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EU Risk Management Plan (Version 4.2)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

Document ID: VV-PVG-121566

EU Risk Management Plan for galcanezumab (INN or common name)

RMP version to be assessed as part of the application: 4.2

Data lock point for this RMP: 10 November 2022

Date of final sign off: See cover page of this document.

Rationale for submitting an updated RMP:

To update the final report commitment date for observational cohort study of exposure to galcanezumab during pregnancy (Study I5Q-MC-B003) from Q4 2025 to Q4 2027 in response to a request for supplementary information posed in the Committee for Medicinal Products for Human Use (CHMP) adoption of conclusions for assessment report for the post-authorisation measure MEA/002.2.

Summary of significant changes in this RMP:

Changed the milestone for the final study report date for study I5Q-MC-B003 from Q4 2025 to Q4 2027 in response to CHMP request for supplementary information in context of adoption of conclusion for assessment report for the post-authorisation measure MEA/002.2. Minor corrections in Part III.2, III.3 and in Part VII Annex 2 to update the due date wording on study progress reports, due to changed PSUR reporting frequency as per EURD list from 1 to 3 years.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Galcanezumab
Pharmacotherapeutic group(s) (ATC Code)	N02CD02
Marketing Authorisation Holder	Eli Lilly and Company
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Emgality
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Humanised IgG monoclonal antibody
	Summary of mode of action: Galcanezumab is a humanised IgG4 monoclonal antibody that binds CGRP and prevents its biological activity without blocking the CGRP receptor.
	Important information about its composition: Galcanezumab is a humanised monoclonal IgG4 antibody produced in Chinese hamster ovary cells. It is provided as a 120-mg/mL solution. Excipients include L-histidine, L-histidine hydrochloride monohydrate, sodium chloride, polysorbate 80, and water for injection.
Hyperlink to the Product Information	See Module 1.3.1
Indication(s) in the EEA	**Current:** Emgality 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:** The recommended dose is 120-mg galcanezumab injected subcutaneously once monthly, with a 240-mg loading dose as the initial dose.
	Proposed: Not Applicable
Pharmaceutical form(s) and strengths	**Current:** • 120-mg solution for injection in a prefilled pen • 120-mg solution for injection in a prefilled syringe
	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = Anatomical Therapeutic Chemical; CGRP = calcitonin gene-related peptide; EU = European Union; IgG = immunoglobulin G; INN = International Nonproprietary Name; PI = package insert; RMP = risk management plan.

Part II: Safety Specification

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

SI.1 Prophylaxis of Migraine

SI.1.1 Incidence

The average annual incidence of any migraine from 1994 to 2002 was 17.6 per 1000 patient years in Danish adults aged 20-49 years (23.4 per 1000 patient years in women and 11.2 per 1000 patient years in men); the average annual incidence of migraine without aura, 12.0 per 1000 patient years, was greater than that of migraine with aura, 5.6 per 1000 patient years (Le et al. 2012). In a UK database study between 1994 and 2001, the estimated incidence rate was 3.69 cases per 1000 person-years for a first diagnosis of migraine in medical records in those aged ≤79 years (Becker et al. 2008). The incidence rate (per 1000 person-years) was highest in 10–19-year-olds (6.43), was relatively stable in those aged 20-49 (approximately 4.5), and lowest in older patients 70-79 years (1.32). Incidence across all ages is greater in women than men, 5.21 and 2.13 per 1000 person-years respectively (Becker et al. 2008).

SI.1.2 Prevalence

A recent systematic review and meta-analysis of community-based and observational studies (n=302 studies involving 6 216 995 participants) reports a global migraine prevalence of 11.6% (6.9% of males and 13.8% of females) and European prevalence of 11.4%; in general, rates were similar across geographies (Woldeamanuel and Cowan 2017). Another review of headache prevalence studies in European countries only reported that the mean prevalence of current migraine in adults was 14.7% (8% of males and 17.6% of females [Stovner and Andree 2010]).

In a prospective survey evaluation of headache disorders, the American Migraine Prevalence and Prevention (AMPP) study; the prevalence of total migraine was estimated to be 11.79% and chronic migraine was estimated to be 0.91% (1.29% of females and 0.48% of males [Buse et al. 2012]). The prevalence of migraine is much lower in older adults aged ≥60 years (6.5% of women and 2.2% of men) than those aged 18-49 years (>20% of women and >6% of men [Buse et al. 2013]). Chronic migraine prevalence decreases from age 50 years and older (Buse et al. 2012).

A review article of epidemiology studies using International Classification of Headache Disorders second edition reports the weighted average 12-month prevalence of chronic migraine to be 0.5% (ranges 0.2% to 2.7%) and of migraine with aura to be 4.4% (ranges 1.2% to 5.8%) (Merikangas 2013). Given the 12-month prevalence weighted average of definite or probable migraine of 18.5% across these studies, migraine with aura therefore represents approximately one-quarter of adult patients with migraine (Merikangas 2013).

SI.1.3 Demographics of the Migraine Population and Risk Factors for the Disease

Data regarding the disease epidemiology and patient demographics are similar in United States and European populations. Patients with migraine are predominantly female (3:1) with a higher prevalence from 18 to 49 years (Buse et al. 2013). Studies conducted in the United States in racially diverse populations have reported migraine prevalence is highest in Caucasians, and lowest in Asian populations (Stewart et al. 1996; Pressman et al. 2016).

Several risk factors for migraine are reported in the literature, these include female sex, younger age (teenagers and younger adults aged less than 50 years have the highest incidence and prevalence) and a family history of migraine (Stewart et al. 2006; Merikangas 2013; Dzoljic et al. 2014). Some comorbidities such as asthma (Martin et al. 2016) and depression (Patten et al. 2008; Modgill et al. 2012) have a bidirectional relationship with migraine. Strong inference of the aetiology is limited as treatment seeking for these primary disorders may increase the opportunity to detect migraine, or vice versa. Obesity has been associated with more frequent and more disabling migraine headache (Bigal et al. 2007); comorbidities such as cardiovascular disease (CVD) or depression, more frequently observed with more severe migraine, may confound this association.

SI.1.4 Main Existing Treatment Options

Migraine can be managed pharmacologically (acute or prophylactic) or non-pharmacologically (relaxation, biofeedback, cognitive behavioural therapy, noninvasive [transcranial magnetic stimulation; supraorbital nerve stimulation] or invasive neuromodulation [occipital nerve stimulation]) (Al-Quliti and Assaedi 2016; Gooriah et al. 2015). Current international guidelines recommend a number of acute and prophylactic medications.

Table SI.1 summarizes migraine prophylactic therapies (drugs of first choice) from the European Federation of Neurological Societies Task Force guidelines on current migraine therapies (Evers et al. 2009). Other commonly used treatments include amitriptyline and botulinum toxin type A.

Table SI.1. Summary of Current Migraine Prophylactic Therapies

Substance	Daily Dose
First Line of Treatment	
Metoprolol	50-200 mg
Propranolol	40-240 mg
Flunarizine	5-10 mg
Valproic acid	500-1800 mg
Topiramate	25-100 mg

Source: Evers et al. 2009.

In addition to prophylactic migraine treatments, patients may also use acute migraine treatments such as triptans and nonsteroidal anti-inflammatory drugs (Al-Quliti and Assaedi 2016).

Absence of migraine treatment may negatively affect the patient's quality of life and can contribute to varying degrees of functional impairment, activity restriction, decreased productivity, and work absence (Al-Quliti and Assaedi 2016).

SI.1.5 Natural History of Migraine in the Untreated Population, Including Mortality and Morbidity

Natural History

Migraine can be a progressive disease; if left untreated, migraine attacks last longer and with greater intensity (Linde et al. 2006). In some patients, the condition can transform from episodic to chronic migraine. An analysis in the AMPP study estimated that this transition occurs at a rate of about 2.5% per year and is associated with increased migraine frequency and use of barbiturates and opioids (Bigal et al. 2008; Lipton 2009). Both incidence and prevalence of migraine decrease with increasing age, particularly from age 50 years and older.

Mortality

Mortality associated with migraine is not well-characterised in the literature, as the condition itself, although debilitating, is not immediately life-threatening or fatal. An Icelandic study determined the hazard ratio (HR) of all-cause mortality in adult patients with migraine was slightly increased when compared to patients without migraine in adjusted analyses (HR=1.15, 95% CI 1.08-1.23 [Gudmundsson et al. 2010]). An increased risk of mortality from CVD was reported in patients with migraine (HR=1.22, 95% CI 1.10-1.36) (Gudmundsson et al. 2010).

Morbidity (Relevant Adverse Events)

Migraine is associated with increased risk of a number of cardiovascular events, which is in turn associated with increased morbidity. The AMPP study included 6102 migraine sufferers and 5243 controls and in adjusted analyses reported significant associations between migraine and: myocardial infarction (OR=2.16, 95% CI 1.70-2.76), stroke (OR=1.54, 95% CI 1.16-2.05), and claudication (OR=2.69, 95% CI 1.98-3.23) (Bigal et al. 2010). These associations were more significant in patients with migraine with aura. Meta-analyses of observational studies identified increased relative risks (RR) of stroke as 2.16 (migraine with aura, RR=2.88; migraine without aura, RR=1.56 [Etminan et al. 2005]). Spector et al. (2010) conducted a meta-analysis of 21 observational studies that examined the risk of ischaemic stroke in patients with migraine and reported an overall pooled effect estimate of 2.04 (95% CI 1.72-2.43 [Spector et al. 2010]).

Suicidal ideation (Ratcliffe et al. 2008) and suicidal attempt (Ratcliffe et al. 2008; Breslau et al. 2012) have been reported to be increased in patients with migraine compared to those without migraine. Limited data are available on suicide in European patients with migraine. Breslau et al. (2012) reported a baseline prevalence of suicide attempt of 9.1% among adult patients aged 25 to 55 years in the United States with migraine (n=496). The 2-year cumulative incidence of suicide attempt was 8.7% compared to 1.3% in controls (Breslau et al. 2012). When adjusted for other confounders, suicide attempt was increased 4-fold (OR=4.43, 95% CI 1.93-10.2) among patients with migraine (Breslau et al. 2012). Another population-based Canadian study found migraine to

be associated with an increased risk of both suicidal ideation and suicide attempt after adjustment for mental disorders and chronic pain comorbidity (Ratcliffe et al. 2008).

