NOVARTIS

Patient Safety & Pharmacovigilance

Erenumab

AMG334

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Erenumab
Product(s) concerned (brand name(s)):	Aimovig
Document status:	Final
Version number:	5.0
Data lock point for this RMP:	Clinical data lock point: 31-Jan-2017 Post-marketing data lock point: 16-May-2024
Date of final sign off:	10-Apr-2025

Rationale for submitting an updated RMP: The EU Risk Management Plan (RMP, v5.0) has been updated to reflect the completion of NIS CAMG334A2023 (PASS Category 3) study.

Summary of significant changes in this RMP:

The table below shows the major modifications/changes for Safety EU RMP v5.0 from EU RMP v4.0.

Part	Major changes compared to RMP v4.0
Part I	No change
Part II	Part II Module SV.1. Post-authorization exposure has been updated to reflect currently available post-authorization exposure. Part II Module SVII.2 has been updated. Part II Module SVII.3 has been updated to include data from Study CAMG334A2023.
Part III	Updated to mark completion of Study CAMG334A2023.
Part IV	No change
Part V	Part V.3 (Table 12-2) has been updated with removal of Study CAMG334A2023 as an additional PV activity.
Part VI	Part VI: Summary of the risk management plan has been updated to reflect the corresponding changes made to Parts II, III and V of the RMP.
Part VII Annexes	
Annex number	**Description of changes**
Annex 4	No change
Annex 6	No change

Others RMP versions under evaluation:

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 4.0

Approved with procedure: EMEA/H/C/004447/R/0024

Date of approval (EC decision): 20-Feb-2023

QPPV name: Dr. Justin Daniels PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

Term/Abbreviation	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AMPP	American Migraine Prevalence and Prevention
AMQ	Amgen MedDRA Query
AMG334	Erenumab
AUC	area under the curve
BDI-II	Beck Depression Inventory-II
BMI	body mass index
BP	blood pressure
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
C_{max}	maximum concentration
CPD(s)	chronic pain disorder(s)
CV	Cardiovascular
CVD	cardiovascular disease
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EM	episodic migraine
EOS	End of study
EPAR	European Public Assessment Report
EU	European Union
HIV	human immunodeficiency virus
IgG	Immunoglobulin G
IP	Investigational product
ISAS	Integrated safety analysis set
iv	intravenous, intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MS	multiple sclerosis
NIS	Non-interventional study
OLE	Open label extension
PFS	prefilled syringe
PK	Pharmacokinetics
Qm	Every four weeks
RMP	Risk Management Plan
SAE	Serious adverse event
sc	Subcutaneous(ly)
SCS	Summary of clinical safety
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA Query

SY	Subject years
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Erenumab (AMG334)
Pharmacotherapeutic group(s) (ATC Code)	N02CD01
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	Aimovig 70 mg solution for injection and 140 mg solution for injection in pre-filled syringe and in pre-filled pen
Invented name(s) in the European Economic Area (EEA)	Aimovig
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Human monoclonal immunoglobulin G2
	Summary of mode of action: Erenumab is a human monoclonal antibody that binds specifically to the calcitonin gene-related peptide (CGRP) receptor. The CGRP receptor is located at sites that are relevant to migraine pathophysiology, such as the trigeminal ganglion. Erenumab potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor, and has no significant activity against other calcitonin family of receptors. CGRP is a neuropeptide that modulates nociceptive signalling and a vasodilator that has been associated with migraine pathophysiology. In contrast with other neuropeptides, CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief. Intravenous infusion of CGRP induces migraine-like headache in patients.
	Important information about its composition: Erenumab is a human IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary cells.
Hyperlink to the Product Information	[Current SmPC]
Indication(s) in the EEA	Current: Aimovig is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.
	Proposed: Not applicable
Dosage in the EEA	Current: Aimovig is administered by subcutaneous (sc) injection. The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks.
	Proposed: Not applicable
	Current: Aimovig is a solution for injection. It is supplied as 70 mg of erenumab in 1.0 mL (70 mg/mL) solution in a single-use pre-

Pharmaceutical form(s) and strengths	filled syringe (PFS) or single-use pre-filled pen (syn. autoinjector) or 140 mg of erenumab in 1.0 mL (140 mg/mL) solution in single use PFS or single use pre-filled pen. Each 140 mg dose is given either as one subcutaneous injection of 140 mg or as two subcutaneous injections of 70 mg.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Prophylaxis of migraine in adults

2.1.1 Epidemiology of the disease

Table 2-1 Summary of Epidemiology of migraine in Adults

Incidence/prevalence	Migraine is the third most common disease in the world (Steiner et al 2013). Approximately 15% of the European and Canadian populations and 12% of the United States population suffer from migraine attacks (Stovner and Andree 2010; Lipton et al 2007).
Demographics of target population	The 1-year sex-stratified prevalence for episodic migraine (EM) was 17.1% for women and 5.6% for men, and for chronic migraine (CM), is 1.3% for women and 0.5% for men (Katsarava et al 2012). The 1-year prevalence peaks in mid-life (30 to 49 years) (26 to 27.3% in women and 8.1 to 9.7% in men) and is lower in children/adolescents and those > 60 years (7.5% in women and 2.5% in men) (Lipton et al 2001). In both sexes, the prevalence of migraine continues to fall at an increasing rate after the mid-60s (Victor et al 2010). The prevalence was found to be lower among black than white people. (Lipton et al 2007; Lipton et al 2002; Lipton et al 2001).
Risk factors for the disease	Migraine has been suggested to be comorbid with several disorders, including vascular diseases, epilepsy, asthma, allergies, irritable bowel syndrome, restless legs syndrome, and various chronic pain syndromes and psychiatric disorders (Vetvik and MacGregor 2017; Chang and Lu 2013; Rodriguez-Sainz et al 2013). First-degree relatives were found to have an increased risk for the same subtype of migraine as the patient, whereas spouses showed an increased risk only for migraine without aura, suggesting that migraine with aura is largely determined by genetic factors, whereas migraine without aura may be determined by a combination of genetic and environmental factors (Russell and Olesen 1995). Low socioeconomic status was also associated with an increased risk for migraine (Winter et al 2012a). A few non-modifiable and modifiable risk factors for migraine progression (or CM) were identified (Bigal et al 2015). Non-modifiable risk factors: • age (highest prevalence in mid-life) • female sex • white race • genetic factors Modifiable risk factors: • obesity • acute medication overuse • caffeine overuse • snoring and sleep apnea • psychiatric comorbidity and stressful life events.

Main treatment options	The treatment of acute migraine includes migraine specific medications and non-specific medications (Gilmore and Michael 2011; Aukerman et al 2002). Specific medications indicated for the acute treatment of migraine: • triptans • ergotamine Non-specific medications: • nonsteroidal anti-inflammatory drugs • opioids Prophylactic medications for prophylaxis of migraine are listed below (Silberstein et al 2009). [Note: all the products within the depicted classes have not been approved by the EMA, some are at the most locally approved in individual countries in the EU across both EM and CM] • beta blockers • selected calcium channel blockers • antidepressants • selected anticonvulsants • angiotensin-converting enzyme and angiotensin receptor antagonists • onabotulinumtoxin A (where approved only for CM)
Mortality and morbidity (natural history)	Migraine is ranked the seventh highest among specific causes of disability globally and the leading cause of disability among neurological disorders (Steiner et al 2013). There is no evidence for a higher all-cause mortality among individuals with migraine compared to non-migraine individuals (Åsberg et al 2016; Schürks et al 2011).

2.1.2 Important co-morbidities

Important co-morbidities include neurological disorders (stroke, epilepsy, vertigo), psychiatric disorders (suicidal ideation and depression), chronic pain disorders (CPD), respiratory disease (allergies/hay fever, and asthma), cardiovascular disease and related risk factors (myocardial infarction [MI], hypertension, and obesity), cerebrovascular disease (stroke and transient ischemic attack [TIA]), and adverse pregnancy/ fetal outcomes (Table 2-2).

Table 2-2 Summary of Epidemiology of Important Comorbidities for Episodic and Chronic Migraine in Adults

Target Population	Important Comorbidities in the Target Population
Cardiovascular diseases (major coronary heart disease, atrial septal aneurysm, hypertension):	
Incidence/prevalence	Migraine is associated with an increased risk of cardiovascular disease (CVD) (Sacco et al 2015); this association is strongest in young women with migraine with aura (Linstra et al 2017). There is evidence that migraine patients are at an increased risk of the following cardiovascular (CV) events when compared to patients without migraine: major cardiovascular disease including ischemic heart disease,

myocardial infarction, angina, coronary revascularization, venous thromboembolism, atrial fibrillation, atrial flutter and cardiovascular disease mortality (Adelborg et al 2018, Kurth et al 2016; Kurth et al 2006; Wang et al 2014).

In studies where migraine with aura was separately assessed, migraine with aura was consistently associated with a higher mortality rate due to cardiovascular diseases (Liew et al 2007, Gudmundsson et al 2010).

Background rates for venous thromboses for CV outcomes in migraine are presented below. Rates were estimated using the Amgen Sentinel system and the Market scan Commercial Claims Database, adult patients ages 18-65 years with migraine were identified from Jan-2010 through Dec-2011 using a combination of ICD-9 diagnosis codes (346.xx) and claims for acute migraine-specific medications (e.g. triptans or ergots) and followed through 30-Sep-2015 (to allow up to 5 years of follow-up).

Incidence rates of CV events in migraine patients per 1000-person years

Event	Event rate (95% CI) per 1000 person-years: Marketscan Database
Venous thromboembolism (including pulmonary embolism)	3.32 (3.24, 3.40)
Angina pectoris	1.56 (1.50, 1.61)
Myocardial Infarction	1.76 (1.70, 1.81)
Transient ischemic attack	3.48 (3.40, 3.56)
Ischemic stroke	2.81 (2.73, 2.88)

Source: Data on File

The table below presents the incidence rates for major coronary heart disease events in women and men with and without migraine. The estimates for men are based on an average of 15.7year follow-up in men 40 to 84 years of age participating in the Physician's Health Study (Kurth et al 2007). The estimates provided for women are based on an average of 10-year follow-up of women ≥ 45 years of age participating in the Women's Health Study (Kurth et al 2006).

