficacy in acute migraine reversal and migraine prevention. None of the small molecule CGRP receptor antagonists have been approved for use in migraine due to difficulties preparing an oral formulation or liver toxicity concerns. Beyond erenumab, anti-CGRP monoclonal antibodies have shown efficacy in migraine prevention in 5 placebo controlled clinical trials.

It was postulated that targeting the CGRP receptor, rather than the ligand, could provide a more consistent therapeutic effect, as monoclonal antibodies targeting the CGRP ligand may require higher concentrations in order to bind to and inhibit CGRP following high-quantity release from stored vesicles during migraine attacks.

In addition, CGRP ligand binds to additional receptors other than the CGRP receptor, such as amylin and adrenomedullin receptor, and the downstream effects of interfering with other CGRP ligand-mediated pathways through non-canonical CGRP receptors are not well understood. CGRP receptor antagonists should therefore allow more selective CGRP blockage without potentially interfering with closely related receptors where CGRP also binds.

## Quality

There are no objections on quality grounds to the approval of Aimovig (erenumab). The evaluator has recommended standard batch release testing as a condition of registration and finalised the quality aspects of the PI. A quality summary will be included in the ACM agenda.

## Nonclinical

There are no nonclinical objections to the registration of erenumab. The evaluator considered treatment-related effects associated with twice weekly injections were minimal and limited to injection site reactions. A Pregnancy Category of B1 was considered appropriate.<sup>6</sup> In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were administered erenumab SC from organogenesis through parturition at exposures up to 16 fold the exposure at the maximum recommended human dose of 140 mg once monthly. Nonclinical sections of the draft PI submitted with the sponsor's response are acceptable to the evaluator.

## Clinical

### Pharmacology

Erenumab is an IgG2 mAb that has high affinity binding to the CGRP receptor. Erenumab exhibited non-linear pharmacokinetics at lower doses and linear PK at higher doses. Exposure increased more than dose proportionally from 1 to 70 mg and appeared to increase approximately dose proportionally from 70 to 210 mg after a single SC administration of erenumab.

On monthly dosing in patients with migraine, SC bioavailability was estimated to be 81.8%. The mean absorption time was 3.36 days, suggesting that the absorption phase is complete in approximately 12 days. The volume of distribution ( $V_d$ ) at steady-state was 7600 mL suggesting limited tissue distribution outside of plasma. The median  $t_{max}$  was 3.9 days. Steady state was generally reached by Week 12 with minimal accumulation (< 2 fold) after 3 doses and the effective half-life was 28 days.

Two elimination phases were observed for erenumab. At low concentrations elimination is predominantly through saturable binding to target (CGRP receptor), while at higher concentrations elimination is largely through a non-specific, non-saturable proteolytic pathway. At the proposed dose of 140 mg SC once monthly, the target-mediated pathway is saturated (peripheral target binding is > 99%) for the entire dosing monthly interval at steady state, suggesting complete blockade of peripheral target (extra-central nervous system). Therefore, total clearance is predominantly linear at 140 mg SC once monthly, and estimated to be 198 mL/d (or 8.25 mL/h), similar to the reported clearance for endogenous IgG.

In the pivotal Phase III Study 20120296 serum concentrations were measured at Day 8, pre-dose at Weeks 4, 12, 16 and 24 doses and at Week 13. The later allowed an estimate of the  $C_{max}$  when erenumab is given monthly.

The mean (SD) concentration at Week 13 for the 140 mg/ month dose group was 19200 ng/mL (7830 ng/mL). Pre dose at Weeks 12, 16 and 24 the mean erenumab serum concentration ranged from 11400 ng/mL at Week 12 to 12800 ng/mL at Week 24.

The population PK analysis reported a CV of erenumab for central volume of distribution of 42%, 27.6% for clearance and 79.5% for absorption rate. Mean serum erenumab concentrations in subjects positive for anti-erenumab antibodies ranged from 62% to

109% of those in subjects negative for anti-erenumab antibodies. In the pivotal Phase III study mean serum trough erenumab concentrations in the 4.6% of subjects who developed binding antibodies were 105% to 44% and 92% to 46% of the mean concentrations for antibody negative subjects in the erenumab 70 mg and erenumab 140 mg groups, respectively across trough time points.

No specific studies were conducted in patients with hepatic or renal impairment. The pop PK analysis showed similar erenumab pharmacokinetics in subjects with mild to moderate renal impairment compared to those with normal renal function. After adjusting for bodyweight, no apparent differences existed in erenumab pharmacokinetics between healthy, chronic migraine and episodic migraine subjects. Other factors including age, eGFR, sex, race, ADA status and SC injection site had minimal impact on the variance (< 10% of variance) of PK parameters.

Interaction studies showed no effect on the PK of ethinyl oestradiol/norgestimate or sumatriptan. Interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes were considered to be unlikely as erenumab is not metabolised by cytochrome P450 enzymes. However, DDIs of erenumab with other prophylactic treatments for migraine were not evaluated.

Erenumab was demonstrated to inhibit a capsaicin induced increase in dermal blood flow compared with placebo.

Immunogenicity was assessed in the early studies as well as in the Phase III studies. Anti-erenumab binding antibodies were detected in 2.6% of patients treated with erenumab 140 mg during the double blind treatment phase of the two placebo controlled migraine studies (Studies 20120295 and 20120296). Neutralising antibodies were not detected in any patient receiving 140 mg SC once monthly in these studies. Evaluation of longer term data through Week 64 of the open label extension phase of episodic migraine Study 20120178 also showed no clinically meaningful impact of anti-erenumab antibodies on efficacy and safety. That study is ongoing with 344 subjects in the open label extension.

The effect of erenumab on blood pressure and on the biomarkers of bone turnover, P1NP and sCTX, were examined in Study 20101268, a Phase Ib ascending dose study in which healthy volunteers and volunteers with migraine received up to 3 monthly doses of erenumab. Significant increases in P1NP were observed at Day 29 in 140 mg erenumab group compared with placebo. The geometric LSM ratio change from Baseline (95% CI; p value) of P1NP (erenumab versus placebo) was 24.07%% (0.45%% to 53.24%; 0.045). This difference wasn't statistically significant at the Day 57 time point however the change was still higher in the erenumab group than in the placebo group.

There was no significant difference between the erenumab groups and placebo group at all measured time points for change in sCTX levels compared with Baseline. Erenumab did not affect blood pressure.

Initial dose-finding explored doses to 70 mg once monthly. As the results from the Phase II Study 20120178, were inconsistent with the doses expected to result in complete inhibition, based on the dermal blood flow model, and to ensure optimal efficacy is achieved with erenumab, a higher dose of 140 mg SC once monthly was also studied.