SI.1.6 Important Co-morbidities

Anxiety and affective disorders such as anxiety, including generalised anxiety disorder and panic disorder, and depression, including major depressive disorder, have been widely reported to occur in patients with migraine at higher frequency than patients without migraine (Breslau and Davis 1993; Becker et al. 2008; Chen et al. 2012; Goulart et al. 2014). The frequency of these disorders (with the exception of panic disorder) is greatest in those patients with more frequent migraine attacks and chronic migraine (Chen et al. 2012; Goulart et al. 2014).

Cardiovascular comorbidities are reported in patients with migraine but vary with age and migraine type. Self-report of any CVD was 14.3% in patients with migraine (15.4% in migraine with aura, 13.7% in patients with migraine without aura) and 10% in subjects with no migraine. The prevalence of any CVD was similar in male and female patients with migraine (Le et al. 2011). Buse et al. (2017) describe the prevalence of any cardiovascular event or condition in participants in the AMPP with episodic migraine as 3.4% in those aged 22 to 39 years, 10.2% in those aged 40 to 59 years, and 22.3% in those aged ≥60 years.

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Nonclinical data reveal no special hazards for humans based on conventional repeat-dose toxicity studies in rats and monkeys with galcanezumab.

SII.1.1 Carcinogenicity

Consistent with regulatory guidelines for biopharmaceuticals, carcinogenicity studies of galcanezumab have not been conducted.

SII.1.1.1 Findings

No galcanezumab-related tumours or precancerous lesions were observed in monkeys that received galcanezumab for 6 months. One female rat administered the highest dose of 250 mg/kg in the 6 month-repeat dose toxicology study was sacrificed in moribund condition on Day 176 due to an inguinal mass, which corresponded microscopically to a fibrosarcoma in the skin/subcutis. This finding occurred at exposures that were approximately 10-fold higher than clinical exposures in patients receiving 240 mg. A carcinoma of the mammary gland was also observed at terminal sacrifice in a female rat receiving the vehicle control.

SII.1.1.2 Relevance to Human Usage

Overall, these nonclinical findings alone are not considered to have relevance to human use. Animal and other studies that have investigated the role of calcitonin gene-related peptide (CGRP) in tumorigenesis have been reported in the literature and do not suggest that chronic treatment with galcanezumab would increase the risk of carcinogenesis. Based on the published incidence of proliferative changes in similarly aged female SD rats, the singular incidence of the fibrosarcoma in the 6-month toxicity study, and the lack of pre-neoplastic changes in any of the galcanezumab toxicity studies conducted in rats and monkeys, the fibrosarcoma is most compatible with spontaneous findings that are unrelated to galcanezumab treatment. Furthermore, the primary and peer review pathologists of the findings in both female rats concluded that these represented incidental neoplasms and were unrelated to galcanezumab treatment.

SII.1.2 Juvenile Toxicology Study

SII.1.2.1 Findings

In a juvenile toxicology study in which rats were administered galcanezumab twice weekly from Postnatal Day 21 through Day 90, various effects on bone parameters were observed and limited to rats at 250 mg/kg. None were considered to be adverse effects of galcanezumab. At the end of the dosing period, male and female rats had a minimal decrease in metaphysis total bone mineral content (BMC) associated with decreases in trabecular BMC and bone mineral density (BMD). In males only, decreases in metaphysis and diaphysis total surface area and diaphysis periosteal circumference were also observed. These effects occurred only in the high dose of 250 mg/kg at exposures that were approximately 50-fold greater than clinical exposures in patients receiving 240 mg.

SII.1.2.2 Relevance to Human Usage

The minimal decrements in total BMC occurred in the absence of changes in cortical bone density, correlative bone histology, or clinical findings supportive of meaningful changes in bone strength, indicating that the minimal changes in femur metaphyseal BMC and BMD were not adverse. No galcanezumab-related bone changes were observed at the end of the recovery period, suggesting that bone alterations identified at the end of the dose period did not persist.

Overall, these findings on the bone in the juvenile toxicity rat study are not considered to have human relevance as the nonadverse findings on BMC and BMD were minimal and reversible and occurred in the absence of histopathology findings or clinical consequences such as impaired use of limbs or fractures. Furthermore, there were no findings suggesting galcanezumab-related effects on bone in the rat and monkey repeat-dose 6-month repeat-dose toxicity studies.

SII.2 Safety Pharmacology

Safety pharmacology endpoints were measured in 6-week and 6-month repeated-dose toxicity studies: blood pressure was not included in the endpoints evaluated. No effects on neurological function, respiration rate, and cardiac function including electrocardiograms, heart rate, and QT intervals, occurred in animals that received galcanezumab.

SII.3 Other Toxicity-Related Information or Data

Not applicable.

Module SIII - Clinical Trial Exposure

Table SIII.1. Exposure to Galcanezumab by Number of Monthly Doses

Cumulative for all Indications[a]		
Number of Monthly Doses	**Patients**	**Person time (Years)**
<3	417	48.6
≥3 to <6	1057	288.6
≥6 to <12	1906	1067.1
≥12 to <18	854	845.1
≥18 to <24	129	194.8
≥24	94	272.0
Total	**4457**	**2716.2**
Prophylaxis of Migraine[b]		
Number of Monthly Doses	**Patients**	**Person time (Years)**
<3	223	32.9
≥3 to <6	1013	271.8
≥6 to <12	1863	1036.9
≥12 to <18	790	768.7
≥18 to <24	109	158.9
≥24	0	0
Total	**3998**	**2269.3**

[a] Overall exposure includes data from completed clinical Trials ART01, CGAB, CGAF, CGAG, CGAH, CGAI, CGAJ, CGAL, CGAM, CGAN, CGAP, CGAR, CGAW, CGAX, and CGBC.

[b] Prophylaxis of migraine exposures includes data from overall exposure data from completed clinical Trials ART01, CGAB, CGAG, CGAH, CGAI, CGAJ, CGAN, CGAP, CGAW, CGAX, and CGBC.

Table SIII.2. Exposure to Galcanezumab by Age Group and Gender

Cumulative for all Indications[a]				
Age group	**Patients**		**Person time (Years)**	
	M	**F**	**M**	**F**
12 to 17 years	0	7	0	2.7
18 to 64 years	943	3431	686.4	2004
65 to 74 years	17	55	6.7	15.9
75 to 84 years	2	2	0.1	0.3
Total	**962**	**3495**	**693.2**	**2023**
Prophylaxis of Migraine[b]				
Age group	**Patients**		**Person time (Years)**	
	M	**F**	**M**	**F**
12 to 17 years	0	7	0	2.7
18 to 64 years	660	3288	367.2	1880.2
65 to 74 years	8	34	4.2	14.6
75 to 84 years	0	1	0	0.3
Total	**668**	**3330**	**371.4**	**1897.8**

Abbreviations: F = female; M = male.

[a] Overall exposure includes data from completed clinical Trials ART01, CGAB, CGAF, CGAG, CGAH, CGAI, CGAJ, CGAL, CGAM, CGAN, CGAP, CGAR, CGAW, CGAX, and CGBC.

[b] Prophylaxis of migraine exposures includes data from overall exposure data from completed clinical Trials ART01, CGAB, CGAG, CGAH, CGAI, CGAJ, CGAN, CGAP, CGAW, CGAX, and CGBC.

Table SIII.3. Exposure to Galcanezumab by Dose per Month

Cumulative for all Indications[a]		
Dose of exposure per month	**Patients**	**Person time (Years)**
5 mg	106	18.0
50 mg	106	17.9
120 mg	2130	1087
240 mg	1596	1113.5
300 mg	519	479.7
Total	**4457**	**2716.2**
Prophylaxis of Migraine[b]		
Dose of exposure per month	**Patients**	**Person time (Years)**
5 mg	68	16.0
50 mg	68	15.7
120 mg	2092	1085.0
240 mg	1596	1113.5
300 mg	174	39.0
Total	**3998**	**2269.3**

[a] Overall exposure includes data from completed clinical Trials ART01, CGAB, CGAF, CGAG, CGAH, CGAI, CGAJ, CGAL, CGAM, CGAN, CGAP, CGAR, CGAW, CGAX, and CGBC.

[b] Prophylaxis of migraine exposures includes data from overall exposure data from completed clinical Trials ART01, CGAB, CGAG, CGAH, CGAI, CGAJ, CGAN, CGAP, CGAW, CGAX, and CGBC.

Table SIII.4. Exposure to Galcanezumab by Ethnic Origin

Cumulative for all Indications[a]		
Ethnic origin	**Patients**	**Person time (Years)**
American Indian or Alaskan	31	16.2
Asian	1079	661.0
Black or African American	311	122.4
Multiple	245	201.4
Native Hawaiian or Other Pacific Islander	6	3.5
Other	8	1.2
White	2762	1704.0
Total	**4442[c]**	**2709.7**
Prophylaxis of Migraine[b]		
Ethnic origin	**Patients**	**Person time (Years)**
American Indian or Alaskan	31	16.2
Asian	1076	660.5
Black or African American	255	113.3
Multiple	205	143.4
Native Hawaiian or Other Pacific Islander	6	3.5
Other	4	0.9
White	2406	1324.9
Total	**3983[c]**	**2262.8**

[a] Overall exposure includes data from completed clinical Trials ART01, CGAB, CGAF, CGAG, CGAH, CGAI, CGAJ, CGAL, CGAM, CGAN, CGAP, CGAR, CGAW, CGAX, and CGBC.

[b] Prophylaxis of migraine exposures includes data from overall exposure data from completed clinical Trials ART01, CGAB, CGAG, CGAH, CGAI, CGAJ, CGAN, CGAP, CGAW, CGAX, and CGBC.

[c] 15 patients with missing race were not counted in this report (1 from CGAI and rest from CGAW).

Module SIV - Populations Not Studied in Clinical Trials

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

Criterion: Patients <18 years of age

Reason for Exclusion: The safety and efficacy for patients <18 years of age has not been studied. To establish the efficacy and safety of this molecule, Phase 3 clinical trials were conducted first in adults.

Is it considered to be included as missing information? No

Rationale: It is not expected that galcanezumab will be used off-label in the paediatric population. Section 4.2 of the summary of product characteristics (SmPC) will clearly state that the safety and efficacy of galcanezumab in children and adolescents aged below 18 years has not yet been established. Additionally, approved alternative therapeutic options are available for the treatment of migraine in paediatric patients. In February 2020, European Medicines Agency (EMA) agreed that Eli Lilly and Company (Lilly) can start to enrol paediatric patients in Phase 3 studies to investigate the efficacy and safety of galcanezumab as a treatment for episodic and chronic migraine.