Incidence/prevalence (continued)

Age-adjusted Incidence Rate of Major Coronary Heart Disease stratified by sex (per 100 000 person-years)

	Major CV events	MI	Coronary revascularization	Angina	Death due to CVD
Men					
No migraine	85	36	-	-	-
Migraine [a]	104	49	-	-	-
Women					
No migraine	200	85	177	137	44
Migraine [a]	248	110	288	256	79
Migraine with aura	383	167	303	231	95

[a] with or without aura

Cumulative Incidence (0-1 year) per 1000 (95% Confidence Intervals) of Major Coronary Heart Disease stratified by age in migraine patients

	MI	IS	PAD	VT	HF
<30 years	-	1.87 (1.35-2.56)	0.05 (0.01-0.3)	0.26 (0.10-0.60)	0.15 (0.05-0.45)
30-39	0.18 (0.04-0.66)	4.20 (3.14-5.55)	0.18 (0.04-0.66)	1.56 (0.95-2.47)	0.36 (0.13-0.91)
40-49	1.12 (0.60-1.97)	7.88 (6.29-9.79)	0.61 (0.26-1.30)	1.54 (0.91-2.51)	0.73 (0.33-1.48)
50-59	2.39 (1.38-3.95)	9.71 (7.46-12.46)	0.51 (0.15-1.47)	2.57 (1.52-4.18)	0.66 (0.23-1.65)
60+	5.90 (3.74-8.97)	24.75 (19.94-30.36)	1.20 (0.42-3.00)	6.46 (4.18-9.63)	4.10 (2.37-6.75)

MI = Myocardial Infarction, IS = Ischaemic Stroke, PAD = Peripheral artery disease, VT = Venous Thromboembolism, HF = Heart Failure

Adelborg et al 2018

The table below presents the prevalence of atrial septal aneurysm. The study by Carerj et al (2003) included 90 patients referred to a Headache Center in Italy. The study by Chambers et al (2013) included 90 migraine patients referred by specialists in London. And the study by Domitrz et al (2014) included 158 patients with migraine recruited from an outpatient migraine clinic in Poland.

	Prevalence atrial septal aneurysm (%)
No migraine[a,b]	1.9 to 6
All migraine[a,c]	15 to 16
Migraine without aura[b]	3.6
Migraine with aura[b]	28.5

[a] Domitrz et al 2014
[b] Carerj et al 2003
[c] Chambers et al 2013

Incidence/ prevalence (continued)

A few studies have reported that migraine is associated with an increased risk of hypertension (Rist et al 2018, Gardener et al 2016; Entonen et al 2014; Bigal et al 2010; Scher et al 2005).

The incidence of hypertension in women with migraine with aura was estimated to be 52.31%, and in women without aura was estimated to be 55.97% (mean follow-up 12.2 years). (Rist et al 2018).

There were several studies, which provided the prevalence of hypertension in migraine and non-migraine patients (table below). The prevalence was higher in CM (18.3% to 33.7%) (Chen et al 2012; Wang et al 2012; Buse et al 2010) than EM (9.8% to 27.9%) patients (Wang et al 2012; Payne et al 2011; Buse et al 2010).

Prevalence hypertension %

	US	Turkey	Finland	Taiwan	China	Brazil
Women no migraine[a]	47.8	-	-	-	-	-
Women migraine[a]	51.2	-	-	-	-	-
No migraine[b]	-	7	11.8	16.6	22.4	34.5
Migraine[b]	-	8	11.6	23.3	34.3	28.3 to 42.6

[a] Schürks et al 2012

[b] Wang et al 2012; Eren et al 2015; Santos et al 2015; Lau et al 2014; and Artto et al 2006

Mortality

Migraine Is associated with a significantly increased risk for cardiovascular disease mortality (hazard ratio 1.37, 1.02 to 1.83) (Kurth et al 2016). In studies where migraine with aura was separately assessed, migraine with aura was associated with a higher mortality rate due to CVD (Gudmundsson et al 2010; Liew et al 2007).

The table below presents the prevalence of CV mortality in a population based cohort study in Australia (n = 2331) over a mean 6-year follow-up.

Prevalence CV mortality %			
	All	Men	Women
No migraine	3.7	4.9	2.8
Migraine	2.3	0	3
Migraine without aura	1.4	0	1.8
Migraine aura	3.1	0	4.2

Cerebrovascular diseases (stroke and transient ischemic attack):

Incidence/prevalence

A systematic review suggests a 2-fold increased risk of ischemic stroke in patients with migraine with aura and a more than 2-fold increased risk of TIA in patients with migraine relative to subjects without migraine (Schürks et al 2009). Being female, age < 45 years, smoking and oral contraceptive use further increased the risk (Schürks et al 2009).

Based on an average of 10-year follow-up of women ≥ 45 years of age participating in the Women's Health Study, the age adjusted incidence rate (per 100 000 person-years) is presented below (Kurth et al 2006).

Age-adjusted Incidence Rate Ischemic Stroke (per 100 000 Person-years)	
Women no migraine	88
Women migraine	71
Women migraine aura	131

The prevalence of stroke in migraine patients was estimated to be around 1.6% to 2.5% (Chen et al 2012; Artto et al 2006). The prevalence in CM was found to be higher than EM in a US study (4.0% vs 2.2%) (Buse et al 2010), but not in a Taiwanese study (0.6% vs 1.2%) (Wang et al 2012).

	The prevalence of TIA was reported to be 1.2% and 0% among EM and CM, respectively, in a Taiwanese cross-sectional survey (Wang et al 2012). No other study reporting the incidence or prevalence of TIA in migraine patients was identified.
Mortality	No study on the mortality rate due to ischemic stroke related causes in migraine patients was identified.
Syncope	Thijs et al (2006) reported that in a Dutch population based study (n=476) that migraine patients have a higher lifetime prevalence of syncope compared to patients without migraine (46% vs 31%; p=0.001).
Psychiatric disorders (depression and suicidal ideation):	
Incidence/prevalence	Patients with migraine were found to be at a higher risk of depression and suicidal ideation than patients without migraine (Nović et al 2016). The risk was found to be further increased in patients with CM relative to patients with EM. The table below shows that the prevalence of depression in migraine patients tends to be higher than in non-migraine patients. Patients with CM have the highest prevalence.

Prevalence of Overall Depression		
	Country	**%**
No Migraine	US[a,b,c]	8.7 to 11.7
	Taiwan[d,e,f]	4.72
	Germany[g]	4.0
Migraine	US[a,b,c]	14.2 to 18.1
	Italy[h]	3.6 to 10.7
	Taiwan[d,e,f]	8.7 to 15.4
	Germany[g]	9.6
EM	US, Taiwan, Italy[i,j,k,l]	6.7 to 25.6
CM	US, Taiwan, Italy[i,j,k,l]	25.2 to 41.2

[a] Winter et al 2012b; [b] Schürks et al 2012; [c] Holroyd et al 2007; [d] Harnod et al 2015; [e] Lau et al 2014; [f] Chen et al 2012; [g] Rhode et al 2007; [h] Beghi et al 2007; [i] Buse et al 2012; [j] Wang et al 2012 [k] Buse et al 2010; [l] Mongini et al 2006.

A meta-analysis suggests a modest positive association between migraine and suicidal ideation (odds ratio [OR] = 1.31, 95% C I= 1.10 to 1.55) after adjusting for potential confounders (Friedman et al 2016). The table below shows the prevalence of suicide, which was estimated based on a population based health survey in Canada (Colman et al 2016).

Prevalence of Suicide (%)		
	No Migraine	Migraine
Suicide Ideation	0.8	2.2
Death by suicide	0.1	0

In a cross-sectional study in Korea, the prevalence of suicidal ideation was estimated to be 17.3% in patients with migraine and 3.8% in patients without migraine (Kim and Park 2014).

Mortality	There is evidence of an association between migraine and suicidal ideation, but not migraine and suicide (Colman et al 2016; Singhal et al 2014; Ilgen et al 2013).
Chronic pain disorders:	
Incidence/prevalence	Chronic pain has been shown to be highly comorbid with other pain disorders (Von Korff et al 2005) and increased headache frequency is correlated with increased comorbidity for chronic pain (Hagen et al 2002). The prevalence of CPD and other pain disorders was found to be higher in CM than in EM patients.

Prevalence of Chronic Pain Disorders (%)	
Episodic migraine[a]	10.6 to 18.9
Chronic migraine[a]	26.5 to 38.3

[a] Wang et al 2012; Payne et al 2011; Buse et al 2010

The prevalence of other pain disorders were consistently found to be higher in CM than EM patients: back pain (66.7% vs 61.0%) (Mongini et al 2006), arthritis (33.6% vs 22.2%), and chronic pain/fibromyalgia/rheumatoid arthritis (40.7% vs 20.1%) (Buse et al 2010).

Mortality	Not applicable.
Adverse pregnancy/fetal outcomes	
Incidence/prevalence	Approximately 75.0% of individuals with migraine are women, and the prevalence of migraine is the highest at reproductive age (Lipton et al 2007). However, limited data are available with regard to the risk of adverse pregnancy/infant outcomes in women with migraine and possible association with migraine treatment. These studies reported an increased risk of low birth weight and pre-term delivery in migraine patients (treated or non-treated) when compared to healthy women. The table below presents the prevalence for these outcomes.

In addition, a study in Sweden (Källén and Lygner 2001) found that women using acute migraine-specific medications (ergots or triptans) have an increased risk of pre-eclampsia when compared to migraine women without treatment.