An integrated summary of efficacy combined monthly migraine days change from Baseline by quartiles of trough concentrations of erenumab at Week 12 in subjects with CM or EM (trough concentrations estimates from the population PK model) from the following studies: EM (Studies 20120296, 20120297, and 20120178) and CM (Study 20120295).

## **Efficacy**

The sponsor assessed efficacy in EM and CM in separate studies. CM is defined as 15 or more headache days per month, at least 8 of which have to be typical migraine days (as

per International Headache Society classification).<sup>14</sup> Extension phases of the Studies 20120178 and 20120297, supportive studies that did not use the proposed 140 mg dose in the double blind treatment phase, and the active treatment phase of Study 20120296 (pivotal EM study) are ongoing.

### ***Chronic migraine***

The pivotal study for prophylaxis of CM was Study 20120295, a multicentre, randomised, double blind, placebo controlled study to evaluate the effect of erenumab compared to placebo on the change from Baseline in monthly migraine days, in subjects with CM. Secondary objectives were to evaluate the effect of erenumab compared to placebo on: the proportion of subjects with at least 50% reduction from Baseline in monthly migraine days; the change from Baseline in monthly acute migraine-specific medication treatment days; in monthly cumulative hours of headache; and on the safety and tolerability of erenumab. Multiple exploratory endpoints including QoL endpoints were also assessed.

This study had 4 phases: screening (up to 3 weeks); Baseline (4 weeks); 12 week double blind treatment; and 12 week follow up. Erenumab 70 mg, erenumab 140 mg, or placebo was administered during the 12 week double blind treatment phase at Day 1 and Weeks 4 and 8. Subjects who completed the 12 week double blind treatment phase were eligible to enrol in an open label extension, Study 20130255. Clinical outcomes assessments were collected by subjects using a handheld electronic diary (eDiary).

The inclusion criteria were assessed during the screening phase prior to enrolment into the Baseline phase as detailed in the study protocol. The main inclusion criteria at screening were:

- Age 18 to 65 years.
- History of migraine with or without aura (with visual, sensory, speech and/or language, retinal or brainstem aura) that experienced > 15 headache days per month, with > 8 migraine days per month.
- Diagnosis of migraine was confirmed according to the International Headache Society classification (2013);<sup>14</sup> based on medical records and/or patient self-report.

The main exclusion criteria at screening were:

- Patients with cluster headaches or hemiplegic headaches.
- CM with continuous pain.
- Unable to differentiate migraine from other headaches.
- Taken opioids or similar analgesics for any indication on > 12 days or butalbital containing analgesic for any indication on > 6 days during past 3 months prior to screening.
- Patients with no therapeutic response to > 3 medication categories for migraine prophylaxis medicines.
- Received Botox in head or neck region in past 4 months.
- Changing dose of any concomitant medications not prescribed for migraine but which may have migraine prophylaxis effects within 1 month prior to screening.
- History or evidence of unstable or clinically significant medical conditions.

The major migraine prophylaxis medication groups, both labelled and off label were not permitted for subjects while on the study. Subjects with coexisting medication overuse of triptans, ergot derivatives, analgesics (but not opioids) and combination drug use were allowed in the study or during the 2 months prior to study commencement.

Inclusion criteria were also assessed during the Baseline phase prior to randomisation into the double blind treatment phase. The main inclusion criteria at Baseline prior to start of the double blind treatment period (all based on the eDiary) were:

- $\geq 15$  headache days of which  $\geq 8$  headache days meet criteria as migraine days during the Baseline phase.
- $\geq 4$  distinct headache episodes, each lasting  $\geq 4$  hours or if shorter, associated with use of a triptan or ergot-derivative on the same calendar day during the Baseline phase.
- At least 80% compliance (for example, must complete eDiary items on at least 23 out of 28 days during the Baseline phase).

The main exclusion criteria prior to the start of double blind treatment period were: development of cluster or hemiplegic headache during Baseline period; taken an opioid or butalbital containing analgesic for any indication for  $> 4$  days during Baseline phase; other exclusion criteria similar to those described at screening.

The primary efficacy endpoint was the change in monthly migraine days from Baseline to the last 4 weeks of the 12 week double blind treatment phase. Secondary endpoints were:

- At least a 50% reduction from Baseline in monthly migraine days in the last 4 weeks of the 12 week double blind treatment phase.
- Change from Baseline in monthly acute migraine-specific medication treatment days in the last 4 weeks of the 12 week double blind treatment phase.
- Change from Baseline in cumulative monthly headache hours in the last 4 weeks of the 12 week double-blind treatment phase.

Approximately 651 subjects were planned to be randomised 3:2:2 to receive placebo, erenumab 70 mg, or erenumab 140 mg monthly every 4 weeks SC. Randomisation was stratified by region (North America versus Other) and medication overuse at Baseline (Yes versus No). To control for multiplicity effects due to the multiple endpoints the hierarchical gate keeping procedures and Hochberg method was used to maintain the 2 sided study wise type I error at 0.05 between the 2 erenumab doses and the primary and secondary endpoints.

The primary endpoint, the change in monthly migraine days from Baseline to the last 4 weeks of the 12 week double blind treatment phase, was initially tested for the erenumab 70 mg treatment group compared to the placebo group at a 2 sided significance level of 0.04. The 140 mg treatment group was initially compared with placebo using a 2 sided significance level of 0.01.

As a gate keeping process, the secondary endpoints were tested statistically using the Hochberg method at significance levels of 0.04 and 0.01 for the erenumab 70 and 140 mg doses, respectively. If the secondary endpoints were statistically significantly different than placebo for one dose of erenumab, the corresponding significance level can be carried over to the primary endpoint test for the other dose of erenumab, and the primary endpoint as re-tested for the other dose of erenumab at a 2 sided significance level of 0.05, followed by comparison of its secondary endpoints at a 2 sided significance level of 0.05 if the primary endpoint is statistically significant at a 2 sided significance level of 0.05.

### *Results*

Of the 953 subjects screened, 286 were enrolled but not randomised; 667 were randomised, 286 to placebo, 191 to erenumab 70 mg and 190 to erenumab 140 mg once monthly. Of these subjects, 660 received 1 or more doses of study treatments and 637 (95.5%) completed the Week 12 assessment. There were few protocol violations, the most frequent being entered study even though entry criteria were not satisfied (4.8%). 612 subjects were included in the per protocol efficacy analysis population.