Criterion: Patients >65 years of age

Reason for Exclusion: The registration studies were conducted in the population with the highest prevalence of migraine. Prevalence of migraine is much lower in older adults aged ≥60 years (6.5% of women and 2.2% of men) compared to those aged 18 to 49 years (>20% of women and >6% of men) (Buse et al. 2013); chronic migraine prevalence decreases above age 50 years (Buse et al. 2012). Patients aged >65 years were also excluded as they are more likely to have comorbidities such as cervical spinal degenerative disease resulting in head and neck pain.

Is it considered to be included as missing information? No

Rationale: Although the number of elderly patients exposed to galcanezumab is too low to draw any definitive conclusions on the product's safety profile in patients >65 years, the prevalence of migraine in this age group is also low and, therefore, not reflective of the anticipated target population. Hence, use in this subpopulation is expected to be very limited and unlikely to represent a safety concern warranting further characterisation.

Criterion: Women Who Are Pregnant

Reason for Exclusion: This is a standard exclusion criterion in clinical development. Although there were no adverse effects on the embryos, foetuses, and offspring demonstrated in nonclinical studies using pregnant rats and rabbits, insufficient information on the effects of galcanezumab on maternal health or the foetus prohibited the inclusion of pregnant women in the development programme. Women of childbearing potential are expected to comprise a significant proportion of the target migraine population. Some studies have shown that CGRP is involved in foeto-placental resistance and an important factor in blood pressure regulation during

pregnancy and low CGRP levels have been associated with pre-eclampsia (Yallampalli and Wimalawansa 1998, Dong et al 2005 and Fei et al 2012). There were a limited number of pregnancies with the original submission (13) in maternal exposure and 2 pregnancies from paternal exposure reported during the clinical development programme so insufficient to exclude potential adverse effects on the foetus or mother during pregnancy.

Is it considered to be included as missing information? Yes (Use in Pregnancy)

Rationale: Not applicable.

Note: Hypertension and pre-eclampsia in pregnant women is classified as an important potential risk.

Criterion: Patients with recent acute cardiovascular events and/or serious cardiovascular risk.

Patients were excluded if they had electrocardiograms showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular risk (including, but not limited to, a corrected QT (QTcB [Bazett's]) interval >470 msec for women and >450 for men), or had a myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, stroke, or deep vein thrombosis/pulmonary embolism within 6 months of screening, or have planned cardiovascular surgery or percutaneous coronary angioplasty. In addition, patients with a lifetime history of stroke were excluded from 2 Phase 3 studies (Studies CGAH and CGAI).

Reason for Exclusion: Patients at risk for acute cardiovascular events and/or serious cardiovascular risk were excluded for the following reasons:

i) Overall safety: to avoid exposing a patient with recent acute cardiovascular events or known serious cardiovascular risk to an investigational drug whose safety profile is not fully established.
ii) To minimise confounding at the case level and improve the interpretation of the cardiovascular data.

Patients who have experienced a recent (within the last 6 months) serious/major cardiovascular event are at increased risk for another event in the initial months after the event. Thus, if such serious events did occur, an assessment of causality would be difficult at the case level. Furthermore, although the frequency of serious cardiovascular events is increased in the migraine population relative to the general population, the incidence is still relatively rare (1 to 2 per 1000 patient years). If such serious events did occur in patients with a recent cardiovascular history, the interpretation of statistical imbalance between treatment groups would also be difficult.

Is it considered to be included as missing information? Yes (Long-term safety)

Rationale: Not applicable

Note: Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events is classified as an important potential risk.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

The size of the galcanezumab-exposed patient populations in prophylaxis of migraine clinical trials (n=3998) means that detection of adverse events with a 95% level of certainty is limited to those which occur at a frequency of >1 in 1333 patients (0.08%).

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

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes[a]

Type of Special Population	Exposure
Pregnant women	Pregnancy was an exclusion criterion in the clinical development programme; however, 13 pregnancies in maternal exposure and 2 pregnancies from paternal exposure were reported during the clinical development programme with the original submission.
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
Patients with hepatic impairment	Galcanezumab has not been specifically studied in patients with hepatic impairment.
Patients with renal impairment[b]	
Mild (60 mL/min ≤ CGCL <90 mL/min)	Number of patients: 599 Patient time (years): 288.2
Moderate (30 mL/min ≤ CGCL <60 mL/min)	Number of patients: 33 Patient time (years): 17.0
Severe (<30 mL/min)	Number of patients: 1 Patient time (years): 0.5
Patients with cardiovascular impairment	458 (147.3 patient time [years]) galcanezumab-treated patients had 1 or more cardiovascular disease medical history or pre-existing conditions (SMQ narrow terms ischaemic heart disease [MI, other ischaemic heart disease], hypertension, cardiac failure, cardiomyopathy, ischaemic CNS vascular conditions, dyslipidaemia, hyperglycaemia/new onset diabetes mellitus).
Immunocompromised patients	Galcanezumab has not been specifically studied in immunocompromised patients.
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical development programme included a representative population of patients with varying disease severity across episodic migraine and chronic migraine.

Type of Special Population	Exposure
Population with relevant different ethnic origin	See Module SIII; patients with an ethnic origin other than White were included in studies of migraine and osteoarthritis of the knee.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not applicable

Abbreviation: CNS= central nervous system; MI = myocardial infarction; SMQ = Standardised Medical Dictionary for Regulatory Activities Queries.

[a] The data presented in this table refer to the original submission for migraine.

[b] N = 2737 patients exposed to galcanezumab including Study I5Q-MC-CGAF. Numbers are based on calculation of creatinine clearance in the studied migraine population at baseline.

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Patient exposure estimates for galcanezumab were calculated by dividing the total number of milligrams sold by the estimated total dose per patient. The estimated total dose per patient was determined by dividing total sales in the US by the estimated number of patients who have received galcanezumab in the US based upon IQVIA's National Prescription Audit (NPA) database. The US total dose per patient was then used as a proxy for other geographic regions because anonymised patient level data is not available in other regions. In addition, the dosing recommendations for galcanezumab are consistent worldwide. For this report, the estimated total dose per patient was:

- Total Dose per Patient = 1259 milligrams (mg)

SV.1.2 Exposure

Cumulatively as of 31 October 2022, there have been 938 765 145 milligrams of galcanezumab sold worldwide. This led to an estimated 745 800 patients exposed to galcanezumab. Table SV.1 provides a cumulative summary of worldwide sales and estimated patient exposure.

Table SV.1. Estimated Cumulative Patient Exposure as of 31 October 2022

Region	Sales (milligrams)	Estimated Patient Exposure (Patients)
Europe	72 216 000	57 300
Japan	52 106 280	41 400
United States	761 661 620	605 100
Other Countries	52 781 245	41 900
Global Totals[a]	**938 765 145**	**745 800**

[a] Due to rounding, numbers presented in this table may not add up precisely to the totals provided.

Exposure data by indication

Lilly currently do not have a data source that would help in estimating the patient exposure across indications for galcanezumab.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Eli Lilly and Company has not observed potential for misuse of galcanezumab for illegal purposes in completed clinical trials. Furthermore, the antibody's mechanism of action and pharmacology do not suggest the potential for abuse or misuse.

Based on the postmarketing experience until 10 November 2022, the cases of abuse, misuse and diversion have been reported very rarely. However, the potential is considered to be negligible.

Module SVII - Identified and Potential Risks

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

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

Data are from Phase 2 and Phase 3 studies of all galcanezumab-treated patients with migraine.

Known risks considered to have minimal clinical impact on patients (in relation to the severity of the indication treated), that require no further characterisation (are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting), and do not impact the risk-benefit profile:

- Constipation: Constipation events were commonly reported in patients treated with any galcanezumab dose in any duration (1.17%). Almost all events were mild or moderate in severity. No serious events were reported. No patients discontinued because of constipation. Most events resolved within the same day or a few days after. However, among the patients reporting constipation, 19% had constipation that persisted for >90 days and was reported as mild-to-moderate in severity. Approximately 34% of patients received corrective treatment and none required surgical intervention.
- Injection site reactions: Injection site reactions, including injection site pain, were commonly reported in patients treated with any galcanezumab dose in any duration (21.62%). The majority (92.0%) of patients reporting treatment-emergent injection site reactions reported events as mild-to-moderate in severity. None of the injection site reactions were classified as serious. Discontinuations because of these adverse events (AEs) were low (0.73%). Most events occurred on the day of treatment administration and resolved in ≤14 days.
- Urticaria: Urticaria is an adverse drug reaction (ADR) and risk that was uncommonly reported in patients treated with any galcanezumab dose in any duration (0.40%). The urticaria reported in all but 2 cases were classified as nonserious. Most events were mild (0.15%) or moderate in severity (0.19%) and resolved. Discontinuations because of urticaria were low (0.19%).
- Adverse outcomes of vertigo: Vertigo is an ADR and was commonly reported in patients treated with any galcanezumab dose in any duration (0.98%) compared with placebo (0.21%). None were associated with adverse outcomes such as falls. Most of the vertigo treatment-emergent adverse events (TEAEs) were mild or moderate in severity (85%), were reported as unrelated by the principal investigator, and resolved. One patient discontinued because of vertigo.

Known risks for which the risk minimisation messages in the product information are adhered by prescribers (for example, actions being part of standard clinical practice in each European Union member state where the product is authorised):

- Unknown at this time

Reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated, or other reasons for considering the risks not important:

- None

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

Important Identified Risk 1: None

Risk-benefit impact: Not applicable

Important Potential Risk 1: Serious Hypersensitivity

Risk-Benefit Impact:

Therapeutic proteins, including monoclonal antibodies, have been associated with hypersensitivity reactions that can be severe and/or associated with serious outcomes including anaphylaxis. They are among the most frequent reactions reported in association with administration of biologic products such as monoclonal antibodies (Clarke 2010).

Events indicative of hypersensitivity to date with galcanezumab have included mainly cutaneous manifestations such as injection site rash, injection site hypersensitivity, allergic dermatitis, pruritus, and urticaria. These were generally judged by the investigators or patients to be of mild or moderate severity and associated with nonserious outcomes and low rates of discontinuation (<1%).

Urticaria is an ADR and likely risk of hypersensitivity. Observed outcomes to date based on frequency, seriousness, and severity are not sufficiently clinically significant to have demonstrated an ostensible impact on benefit-risk at this time.