Prevalence of Pregnancy Complications (%)			
	Migraine Triptans / Sumatriptan	Migraine No treatment	No migraine
Low birth weight[a,b] < 2500g	3.4 to 4.3	5.8 to 6.0	1.9 to 4
Preterm delivery[a,b]	6.3 to 14.7	3.4 to 9.9	5.9 to 7.3
Major congenital[b]	5.7	6	5.1

[a] Olesen et al 2000; [b] Nezvalova-Henriksen et al 2010

In a population-based database study in Taiwan, women with migraine were found to be at a higher risk for giving birth to infants with low-birth weight (OR = 1.16, 95% [confidence interval] CI = 1.03 to 1.31, p = 0.014), experience a preterm delivery (OR = 1.24, 95% CI = 1.13-1.39, p < 0.001), pre-eclampsia (1.34 [95% CI = 1.02-1.77,

p = 0.027)], or delivery by caesarean section for preterm births (OR = 1.16, 95% CI = 1.07-1.24, p < 0.001) (Chen et al, 2010). A meta-analysis found that triptan-exposed migraine patients had a higher risk of spontaneous abortions and migraine patients without triptan treatment had a higher risk of congenital malformations relative to healthy patients (Marchenko 2015).

Mortality: Not applicable.

Asthma/allergy

Incidence/prevalence: Several epidemiologic and clinical-based studies have demonstrated an association of migraine with asthma and allergy (Aamodt et al 2007; Davey et al 2002; Strachan et al 1996; Chen and Leviton 1990). The table below presents the prevalence of asthma in different countries. The study by Chen et al (2012) is the only one matched for age, gender, urbanization level of residence and income.

Prevalence of Asthma		
	Country	%
No migraine	Taiwan[a]	1.2
	Turkey[b]	5
Migraine	Turkey[b]	3.9
EM	US[c]	17.2
CM	Taiwan[a]	3.5
	US[c]	24.4

[a] Chen et al, 2012; [b] Eren et al 2015; [c] Buse et al 2010

In a Finnish study, the prevalence of allergy was reported to be 34.0% and 22.0% in migraine patients with and without family history of migraine, respectively (Artto et al 2006). In a US study, CM patients were found to have higher prevalence of asthma (24.4%) and allergy (59.9%) than EM patients (17.2% and 50.7%, respectively) (Buse et al 2010).

Mortality: Not applicable.

Obesity

Incidence/prevalence: Obesity has been shown to be associated with both episodic and chronic headache among reproductive age subjects in multiple studies. However, such association was not observed in post-reproductive-aged individuals (Evans et al 2012), which may be due to the different impact or implication of a given body mass index (BMI) for younger vs older individuals and the insufficiency of BMI in indicating adiposity in an older population (Peterlin et al 2010; Prentice and Jebb 2001).

The table below presents the incidence of obesity (BMI ≥ 30 kg/m^2) after 12.9 years of follow-up in a US prospective cohort study (Winter et al, 2012b).

Incidence of Obesity (%)	
No migraine	3.7
Migraine	4.5

Prevalence of Obesity		
	Countries	%

No migraine	Australia, Brazil, Canada, France, Germany, Italy, Spain, Sweden, Taiwan, UK, USA[a,b,c,d]	17 to 24.5
Migraine	Australia, Brazil, Canada, France, Germany, Italy, Spain, Sweden, Taiwan, UK, USA[a,b,c,d]	16.5 to 25.8
CM	Germany[c,e]	19.7 to 24.3
	US[f]	25.5
EM	Germany[c,e]	12.0 to 17.6
	US[f]	21.0

[a] Santos et al 2015; [b] Schürks et al 2012; [c] Payne et al 2011; [d] Mattsson 2007; [e] Schramm et al 2013; [f] Buse et al 2010

Mortality: Not applicable.

Irritable bowel syndrome

Incidence/prevalence: The incidence rate of irritable bowel syndrome was estimated to be 73.87 per 10 000 person-years in individuals with migraine and 30.14 per 10 000 person-years in individuals without migraine in a Taiwanese study (Lau et al 2014).

The prevalence of celiac disease was reported to be 4.4% in individuals with migraine and 0.4% in individuals without migraine in an Italian study (Gabrielli et al 2003).

Mortality: Not applicable.

Multiple sclerosis

Incidence/prevalence: Several studies support the association of migraine and multiple sclerosis (MS) (Gelfand et al 2013; Pakpoor et al 2012). A meta-analysis concluded that MS patients are more than twice as likely to report migraine than controls with no neurological conditions (OR = 2.60 (95% CI 1.12 to 6.04) (Pakpoor et al 2012). Most of the studies, except one, had MS patients as their population of study.

The only cohort study identified that assessed a migraine population was the study by Kister et al (2012), who estimated the incidence of MS in patients with migraine using data from the Prospective Nurses' Health Study II. The authors concluded that the women with pre-existing migraine have a statistically significant 39% higher risk of developing MS compared with women without migraine after adjusting for confounders.

The table below presents the cumulative incidence of developing MS in women over a 15-year follow-up.

Cumulative incidence of developing MS in women %			
No migraine	Taiwan	0.32	Kister et al 2012
Migraine	Taiwan	0.47	Kister et al 2012

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage

Study Type	Key Safety Finding	Relevance to Human Usage
Repeat-dose toxicity	In the repeat-dose toxicology studies, anti-erenumab binding and/or neutralizing antibodies were observed in few animals with associated light microscopic changes consistent with immune mediated pathology secondary to development of circulating anti erenumab immune complexes.	Administration of human proteins to cynomolgus monkeys is often associated with development of antibodies to the human protein, but antigenicity in animal models has low predictive value and overestimates immunogenicity rates and the incidence of adverse immune-mediated events in human subjects (Ponce et al 2009; Bugelski and Treacy 2004; Koren et al 2002).
Safety Pharmacology	There were no biologically significant erenumab-related changes in heart rate, blood pressure (BP), body temperature, respiration rate, electrocardiographic, or neurological assessments.	There were no erenumab-related changes in hemodynamic parameters animals treated with up to 38-fold (based on C_{max}) over the therapeutic dose of 140 mg qm.
Reproductive/development	There were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive organs) in chronic toxicology study in sexually mature monkeys at systemic exposures (based on AUC) up to 123-fold higher than the clinical dose of 140 mg qm. In an enhanced prenatal/postnatal developmental toxicity study in female cynomolgus monkeys, erenumab was well tolerated with no evidence of maternal toxicity, no effects on fetal/infant losses, and no effects on infant growth or development through 6 months postpartum with doses which provide exposure margins of 17-fold (based on AUC) over the therapeutic dose of 140 mg qm.	Erenumab, like other IgG antibodies, crosses the placental barrier (Moffat et al 2014; Hurley and Theil 2011; Van de Perre 2003). Animal studies are not always predictive of human response and therefore, it is not known whether erenumab can cause fetal harm when administered to a pregnant woman.
Genotoxicity	The mutagenic potential of erenumab has, in alignment	There were no nonclinical safety findings in the repeat dose

	with the relevant regulatory guidance ICH S2 (R1) not been evaluated; monoclonal antibodies are not expected to enter cell nuclei and interact with or alter DNA or chromosomes.	toxicology studies with doses which provide exposure margins of 123-fold (based on AUC) over the therapeutic dose of 140 mg qm. Genotoxicity testing is not applicable to biologics per ICH S2 (R1) guidance.
Carcinogenicity	No nonclinical studies were conducted to assess carcinogenic risk as these assays are not feasible for erenumab because it is a monoclonal antibody that does not have biologic activity in rodents. There is no direct evidence linking CGRP-receptor antagonism and malignancy. The assessment based on weight of evidence from available scientific literature on immune function, cell proliferation and phenotypic characteristics of knockout models concludes that chronic clinical use of erenumab will not be associated with a carcinogenic risk.	There was no evidence of histopathological changes of neoplasia including, cellular hypertrophy, cellular hyperplasia, tissue injury and/or inflammation in the repeat dose toxicology studies with doses which provide exposure margins of 123-fold (based on AUC) over the therapeutic dose of 140 mg qm.

Table 3-2 Conclusions on Safety Concerns Based on Nonclinical Data

Safety Concerns
Important identified risks (confirmed by clinical data)
Not applicable
Important potential risks (not refuted by clinical data or are of unknown significance)
Not applicable
Missing information
Not applicable

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII.2. Clinical trial exposure

A total of 2537 subjects/migraine patients (2310.3 SY of exposure) have been exposed to at least 1 dose of erenumab: 2128 subjects have been exposed to 70 mg (1673.1 SY of exposure) at any time and 1198 subjects have been exposed to 140 mg (589.4 SY of exposure) at any time (Table 4-1). Note that the 140 mg dose was administered as 2 injections of 70 mg. Clinical trial exposure in this RMP is presented till data lock point of EU RMP version 1.4 of original submission (31Jan2017).

Table 4-1 SIII.1: Summary of Subject-years of Exposure to erenumab by Dose Level (Integrated Safety Analysis Set – erenumab Subjects Only)

	12-Week Placebo-controlled Pool		24-Week Placebo-controlled Pool		Erenumab through OLE Pool		Erenumab Long-term Pool		All Subjects	
Dose level of Erenumab	n	Subject-years	n	Subject-years	n	Subject-years	n	Subject-years	n	Subject-years
7 mg	108	24.4	0	0.0	0	0.0	0	0.0	108	24.4
21 mg	105	23.5	0	0.0	0	0.0	0	0.0	105	23.5
70 mg	893	200.7	314	137.5	2128	1673.1	1069	1209.4	2128	1673.1
140 mg	507	114.3	319	139.4	1198	589.4	817	420.6	1198	589.4
70 mg and / 140 mg	1400	315.0	633	276.9	2499	2262.5	1198	1630.1	2499	2262.5
All doses	1613	362.9	633	276.9	2499	2262.5	1198	1630.1	2537	2310.3

Integrated safety analysis set (ISAS): all subjects in the studies/pool who have received at least one dose of investigational product (IP).

n = number of subjects with available data. Subject-years = time from first dose of erenumab through MIN (last IP dose date +27, data cut-off date, end of study (EOS) date).