At Baseline, 82.8% of subjects were women, mean age was 42.1 years (range 18 to 66 years) and mean BMI was 26.1 kg/m<sup>2</sup>, 50.4% had used prophylactic topiramate and 23.7 had used onabotulinum toxin. Overall, the mean number of monthly headache days was 20.5 days, monthly acute migraine specific medication use in days was 9.3 days, the mean disease duration of migraine with or without aura was 21.7 years. MPFID, a measure of mean physical impairment and everyday activities was assessed at Baseline and throughout the study. MPFID scores range from 0 to 100 with higher scores indicating higher disease burden. At Baseline, mean MPFID scores ranged from 16.74 (140 mg erenumab group) to 29.88 (placebo group). Baseline demographic and disease characteristics were similar across treatment groups, 66.3 to 69.9% of subjects across the groups had failed  $\geq 1$  prior migraine prophylaxis treatment and medication overuse was reported for 41.1% of randomised subjects at Baseline. Approximately half of the randomised subjects were in North America (47.2%) and half were in other regions (52.8%).

Mean reductions in MMD from Baseline to the last 4 weeks of the 12 week double blind treatment period occurred in all groups, with a mean reduction of 4.24 days in the placebo group, 6.63 days in the erenumab 70 mg group and 6.53 days in the erenumab 140 mg group. Adjusted analysis using a generalised linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region and medication overuse, and Baseline value as covariates and assuming a first order auto regressive covariance structure gave a LSM reduction of 4.18 days for placebo, 6.64 for erenumab 70 mg and 6.63 for erenumab 140 mg. Comparisons of both erenumab doses with placebo were statistically significant ( $p < 0.001$ ). The LSM treatment difference of about 2.5 days in a 4 week period was on a background mean of around 20 headache days per month.

The following subgroup analyses for the primary endpoint showed evidence of greater efficacy with the 140 mg dose over the 70 mg dose:

- Patients who had used prophylactic topiramate (-2.96, -5.49 and -7.08, in the placebo, erenumab 70 mg and erenumab 140 mg groups, respectively) compared to those who had not (-5.61, -7.59 and -6.17, respectively).
- Had disease duration  $>$  median of 21 years (-3.91, -5.58 and -7.15, respectively compared to those who had duration  $<$  21.7 years (-4.45, -7.58 and -6.02, respectively).
- Those who had failed  $> 1$  or  $> 2$  prophylactic medications.

Statistical comparisons for the primary efficacy endpoint between the 70 mg and 140 mg dose groups within these subgroups were not performed. Confidence intervals for difference from placebo for the two groups widely overlapped.

The proportion of subjects with a  $\geq 50\%$  reduction in monthly migraine days from Baseline to the last 4 weeks of the 12 week double blind treatment phase was 23.5%, 39.9% and 41.2% for the placebo, erenumab 70 mg and erenumab 140 mg groups, respectively. Both erenumab dose groups were statistically superior to placebo ( $p < 0.001$ ) for this major secondary endpoint with approximately ( $\sim$ ) 16% more subjects taking either dose of erenumab experiencing a  $> 50\%$  reduction in migraine days per month. While there was a small percentage difference between the erenumab doses, favouring the higher dose, no statistical comparisons were performed. Of note, while the unadjusted data showed no statistically significant mean difference in the change in cumulative monthly headache hours from Baseline for erenumab 70 mg and 140 mg compared with placebo, the adjusted analysis showed a statistically significant difference for the 140 mg dose.

Timing of onset of reduction in monthly migraine days at Weeks 4 and 8 of the double blind treatment period were assessed as exploratory analyses. Both doses of



erenumab were superior to placebo at both these assessments with the difference in mean migraine days from 2.36 to 2.89 across the dose groups and months assessed. The 140 mg dose group had a larger difference from placebo at both these assessment periods. Similarly for the 50% responder rates, change from Baseline in monthly acute migraine specific medication treatment days at both assessment periods. Maximal response appeared to be achieved by Week 8.

Change from Baseline scores at Week 12 for patient reported outcomes assessing extent of disability tended to favour erenumab and most of them were statistically significant from placebo. Differences from placebo were larger with the higher erenumab dose and there were no statistical comparisons between the erenumab doses. MPFID was not included in that table, however few patients in each group completed that assessment and differences from placebo were not statistically significant.

A subgroup analysis of subjects with medication overuse, excluding opioid overuse, at Baseline (41% of subjects) was conducted. There were 268 of these subjects, 113 were randomised to placebo, 77 to erenumab 70 mg and 78 to erenumab 140 mg. Erenumab treatment groups had statistically significantly higher 50% responder rates than placebo at Weeks 4, 8 and 12. The differences at Week 12 were 18.7% for the 70 mg erenumab group and 16.9% for the 140 mg erenumab group.

Similarly the change from Baseline in monthly migraine days for this subgroup showed reductions greater than the reductions in the placebo group that were apparent from Week 4.

### ***Episodic migraine***

Study 20120296 was a Phase III, multicentre, randomised, stratified, double blind, placebo controlled, parallel group study to evaluate the effect of erenumab compared to placebo in subjects with EM. This study had a screening of up to 3 weeks, a Baseline phase of 4 weeks, and a double blind Treatment phase of 24 weeks. Subjects were then re-randomised for a 28 week 'Active treatment' phase and a 12 week Follow up phase. During the double blind period subjects received erenumab 140 mg, erenumab 70 mg or placebo once monthly as in Study 20120295.

Subjects were then re-randomised to receive erenumab 70 mg or erenumab 140 mg (actual dose blinded) during the 28 week active treatment phase at Weeks 24, 28, 32, 36, 40, 44 and 48. The active treatment phase had not been completed by the majority of subjects when the main (interim) study report was completed in February 2017. An abbreviated report dated 19 January 2018 provided an 8 page synopsis of the final results for the active treatment phase.

The inclusion criteria differed from Study 20120295 primarily in the frequency of migraine episodes. For screening, subjects were required to have a migraine frequency from 4 to < 15 migraine days per month and total headache frequency (that is, migraine and non-migraine headache) of < 15 days per month on average across the 3 months prior to screening. For inclusion in the double blind randomised phase the migraine and headache frequencies had to be confirmed and at least 80% compliance with eDiary completion. Exclusion criteria were similar to those of Study 20120295 except that subjects were permitted to take stable doses of prophylactic migraine medication (though only 0.03% did) and patients who had failed more than 2 of 7 listed prophylactic migraine medication categories were excluded compared with failure of more than 3 of 8 prophylactic migraine medication categories in Study 20120295. An e-dairy was used to collect clinical outcome assessments. The primary efficacy endpoint was the change from Baseline in mean MMD over the last 3 months (Months 4, 5 and 6) of the double blind treatment phase. Secondary endpoints were:

- Achievement of at least a 50% reduction from Baseline in mean monthly migraine days over the last 3 months (Months 4, 5, and 6) of the double blind treatment phase.
- Change from Baseline in mean monthly acute migraine specific medication treatment days over the last 3 months (Months 4, 5, and 6) of the double blind treatment phase.
- Change from Baseline in mean monthly average physical impairment domain scores over the last 3 months (Months 4, 5, and 6) of the double blind treatment phase as measured by the MPFID.
- Change from Baseline in mean monthly average impact on everyday activities domain scores over the last 3 months (Months 4, 5, and 6) of the double blind treatment phase as measured by the MPFID.