Based on therapeutic monoclonal antibody class effects and pharmacological plausibility, there is potential for more concerning manifestations of hypersensitivity, such as anaphylaxis. Although no cases of galcanezumab-related anaphylaxis have been reported, galcanezumab is a humanised monoclonal antibody. Therefore, there is a potential risk for serious hypersensitivity reactions in clinical practice after exposure in high numbers of patients and over extended periods of treatment for a chronic condition such as migraine. Such events are usually unpredictable and not preventable but are generally well managed in clinical practice. However, should serious hypersensitivity reactions, including anaphylaxis, occur sufficiently frequently and with clinically concerning adverse outcomes, then there would be a likely impact on benefit-risk, taking into account the nature of the condition being treated. If the frequency of any serious hypersensitivity reactions remains very low and well managed in clinical practice, then the impact on benefit-risk will remain minimal.

Important Potential Risk 2: Serious Cardiovascular Outcomes in Patients at High Risk of Cardiovascular and Cerebrovascular Events

Risk-Benefit Impact:

Cardiovascular comorbidities and risk factors for cardiovascular events, such as hypertension, are reported to be higher in patients with migraine than in the nonmigraine population (Le et al. 2011; Chen et al. 2012). In observational studies, cardiovascular outcomes, including ischaemic stroke, transient ischaemic attack, ischaemic heart disease, and myocardial infarction, have been reported to have increased RR in the migraine population compared to the nonmigraine population (Kurth et al. 2006; Becker et al. 2007; Sacco et al. 2015; Peng et al. 2017).

Patients with a medical history or pre-existing CVD or risk factors for cardiovascular events were included in the Phase 3 clinical trials, with approximately 17% to 19% of patients identified with pre-existing cardiac risk factors. However, patients with recent acute cardiovascular events and/or serious cardiovascular risk occurring within the 6 months before enrolment were excluded from these migraine trials. In addition, patients with a lifetime history of stroke were excluded from 2 Phase 3 studies (Studies CGAH and CGAI). As a result, the cardiovascular safety of galcanezumab in migraine patients at high CV risk is uncertain given that nonclinical studies suggest that CGRP plays an important role in facilitating vasodilatation to various stimuli including acute ischaemia (Russell et al. 2014) and the target population is at higher risk of ischaemic cardiovascular outcomes. Taking into account these theoretical considerations and lack of experience in this subpopulation of patients, use in migraine patients at high risk for cardiovascular and cerebrovascular events will be classified as an important potential risk.

Data from the clinical development programme reported in this Marketing Authorisation Application have not demonstrated a signal for serious cardiovascular events for up to 1 year of exposure to galcanezumab. Therefore, there is no current evidence that serious cardiovascular risk is either an adverse effect of galcanezumab nor has any impact on the benefit-risk profile of galcanezumab. However, relatively few patients have been exposed for up to 1 year and long-term data in a chronic condition such as migraine are missing, so the implications of chronic CGRP inhibition in patients remain uncertain.

As a result of these considerations, the potential may exist for serious cardiovascular outcomes to occur in clinical practice after exposure in higher numbers of patients and over more extended periods of prophylactic treatment for a chronic condition like migraine. Should serious outcomes such as ischaemic stroke, or myocardial infarction occur with sufficient frequency and at rates higher than expected for the target population, then there would be a likely negative impact on benefit-risk, in the context of the prevention of a debilitating, but nonlife-threatening condition such as migraine. If the frequency of adverse cardiovascular events remains very low, with no clear causal association to treatment and well managed in clinical practice, then the impact on benefit-risk will remain minimal.

Important Potential Risk 3: Hypertension during Pregnancy and Pre-eclampsia

Risk-Benefit Impact:

The majority of patients with migraine are females of child-bearing age; therefore, pregnancy is likely to occur in women who are exposed to galcanezumab. In addition, women with migraine have been found to be at increased risk of developing hypertensive disorders such as pre-eclampsia in pregnancy compared to women without migraine (Banhidy et al. 2007; Facchinetti et al. 2009).

CGRP and other endothelial dysfunction mediators have been investigated for their roles in contributing to the vascular adaptations during pregnancy including the outcomes of gestational hypertension and pre-eclampsia (Fei et al. 2012). Systemic levels of CGRP levels change during pregnancy, increase during pregnancy, peak during the last trimester and decrease after delivery (Yadav et al. 2014). However significantly lower increases in CGRP levels during pregnancy have been observed in pregnancies which were pre-eclamptic compared with normotensive pregnancies, suggesting that this may implicate a role of lower CGRP in pre-eclampsia (Fei et al. 2012; Yadav et al. 2014).

Pre-eclampsia is a serious condition and both pregnancy-induced hypertension and pre-eclampsia are associated with premature birth and lower birth-weight infants (Fei et al. 2012). In severe cases of pre-eclampsia, there are risks of foetal growth retardation and maternal death (Fei et al 2012; Yadav et al. 2014).

Data from the clinical development programme reported in this Marketing Authorisation Application have not demonstrated a signal for hypertension or pre-eclampsia in pregnant women treated with galcanezumab. The one case of pre-eclampsia noted in clinical development represents 6.25% of the 16 maternal pregnancies reported in total since the original submission, and this is consistent with background rates for pre-eclampsia which affects approximately 2 to 8% of all pregnancies (WHO, 1988). Therefore, there is no current evidence that hypertension and/or pre-eclampsia are either adverse effects or have any impact on the benefit-risk profile of galcanezumab. However, the clinical trial experience of galcanezumab exposure in pregnancy currently is too limited to draw any definitive conclusions and exposure in pregnancy in everyday clinical practice is likely.

As hypertension and pre-eclampsia is an important potential risk, based on the theoretical considerations described, the current impact on benefit-risk is negligible. Over time and with increased clinical experience, however, should serious outcomes impacting either the mother or foetus occur in clinical practice sufficient to suspect a causal association with treatment, then a negative impact on benefit-risk would be likely, in the context of migraine prevention. If the frequency of these conditions remains very low, within rates expected for the target population, well managed in clinical practice, and with no clear causal association to galcanezumab, then the impact on benefit-risk will remain minimal.

Missing Information 1: Use in Pregnancy

Risk-Benefit Impact:

The current data are too limited to draw conclusions about the effect of galcanezumab exposure during pregnancy in humans. Studies in animals did not show evidence of embryolethality, teratogenicity, or foetotoxicity. In addition, no effect was observed at any dose level on female or male fertility in animal studies. However, there are limited safety data on the use of galcanezumab in pregnant women or in women exposed via a male partner treated with galcanezumab, as pregnant women were excluded from entering clinical studies. Pregnancy occurring during a clinical study was a criterion for permanent discontinuation in all galcanezumab studies.

Nonclinical studies show no evidence of adverse effects in pregnancy or on the foetus to warrant a contraindication. Labels will reflect that there are insufficient human data to establish the safety of galcanezumab during pregnancy. However, despite a labelling recommendation for contraception in females of childbearing potential during treatment, it is likely that women exposed to galcanezumab will become pregnant in routine clinical practice, as the indicated population is predominantly women of childbearing potential.

Galcanezumab use during pregnancy is considered to be a safety concern requiring further study in a larger population than in clinical development because of the limited data on pregnancy outcomes. If data demonstrate that such use is associated with clinically significant adverse outcomes to the mother, foetus, or baby, this would potentially impact the benefit-risk in the context of use in migraine prophylaxis.

Missing Information 2: Long-Term Safety Including Malignancies

Risk-Benefit Impact:

The maximum treatment exposure duration is 12 monthly doses in the migraine clinical development programme. Serious cardiovascular outcomes with long-term use have been classified as an important potential risk. Current data have not identified any other specific safety concern with long-term use that would require specific study or additional risk minimisation actions. There has been no patient exposure outside of the clinical development programme. Migraine is a chronic condition and it is anticipated that prophylactic treatment will continue for long periods of time. Given the uncertainties regarding long-term use of galcanezumab, long-term safety is considered worthy of further study. This would allow the systematic collection of more data on outcomes in a larger population and for longer periods of time than was possible in clinical development. If the data demonstrate that long-term use is associated with clinically significant adverse outcomes or morbidity (such as malignancy), this would potentially impact the benefit-risk in the context of the prophylactic treatment of a debilitating, but nonlife-threatening condition such as migraine.

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

Not applicable.

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

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Serious Hypersensitivity

Potential mechanisms:

The administration of a therapeutic protein may be associated with hypersensitivity reactions. As a humanised monoclonal antibody, galcanezumab would be expected to carry risks for hypersensitivity reactions. These reactions may be "immediate," usually occurring within 1 hour up to 6 hours from last administration, which often manifest as isolated symptoms such as urticaria or angioedema (possibly as severe as anaphylaxis), or "delayed" reactions, which commonly occur many days after treatment, may involve a delayed T-cell-dependent allergic mechanism, and can manifest as maculopapular exanthemas or delayed urticaria.

Evidence source(s) and strength of evidence:

Antidrug antibody levels that developed after starting galcanezumab did not appear to impact its safety profile in patients who had reported hypersensitivity events. This applied regardless of duration of galcanezumab exposure and magnitude of the antidrug antibody levels measured.

The current evidence is from the clinical development programme and from postmarketing reports. In the clinical development programme, hypersensitivity events were observed at a higher incidence in galcanezumab-treated patients compared to placebo. This finding was consistently observed across all the clinical trials with galcanezumab, and the evidence was considered sufficient to conclude that some hypersensitivity reactions (urticaria, pruritus, and injection site reactions) were adverse effects of the product. The profile in the clinical development programme has been mainly characterised by skin events (urticaria and pruritus) which were mild or moderate in severity and associated with nonserious outcomes.

Relatively low patient exposure in the trials did not allow detection of rare hypersensitivity events. However, post-marketing cases of serious hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported.

Characterisation of the risk:

Frequency

- Incidence: There were no anaphylactic reactions or serious hypersensitivity AEs (immediate or delayed) across all galcanezumab dose groups during the double-blind treatment phase. Two serious cases (0.08%) of urticaria were reported outside the

randomised phase of the programme. The events of serious hypersensitivity in the galcanezumab spontaneous database are rarely reported.

Data Source: Integrated data from migraine clinical trial population at initial submission (randomised, open-label, and post treatment phases); Lilly Safety System spontaneous database cumulatively through 10 November 2022.

Severity

Among all the galcanezumab-treated patients with migraine who reported hypersensitivity events, 96.9% reported mild or moderate events (191/197); 6 patients reported a severe hypersensitivity event (pruritus, rash, hypersensitivity, and urticaria).

Data Source: Integrated data from migraine clinical trial population at initial submission (randomised, open-label, and post treatment phases).