12-Week Placebo-controlled Pool: all subjects from studies 20120178, 20120295, 20120296, and 20120297 in the ISAS.

24-Week Placebo-controlled Pool: all subjects from study 20120296 in the ISAS.

Erenumab through OLE pool: all subjects enrolled in studies 20120178, 20120295, 20130255, 20120296, and 20120297 who received at least one dose of erenumab (70 mg or 140 mg).

Erenumab long-term pool: all subjects in the erenumab through OLE pool who have a minimum of 1 year's continuous exposure (phases combined) to erenumab (70 mg, 140 mg or both).

All subjects: all subjects from studies 20120178, 20120295, 20130255, 20120296, and 20120297 in the ISAS.

Total exposure time is summed across phases/studies. The erenumab through OLE pool and the erenumab long-term pool will only summarize exposure to erenumab 70 mg and/or erenumab 140 mg. OLE = Open Label Extension.

Source: SCS Table 4

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 ≥ 3 months, 2066 subjects (81.4%) were exposed to erenumab for ≥ 6 months, and 1214 subjects (47.8%) were exposed to erenumab for ≥ 12 months (Table 4-2).

Table 4-2 SIII.2: Overall Extent of Exposure to Erenumab by Duration of Exposure and Doses Received (Integrated Safety Analysis Set - Erenumab Subjects Only)

	12-Week Placebo-controlled Pool (N = 1613)	24-Week Placebo-controlled Pool (N = 633)	Erenumab through OLE Pool (N = 2499)	Erenumab Long-term Pool (N = 1198)	All Subjects (N = 2537)
Duration of exposure (weeks)					
N	1613	633	2499	1198	2537
Mean	11.7	22.8	47.2	71.0	47.5
SD	1.2	3.9	31.6	29.0	33.0
Median	12.0	24.0	46.4	53.0	46.4
Q1, Q3	11.9, 12.0	23.7, 24.0	25.6, 52.7	52.0, 65.9	24.9, 52.7
Min, Max	1, 15	2, 26	0, 159	46, 159	0, 159
Duration of exposure by time - n (%)					
≥ 1 dose	1613 (100.0)	633 (100.0)	2499 (100.0)	1198 (100.0)	2537 (100.0)
≥ 3 months	1556 (96.5)	609 (96.2)	2358 (94.4)	1198 (100.0)	2392 (94.3)
≥ 6 months	0 (0.0)	581 (91.8)	2057 (82.3)	1198 (100.0)	2066 (81.4)
≥ 12 months	0 (0.0)	0 (0.0)	1198 (47.9)	1198 (100.0)	1213 (47.8)
≥ 18 months	0 (0.0)	0 (0.0)	287 (11.5)	287 (24.0)	291 (11.5)
Doses received - n (%)					
1	26 (1.6)	11 (1.7)	55 (2.2)	0 (0.0)	58 (2.3)
2-3	1587 (98.4)	28 (4.4)	174 (7.0)	0 (0.0)	202 (8.0)
4-6	0 (0.0)	594 (93.8)	365 (14.6)	0 (0.0)	366 (14.4)
7-13	0 (0.0)	0 (0.0)	1327 (53.1)	620 (51.8)	1323 (52.1)
14-20	0 (0.0)	0 (0.0)	298 (11.9)	298 (24.9)	306 (12.1)
≥ 21	0 (0.0)	0 (0.0)	280 (11.2)	280 (23.4)	282 (11.1)

Integrated safety analysis set (ISAS): all subjects in the studies/pool who have received at least one dose of IP.

N = Number of subjects in the analysis set; n = number of subjects with available data; % = n/N * 100.

12-Week Placebo-controlled Pool: all subjects from studies 20120178, 20120295, 20120296, and 20120297 in the ISAS.

24-Week Placebo-controlled Pool: all subjects from study 20120296 in the ISAS.

Erenumab through OLE pool: all subjects enrolled in studies 20120178, 20120295, 20130255, 20120296, and 20120297 who received at least one dose of erenumab (70 mg or 140 mg).

Erenumab long-term pool: all subjects in the erenumab through OLE pool who have a minimum of 1 year's continuous exposure (phases combined) to erenumab (70 mg, 140 mg or both).

All subjects: all subjects from studies 20120178, 20120295, 20130255, 20120296, and 20120297 in the ISAS.

	12-Week Placebo-controlled Pool (N = 1613)	24-Week Placebo-controlled Pool (N = 633)	Erenumab through OLE Pool (N = 2499)	Erenumab Long-term Pool (N = 1198)	All Subjects (N = 2537)

Total exposure time is summed across phases/studies. The erenumab through OLE pool and the erenumab long-term pool will only summarize exposure to erenumab 70 mg and/or erenumab 140 mg

Duration of exposure by time is defined as: ≥ 3 months - subjects receiving week 8 dose or later; ≥ 6 months - subjects receiving week 20 dose or later; ≥ 12 months - subjects receiving week 48 dose or later and ≥ 18 months - subjects receiving week 72 dose or later.

OLE = Open Label Extension.

Source: SCS Table 5

For subjects with continuous exposure, 1598 (63.0%) received 70 mg and 768 (30.3%) received 140 mg for ≥ 6 months; 682 (26.9%) and 134 (5.3%) received 70 mg and 140 mg for ≥ 12 months, respectively (Table 4-3).

Table 4-3 SIII.3: Overall Extent of Continuous Exposure to erenumab (Integrated Safety Analysis Set – erenumab Subjects Only)

	Number of subjects exposed to erenumab (N=2537)			
	≥ 3 months	≥ 6 months	≥ 12 months	≥ 18 months
Dose level	n (%)	n (%)	n (%)	n (%)
Any dose	2392 (94.3)	2066 (81.4)	1213 (47.8)	291 (11.5)
70 mg	1969 (77.6)	1598 (63.0)	682 (26.9)	287 (11.3)
140 mg	1067 (42.1)	768 (30.3)	134 (5.3)	0 (0.0)
70 mg and/or 140 mg	2358 (92.9)	2057 (81.1)	1198 (47.2)	287 (11.3)

Integrated safety analysis set (ISAS): all subjects in the studies/pool who have received at least one dose of IP.

N = Number of subjects in the analysis set; n = number of subjects with available data; % = n/N * 100.

Subjects in the 70 mg and/or 140 mg received either 70 mg, 140 mg or a combination of both doses.

Duration of exposure is defined as: ≥ 3 months - subjects receiving week 8 dose or later; ≥ 6 months - subjects receiving week 20 dose or later; ≥ 12 months - subjects receiving week 48 dose or later and ≥ 18 months - subjects receiving week 72 dose or later.

Source: SCS Table 6

Table 4-4 SIII.4: Cumulative Subject Exposure to erenumab in Completed erenumab Trials, by Age Group and Sex (Safety Analysis Set)

	Male		Female		Total	
Age Group	Number of Subjects	Subject-Years	Number of Subjects	Subject-Years	Number of Subjects	Subject-Years
Healthy volunteers						
>0 to <18 years	0	0.0	0	0.0	0	0.0
18 to <65 years	350	29.86	263	20.56	613	50.42
≥ 65 years	0	0.0	0	0.0	0	0.0
Total	350	29.86	263	20.56	613	50.42
Migraine patients						

	Male		Female		Total	
Age Group	Number of Subjects	Subject-Years	Number of Subjects	Subject-Years	Number of Subjects	Subject-Years
>0 to <18 years	0	0.0	0	0.0	0	0.0
18 to <65 years	57	12.51	339	76.76	396	89.27
≥ 65 years	0	0.0	0	0.0	0	0.0
Total	57	12.51	339	76.76	396	89.27
Women with hot flashes associated with menopause						
>0 to <18 years	-	-	0	0.0	0	0.0
18 to <65 years	-	-	50	3.83	50	3.83
≥ 65 years	-	-	0	0.0	0	0.0
Total	-	-	50	3.83	50	3.83
All						
>0 to <18 years	0	0.0	0	0.0	0	0.0
18 to <65 years	407	42.37	652	101.16	1059	143.52
≥ 65 years	0	0.0	0	0.0	0	0.0
Total	407	42.37	652	101.16	1059	143.52

Subjects who received at least one dose of erenumab were included in the analysis.

Length of exposure is calculated up to MIN (last IP dose date +27, EOS date, snapshot date).

The completed studies included are: 20101267, 20101268, 20120130, 20120180, 20120295, 20150149, 20140255, 20140477, 20150334.