### Results

1492 subjects were screened, 955 randomised to the double blind treatment phase and 952 subjects (99.7%) received 1 or more doses of study treatment. Of these 858 subjects (89.8%) completed the double blind treatment phase of the study (that is completed the Week 24 follow up assessment) and 97 (10.2%) discontinued the double blind treatment phase.

In the subsequent active treatment phase, 844 subjects received 1 or more doses of study treatment. As of the data cut-off date (5 September 2016), 91 subjects (9.5%) had completed the active treatment phase of the study, 716 subjects (75.0%) continued in the active treatment phase and 37 subjects (3.9%) discontinued the active treatment phase (protocol specified criteria, subject request and lost to follow up).

The demographic characteristics were similar to those of Study 20120295. The majority of subjects were women and mean age was 41 years. The mean (SD) number of migraine days and number of monthly headache days was 8.3 (2.5) and 9.2(2.6), respectively. The mean (SD) disease duration of migraine with or without aura was 19.9 (12.2) years and the mean (SD) monthly acute migraine specific medication use at Baseline was 3.4 (3.4) days. Just over one half of subjects in each treatment group (55.8%, 55.2% and 58.6% in the placebo, erenumab 70 mg and erenumab 140 mg groups, respectively) were migraine prophylactic medication naïve at Baseline.

Overall, topiramate (48.1% of subjects), beta blockers (47.7%), other (31.4%) and tricyclic antidepressants (30.9%) were the most frequently used prior prophylactic medication categories. During the study current migraine prophylactic treatments were taken by 10, 9 and 8 subjects in placebo, 70 mg and 140 mg groups, respectively. Mean Baseline MPFID was 12 to 13, indicating limited scope for improvement in physical function.

All treatment groups had a mean reduction in monthly migraine days from Baseline to the last 3 months of the double blind treatment period. In the placebo group mean monthly migraine days reduced from 8.25 to 6.33, a 1.95 day reduction. In the 70 mg erenumab group the reduction was from 8.31 to 4.95, a 3.36 day reduction and in the 140 mg erenumab group the reduction was from 8.33 to 4.48, a 3.96 day reduction. The difference from placebo in adjusted mean change from Baseline in the number of migraine days per month showed similar results to the unadjusted data and both doses of erenumab were statistically significantly superior to placebo. There was no statistical comparison between doses of erenumab for the primary efficacy endpoint. Various sensitivity analyses also confirmed statistical superiority of each dose over placebo.

The responder rates were 26.6% in the placebo group, 43.3% in the 70 mg dose group and 50% in the 140 mg dose group. The comparisons of each erenumab dose group with placebo were also statistically significant ( $p < 0.001$  for each comparison). There were small absolute reductions in the mean number of migraine treatment days, however this came from a fairly low base mean of from 3.24 to 3.43 days across the treatment groups. The difference from placebo in reduction of migraine treatment days was 0.94 days for the

70 mg group and 1.42 days for the 140 mg group. These reductions were also statistically significant ( $p < 0.001$  for both comparisons). The physical impairments scores also showed statistical superiority of both doses of erenumab over placebo.

Exploratory analyses included assessment of the proportion of subjects with a complete response, that is, no migraine days. This varied from 2.8% in the placebo group to 5% in the erenumab 140 mg dose group.

Of the 955 subjects randomised into the study, 845 (88.5%) entered the active treatment phase and were re-randomised to blindly receive active treatment phase erenumab 70 mg ( $n = 421$ ) or erenumab 140 mg ( $n = 424$ ). 764 (90.4%) subjects completed the active treatment phase that is received the final Week 48 dose. The proportion of subjects who achieved a  $\geq 50\%$  reduction in monthly migraine days from Baseline to Week 52 was 61.0% in the All erenumab 70 mg group and 64.9% in the All erenumab 140 mg group. This is a further 17.7% increase in responder rates from the end of the double blind treatment period for the 70 mg group and a further 14.9% increase in responder rates for the 140 mg group.

### Supportive studies

There were 2 studies that did not assess the proposed dose regimen. Studies 20120297 and 20120178 included a 70 mg once monthly erenumab dose regimen. Both studies showed this dose resulted in a mean of approximately 1 additional migraine free day per month compared with placebo in the last 4 weeks of a 12 week double blind treatment period for subjects with EM. For Study 20120178 the planned interim analysis that evaluated the long term efficacy and safety of erenumab after the double blind treatment phase and through Week 64 of the open label treatment phase were provided and suggest persistence of efficacy.

Study 20130255 is the open label extension of Study 20120295, the pivotal study for CM. At the time of data cut-off, 225 subjects (36.9%) had completed the study and no analysis of ongoing efficacy was available from the interim study report.

### Safety

Data from studies in CM and EM were combined in the primary safety analysis. Overall, 3150 subjects were exposed to at least 1 dose of erenumab and of these subjects, a total of at least 2537 were subjects with migraine (included in the integrated analysis) and 613 were healthy subjects. The mean (SD) duration of exposure was 47.5 (33.0) weeks for subjects exposed to any dose of erenumab. 1213 subjects were exposed to erenumab for  $\geq 12$  months. For subjects with continuous exposure, 1598 received 70 mg and 768 received 140 mg for  $\geq 6$  months and 682 and 134 respectively received 70 mg and 140 mg for  $\geq 12$  months. Two deaths were reported; both occurred in the open label treatment phase and had confounding features, and both were considered by the investigator as unrelated to study treatment.

The majority of subjects in the Integrated safety analysis set were female (83.8%) and Caucasian (91.0%) with mean (SD) age of 41.5 (11.2) years. Almost all subjects used acute headache medications (2601 subjects, 97.9%); 1746 subjects (65.7%) used acute migraine specific medications during the Baseline period and 1391 subjects (52.4%) had previously or concurrently been treated with a prophylactic migraine medication.

Erenumab appears not to be associated with SAEs. AEs in the integrated safety analysis that met predefined numerical imbalance criteria included constipation, injection site pain, injection site erythema, bronchitis, muscle spasms and generalised pruritus. For all but injection site reactions, the incidence of these events was numerically higher in the 140 mg dose group compared to the 70 mg group. However, majority of these events were mild to moderate in severity and did not lead to study discontinuation. Incidences for the

double-blind, placebo controlled periods (Studies 20120178, 20120295, 20120296 and 20120297) through to Week 12 are summarised in Table 10.