Risk factors and risk groups:

Patients with a history of hypersensitivity to monoclonal antibodies or therapeutic proteins were excluded from the clinical development programme, therefore it is not known if previous hypersensitivity to another biological product constitutes a risk factor for treatment with galcanezumab.

No significant dose-response has been observed between the galcanezumab 120 mg and the 240 mg dose groups in the frequency of hypersensitivity TEAEs. No trend for an increase in the by-monthly frequency of hypersensitivity events is evident with additional exposure to galcanezumab.

Preventability:

Hypersensitivity is neither predictable nor preventable. No correlation with antibody formation has been observed. If a serious hypersensitivity reaction occurs, galcanezumab should be discontinued immediately and appropriate therapy should be initiated.

Impact on the risk-benefit balance of the product:

Hypersensitivity events were observed at a higher incidence in galcanezumab-treated patients than placebo across all the clinical trials with galcanezumab to warrant labelling of some hypersensitivity reactions (urticaria, pruritus, injections site reactions) as an adverse effect of the product. The profile to date is largely characterised by cutaneous events (urticaria and pruritus), which are mild or moderate in severity and associated with nonserious outcomes. Serious hypersensitivity reactions, such as anaphylaxis and angioedema, have been determined to be adverse effects of galcanezumab treatment based on postmarketing data but the impact on the individual patient is still considered to be low as these events are rare, easily detectable and generally well managed in everyday clinical practice.

Public health impact:

Galcanezumab-treated patients experienced severe hypersensitivity reactions at an incidence of 0.2%. The incidence of serious hypersensitivity events (2 cases of urticaria) was 0.08%. Although postmarketing events of serious hypersensitivity reactions have also been reported, the impact on public health is considered to be low as they are currently reported rarely and are well managed in everyday clinical practice.

Important Potential Risk: Serious Cardiovascular Outcomes in Patients at High Risk of Cardiovascular and Cerebrovascular Events

Potential Mechanisms:

The putative mechanism for serious cardiovascular outcomes is chronic inhibition of CGRP, which in nonclinical models suggest that CGRP plays an important role in facilitating vasodilation to various stimuli including acute ischaemia (MaassenVanDenBrink et al. 2016).

Evidence Source(s) and Strength of Evidence:

Data from the clinical development programme reported in this Marketing Authorisation Application have not demonstrated a signal for serious cardiovascular events for up to 1 year of exposure to galcanezumab. There is therefore no current evidence that serious cardiovascular risk either is an adverse effect of galcanezumab or has any ostensible impact on the benefit-risk profile.

Patients with a medical history or pre-existing CVD, or risk factors for cardiovascular events were included in the Phase 3 clinical trials, with approximately 17% to 19% of patients identified with pre-existing cardiac risk factors. However, patients with recent acute cardiovascular events and/or serious cardiovascular risk within the 6 months before enrolment were excluded from the Phase 3 migraine trials. In addition, patients with a lifetime history of stroke were excluded from 2 Phase 3 studies. As a result, the cardiovascular safety of the product in the migraine patient population at high cardiovascular risk is uncertain given that nonclinical studies suggest that CGRP plays an important role in facilitating vasodilatation to various stimuli including acute ischaemia (Russell et al. 2014), and the target population is at higher risk of ischaemic cardiovascular outcomes such as myocardial infarction or stroke. Based on these theoretical considerations, use in migraine patients at high risk for cardiovascular and cerebrovascular events will be classified as an important potential risk.

Characterisation of the Risk:

Frequency

- Incidence: Overall incidence of cardiovascular TEAEs in galcanezumab-treated patients (n=2586) as identified by 9 different Standardised Medical Dictionary for Regulatory Activities Queries (narrow search):
    - cardiac arrhythmias 0.54%
    - cardiac failures 0.04%

  - cardiomyopathy 0.0%
  - central nervous system vascular disorders 0.04%
  - embolic or thrombotic events 0.19%
  - hypertension 1.28%
  - ischaemic heart disease 0.12%
  - pulmonary hypertension 0.0%
  - torsade de pointes/QT prolongation 0.15%
- Incidence and confidence intervals:
  - incidence of cardiovascular serious AEs: 0.21% (placebo-controlled period)
  - incidence of cardiovascular serious AEs: 0.23% (overall migraine database)
  - exposure adjusted incidence rate:
    - acute myocardial infarction: 0.13 x 100 PY (CI 0.02, 0.46)
    - transient ischaemic attack: 0.06 x 100 PY (CI 0.00, 0.35)

Data source: Integrated data from migraine clinical trial population at initial submission (randomised, open label, and posttreatment phases) using 9 different Standardised Medical Dictionary for Regulatory Activities Queries (cardiac arrhythmias, cardiac failure, cardiomyopathy, central nervous system vascular disorders, embolic and thrombotic events, hypertension, ischaemic heart disease, pulmonary hypertension, torsade de pointes/QT prolongation).

Risk Factors and Risk Groups:

No specific risk factors have been identified for cardiovascular outcomes in patients treated with galcanezumab.

Preventability:

Serious adverse cardiovascular outcomes are unlikely to be preventable, particularly in the absence of identified risk factors in the target population that could be considered specific to treatment.

Impact on the Risk-Benefit Balance of the Product:

The potential could exist for serious cardiovascular outcomes to occur in clinical practice after exposure in higher numbers of patients and over more extended periods of treatment for a chronic condition like migraine. Should serious outcomes, such as ischaemic stroke or myocardial infarction, occur sufficiently frequently and at rates higher than expected for the target population, then there would be a likely negative impact on benefit-risk, in the context of the prophylactic treatment of a debilitating, but nonlife-threatening condition such as migraine.

If the frequency of adverse cardiovascular events remains very low, with no clear causal association to treatment and well managed in usual clinical practice, then the impact on benefit-risk will remain minimal.

Public Health Impact:

The clinical trial programme did not identify an increased incidence of serious cardiovascular events such as acute myocardial infarction and transient ischaemic attack in patients exposed to galcanezumab above what is expected in a migraine population (<2 per 1000 patient years; Hall et al. 2004; Kurth et al. 2006; Becker et al. 2007). Therefore, the current data do not suggest a significant impact on public health.

Important Potential Risk: Hypertension during Pregnancy and Pre-eclampsia

Potential Mechanisms:

Systemic levels of CGRP change during pregnancy, increase during pregnancy, peak during the last trimester and decrease after delivery (Yadav et al. 2014). CGRP and other endothelial dysfunction mediators have been investigated for their roles in contributing to the vascular adaptations during pregnancy including the outcomes of gestational hypertension and pre-eclampsia (Fei et al. 2012). Significantly lower increases in CGRP levels during pregnancy have been observed in pregnancies which were pre-eclamptic compared with normotensive pregnancies, suggesting that this may implicate a role of lower CGRP in pre-eclampsia (Fei et al. 2012; Yadav et al. 2014).

Evidence Source(s) and Strength of Evidence:

The majority of patients with migraine are females of child-bearing age; therefore, pregnancy is likely to occur in women who are exposed to galcanezumab. In addition, women with migraine are thought to be at an increased risk for pre-eclampsia compared to women without migraine, due to disordered reactivity of the blood vessels and abnormal platelet activity (Adeney and Williams, 2006). Studies performed in multiple countries have demonstrated that women with migraine experience a 1.4 - 4.0-fold increased risk of pre-eclampsia relative to non-migraine controls (Banhidy et al. 2007; Sanchez et al. 2008; Facchinetti et al. 2009).

There was no evidence of an increased risk of hypertension or pre-eclampsia in patients exposed to galcanezumab in pregnancy during clinical development; however, experience in pregnancy was very limited. In clinical trials, of 16 pregnancies reported, one mother experienced pre-eclampsia (6.25% of pregnancies). This is consistent with the World Health Organisation's global estimate of pre-eclampsia in the general population (2-8%) (WHO, 1988). Given the biological mechanism of galcanezumab and the role of CGRP in pregnancy, there is a theoretical rationale for including hypertension and pre-eclampsia, as an important potential risk among women with migraine who are exposed to galcanezumab during pregnancy.

Characterisation of the Risk:

Incidence: In clinical trials, of 16 pregnancies reported where a mother was exposed to galcanezumab, one mother experienced pre-eclampsia (6.25% of pregnancies).

Data Source: Data from Phase 3 migraine prevention clinical studies at the time of the original marketing application.

Risk Factors and Risk Groups:

Other than the subset of treated migraine patients who become pregnant who, in general are at higher risk of hypertension in pregnancy or pre-eclampsia, no specific risk factors have been identified for galcanezumab as experience of pre-eclampsia is confined to one case (6.25%).

Preventability:

Current experience of the use of galcanezumab in pregnancy and hypertension /pre-eclampsia is too limited to provide data on the predictability of the potential risk or factors that could increase the risk. Routine management of pregnancy, irrespective of any treatment received, includes regular blood pressure monitoring as a standard measure (NICE [WWW]). In these circumstances, it would be expected that clinically concerning increases in BP as a possible predictor of pre-eclampsia would be detected as part of standard clinical practice.

Impact on the Risk-Benefit Balance of the Product:

Pre-eclampsia is a serious condition and both pregnancy-induced hypertension and pre-eclampsia are associated with premature birth and lower birth-weight infants (Fei et al. 2012). In severe cases of pre-eclampsia, there are risks of foetal growth retardation and maternal death (Fei et al 2012; Yadav et al. 2014).

Data from the clinical development programme reported at the time of the original marketing application have not demonstrated a signal for hypertension or pre-eclampsia in pregnant women treated with galcanezumab. The one case of pre-eclampsia noted in clinical development represents 6.25% of the 16 pregnancies reported and this is consistent with background rates for pre-eclampsia which affects approximately 2-8% of all pregnancies (WHO, 1988). Therefore, there is no current evidence that hypertension and/or pre-eclampsia are either adverse effects or have any impact on the benefit-risk profile of galcanezumab. However, the clinical trial experience of galcanezumab exposure in pregnancy currently is too limited to draw any definitive conclusions and exposure in pregnancy in everyday clinical practice is likely.

As hypertension and pre-eclampsia is an important potential risk, based on the theoretical considerations described, the current impact on benefit risk is negligible. Over time and with increased clinical experience, however, should serious outcomes impacting either the mother or foetus occur in clinical practice sufficient to suspect a causal association with treatment, then a negative impact on benefit-risk would be likely, in the context of migraine prevention If the frequency of these conditions remains very low, within rates expected for the target population, well managed in clinical practice, and with no clear causal association to galcanezumab, then the impact on benefit-risk will remain minimal.