Source: Core RMP v2 Table 7

Table 4-5 SIII.5: Demographic and Baseline Characteristics (Integrated Safety Analysis Set)

		Erenumab			
	Placebo (N = 1043)	7 mg or 21 mg (N = 213)	70 mg (N = 893)	140 mg (N = 507)	Total (N = 2656)
Age (years)					
N	1043	213	893	507	2656
Mean	41.8	40.0	41.7	41.3	41.5
SD	11.1	11.6	11.2	11.2	11.2
Median	42.0	41.0	43.0	43.0	42.0
Q1, Q3	33.0, 50.0	30.0, 50.0	34.0, 50.0	33.0, 50.0	33.0, 50.0
Min, Max	18, 66	18, 60	18, 65	18, 65	18, 66
Sex - n (%)					
Male	174 (16.7)	41 (19.2)	138 (15.5)	76 (15.0)	429 (16.2)
Female	869 (83.3)	172 (80.8)	755 (84.5)	431 (85.0)	2227 (83.8)
Ethnicity - n (%)					
Hispanic/Latino	86 (8.2)	18 (8.5)	55 (6.2)	32 (6.3)	191 (7.2)
Not Hispanic/Latino	957 (91.8)	195 (91.5)	838 (93.8)	475 (93.7)	2465 (92.8)
Race - n (%)					
American Indian or Alaska Native	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.1)
Asian	14 (1.3)	1 (0.5)	11 (1.2)	4 (0.8)	30 (1.1)
Black or African American	74 (7.1)	16 (7.5)	59 (6.6)	24 (4.7)	173 (6.5)
Multiple	4 (0.4)	0 (0.0)	3 (0.3)	0 (0.0)	7 (0.3)
Native Hawaiian or Other Pacific Islander	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.1)
White	934 (89.5)	195 (91.5)	813 (91.0)	475 (93.7)	2417 (91.0)
Other	13 (1.2)	1 (0.5)	7 (0.8)	2 (0.4)	23 (0.9)
Region - n (%)					
North America	544 (52.2)	115 (54.0)	471 (52.7)	248 (48.9)	1378 (51.9)
Other[a]	499 (47.8)	98 (46.0)	422 (47.3)	259 (51.1)	1278 (48.1)

[a] Other includes Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Norway, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, the Netherlands.
Integrated safety analysis set: all subjects in the studies/pool who have received at least one dose of IP.
N = Number of subjects in the analysis set; n = Number of subjects with non-missing values; % = n/N × 100.
Source: SCS Table 10

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Hypersensitivity to the active substance or to any of the excipients	This is a standard precautionary measure for any new biological until additional clinical experience has been gained.	No	Across the clinical development program, there were no cases of serious hypersensitivity events attributed to erenumab. There were no noticeable imbalances in any hypersensitivity events between placebo and erenumab.
Older than 50 years of age at migraine onset	To ensure a homogenous disease population and interpretability of efficacy results, as older individuals with different types of new onset headache disorders are sometimes misdiagnosed with migraine. Migraine onset is typically during adolescence, and in most cases, occurs by 40 years of age. When “migraine” onset occurs after age 50, the diagnosis should be questioned given a higher probability of secondary headache disorders in this population.	No	It is rare, but not impossible, for migraine onset to occur later in life. In patients who have late onset migraine, the pathophysiology is considered to be the same as earlier onset migraine.
Adults > 65 years of age upon entry into screening	To ensure a homogenous disease population and interpretability of results. Erenumab	No	Migraine gets attenuated with increasing age and the need for migraine prophylaxis is lower in elderly patients >65 years.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	development has focused on establishing safety and efficacy in a general population that did not include special populations.		Clinical trial data did not show age dependent AEs, and given that migraine attenuates in the elderly and that we inform prescribers in the SmPC, this is not a missing information or a risk that would need to be managed further.
No therapeutic response with > 2 of 7 (EM) or > 3 of 7 (CM) protocol-defined medication categories for prophylactic treatment of migraine after an adequate therapeutic trial.	To exclude subjects who have demonstrated a general nonresponse to available prophylactic treatment approach, which if included might obscure interpretability of overall efficacy results.	No	Nonresponse to prior treatment with other medications is not expected to have an impact on the safety.
Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain)	To ensure a homogenous disease population and interpretability of results, as subjects with other active pain disorders may confound efficacy results.	No	In patients with chronic pain and migraine, the pathophysiology of migraine is considered to be the same as in migraine patients without chronic pain.
History of major psychiatric disorder (such as schizophrenia and bipolar disorder), or current evidence of depression based on a Beck Depression Inventory-II (BDI-II) total score > 19 at screening. Subjects with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable with BDI-II ≤ 19 and are taking no more than 1 medication for each disorder. Subjects must	Patients with a major psychiatric disorder or unstable depression or anxiety, as well as subjects with BDI II total score > 19 at screening, would be at increased risk of noncompliance with the protocol; and therefore, their inclusion might result in a higher dropout rate and/or make interpretation of efficacy data difficult. Inclusion of patients with unstable depression and anxiety may confound safety	No	Given the very low central nervous system penetration (< 1%) by monoclonal antibodies such as erenumab due to the blood brain barrier (Pardridge 2007; Rubenstein et al 2003), exacerbation of an underlying psychiatric condition would not be expected.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
have been on a stable dose within the 3 months prior to the start of the baseline phase.	assessment of erenumab.		
History of seizure disorder or other significant neurological conditions other than migraine. Note: A single childhood febrile seizure is not exclusionary.	Inclusion of patients with seizure disorders may confound safety assessment of erenumab.	No	Given the very low central nervous system penetration (< 1%) by monoclonal antibodies such as erenumab due to the blood brain barrier (Pardridge 2007; Rubenstein et al 2003), exacerbation of an underlying seizure or other neurological disorder would not be expected.
Human immunodeficiency virus (HIV) infection by history	Inclusion of this condition would interfere with an appropriate assessment of efficacy and safety because this condition and its treatment are associated with an increase in adverse events.	No	Erenumab is not an immunomodulator and is not expected to have an effect on B or T cell function.
Hepatic disease by history or total bilirubin ≥ 2.0 x upper limit of normal (ULN) or alanine transaminase or aspartate aminotransferase ≥ 3.0 x ULN, as assessed by the central laboratory at initial screening	Inclusion of this condition would interfere with an appropriate assessment of safety.	No	The liver is not a major route of IgG elimination. No evidence of hepatic toxicity (either by histopathology or transaminase elevation) was observed with repeated-dose erenumab administration in nonclinical toxicology studies in cynomolgus monkeys up to 6 months corresponding to approximately a 123-fold margin over the clinical dose of 140 mg
Significantly impaired renal function as determined by an estimated glomerular filtration rate (eGFR) of ≤	Inclusion of this condition would interfere with an appropriate assessment of safety.	No	Population pharmacokinetic analysis of integrated data from the erenumab clinical trials did not reveal a difference in

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
30 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease equation as assessed by the central laboratory at screening			the pharmacokinetics of erenumab in patients with mild or moderate renal impairment relative to those with normal renal function. No dose adjustment is recommended in patients with renal impairment since erenumab, as a human immunoglobulin G, is not excreted by the kidneys and renal clearance is not a major clearance pathway for erenumab.
MI, cerebrovascular accident, TIA, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening	Inclusion of these conditions would interfere with an appropriate assessment of safety profile for the majority of the indicated population because these conditions and their treatments are associated with an increase in adverse events.	No	A review of the non-clinical and clinical data did not identify an increased risk of cardiovascular events in subjects treated with erenumab. Because CGRP is a vasodilator, inhibition of the CGRP effects may theoretically interfere with compensatory vasodilation, particularly in ischemia related diseases, therefore the use in patients with MI, cerebrovascular accident, TIA, unstable angina is considered as an important potential risk.
Botulinum toxin injections (or treatment) in the head and/or neck region within 4 months prior to screening/the start of the baseline phase or during the baseline phase	To ensure a homogenous disease population and interpretability of efficacy results. A wash out/recovery period after prior botulinum toxin treatment was required before initiating treatment with erenumab to ensure clinical study efficacy results were not confounded by recent	No	It is not expected to have an impact on the safety.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
	botulinum toxin exposure. Four months is considered sufficient for any effect of botulinum toxin injection of the head/neck to have worn off.		
The subject is at risk of self-harm or harm to others as evidenced by past suicidal behavior or selection of items 4 or 5 on the Columbia Suicide Severity Rating Scale assessed at screening.	Inclusion of such patients could make it difficult to ascertain whether treatment emergent suicidal ideation and behavior was related to erenumab vs a preexisting risk.	No	A review of the safety data did not find increased risk of suicidal behaviors in subjects treated with erenumab.
Malignancy within the 5 years prior to screening, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ	Inclusion of patients with a high chance of malignancy recurrence could make it difficult to ascertain whether treatment emergent malignancy events were related to erenumab.	No	A review of the safety data did not find increased risk of malignancy in subjects treated with erenumab.
Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates)	Patients with alcoholism and drug abuse are less likely to be compliant with the protocol and might have adverse events associated with their addiction (e.g., hepatotoxicity).	No	The liver is not a major route of IgG elimination. No evidence of hepatic toxicity (either by histopathology or transaminase elevation) was observed with repeated-dose erenumab administration in nonclinical toxicology studies in cynomolgus monkeys up to 6 months corresponding to approximately a 123-fold margin over the clinical dose of 140 mg. Similarly, in the clinical program, there was no evidence of hepatotoxicity based on review of either hepatic disorder events or

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			review of hepatic laboratory data.
Pregnant or a female expecting to conceive during the study, including through 16 weeks after the last dose of investigational product	Due to potential safety concerns in pregnant women, enrollment in clinical studies is not generally permitted	Yes	Not applicable
Breastfeeding or a female expecting to breastfeed during the study, including through 16 weeks after the last dose of investigational product	Due to potential safety concerns in lactating women, enrollment in clinical studies is not generally permitted	No	No data are available on the potential transfer of erenumab in the breast milk, however, higher exposure in utero in nonclinical studies had no adverse effects on the neonate/infant. It is known that there is low transfer of immunoglobulins such as erenumab to milk and there is also limited systemic uptake into the neonatal and infant circulation.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Table 5-2 Limitations Common to All Clinical Trials

Ability to Detect Adverse Drug Reactions (ADRs)	Limitation of Trial Program	Discussion of Implications for Target Population
Rare ADRs	A total of 2537 subjects were exposed to erenumab in the clinical study program.	If zero incidence was observed for a given ADR in the clinical program (i.e., a rare ADR), using the 3/n rule, it was concluded with 95% confidence that the true incidence rate will be lower than 3/2537 (0.0012).
ADRs due to prolonged exposure	No subjects were exposed to erenumab for ≥ 3 years in the clinical study program. A total of 291 subjects were exposed to erenumab for ≥ 18 months in the clinical study program.	As the exposure duration was less than 3 years to date in the clinical study program, there has been no opportunity to observe ADRs that might occur with prolonged exposure or prolonged latency.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-3 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure/Representation in Clinical Trial Program
Pediatric patients	The safety of erenumab has not yet been established in pediatric patients. Erenumab will be evaluated in pediatric subjects in separate studies.
Geriatric patients > 65 years old	No migraine subjects > 65 years old were enrolled in the erenumab clinical program. Overall, migraine prevalence decreases after age 50 years and in women after menopause, unless estrogen replacement therapy is administered. In both sexes, the prevalence of migraine continues to fall at an increasing rate in the age of mid-60s (Victor et al 2010).
Pregnant women	Pregnant women were excluded from the clinical trials, though a small number of pregnancies has been reported in the erenumab clinical program. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Animal studies are not always predictive of human response and it is therefore not known whether erenumab can cause fetal harm when administered to a pregnant woman. As a precautionary measure, it is preferable to avoid the use of erenumab during pregnancy.