**Table 10: Adverse event incidences across study groups**

Adverse reaction term	Placebo n = 1043 (%)	Erenumab 70 mg n = 893 (%)	Erenumab 140 mg n = 507 (%)
Injection site reactions	33 (3.2)	50 (5.6)	23 (4.5)
Constipation	11 (1.1)	12 (1.3)	16 (3.2)
Pruritus	5 (0.5)	6 (0.7)	9 (1.8)
Muscle spasms	4 (0.4)	1 (0.1)	10 (2.0)

There was no evidence of an effect on the liver, kidneys or haematology assessments, nor was there a signal for increased malignancy or psychiatric disorders including suicidality.

There was also no signal for an increase in CV disorders. The population had considerable risk factors for CV disease but were generally in early middle age and have not received long term treatment.

There was no increase in immune system disorders or hypersensitivity. There was an indication of a possible association between pruritus and increasing dose of erenumab as shown above. The significance of this is unclear.

Nineteen maternal exposures to erenumab during pregnancy had been reported to 31 January 2017. There were been 3 full term births without complications, 1 full time birth with complications (no reported birth complications or congenital anomalies but was admitted to the neonatal intensive care unit for 4 days (reason for admission not known), one preterm birth, 2 elective terminations and 2 spontaneous abortions. 10 pregnancy outcomes were unknown. The effect of withdrawal hasn't been systematically examined. As noted by the clinical evaluator, this issue should be included in the missing information for safety concerns in the RMP.

## RMP evaluation

The RMP evaluator has recommended that the 5 year extension Study 20120178 should be included in the ASA as an additional pharmacovigilance activity for Missing Information 'Long term safety'. In addition, the sponsor should provide a planned submission date for that study. When available a revised RMP which considers the study outcomes should be submitted to the TGA for review. The sponsor agreed to submit the final study report and advised it is planned to be available in the last quarter of 2020.

The RMP evaluator recommended the inclusion of a 'black triangle' on the PI, consistent with erenumab being a new biological entity. The PI also requires formatting to be consistent with current requirements. Routine pharmacovigilance activities have been proposed for erenumab. The following condition of registration has been proposed:

- The Aimovig EU-Risk Management Plan (RMP) (version 1.0, dated 11 May 2017, data lock point 31 January 2017), with ASA (version 1.0, dated 8 June 2017), included with the submission, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).
- Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.
- The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes.  
  
Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Aimovig (erenumab) is to be included in the Black Triangle Scheme. The PI and CMI for Aimovig must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

## Risk-benefit analysis

### Delegate's considerations

#### *Discussion*

The decision to propose a dose regimen of 140 mg once monthly was made relatively late in the clinical development program. The sponsor has advised that a post-approval change procedure to register the 140 mg/mL strength is planned for submission immediately after the initial approval of the product. Only 1 of the Phase III studies (Study 20120296) included the proposed dose regimen. The proposed dose regimen of 140 mg once monthly was also administered in Study 200120295, a large Phase II study and was added to the extension phase of Study 20120278.

Evidence of increased efficacy of the 140 mg dose compared to the 70 mg dose is limited but is most clearly suggested where there is a positive correlation between trough serum levels of erenumab and difference from placebo in mean reduction from Baseline in migraine days per month. In Study 20120295 only the subgroups of patients who had failed prior prophylactic treatment, had used prior topiramate or had disease duration median of > 21 years had noticeable larger reductions in migraine days with the higher dose. The differences were not large and there were no statistical comparisons between the dose groups within these subgroups. Of note, the exploratory analysis of the endpoint of change in cumulative monthly headache hours from Baseline for erenumab 70 mg and 140 mg compared with placebo showed a statistically significant difference for the higher dose but not the lower dose for the adjusted analysis only. The clinical evaluator suggested, it may be more prudent to use the higher dose only in the above subgroups of patients while the option of the lower 70 mg dose could be made available for most other subgroups of patients.

In response to a question from the evaluator the sponsor provided a case for all patients to be treated with the 140 mg once monthly dose regimen. At this stage the Delegate

proposes that the all patients commencing treatment begin with 70 mg once monthly. If after 3 months the response is inadequate the dose could be increased to 140 mg once monthly. If after a further 3 months the response remains inadequate then treatment with erenumab should be reconsidered.

While the primary endpoint in all the efficacy studies involved changes from Baseline in mean migraine days per month, the relevant EU guideline recommends that for migraine prophylaxis trials the primary endpoint should be the frequency of attacks within a pre-specified period. For example the mean frequency of attacks per 4 weeks or during the final 4 weeks of a 3 month study duration. The sponsor has not adopted that recommendation but rather has assessed changes from Baseline in mean migraine days per month. That parameter is the second of a list of possible secondary endpoints listed in the guideline. From a clinical point of view it seems most likely that patients and healthcare providers would be more interested in the response rates that is  $\geq 50\%$  reduction in the number of migraine days per month as that measure provides a good indication of the proportion of patients that can expect a clinically meaningful reduction in the effect of migraine on their daily lives.

From the pivotal EM efficacy Study 20120296, the mean difference from placebo in change in mean number of migraine days per 4 weeks for subjects taking the proposed 140 mg once monthly dose regimen was about 2 days. On a background mean Baseline frequency of about 8 days a month, this is about a 25% relative reduction in migraine days overall. However about 24% of patients more than placebo had a 50% reduction in their number of migraine days (50% for erenumab versus 26.6 % for placebo). This suggests quite a large variability in the extent of response across the treatment groups. This is seen in the quartile 1 and 3 results for the primary efficacy endpoint.

While the full final report with efficacy data to Week 48 in Study 20120296 was provided only as a synopsis the results suggested a further increase in response rates with extended continuous treatment with erenumab.

For patients with CM the absolute reduction in the number of migraine days after 12 weeks of treatment was about 2.5 days but on a Baseline mean of around 20 migraine days per month. While the absolute reduction in mean migraine days is similar, these patients received proportionately a much smaller benefit than those with EM. The relative reduction in mean migraine days per months is  $\sim 12.5\%$ . However about 16% more subjects taking erenumab had a 50% reduction in the number of migraine days per month from Baseline.

Currently there are no major safety issues with erenumab however long term data are very limited. Given the benefits from treatment are highly variable in a condition which also varies in severity over time without therapeutic intervention, it is reasonable that patients with CM should not continue with erenumab if they do not have a least a reduction of 2 days in their MMD frequency after a trial. Current Australian guidelines for treatment trials for migraine prophylaxis treatment recommend a trial of 8 to 12 weeks. This should also apply to erenumab. Additionally, efficacy results from open label treatment for the 70 mg dose but not the 140 mg dose were made available.