Public Health Impact:

Pre-eclampsia affects approximately 2-8% of all pregnancies (WHO, 1988). The existing data on pre-eclampsia in patients who were exposed to galcanezumab is limited to one case, therefore the population-level impact is not readily quantifiable but overall is expected to be very low.

SVII.3.2 Presentation of the Missing Information

Missing Information: Use in Pregnancy

Evidence Source:

Galcanezumab clinical studies excluded women who were pregnant, and pregnancy was a criterion for permanent discontinuation in all studies. Although there were a number of pregnancy exposures in the clinical development programme, there are insufficient data to establish the safety of galcanezumab during pregnancy in humans. Studies in animals did not show evidence of embryolethality, teratogenicity, or foetotoxicity.

Population in Need of Further Characterisation:

The indicated population is approximately 80% female, many of whom are of childbearing age. Therefore, given the limitations of the existing evidence, further understanding of the use of galcanezumab in female patients with migraine who are pregnant, foetal exposure to galcanezumab, and the pregnancy/infant outcomes is warranted.

Missing Information: Long-Term Safety Including Malignancies

Evidence Source:

The long-term safety of galcanezumab beyond 1 year has not been evaluated through the clinical trial programme. As migraine is a chronic condition, long-term use is anticipated in routine clinical practice.

Population in Need of Further Characterisation:

Migraine is a chronic medical condition and use in this condition even up to one year is limited to 279 patients. Given that exposure data up to12 months are limited and data for a longer duration of treatment is not available from the clinical trials, the evidence for safety in long-term galcanezumab use is not available.

It could be anticipated that with long-term use, adverse effects which are infrequent, and/or have a longer latency period such as malignancy, and/or are infrequent among migraine patients could occur. In these circumstances, prolonged use of galcanezumab in the target migraine population in clinical practice warrants further characterisation.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Serious hypersensitivity
Important potential risks	Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events Hypertension during pregnancy and pre-eclampsia
Missing information	Use in pregnancy Long-term safety including malignancies

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

- Serious hypersensitivity
  - allergy follow-up form: to further characterise allergic reactions and associated events
  - anaphylaxis follow-up form: to further characterise anaphylaxis reactions and associated events
  - angioedema follow-up form: to further characterise angioedema reactions and associated events
- Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events
  - cardiac disorder follow-up form: to further characterise serious cardiovascular reactions and associated events
  - cerebrovascular accident follow-up form: to further characterise cerebrovascular accident reactions and associated events
- Pregnancy
  - Pregnancy data collection maternal follow-up form: to further characterise use in pregnancy
  - Pregnancy data collection paternal follow-up form: to further characterise use in pregnancy
  - Pregnancy outcome maternal follow-up form: to further characterise use in pregnancy
  - Pregnancy outcome paternal follow-up form: to further characterise use in pregnancy
  - Breastfeeding form: to further characterise use in breastfeeding
- Cancer-Neoplasm
  - Cancer/neoplasm follow-up form: to further characterise cancer/neoplasms and associated events
- Peripheral vascular disease
  - Peripheral vascular disease follow-up form: to further characterise peripheral vascular disease events

III.2 Additional Pharmacovigilance Activities

Observational Cohort Study of Exposure to Galcanezumab during Pregnancy among Women with Migraine

Study Short Name and Title: Cohort Study of Exposure to Galcanezumab during Pregnancy

Rationale and Study Objectives:

Pregnant women were not included in the clinical development programme; however, the indicated population is predominantly women, many of whom are of childbearing age. The population of pregnant women treated with galcanezumab is therefore one which warrants further characterisation, as effects on the foetus after exposure in utero are unknown. For risk management purposes, this represents missing information as adverse outcomes in pregnancy could impact benefit-risk. Additionally, some non-clinical studies have shown that CGRP is an important factor in blood pressure regulation during pregnancy and that low CGRP levels have been associated with pre-eclampsia. Given that there is a theoretical basis for hypertension during pregnancy and pre-eclampsia, these are considered to be important potential risks. This post-authorisation observational study will actively monitor exposure to galcanezumab during pregnancy among women with migraine or cluster headache, study the incidence of pregnancy outcomes (including hypertension during pregnancy and pre-eclampsia) in women with galcanezumab exposure, and compare the incidence of pregnancy outcomes to other women with migraine, including those receiving other prophylactic medication for the treatment of migraine.

Study Design:

This study will use administrative data to actively monitor exposure to galcanezumab during pregnancy in women with migraine or cluster headache. Exposure to other prophylactic migraine medication will also be monitored and described.

A cohort study design will be used to describe the incidence of hypertension during pregnancy and pre-eclampsia, as well as other pregnancy outcomes including maternal, foetal, and/or infant outcomes, in pregnancies with exposure to galcanezumab.

The incidence of pregnancy outcomes (maternal, foetal, and/or infant outcomes) in pregnancies with exposure to galcanezumab will be compared descriptively to other women with migraine, and women with migraine treated with other prophylactic migraine medication.

Medical record review will be used to obtain additional information on outcomes and confounders where feasible.

Study Population:

The study population is pregnant adult women with a diagnosis of migraine or cluster headache. Exposure to prophylactic migraine medication will be identified through pharmacy and medical claims within 5 half-lives (135 days) before the estimated start of pregnancy or during pregnancy.

Milestones:

A study protocol is included in Annex 3, Part C; the proposed milestones and anticipated due dates are as follows:

Milestone	Anticipated Due Date
Protocol submission within 6 months of EU Commission Decision	Q2 2019
Study progress reports	To be provided annually[a]
Interim study report	Q4 2022
Final study report submission (EMA)	Q4 2027
Final study report submission (FDA)	Q4 2027

Abbreviations: EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; Q = quarter.

[a] Details of progress reports, including delivery dates, will be provided in the protocol.

A Retrospective Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in European Patients Treated for Migraine in the Course of Routine Clinical Care.

Study Short Name and Title: Galcanezumab European Drug Utilisation and Safety Outcomes Study

Rationale and Study Objectives:

The longer-term safety of galcanezumab (beyond 1 year) has not been established through the clinical trial programme. As migraine is a chronic condition, potential longer-term use beyond 1 year is anticipated in routine clinical practice. Therefore, adverse effects which are infrequent, have a longer latency period such as malignancy, and/or are infrequent among migraine patients such as serious hypersensitivity could occur. Additionally, patients with recent acute cardiovascular events and/or serious cardiovascular risk, as well as patients over the age of 65, were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation.

The primary objective of this study is to evaluate the utilisation and long-term safety of galcanezumab in Europe, including cases of cardiovascular safety and malignancy, and other rare safety events such as serious hypersensitivity, in routine clinical practice.

The secondary objective is to provide context for incidence rates of safety events seen in the galcanezumab cohort by describing the incidence rates observed in a comparator cohort and, when feasible, to conduct comparative safety analyses of serious cardiovascular events, serious hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control.

Primary Objective:

To describe in real-world clinical practice, in Europe:

- the utilisation of galcanezumab
- the incidence of serious cardiovascular outcomes among patients at high risk of cardiovascular events and patients who receive long-term galcanezumab treatment
- the incidence of safety outcomes among patients ≥65 years of age
- the incidence of serious hypersensitivity reactions such as anaphylaxis in patients who receive galcanezumab
- the incidence of malignancy in patients exposed to galcanezumab
    - to confirm the safety profile in real-world practice over a period of up to 5 years

Secondary Objective:

The secondary objective is to provide context for incidence rates of safety events seen in the galcanezumab cohort by describing the incidence rates observed in a comparator cohort and, when feasible, to conduct comparative safety analyses of serious cardiovascular events, serious hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control.

Study Design:

The primary objectives will be conducted within a European cohort of galcanezumab users, with exposures to galcanezumab identified from pharmacy records and safety outcomes identified through medical claims or records.

Patient duration of exposure cannot be accurately estimated at this time, and limitations in patient follow-up exist in real-world data sources such as patients switching between treatment providers. It is intended to initiate patient follow-up from the start of exposure until the patient discontinues therapy, is lost to follow-up, or occurrence of an event, at which point they will be censored. Medical record review will complement the database analysis where feasible to obtain additional information on confounders.

The proposed study is an observational cohort study utilising secondary data sources. Country-specific cohorts of patients with migraine who have received treatment with galcanezumab will be identified from national databases in Europe. The utilisation of galcanezumab and the incidence of relevant safety outcomes will be described overall and within populations of special interest (patients with recent acute cardiovascular events and/or serious cardiovascular risk prior to initiating galcanezumab, and patients ≥65 years of age).

Study Population:

All patients initiating treatment with galcanezumab and who have 6 months of baseline information prior to the start of treatment will be eligible for the study. The 6-month baseline requirement provides an opportunity to assess baseline characteristics and to identify patients of special interest (patients with recent acute cardiovascular events and/or serious cardiovascular risk prior to initiating galcanezumab and patients ≥65 years of age).

Milestones:

A study protocol is included in Annex 3, Part C; the proposed milestones are as follows:

Milestone	Anticipated Due Date
Protocol Submission within 6 months of EU Commission Decision	Q2 2019
Study progress reports	To be provided annually[a]
Interim study report	Q4 2023
Final study report submission	Q4 2026

Abbreviations: EU = European Union; Q = quarter.

[a] Details of progress report, including delivery dates, will be provided in the protocol.

A Retrospective Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in US Patients Treated for Migraine in the Course of Routine Clinical Care

Study Short Name and Title: Galcanezumab US Drug Utilisation and Safety Outcomes Study

Rationale and Study Objectives:

The longer-term safety of galcanezumab (beyond 1 year) has not been established through the clinical trial programme. As migraine is a chronic condition, potential longer-term use beyond 1 year is anticipated in routine clinical practice. Therefore, adverse effects which are infrequent, have a longer latency period such as malignancy, and/or are infrequent among migraine patients such as serious hypersensitivity could occur. Additionally, patients with recent acute cardiovascular events and/or serious cardiovascular risk, as well as patients over the age of 65, were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation.

The objective of this study is to evaluate the utilisation and long-term safety of galcanezumab in the United States, including cardiovascular safety and malignancy, and other rare safety events such as serious hypersensitivity, in routine clinical practice.

The secondary objective is to conduct comparative safety analyses of specific outcomes using patients initiated on other prophylactic migraine medication as controls. Safety events observed in the primary objective will inform the design of comparative analyses.