Breastfeeding woman	Lactating women were excluded from the clinical trials. There were no reports of women taking erenumab while breastfeeding in the erenumab clinical program.
Patients of different race or ethnic origin	While most subjects enrolled in clinical studies were White, subjects from other races or ethnicities were also enrolled in the clinical studies (Table 4-5). In the clinical studies, adverse events, serious adverse events, and adverse events leading to discontinuations by race were consistent with overall results. In addition, pharmacokinetics (PK) of erenumab was found to be similar between Japanese and White healthy subjects.
Patients with severe renal impairment	Population pharmacokinetic analysis of integrated data from the erenumab clinical trials did not reveal a difference in the pharmacokinetics of erenumab in patients with mild or moderate renal impairment relative to those with normal renal function. Elimination of erenumab likely occurs via 2 mechanisms: nonspecific catabolism (as for other IgGs) and degradation of the erenumab-CGRP receptor complex. The pharmacokinetics of monoclonal antibodies are not expected to be modified by impaired renal function.
Patients with moderate to severe hepatic impairment	No pharmacokinetic studies of erenumab have been conducted in patients with hepatic impairment. Elimination of erenumab likely occurs via 2 mechanisms: nonspecific catabolism (as for other IgG) and degradation of the erenumab-CGRP receptor complex. Thus, the pharmacokinetics of erenumab are not expected to be affected by hepatic impairment, and studies in these conditions are not planned.

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

Novartis

Novartis' estimates of post-marketing patient exposure (excluding US and Japan) are based on unit sales data and the use of the following formula:

Exposure = units sold for 70 and 140 mg/1 mL divided by 12 months = patient-years

Amgen

Amgen's estimates of post-marketing patient exposure are in part based on unit sales data (e.g., vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of person-count (when feasible) or person-time using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

Post-marketing patient exposure estimates are reported overall and for the geographical regions of United States and Japan.

6.1.2 Part II Module SV.1.2. Exposure

Cumulatively, since the IBD (17-May-2018) of erenumab up to the PSUR DLP (16-May-2024), the estimated exposure to erenumab worldwide in the marketed setting has been 1459002 patient-years, of which [redacted] patient-years were from the EU region.

The world-wide cumulative number of patient-years of exposure to erenumab through commercial distribution is shown in Table 6-1 below:

Table 6-1 Cumulative exposure from marketing experience (patient-years)

	EU Region*	USA and Japan	ROW	Total
Erenumab Solution for injection	[redacted]	[redacted]	[redacted]	1459002

*EU region includes European Union countries, Switzerland, and Iceland
ROW: Rest of the World, including Canada; USA: United States of America
This table includes cumulative data obtained from 17-May-2018 to 16-May-2024
Source of data: Worldwide sales volume data from Novartis and Amgen

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Animal studies assessing the effects of erenumab at low and high doses did not reveal any erenumab-related neurobehavioral effects that would suggest a propensity to misuse or abuse. An assessment of events received from human studies to date did not reveal any patterns suggesting mood alterations within the psychiatric disorders system organ class that would encourage abuse.

Given the low potential for central nervous system penetration with erenumab, and the lack of evidence for abuse liability from preclinical/clinical studies to date, it can be concluded that there is no evidence to suggest a potential for drug abuse or misuse.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse drug reactions (ADRs) are identified risks. The ADRs identified during the 12-week, placebo controlled period included injection site reactions (e.g. injection site pain, injection site erythema), constipation, muscle spasm, and pruritus. They occurred at a low frequency and in absence of any serious consequence. Hence, none of these ADRs qualify as important identified risks.

Hypersensitivity

As with any large molecule therapeutic agent, administration of erenumab may result in systemic reactions including immune-mediated erenumab hypersensitivity. For events of erenumab hypersensitivity, a search strategy using the MedDRA standardized medical query (SMQs) for hypersensitivity, anaphylactic reactions and Amgen MedDRA Queries (AMQs) for rash and urticaria were used to identify relevant adverse events. Additionally, the algorithmic anaphylactic reaction SMQ was also reviewed.

In the integrated 12-week double blind placebo control data, subject incidence rates of AEs mapping to the hypersensitivity SMQ were 1.9% in the placebo group, 2.0% in the 70-mg group, and 2.2% in the 140-mg group. The most frequently reported (> 2% All erenumab) adverse events terms in this SMQ were rash, rash maculo-papular, and eczema. Two SAEs of hypersensitivity were reported in placebo, and no SAE of hypersensitivity was reported with erenumab. No significant differences were observed with long-term exposure. (SCS Section 2.1.9.2.2.1).

Review of the anaphylactic reaction SMQ did not identify any probable anaphylactic reactions without an alternative etiology (e.g. anaphylaxis due to penicillin, insect sting, or unknown food allergy) (SCS Section 2.1.9.2.2.2). Similarly, for rash and urticaria, the data do not indicate that subjects treated with erenumab are at increased risk of either event (SCS Sections 2.1.9.2.2.4 and SCS Section 2.1.9.2.2.5).

Overall, the clinical data do not indicate an increased risk of hypersensitivity reactions with erenumab.

Immunogenicity

Overall, in the completed and on-going Phase I, II and III clinical studies as of the original submission, 7.2% (242 of 3361) of erenumab dosed subjects (dose range from 1 mg to 280 mg) developed anti-AMG334 binding antibodies, and 0.8% (28 of 3361) developed anti-AMG334 neutralizing antibodies.

Across four placebo-controlled migraine Phase II and III studies (20120178, 20120295, 20120296, and 20120297), 6.3% (56 of 884) subjects treated with the 70 mg qm (every 4 weeks) sc dose during the double-blind treatment phase developed anti-AMG334 antibodies (3 of which had neutralizing activity). In the pivotal studies 20120295 and 20120296, a total of 2.6% (13 of 504) subjects treated with the 140 mg qm sc dose during the double-blind treatment phase developed anti-AMG334 antibodies (none of which had neutralizing activity).

Three analyses examined the potential clinical impact of anti-AMG334 antibodies on PK, clinical efficacy, and clinical safety of erenumab. These impact analyses utilized data pooled from 4 placebo-controlled migraine studies (20120178, 20120295, 20120296 and 20120297) and the open-label extension study 20130255, and included subjects treated with doses of erenumab other than 140 mg. The results were summarized as follows:

- Mean trough levels of erenumab (week 12) among subjects developing anti-AMG334 antibodies were 40% (for 140 mg dose group) and 35% (for the 70-mg group) lower than in antibody-negative subjects.
- The mean change from baseline in monthly migraine days (MMD) was similar for anti-AMG334 binding antibody-positive subjects compared with those who remained antibody-negative. While the number of subjects with anti-AMG334 neutralizing antibodies is limited, their reduction in monthly migraine days is within the range of those for anti-AMG334 antibody-negative subjects.
- There was no impact of anti-AMG334 antibody development on safety (Injection site reactions AMQ, Hypersensitivity MedDRA SMQ, and immune disorders system organ class [SOC]).

In conclusion, the incidence of anti-AMG334 antibody development is low. There was no clinically meaningful impact on either efficacy or safety. The safety profiles of the subjects who tested positive for anti-AMG334 antibodies were found to be consistent with the safety profiles of antibody-negative subjects (Integrated Immunogenicity Report in Module 5.3.5.3).

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 8-1 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
None	Not applicable

Table 8-2 Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack,	Although the available nonclinical, preclinical and clinical evidence to date including a treadmill study to assess patients with chronic stable angina did not show cardiovascular safety issues, it is recognized that there is no clinical information on use in migraine patients with myocardial infarction, cerebrovascular accident, transient ischemic attack, and angina unstable or coronary artery

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
angina unstable and poorly controlled hypertension	bypass surgery or other revascularization procedure within 12 months prior to study entry. Calcitonin gene related peptide (CGRP) is a potent vasodilator. Hence, there is a theoretical concern that inhibition of CGRP effects may result in lack of compensatory vasodilation, particularly in the context of the coronary circulation during ischemia-related diseases/conditions. However, it is important to recognize that CGRP is one of a number of neuropeptides including adrenomedullin, kinins, natriuretic peptides, and urocortins that function as cardioprotective vasodilatory mediators (Burley et al 2007). The relative importance of CGRP in vasodilation, as compared to other neuropeptides and paracrine factors, remains unclear. Moreover, the precise extent of the role played by the canonical CGRP receptor in mediating vasodilatory mechanisms remains unknown as CGRP binds to several other receptors, such as the amylin 1 receptor to which it binds with similar potency as amylin (Bailey et al 2012, Juaneda et al 2000) and erenumab selectively binds to the CGRP receptor. Thus, the relative importance of the CGRP receptor pathway among the other vasodilatory pathways that may be activated during myocardial ischemia has not been established. A few patients reached a post-baseline systolic BP > 160mmHg and these patients were already hypertensive or pre-hypertensive (defined as systolic BP ≥ 140mmHg or diastolic BP ≥ 90mmHg) at baseline and had medical history of hypertension or other confounding factors.