Only a synopsis of efficacy for long term treatment with the 140 mg dose has been provided. At the time the submission was written 134 patients had received erenumab 140 mg monthly for  $\geq 12$  months, 103 with EM and 31 with CM. This is only just above the minimum recommended for medication for long term use in the EU guidelines.

Erenumab has not been assessed in patients with fewer than 4 migraine days per month. The extent of benefit these patients may receive is not known and the Delegate considers that erenumab should not be made available to those patients, at least not until longer term data are available in patients with more frequent migraine.

**Table 11: Study 20120295 in CM; responder rate -  $\geq$  50% reduction in MMD from Baseline to Week 12 (for medication overuse 'Yes' subgroup)**

	Placebo N=113	Erenumab 70 mg N= 77	Erenumab 140 mg N=78
Baseline N Mean migraine days per month (SD)	113 19.57(4.42)	77 18.76 (4.56)	78 18.84 (4.52)
Week 12 (month 3) Responder - n (%) % Difference from placebo	20 (17.7)	28 (36.4) 18.7	27 (34.6) 16.9
Adjusted odds ratio (erenumab vs. placebo) <sup>a</sup> (95% CI) p		2.67 (1.36, 5.22) 0.004	2.51 (1.28, 4.94) 0.007

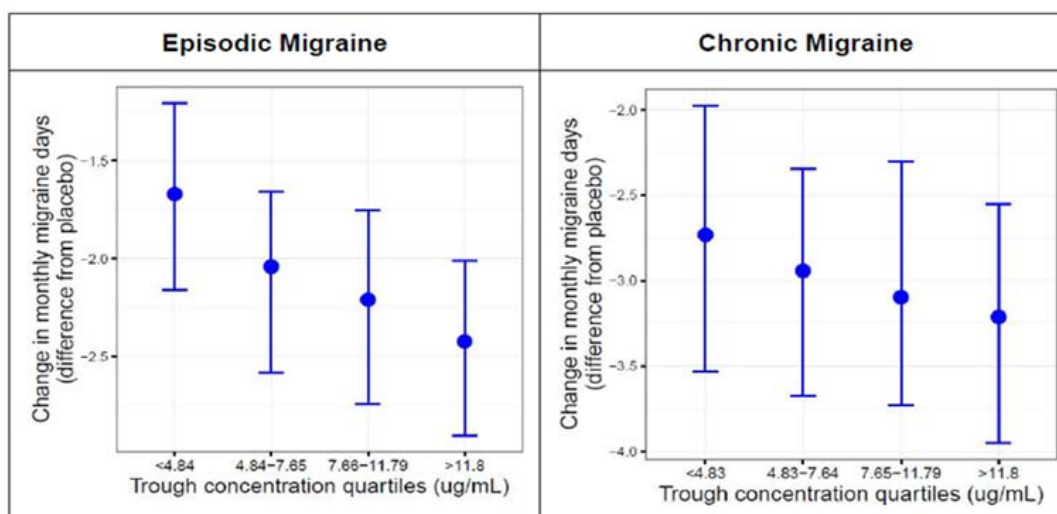
<sup>a</sup> The adjusted odds ratios and p-values are obtained from a Cochran-Mantel-Haenszel test after the missing data are imputed as non-response, stratified by stratification factor region. P-values for pairwise comparisons are nominal p-values obtained from the CMH test using data including placebo and corresponding erenumab dose group only.

**Table 12: Change from Baseline in monthly migraine days Week 12 for medication overuse 'Yes' subgroup**

	Placebo N=113	Erenumab 70 mg N= 77	Erenumab 140 mg N=78
Baseline N Mean (SD)	113 19.57(4.42)	77 18.76 (4.56)	78 18.84 (4.52)
Week 12 (month 3) N Mean (SD)	108 15.81(7.44)	72 12.19 (6.95)	77 12.34 (7.51)
Change from baseline at week 12 Mean (SD)	-3.64	-6.53	-7.51
Adjusted analysis <sup>a</sup> LSM estimate (95% CI of LSM)	-3.53 (-4.64, -2.43)	-6.63 (-7.97, -5.29)	-6.63 (-4.81, -1.39)
Difference in LSM (95% CI of difference) p		-3.10 (-4.83, -1.37) <0.001	-3.10 (-4.81, -1.39) <0.001

<sup>a</sup> Adjusted analysis utilises a generalised linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors region, and baseline value as covariates and assuming a first-order autoregressive covariance structure. P-values for pairwise comparisons are nominal p-values without multiplicity adjustment.

**Figure 3: Monthly migraine days change from Baseline by quartiles of trough concentrations at Week 12 in subjects with CM and EM (trough concentration estimates from population PK model: mean MMD plus or minus 95% confidence interval exposure response model)**



### Summary of issues

1. The optimum dose regimen is not clear as there is irregular evidence of a clinically significant increase in benefit with doubling of the erenumab dose from 70 mg once monthly to 140 mg once monthly.
2. Comparative efficacy data against placebo was provided only to 24 weeks. A synopsis of the final results for 48 weeks of active treatment was supplied but there is no 48 week comparison with placebo.

Erenumab has been proposed as a prophylactic treatment. This suggests long term use is intended. A decision on how long a patient is going to be treated needs to be made by the treating physician for each individual patient. It is standard practice for prophylactic treatment of migraine that treatment continuation needs to be re-evaluated in intervals of 3 to 6 months as per Australian Therapeutic Guideline, 'Neurology.'

3. Intermittent use of a mAb is not usual for other indications. Data on the effect of intermittent use has not been provided to the TGA, nor does it appear that the sponsor plans to assess benefit and risk when erenumab is used intermittently.
4. Placebo response rates were quite large with a 50% responder rate of 29.4% in Study 20120296, the pivotal study for EM. This is likely to make it difficult to determine which patients are benefiting from active treatment.
5. In the clinical trials, however differences from placebo in the reduction from Baseline in the mean number of migraine days per month were consistent across studies. The absolute difference was around 2 days per month for both EM and CM. This extent of benefit is relatively large for patients with EM but small for patients with CM.
6. A proportion of patients with either EM or CM receive a substantial benefit from treatment. About 16% more subjects with CM taking erenumab than placebo had a 50% reduction in the number of migraine days per month (from a mean of 20 days at Baseline). For subjects with EM 23.4% more subjects taking erenumab than placebo had a 50% reduction in the number of migraine days per month (from a mean of 8.3 days).



7. For subjects with CM and medication overuse the mean extent of benefit was similar to that of the overall CM population (the subgroup analyses of key efficacy endpoints is discussed).