Primary Objective:

To describe in real-world clinical practice, in the United States:

- the utilisation of galcanezumab
- the incidence of serious cardiovascular outcomes among patients at high risk of cardiovascular events and patients who receive long-term galcanezumab treatment
- the incidence of safety outcomes among patients ≥65 years of 0 age
- the incidence of serious hypersensitivity reactions such as anaphylaxis in patients who receive galcanezumab
- the incidence of malignancy in patients exposed to galcanezumab

- to confirm the safety profile in real-world practice over a period of up to 5 years

The secondary objective is to conduct comparative safety analyses of specific outcomes using patients initiated on other prophylactic migraine medication as controls.

Secondary Objective:

Based on the number of outcome events observed, the aim is to conduct comparative safety analyses of cardiovascular events, serious hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control.

Study Design:

This observational cohort study will use US administrative data supplemented with health record data, as available, to monitor exposure to galcanezumab in routine clinical practice and to evaluate long-term safety. Information from medical records will be used to validate claims algorithms and can also be used to obtain additional information on confounders.

Study Population:

Adult patients with a diagnosis of migraine or cluster headache who initiate treatment with galcanezumab will be eligible for the cohort for the primary objective. For comparative analyses (secondary objective), adult patients with migraine who initiated treatment with another prophylactic migraine medication will be identified as controls.

Milestones:

A study protocol is included in Annex 3, Part C; the proposed milestones are as follows:

Milestone	Anticipated Due Date
Protocol Submission within 6 months of EU Commission Decision	Q2 2019
Study progress reports	To be provided annually[a]
Interim study report	Q4 2024
Final study report submission	Q4 2026

Abbreviations: EU = European Union; Q = quarter.

[a] Details of progress report, including delivery dates, will be provided in the protocol.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study (study short name, and title) Status (planned/ongoing)	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones (required by regulators)**	**Due Dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation (key to benefit-risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit-risk)				
None				

Category 3 – Required additional pharmacovigilance activities (by the competent authority)				
Cohort Study of Exposure to Galcanezumab during Pregnancy (Ongoing)	To actively monitor exposure to galcanezumab during pregnancy among women with migraine or cluster headache, using administrative (secondary) data. To study the incidence of pregnancy outcomes (including hypertension during pregnancy and pre-eclampsia) among women exposed to galcanezumab during pregnancy in comparison to women receiving other prophylactic migraine medication.	- Hypertension and pre-eclampsia during pregnancy - Use during pregnancy	Protocol submission Study progress reports Final report (EMA) Final report (FDA)	Q2 2019 To be provided annually Anticipated Q4 2027 Anticipated Q4 2027
Galcanezumab European Drug Utilisation and Long-term Safety Outcomes Study (Ongoing)	To describe, in real-world clinical practice, the utilisation of galcanezumab in Europe, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardiovascular events, and malignancies. The secondary objective is to provide context for incidence rates of safety events seen in the galcanezumab cohort by describing the incidence rates observed in a comparator cohort and, as feasible, to conduct comparative safety analyses of serious cardiovascular events, serious hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control.	- Long-term safety, including malignancy - Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events - Serious hypersensitivity reactions.	Protocol submission Study progress reports Interim study report Final report	Q2 2019 To be provided annually Q4 2023 Anticipated Q4 2026
Galcanezumab US Drug Utilisation and Safety Outcomes Study (Ongoing)	To describe, in real-world clinical practice, the utilisation of galcanezumab in the US, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious	- Long-term safety, including malignancy - Serious cardiovascular outcomes in patients at high risk of	Protocol submission Study progress reports	Q2 2019 To be provided annually

	cardiovascular events, and malignancies. Another objective is to understand the risk of specified safety events in patients receiving galcanezumab relative to adult patients who initiated treatment with another prophylactic migraine medication.	cardiovascular and cerebrovascular events - Serious hypersensitivity reactions	Interim study report Final report	Anticipated Q4 2024 Anticipated Q4 2026

Abbreviations: EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; Q = quarter.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Serious hypersensitivity	Routine risk communication: • SmPC Section 4.8 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.3 includes a contraindication in patients with known hypersensitivity to galcanezumab or to any of the excipients. • SmPC Section 4.4 provides guidance to discontinue galcanezumab and start appropriate therapy if a serious hypersensitivity reaction occurs. Other Routine risk minimisation measures beyond the Product Information: • Pack size: Not applicable • Legal status: Not applicable

Abbreviations: PL = package leaflet; SmPC = summary of product characteristics.

Safety Concern	Routine Risk Minimisation Activities
Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events	Routine risk communication: • None proposed Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 states that patients with certain major cardiovascular diseases were excluded from clinical studies and cross-references to section 5.1 for additional details on these patients. • PL Section 2 advises patients to inform their HCP if they have serious cardiovascular disease. Other Routine risk minimisation measures beyond the Product Information: • Pack size: Not applicable • Legal status: Not applicable

Abbreviations: HCP = health care professional; PL = package leaflet; SmPC = summary of product characteristics.

Safety Concern	Routine Risk Minimisation Activities
Hypertension during pregnancy/pre-eclampsia	Routine risk communication: • None proposed beyond wording on use in pregnancy in SmPC Section 4.6 and section 2 of the Package Leaflet Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed Other Routine risk minimisation measures beyond the Product Information: • Pack size: Not applicable • Legal status: Not applicable

Abbreviations: SmPC = summary of product characteristics.

Safety Concern	Routine Risk Minimisation Activities
Use in pregnancy	Routine risk communication: • SmPC Section 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: In SmPC Section 4.6, guidance is provided that: • It is specifically recommended that women of childbearing potential use an effective method of contraception during treatment and for at least 5 months after treatment. • As a precautionary measure, it is preferable to avoid the use of galcanezumab during pregnancy. • Treatment during breastfeeding could be considered following the first few days after birth only if clinically needed. • PL Section 2 advises women to avoid becoming pregnant while using galcanezumab and also recommends the use of contraception while using Emgality and for at least 5 months after the last Emgality dose. Women who are breast-feeding or planning to breast-feed are advised to talk to their doctor before using this medicine. Other routine risk minimisation measures beyond the product information: • Pack size: Not applicable • Legal status: Not applicable

Abbreviations: PL = package leaflet; SmPC = summary of product characteristics.

Safety Concern	Routine Risk Minimisation Activities
Long-term safety including malignancies	Routine risk communication: • SmPC Section 5.3

Abbreviations: SmPC = summary of product characteristics

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious hypersensitivity	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.3 and PL Section 2 includes a contraindication in patients with known hypersensitivity to galcanezumab or to any of the excipients Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 provides guidance to discontinue galcanezumab and start appropriate therapy if a serious hypersensitivity reaction occurs • PL Section 4 provides guidance to the patient to stop using galcanezumab and tell their doctor if they think that they have had an allergic reaction.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Spontaneous case AE follow-up forms for suspected adverse reactions (allergy, anaphylaxis, and angioedema). • Routine review of EudraVigilance data will be performed in conjunction with Lilly's routine signal evaluation processes. Additional pharmacovigilance activities: • A Retrospective Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in European Patients treated for Migraine in the Course of Routine Clinical Care o To describe, in real-world clinical practice, the utilisation of galcanezumab in Europe, and the incidence of important safety outcomes such as **serious hypersensitivity** and long-term safety including serious cardiovascular events, and malignancies. o To understand the risk of specified safety events in adult patients receiving galcanezumab relative to other adult patients who initiated treatment with other prophylactic migraine medication, as feasible, given the availability of data. • A Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in US Patients Treated for Migraine in the Course of Routine Clinical Care. o To describe, in real-world clinical practice, the utilisation of galcanezumab in the US, and the incidence of important safety outcomes such as **serious hypersensitivity** and long-term safety including serious cardiovascular events, and malignancies. o To understand the risk of specified safety events in patients receiving galcanezumab relative to adult patients who initiated treatment with another prophylactic migraine medication.
Serious cardiovascular outcomes in patients at high	Routine risk minimisation measures: • None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
risk of cardiovascular and cerebrovascular events	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 states that patients with certain major cardiovascular diseases were excluded from clinical studies and cross-references to section 5.1 for additional details on these patients. PL Section 2 advised patients to inform their HCP if they have serious cardiovascular disease	• Spontaneous case AE follow-up forms for suspected adverse reactions (serious cardiovascular reactions and associated events, serious cerebrovascular accident reactions, and associated events). • Routine review of EudraVigilance data will be performed in conjunction with Lilly's routine signal evaluation processes. Additional pharmacovigilance activities: • A Retrospective Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in European Patients treated for Migraine in the Course of Routine Clinical Care o To describe, in real-world clinical practice, the utilisation of galcanezumab in Europe, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including **serious cardiovascular events**, and malignancies. o To understand the risk of specified safety events in adult patients receiving galcanezumab relative to other adult patients who initiated treatment with other prophylactic migraine medication, as feasible, given the availability of data. • A Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in US Patients Treated for Migraine in the Course of Routine Clinical Care. o To describe, in real-world clinical practice, the utilisation of galcanezumab in the US, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including **serious cardiovascular events**, and malignancies. o To understand the risk of specified safety events in patients receiving galcanezumab relative to adult patients who initiated treatment with another prophylactic migraine medication.
Hypertension during pregnancy/pre-eclampsia	Routine risk minimisation measures: • None proposed Routine risk minimisation activities recommending specific clinical measure to address the risk: • None proposed beyond wording proposed for	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Spontaneous case AE follow-up forms for suspected pregnancy exposures and associated events and outcomes including hypertension/pre-eclampsia. Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	use in pregnancy in SmPC 4.6.	• Observational Cohort Study of Exposure to Galcanezumab during Pregnancy among Women with Migraine o To actively monitor exposure to galcanezumab during pregnancy among women with migraine o To study the incidence of **hypertension during pregnancy, pre-eclampsia**, and other relevant pregnancy outcomes among women exposed to galcanezumab during pregnancy in comparison to women receiving other prophylactic migraine medication.
Use in pregnancy	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.6 guidance is provided that as a precautionary measure, it is preferable to avoid the use of galcanezumab during pregnancy. Emgality could be considered during breastfeeding only if clinically needed. It also specifically recommends that women of childbearing potential use an effective method of contraception during treatment and for at least 5 months after treatment. • PL Section 2 advised women to avoid becoming pregnant while using galcanezumab and also recommends using contraception while using Emgality and for at least 5 months after last Emgality dose. Women who are breast-feeding or planning to breast-feed are advised to talk to their doctor before using this medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Prospective follow-up forms reporting pregnancies to monitor the incidence of adverse maternal and foetal outcomes after exposure to galcanezumab during pregnancy • Attention to pregnancies when undertaking signal management in the Food and Drug Administration Adverse Event Reporting System Additional pharmacovigilance activities: • Observational Cohort Study of Exposure to Galcanezumab during Pregnancy among Women with Migraine o To actively monitor exposure to galcanezumab during pregnancy among women with migraine, using administrative (secondary) data. o To study the incidence of hypertension during pregnancy pre-eclampsia, and other relevant pregnancy outcomes among women exposed to galcanezumab during pregnancy in comparison to women receiving other prophylactic migraine medication.
Long-term safety including malignancies	Routine risk minimisation measures: • SmPC Section 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting signal detections: • Spontaneous case AE follow-up forms for suspected adverse reactions (cancer-neoplasm)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Additional pharmacovigilance activities: • A Retrospective Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in European Patients treated for Migraine in the Course of Routine Clinical Care o To describe, in real-world clinical practice, the utilisation of galcanezumab in Europe, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardiovascular events, and **malignancies**. o To understand the risk of specified safety events in adult patients receiving galcanezumab relative to other adult patients who initiated treatment with other prophylactic migraine medication, as feasible, given the availability of data. • A Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in US Patients Treated for Migraine in the Course of Routine Clinical Care o To describe, in real-world clinical practice, the utilisation of galcanezumab in the US, and the incidence of important safety outcomes such as serious hypersensitivity and long-term safety including serious cardiovascular events, and malignancies. o To understand the risk of specified safety events in patients receiving galcanezumab relative to adult patients who initiated treatment with another prophylactic migraine medication.