Table 8-3 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Use in pregnant women (including those at risk of pre-eclampsia)	Migraine predominantly affects women (around 75% of migraine patients), most of them at reproductive age. No clinical studies of erenumab have been conducted in pregnant women. Overall, the number of pregnancies and outcomes reported are too limited to evaluate and conclude on the effects of erenumab on pregnancies. However, based on the events reported to date no safety concern has been identified. Furthermore, the data from the preclinical studies, Phase I studies that included continuous ambulatory blood pressure monitoring, a dedicated triptan interaction study, and the integrated analysis of Phase II and III clinical trials indicate that there is no clinically relevant effect of erenumab on blood pressure.
Long-term safety	Long term safety was assessed using integrated safety data (subjects with a minimum of 1-year exposure to at least 1 dose of 70 mg or 140 mg erenumab from the clinical studies 20120178, 20120295/20130255, and 20120296). This pool had 1198 patients who might switch from one dose to another dose. There were 682 patients and 134 patients who received ≥ 12 months of continuous exposure to 70 mg and 140 mg, respectively. To date, no

	safety concerns have been identified in patients with long-term use of erenumab. Data on longer term safety will be further collected in the 20120178 extension study up to 5 years.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There was no change in safety concerns since the last update.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Important potential risk: Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension.

Table 8-4 Clinical trial data of cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension[α]

[α]Note: As patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, and angina unstable within 12 months prior to screening were excluded from the clinical trials, the table is only presenting the cardiovascular events reported in patients without these pre-existing conditions. Furthermore, the hypertension events in all patients regardless of their baseline blood pressure values are presented in the table. Analysis is based on the 12-week placebo-controlled pool.

	Placebo N=1043 n (%) 95% CI*	Erenumab N=1613 n (%) 95% CI*	Risk Difference (Erenumab−Placebo) 95% CI[#]
SMQ - Ischaemic heart disease (narrow and broad)			
Number of subjects with at least one event	1 (0.1) (0.002, 0.533)	3 (0.2) (0.038, 0.543)	0.0009 (−0.0037, 0.0046)
Maximum grade			
Grade 1	0	0	
Grade 2	1 (0.1)	2 (0.1)	
Grade 3	0	0	
Grade 4	0	1 (0.1)	
SAEs	0	0	
Outcome of Serious Adverse Event			
Recovered/resolved	0	0	
Recovering/resolving	0	0	

Not recovered/not resolved	0	0	
Recovered/resolved with sequelae	0	0	
Fatal	0	0	
Unknown	0	0	
SMQ - Ischaemic central nervous system vascular conditions (narrow)			
Number of subjects with at least one event	0 (0.0) (0.000, 0.353)	2 (0.1) (0.015, 0.447)	0.00124 (−0.0025, 0.0045)
Maximum grade			
Grade 1	0	0	
Grade 2	0	1 (0.1)	
Grade 3	0	1 (0.1)	
Grade 4	0	0	
SAEs	0	1 (0.1)	
Outcome of Serious Adverse Event			
Recovered/resolved	0	0	
Recovering/resolving	0	0	
Not recovered/not resolved	0	1 (0.1)	
Recovered/resolved with sequelae	0	0	
Fatal	0	0	
Unknown	0	0	
SMQ – Hypertension			
Number of subjects with at least one event	9 (0.9) (0.395, 1.632)	9 (0.6) (0.255, 1.057)	−0.0031 (−0.0112, 0.0034)
Maximum grade			
Grade 1	3 (0.3)	3 (0.2)	
Grade 2	5 (0.5)	3 (0.2)	
Grade 3	1 (0.1)	3 (0.2)	
Grade 4	0	0	
SAEs	0	0	
Outcome of Serious Adverse Event			
Recovered/resolved	0	0	
Recovering/resolving	0	0	
Not recovered/not resolved	0	0	
Recovered/resolved with sequelae	0	0	
Fatal	0	0	
Unknown	0	0	

Numbers (n) represent counts of subjects with at least one event.

[#]: NewCombe method is used.

[*]: Exact confidence interval.

Unknown includes AE outcome as unknown or missing.

MedDRA version 20.0.

Source: Attachment to Annex 7 Table 8-4

Table 8-5 Important potential risk Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension: Other details

Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	**Details**
Potential mechanisms	Calcitonin gene related peptide (CGRP) is a vasodilator and there is a theoretical concern that inhibition of the CGRP effects may result in lack of compensatory vasodilation particularly in the context of the coronary circulation during ischemic-related conditions. However, the precise extent of the role played by the canonical CGRP receptor in mediating vasodilatory mechanisms remains unknown as CGRP binds to several other receptors, such as the amylin 1 receptor to which it binds with similar potency as amylin (Bailey et al 2012, Juaneda et al 2000) and erenumab selectively binds to the CGRP receptor. Furthermore, it is important to recognize that CGRP is one of a number of neuropeptides including adrenomedullin, kinins, natriuretic peptides, and urocortins that function as cardioprotective vasodilatory mediators (Burley et al 2007); The relative importance of CGRP in vasodilation remains unclear.
Evidence source(s) and strength of evidence	A comprehensive assessment of CV safety in over 2500 patients in the erenumab clinical Phase II/III program including cardiovascular, cerebrovascular and peripheral vascular AEs, BP assessments and electrocardiograms. The program employed an external, independent Cardiovascular Events Committee to adjudicate the selected CV, cerebrovascular, and peripheral vascular AEs. While patients with recent (i.e., within the last 12 months) cardiovascular events such as MI, stroke, TIA, unstable angina, coronary artery bypass surgery or other revascularization procedures were excluded, patients with risk factors for cardiovascular disease (e.g., diabetes, hypertension, and hyperlipidemia) were allowed to participate. Over 70% of subjects had 1 or more baseline cardiovascular risk factor(s) while approximately 30% of subjects had 2 or more. The summation of this evaluation demonstrated no evidence of a relationship between erenumab and cardiovascular, cerebrovascular, and peripheral vascular events in both individual and aggregate

Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	**Details**
	AEs. In the subjects with 2 or more CV risk factors at baseline, the incidence of AEs was slightly higher than in subjects with 0 or 1 CV risk factor at the baseline, but similar to the placebo and across treatment groups. No relevant differences were observed between these subgroups in the most frequent AEs or AEs associated with cardiac disorders. Looking at the effect on BP, there was no clinically meaningful difference in either systolic or diastolic BP or in the frequency of increased blood pressure AEs with erenumab versus placebo. A few patients reached a post-baseline systolic BP > 160mmHg and these patients were already hypertensive or pre-hypertensive (defined as systolic BP ≥ 140mmHg or diastolic BP ≥ 90mmHg) at baseline and had medical history of hypertension or other confounding factors. There were no relevant differences in change in CV medication observed between erenumab and placebo.
Characterization of the risk:	An extensive nonclinical and clinical evaluation of the CV risk was undertaken during the development of erenumab. The nonclinical risk evaluation specifically evaluated the effect of CGRP receptor inhibition on the theoretical risk of abrogation of compensatory vasodilation and included an ex vivo study of human coronary arteries and a dedicated cardiovascular study in cynomolgus monkey. In the ex vivo study, isolated human coronary arteries were exposed to sumatriptan or erenumab to examine the effects on coronary vasoconstriction. Sumatriptan demonstrated a concentration dependent contraction of the proximal and distal coronary arteries while erenumab did not cause any change to coronary vascular contractile tone. To evaluate the effect of erenumab on vascular tone in vivo, a dedicated cardiovascular study in cynomolgus monkeys (Study 113726) was conducted. Erenumab at maximum doses up to 225 mg/kg was not associated with any mean increase in BP. These observations are in line with the published literature wherein the majority of in vitro and in vivo studies report no effect of inhibition of the CGRP receptor in the setting of myocardial ischemic injury (Regan et al 2009, Wu et al 2001, Chai et al 2006, Sekiguchi et al 1994). Thus, in both ex vivo and in vivo nonclinical experiments, erenumab or other modes that inhibit the CGRP receptor had no adverse effect on vascular tone and/or blood pressure. To directly address the hypothesis that the loss of compensatory vasodilation due to inhibition of CGRP effects could lead to ischemia, an exercise treadmill study was performed in patients with chronic stable angina. Study

Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	Details
	20140254 evaluated the effect of 140 mg erenumab iv compared to placebo iv on exercise capacity in subjects with stable angina as measured by total exercise time during an exercise treadmill test. The secondary endpoints were exercise-induced angina ST-segment depression. Baseline CV risk factors for these patients were that all (100%) subjects had coronary artery disease, 40% had prior myocardial infarction, 62% had a prior percutaneous cardiac interventional procedure, 33% had a history of coronary artery bypass surgery, about 24% had prior cerebrovascular disease/peripheral arterial disease. The iv administration achieved high exposures to erenumab, its concentrations at the end of the treadmill test were at least twice that with monthly sc administered erenumab 140 mg. There was no difference in total exercise time between subjects who received erenumab and those who received placebo. 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]), supporting the hypothesis that erenumab does not decrease exercise capacity compared to placebo in subjects at risk of MI. There were no significant differences in the secondary endpoints as well as compared to placebo. This absence of compensatory vasodilation would manifest in circumstances when the demand for increased perfusion cannot be met, such as in patients with coronary artery disease during exercise. Furthermore, to rigorously evaluate the potential effect of erenumab on BP, two studies were conducted. Study 20140255 assessed the effects of sc sumatriptan (ImitrexTM) alone and the effects of a single intravenous (iv) dose of erenumab and sc sumatriptan concomitant therapy on resting blood pressure in healthy subjects. The results demonstrated no clinically meaningful differences in time weighted averages of mean arterial pressure or systolic and diastolic blood pressure between subjects who received sumatriptan alone and those who received concomitant sumatriptan and erenumab. Study 20101268 evaluated the effect of erenumab on the change in blood pressure that was collected through 24-hour ambulatory blood pressure monitoring in healthy subjects and migraine patients. There was no statistically significant difference in least square mean 24-hour blood pressure and nocturnal or the diurnal pattern of blood pressure between healthy or migraine subjects in the erenumab groups and the placebo group. The non-interventional study AMG334A2023 examined patient characteristics and drug utilization patterns using

Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	**Details**
	health care data from population registries in Denmark, Finland, Norway and Sweden from 2018 to 2022. The population consisted of adults on prophylactic migraine medications, whereas for the exploratory pregnancy analyses also patients on acute migraine medications and patients not receiving migraine treatment were included. There were very low rates of other CV events (myocardial infarction, artery revascularization, ischemic/haemorrhagic stroke, ischemic attack, CV death, MACE) overall. The most frequent CV outcome was hypertension for all treatment cohorts, during the follow-up, the crude rates per 1000 person-years of hypertension, regardless of previous history of hypertension, were 130 in the erenumab cohort, 161 in the non-erenumab CGRP antagonist cohort, 259 in the botulinum toxin cohort, and 454 in the other prophylactic migraine medication cohort. This rate was lower than in non-erenumab CGRP antagonist, botulinum toxin and other prophylactic migraine medication cohorts, however, no formal comparative analyses were performed.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to erenumab has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Preventability	Information is not available as the risk remains theoretical and need further characterization.
Impact on the benefit-risk balance of the product	In this study (CAMG334A2023) with over 20500 patients initiating erenumab treatment, the reported unadjusted incidence rate of hypertension seemed to be in comparable level between the migraine cohorts (no statistical comparison was performed). The benefit-risk balance of erenumab for the indication of the prophylaxis of migraine in adults remains unaltered. The study CAMG334A2023 was descriptive and not designed to assess the benefit-risk balance of erenumab. This risk will continued to be evaluated in the post-marketing real-world setting.
Public health impact	Migraine is associated with an increased risk of CV outcomes, including ischemic heart disease, transient ischemic attack, ischemic stroke, myocardial infarction, angina, coronary revascularization, and cardiovascular disease mortality (Bigal et al 2010, Kurth et al 2009, Rose et al 2004, Schurks et al 2009, Velentgas et al 2004, Wang et al 2014), especially in women and in patients presenting aura (Gudmundsson et al 2010, Kurth et al 2006, Linstra et al 2017). The public health impact of erenumab in worsening such conditions is unknown.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 8-6 Use in pregnant women (including those at risk of preeclampsia)

Use in pregnant women (including those at risk of pre-eclampsia)	Details
Evidence source	CGRP among other factors plays an important role in regulating blood pressure and maintaining normal fetoplacental development, fetal survival, and vascular adaptations during pregnancy. Hence, there is a theoretical concern that inhibition of CGRP effects could have adverse effects on the blood pressure and fetoplacental development for pregnant women. Available evidence from an enhanced pre- and post-natal development (ePPND) study in cynomolgus monkeys did not show erenumab-related changes in clinical signs, food consumption, body weights, gestation length, or pregnancy outcomes (i.e., fetal or infant losses) and no effects on infant growth or development through 6 months postpartum. In human studies, the role of CGRP in pre-eclamptic women has not been established. Some studies showed the absence of differences in serum CGRP levels between pre-eclamptic and normotensive women (Kraayenbrink et al 1993; Schiff et al 1995). 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 migraine patients. There was no statistically significant difference in least square mean 24-hour BP and nocturnal BP between healthy or migraine subjects in the erenumab groups and the placebo group. The integrated analysis indicated that there is no clinically relevant effect of erenumab on BP in the Phase II and III clinical studies. No clinical studies of erenumab have been conducted in pregnant women. Overall, the number of pregnancies and outcomes reported are too limited to evaluate and conclude on the effects of erenumab on pregnancies. However, based on the events reported to date no safety concern has been identified.
Anticipated risk/ consequence of the missing information:	There is a limited amount of data from the use of erenumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Pregnancy outcome data will be collected in the intensive monitoring program. In Study CAMG334A2023 an exploratory analysis was included to assess if pregnant women are being prescribed erenumab, in addition the unadjusted maternal pregnancy outcomes were estimated. Across the 4 Nordic countries (Denmark, Finland, Norway, Sweden), between August 2018 and September 2022, there were 208 pregnancies exposed to erenumab. Among these erenumab-exposed pregnancies, the prevalence of any hypertensive disorders of pregnancy was 6.7% and the prevalence of gestational diabetes was 6.3%. There were no stillbirths. These exploratory analyses were not designed to assess the safety of erenumab during pregnancy but rather to inform the calculation of statistical power for future studies.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

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

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

Overall, Novartis considers routine pharmacovigilance activities are sufficient in the post-authorization setting for erenumab, combined with the data from the ongoing and additional long-term safety studies.

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Intensive monitoring of pregnancy outcomes to collect maternal data at every trimester and infant data from birth until 1 year with at least 4 follow-up attempts by all available means of contact (phone, e-mail, letter, fax, etc.) at each time point. The primary pregnancy outcome of interest is major congenital malformations, which is defined as any chromosomal defects, amniotic bands, metabolic disorders or structural malformations. Structural malformation includes any congenital anomaly in central nervous system, cardiovascular, urinary, musculoskeletal, upper alimentary tract & gastrointestinal systems or in genital organs, or any occurrence of oral clefts.

10.2 Part III.2. Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities.

10.3 Part III.3. Summary Table of additional pharmacovigilance activities

Not applicable

11 Part IV: Plans for post-authorization efficacy studies

Not applicable.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	Routine risk communication: SmPC Section 5.1 (Pharmacodynamic properties) SmPC Section 4.4 (Special warnings and precautions for use)
Use in pregnant women (including those at risk of pre-eclampsia)	Routine risk communication: SmPC Section 4.6 (Fertility, pregnancy and lactation)

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension	Routine risk minimization measures: SmPC Section 5.1 (Pharmacodynamic properties) SmPC Section 4.4 (Special warnings and precautions for use) Additional risk minimization measures: None	Routine pharmacovigilance activities beyond ADRs reporting and signal detection: None Additional pharmacovigilance activities: None
Use in pregnant women (including those at risk of pre-eclampsia)	Routine risk minimization measures: SmPC Section 4.6 (Fertility, pregnancy and lactation)	Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	Intensive monitoring of pregnancy outcomes Additional pharmacovigilance activities: None

13 Part VI: Summary of the risk management plan - Aimovig (Erenumab)

This is a summary of the risk management plan (RMP) for Aimovig. The RMP details important risks of Aimovig, how these risks can be minimized, and how more information will be obtained about Aimovig's risks and uncertainties (missing information).

Aimovig's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Aimovig should be used.

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

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

13.1 Part VI: I. The medicine and what it is used for

Aimovig is authorized for the prophylaxis of migraine in adults who have at least 4 migraine days per month (see SmPC for the full indication). It contains erenumab (a human IgG2 monoclonal antibody) as the active substance and it is given by sc injections.

Further information about the evaluation of Aimovig's benefits can be found in Aimovig's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004447/human_med_002275.jsp

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Aimovig, together with measures to minimize such risks and the proposed studies for learning more about Aimovig's risks, are outlined below in Table 13-2.

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

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

Together, these measures constitute routine risk minimization measures.

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

13.2.1 Part VI: II.A: List of important risks and missing information

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

Table 13-1 List of important risks and missing information

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

13.2.2 Part VI: II.B: Summary of important risks and missing information

Table 13-2 Important potential risk: Cardiovascular outcomes in patients with pre-existing myocardial infarction, cerebrovascular accident, transient ischemic attack, angina unstable and poorly controlled hypertension

Evidence for linking the risk to the medicine	A comprehensive assessment of CV safety in over 2500 patients in the erenumab clinical Phase II/III program including cardiovascular, cerebrovascular and peripheral vascular AEs, BP assessments and electrocardiograms. The program employed an external, independent Cardiovascular Events Committee to adjudicate the selected CV, cerebrovascular, and peripheral vascular AEs. While patients with recent (i.e., within the last 12 months) cardiovascular events such as MI, stroke, TIA, unstable angina, coronary artery bypass surgery or other revascularization procedures were excluded, patients with risk factors for cardiovascular disease (e.g., diabetes, hypertension, and hyperlipidemia) were allowed to participate. Over 70% of subjects had 1 or more baseline cardiovascular risk factor(s) while approximately 30% of subjects had 2 or more. The summation of this evaluation demonstrated no evidence of a relationship between erenumab and cardiovascular, cerebrovascular, and peripheral vascular events in both individual and aggregate AEs. In the subjects with 2 or more CV risk factors at baseline, the incidence of AEs was slightly higher than in subjects with 0 or 1 CV risk factor at the baseline, but similar to the placebo and across treatment groups. No relevant differences were observed between these subgroups in the most frequent AEs or AEs associated with cardiac disorders. Looking at the effect on BP, there was no clinically meaningful difference in either systolic or diastolic BP or in the frequency of increased blood pressure AEs with erenumab versus placebo. A few

	patients reached a post-baseline systolic BP > 160mmHg and these patients were already hypertensive or pre-hypertensive (defined as systolic BP ≥ 140mmHg or diastolic BP ≥ 90mmHg) at baseline and had medical history of hypertension or other confounding factors. There were no relevant differences in change in CV medication observed between erenumab and placebo.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to erenumab has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	Routine risk minimization measures- SmPC Section 5.1 (Pharmacodynamic properties) SmPC Section 4.4 (Special warnings and precautions for use) Routine pharmacovigilance activities beyond ADRs reporting and signal detection - None Additional risk minimization measures – None
Additional pharmacovigilance activities	None

Table 13-3 Missing information: Use in pregnant women (including those at risk of pre-eclampsia)

Risk minimization measures	Routine risk minimization measures- SmPC Section 4.6 (Fertility, pregnancy and lactation) Routine pharmacovigilance activities beyond ADRs reporting and signal detection - Intensive monitoring of pregnancy outcomes Additional risk minimization measures – None
Additional pharmacovigilance activities	None

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Aimovig.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Aimovig.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

None.

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.