### **Proposed action**

The Delegate had no reason to say, at the time, that the application for Aimovig should not be approved for registration, subject to negotiation of the PI and other conditions of registration.

### **Request for ACM advice**

The Advisory Committee on Medicines (ACM) is requested to provide advice on the following specific issues:

1. Does the committee consider that the available evidence supports a dose regimen of 70 mg once monthly with an increase to 140 mg once monthly only if there is an inadequate response?
2. Does the committee consider that long term use should not be permitted until the full report of the 12 month efficacy data from Study 20120296 is submitted to the TGA for evaluation?
3. Should patients be required to have a mandatory minimal treatment response to qualify for treatment beyond an initial period?

While this approach would reduce the number of patients receiving no or minimal benefit receiving ongoing treatment it is not clear what parameter should be measured to assess response to treatment, when it should be assessed, and what degree of response would be an appropriate minimum. Would the committee like to suggest appropriate limits?

4. Intermittent use of a mAb is not generally recommended. What are the committee's thoughts on intermittent use of erenumab as migraine prophylaxis?
5. Does the committee consider a minimum number of migraines per month or migraine days should be required prior to commencing erenumab treatment?
6. Erenumab is a new medicine and the first mAb to manage migraine. Should potential patients be required to have failed other prophylaxis treatments prior to being considered for erenumab?
7. Small numbers of subjects were taking concomitant migraine prophylaxis medications in the clinical trials. Does the committee consider that available evidence supports concurrent administration of erenumab with other migraine prophylactic medications?

### **Response from sponsor**

The sponsor welcomes the Delegate's and clinical evaluator's recommendation to approve Aimovig (erenumab). The Delegate has sought ACM advice on seven specific issues related to this application. The sponsor takes the opportunity in this pre-ACM response to acknowledge the revised proposed indication recommended for approval by the clinical evaluator and present our comments on each of these specific issues for consideration by ACM in the below section.

### ***Revised proposed indication***

The clinical evaluator, in their overview, has proposed a revised indication for Aimovig. In order to assure that the wording of the proposed indication in Australia is an accurate

representation of the submitted data, a reference to the 'Clinical trials' and 'Dosage and administration' sections of the PI is included. The revised proposed indication for ACM consideration is as follows:

*Aimovig is indicated for prophylaxis of migraine in adults. (Refer to 'Clinical trials' and 'Dosage and administration' for available data in chronic and episodic migraine).*

The sponsor believes that the proposed revised indication for Aimovig is appropriate and supported by the body of submitted clinical evidence.

#### **ACM advice sought on specific issues from the Delegate's overview**

[Information redacted]

#### **Concluding remarks**

The sponsor welcomes the Delegate's and clinical evaluator's recommendation to approve Aimovig (erenumab) for prophylaxis of migraine. We agree that there could be a place for 70 mg once monthly dose in clinical practice and that this would be an appropriate starting dose for some patients. However, the evidence presented in pivotal trial clearly shows that some patients will benefit more from a 140 mg once monthly starting dose, specifically patients who have failed prior prophylactic therapy and have few remaining treatment options. Long term efficacy data up to 12 months support the long term use of the erenumab. Safety and tolerability of both doses over 12 months were comparable to placebo. Hence, the restrictions proposed by the Delegate are not warranted. The proposed revised posology wording: 'The recommended dose of Aimovig is 70 mg or 140 mg administered once every 4 weeks. Some patients, especially patients who failed at least one other prophylactic pharmacotherapy, may benefit from a dose of 140 mg every 4 weeks' includes the TGA clinical evaluator's suggestion to use the higher dose in patients who failed prior treatment. This proposal is supported by the evidence presented in our submission and we believe will better meet the needs of all migraine patients and the specialists who will treat these patients. The sponsor seeks to discuss the final wording of the dosage with the Delegate in the post-ACM phase.

The sponsor looks forward to the ACM's deliberation in this matter.

#### **Advisory committee considerations<sup>63</sup>**

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Aimovig solution for injection containing 70 mg in 1.0 mL (70 mg/mL) of erenumab to have an overall positive benefit-risk profile for the revised proposed indication:

*Aimovig is indicated for prophylaxis of migraine in adults.*

The sponsor proposed indication at the time the ACM considered this application was:

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<sup>63</sup> The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

*Aimovig is indicated for prophylaxis of migraine in adults. (Refer to 'Clinical trials' and 'Dosage and administration' for available data in chronic and episodic migraine).*

In providing this advice the ACM:

- Agreed that there was a dose-response relationship observed particularly in the episodic migraine trials and that some patients would benefit from the higher dose (140 mg).
- Was of the view that long term use should be permitted based on the current safety data but the patient's response should be monitored and re-assessed at appropriate intervals.
- Advised that the Sponsor should monitor off label use in paediatric patients with migraine when erenumab is registered.
- Noted that fewer migraine days were not the only indicator of response and therefore a minimal treatment response was difficult to quantify.
- Agreed that it was consistent with current Guidelines to use erenumab for a period of time, cease then restart if required.
- Noted that specifying a minimum number of migraines per month in order to commence treatment with erenumab is too narrow and does not take into account other factors such as patient's quality of life.
- Was of the view that is highly likely that erenumab would be used as a second line treatment and therefore it was not necessary to specify that patients should have failed other prophylactic treatments.
- Agreed that erenumab should not be restricted for use as monotherapy as there does not appear to be a safety risk with concurrent use of current prophylactic therapies.
- Was of the view that treatment should be initiated by neurologists/headache specialists but that ongoing treatment could be prescribed by general practitioners.

#### ***Proposed conditions of registration***

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Include the ongoing 5 year extension Study 20120178 as a condition of registration.
- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA.
- Negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

#### ***Proposed PI/CMI amendments***

The ACM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Modify the proposed dosing statement as follows:
  - *'The recommended dose of Aimovig is 70 mg or 140 mg administered once every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks.'*
- Consideration for use of erenumab as a second line agent be included under the Precautions Section of the PI

- Wording regarding quality of life assessment in addition to assessment of the number of migraine days be included instead of information regarding the exploratory endpoints in the Clinical Trials section.

### ***Specific advice***

The ACM advised the following in response to the delegate's specific questions on the submission:

- 1. Does the committee consider that the available evidence supports a dose regimen of 70 mg once monthly with an increase to 140 mg once monthly only if there is an inadequate response?***

The ACM noted that the proposed dosage regimen was now 70 mg or 140 mg every 4 weeks, as opposed to once a month. The ACM considered that there was a dose-response relationship as demonstrated by the clinical trials (Studies 20120295 (CM)) and 21020296 (EM)), which was more evident in the episodic migraine trial. The ACM was of the view that some patients may require a higher starting dose and that flexibility was required to allow physician discretion to prescribe the appropriate dosage. The ACM noted the Sponsor's proposed wording regarding the dosage 'The recommended dose of Aimovig is 70 mg or 140 mg administered once every 4 weeks. Some patients, especially patients who failed at least one other prophylactic pharmacotherapy, may benefit from a dose of 140 mg every 4 weeks' and considered that the second part of the statement should be simplified as follows: '*Some patients may benefit from a dose of 140 mg every 4 weeks*'.

- 2. Does the committee consider that long term use should not be permitted until the full report of the 12 month efficacy data from Study 20120296 is submitted to the TGA for evaluation?***

The ACM noted there is an ongoing 5 year extension Study 20120178 which will be included as an additional pharmacovigilance activity in the sponsor's RMP (ASA). The ACM advised that this extension study should also be included as a condition of registration. The ACM considered that the sponsor should commit to involvement with an international migraine database, so that intermittent versus long term use could be part of the sub-analyses for this ongoing long term study.

The ACM was of the view that based on the safety data to date, that long term use of erenumab should be permitted but the patient's response should be monitored and the patient re-assessed at appropriate intervals.

The ACM also noted that no paediatric patients will be included in this long-term study and there are no current studies in paediatrics. The ACM was informed that Phase III paediatric studies were deferred until full Phase III data in adults is available, which will allow the establishment of the benefit-risk in migraine as well as a decision on dosing before starting the paediatric program.

The ACM advised that the sponsor should monitor for off label use in paediatric migraine patients when erenumab is marketed in Australia.

- 3. Should patients be required to have a mandatory minimal treatment response to qualify for treatment beyond an initial period? While this approach would reduce the number of patients receiving no or minimal benefit receiving ongoing treatment it is not clear what parameter should be measured to assess response to treatment, when it should be assessed, and what degree of response would be an appropriate minimum. Would the committee like to suggest appropriate limits?***

The ACM advised that fewer migraine days was not the only indicator of response and therefore a minimal treatment response was difficult to quantify. In addition, a mandatory

minimal treatment response such as the number of migraine days was too narrow an approach and does not take into account other factors. Other dimensions indicative of response include patient's quality of life or less severe headaches even if the number of migraine days remained the same.

The ACM discussed the following options which could be considered as a minimal treatment response to qualify for treatment:

- A headache diary prior to and after treatment with a reduction of 50% migraine days in 3 months from commencement (similar to Botox criteria).
- A quality of life score such as the HIT-6 score with a score reduction of > 3 after 3 months compared to pre-treatment considered as a clinically significant response.

However, overall, the ACM considered that a mandatory minimal treatment response was too narrow an approach and does not take into account the many factors involved in a response to treatment. The ACM agreed that treatment should only continue if effective and that an appropriate time for assessment of response is after 8 to 12 weeks of treatment.

**4. *Intermittent use of a mAb is not generally recommended. What are the committee's thoughts on intermittent use of erenumab as migraine prophylaxis?***

The ACM advised that in terms of rational use of medicine erenumab could be used for a period of time, ceased and then restarted if necessary, which is in accordance with the current Therapeutic Guidelines (Neurology) recommendation for the prophylactic treatment of migraine.

The ACM noted that patients with long standing migraine are generally compliant with their medication and that any issues with compliance to current prophylactics are due to poor tolerability, interactions and lack of effectiveness, rather than any fluctuating need for ongoing treatment.

The ACM noted that there are no data with regards to implications for the development of immunogenicity or formation of antibodies with intermittent use.

**5. *Does the committee consider a minimum number of migraines per month or migraine days should be required prior to commencing erenumab treatment?***

The ACM noted that although patients in the clinical trials had a minimum of 4 migraine days per month prior to initiating erenumab, specifying this as a minimum requirement to commence treatment is too narrow a requirement and does not take into account other factors such as patient's quality of life. In addition, some patients with more than 4 migraine days per month may not need to be treated with erenumab.

However, the ACM was of the view that initial prescribing of erenumab should be restricted to physicians who specialise in the treatment of migraine but that general practitioners should be allowed to prescribe ongoing therapy in order to facilitate equity of access. It would be preferable to use the clinical judgment of these specialists to assess if a patient would be a suitable candidate for erenumab rather than using the number of migraine days to restrict initial prescribing of erenumab. The ACM was of the view that the indication should not state that prescribing should be restricted to specialists as the evidence presented did not support this.

The ACM advised that wording regarding quality of life assessment in addition to assessment of the number of migraine days be included instead of information regarding the exploratory endpoints in the Clinical Trials section of the PI.

**6. *Erenumab is a new medicine and the first mAb to manage migraine. Should potential patients be required to have failed other prophylaxis treatments prior to being considered for erenumab?***

The ACM was of the view that erenumab would be most likely used by clinicians as a second-line therapy as it is a new therapy and it is given by injection rather than orally. Therefore, it is not necessary to specify that patients should have failed other prophylactic treatments. However, the ACM considered that information regarding preference for use of erenumab as a second-line agent could be included under the Precautions Section of the PI.

**7. *Small numbers of subjects were taking concomitant migraine prophylaxis medications in the clinical trials. Does the committee consider that available evidence supports concurrent administration of erenumab with other migraine prophylactic medications?***

The ACM considered that as there were many medicines available for prophylactic treatment of migraine that it was not pragmatic to prevent concurrent administration of these treatments. In addition, it would not be feasible to investigate systematically combination use of erenumab with all the agents currently available. If there are any DDIs of concern this will come to light in the post-market safety reports. The ACM considered that the risk-benefit of erenumab is acceptable and that to date there are no long term safety concerns.

## **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Aimovig (erenumab) 70 mg/mL solution for injection in prefilled pen and prefilled syringe, for the following indication:

*Aimovig is indicated for prophylaxis of migraine in adults.*

### **Specific conditions of registration applying to these goods**

- Aimovig (erenumab) is to be included in the Black Triangle Scheme. The PI and CMI for Aimovig must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Aimovig EU-RMP (version 1.0, dated 11 May 2017, data lock point 31 January 2017), with ASA (version 1.0, dated 8 June 2017), included with submission PM-2017-02174-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes.

- Batch release testing and compliance with Certified Product Details (CPD):
  - It is a condition of registration that all batches of Aimovig imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
  - It is a condition of registration that each batch of Aimovig imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index>.
  - The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact [Biochemistry.Testing@health.gov.au](mailto:Biochemistry.Testing@health.gov.au) for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at <https://www.tga.gov.au/publication/testing-biological-medicines>.
  - This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until the sponsor is notified in writing of any variation.
  - The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

## Attachment 1. Product Information

The PI for Aimovig approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Therapeutic Goods Administration**

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