Abbreviations: AE = adverse event; HCP = health care provider; GVP = good pharmacovigilance practice; PL = package leaflet; SmPC = summary of product characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Emgality (Galcanezumab)

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

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

This summary of the RMP for Emgality should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Emgality's RMP.

I - The Medicine and What It is Used for

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

Further information about the evaluation of Emgality's benefits can be found in Emgality's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage [this line should be only edited by EMA link to the EPAR summary landing page].

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

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

Measures to minimise the risks identified for medicinal products include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of Important Risks and Missing Information

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

List of Important Risks and Missing Information	
Important identified risks	Serious hypersensitivity
Important potential risks	Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events Hypertension during pregnancy and pre-eclampsia
Missing information	Use in pregnancy Long-term safety including malignancies

II.B Summary of Important Risks

Important Identified Risk: Serious Hypersensitivity	
Evidence for linking the risk to the medicine	Antidrug antibody levels that developed after starting galcanezumab did not appear to impact its safety profile in patients who had reported hypersensitivity events. This applied regardless of duration of galcanezumab exposure and magnitude of the antidrug antibody levels measured. The current evidence is from the clinical development programme and from postmarketing reports. In the clinical development programme, hypersensitivity events were observed at a higher incidence in galcanezumab-treated patients compared to placebo. This finding was consistently observed across all the clinical trials with galcanezumab, and the evidence was considered sufficient to conclude that some hypersensitivity reactions (urticaria, pruritus, and injection site reactions) were adverse effects of the product. The profile in the clinical development programme has been mainly characterised by skin events (urticaria and pruritus), which were mild or moderate in severity and associated with nonserious outcomes. Relatively low patient exposure in the trials did not allow detection of rare hypersensitivity events. However, post-marketing cases of serious hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria, have been reported.
Risk factors and risk groups	Patients with a history of hypersensitivity to monoclonal antibodies or therapeutic proteins were excluded from the clinical development programme, therefore it is not known if previous hypersensitivity to another biological product constitutes a risk factor for treatment with galcanezumab. No significant dose-response has been observed between the galcanezumab 120 mg and the 240 mg dose groups in the frequency of hypersensitivity TEAEs. No trend for an increase in the by-monthly frequency of hypersensitivity events is evident with additional exposure to galcanezumab.

Important Identified Risk: Serious Hypersensitivity	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 and PL Section 2 • SmPC Section 4.3 includes a contraindication in patients with known hypersensitivity to galcanezumab or to any of the excipients. • SmPC Section 4.4 provides guidance to discontinue galcanezumab and start appropriate therapy if a serious hypersensitivity reaction occurs. • PL Section 4 provides guidance to the patient to stop using galcanezumab and tell their doctor if they think that they have had an allergic reaction.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Galcanezumab European Drug Utilisation and Safety Outcomes Study Galcanezumab US Drug Utilisation and Safety Outcomes Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: PL = package leaflet; SmPC = summary of product characteristics; TEAEs = treatment-emergent adverse events.

Important Potential Risk: Serious Cardiovascular Outcomes in Patients at High Risk of Cardiovascular and Cerebrovascular Events	
Evidence for linking the risk to the medicine	Data from the clinical development programme reported in this Marketing Authorisation Application have not demonstrated a signal for serious cardiovascular events for up to 1 year of exposure to galcanezumab. There is therefore no current evidence that serious cardiovascular risk either is an adverse effect of galcanezumab nor has any ostensible impact on the benefit-risk profile. However, relatively few patients have been exposed for up to 1 year and long-term data in a chronic condition such as migraine are missing, so the implications of chronic CGRP inhibition in patients remain uncertain. This uncertainty notably relates to cardiovascular safety given that nonclinical studies suggest that CGRP plays an important role in facilitating vasodilatation to various stimuli including acute ischaemia and the target population is at higher risk of ischaemic cardiovascular outcomes. Patients with a medical history or pre-existing CVD, or risk factors for cardiovascular events were included in the Phase 3 clinical trials, with approximately 17% to 19% of patients identified with pre-existing cardiac risk factors. However, patients with recent acute cardiovascular events and/or serious cardiovascular risk within the 6 months before enrolment were excluded from the Phase 3 migraine trials. In addition, patients with a lifetime history of stroke were excluded from 2 Phase 3 studies. As a result, the cardiovascular safety of the product in the migraine population at higher risk represents a gap in knowledge.
Risk factors and risk groups	No specific risk factors have been identified for cardiovascular outcomes in patients treated with galcanezumab.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4 states that patients with certain major cardiovascular diseases were excluded from clinical studies and cross-references to section 5.1 for additional details on these patients. • PL Section 2 advises patients to inform their HCP if they have serious cardiovascular disease.

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Galcanezumab European Drug Utilisation and Safety Outcomes Study Galcanezumab US Drug Utilisation and Safety Outcomes Study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: Hypertension During Pregnancy and Pre-eclampsia	
Evidence for linking the risk to the medicine	The majority of patients with migraine are females of child-bearing age; therefore, pregnancy is likely to occur in women who are exposed to galcanezumab. In addition, women with migraine are thought to be at an increased risk for pre-eclampsia compared to women without migraine, due to disordered reactivity of the blood vessels and abnormal platelet activity. Studies performed in multiple countries have demonstrated that women with migraine experience a 1.4 - 4.0-fold increased risk of pre-eclampsia relative to non-migraine controls. There was no evidence of an increased risk of hypertension or pre-eclampsia in patients exposed to galcanezumab in pregnancy during clinical development; however, experience in pregnancy was very limited. Of 16 pregnancies reported, one mother experienced pre-eclampsia (6.25% of pregnancies). This is consistent with the World Health Organisation's global estimate of pre-eclampsia in the general population (2-8%). Given the biological mechanism of galcanezumab and the role of CGRP in pregnancy, there is a theoretical rationale for including hypertension and pre-eclampsia, as an important potential risk among women with migraine who are exposed to galcanezumab during pregnancy.
Risk factors and risk groups	Other than the subset of treated migraine patients who become pregnant who, in general are at higher risk of hypertension in pregnancy or pre-eclampsia, no specific risk factors have been identified for galcanezumab as experience of pre-eclampsia is confined to one case (6.25%). Preventability: Current experience of the use of galcanezumab in pregnancy and hypertension /pre-eclampsia is too limited to provide data on the predictability of the potential risk or factors that could increase the risk. Routine management of pregnancy, irrespective of any treatment received, includes regular blood pressure monitoring as a standard measure. In these circumstances, it would be expected that clinically concerning increases in BP as a possible predictor of pre-eclampsia would be detected as part of standard clinical practice.
Risk minimisation measures	Routine risk minimisation measures • None beyond proposed wording for use in pregnancy in SmPC Section 4.6 and section 2 of the PL.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Cohort Study of Exposure to Galcanezumab during Pregnancy See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: BP = blood pressure; CGRP = calcitonin gene-related peptide; CVD = cardiovascular disease; EU = European Union; GVP = good pharmacovigilance practice; HCP = health care professional; SmPC = summary of product characteristics.

Missing Information: Use in Pregnancy	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 provides guidance that as a precautionary measure, it is preferable to avoid the use of galcanezumab during pregnancy. Emgality could be considered during breastfeeding only if clinically needed. It is specifically recommended that women of childbearing potential use an effective method of contraception during treatment and for at least 5 months after treatment. • PL Section 2 advises women to avoid becoming pregnant while using galcanezumab and also recommends using contraception while using Emgality and for at least 5 months after the last Emgality dose. Women who are breast-feeding or planning to breast-feed are advised to talk to their doctor before using this medicine.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Cohort Study of Exposure to Galcanezumab during Pregnancy See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: SmPC = summary of product characteristics.

Missing Information: Long-Term Safety Including Malignancies	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 5.3
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Galcanezumab European Drug Utilisation and Safety Outcomes Study Galcanezumab US Drug Utilisation and Safety Outcomes Study See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: SmPC = summary of product characteristics.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Emgality.

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

Study short name: Cohort Study of Exposure to Galcanezumab during Pregnancy

Purpose of the study:
Pregnant women were not included in the clinical development programme; however, the indicated population is predominantly women, many of whom are of childbearing age. The population of pregnant women treated with galcanezumab is therefore one which warrants further characterisation, as effects on the foetus after exposure in utero are unknown. For risk management purposes, this represents missing information as adverse outcomes in pregnancy could impact benefit-risk. Additionally, some non-clinical studies have shown that CGRP is an important factor in blood pressure regulation during pregnancy and that low CGRP levels have been associated with pre-eclampsia. Given that there is a theoretical rationale for hypertension during pregnancy and pre-eclampsia, these are considered to be important potential risks. This post-authorisation observational study will actively monitor exposure to galcanezumab during pregnancy among women with migraine or cluster headache, study the incidence of pregnancy outcomes (including hypertension during pregnancy and pre-eclampsia) in women with galcanezumab exposure, and compare the incidence of pregnancy outcomes to other women with migraine, including those receiving other prophylactic medication for the treatment of migraine.

Study short name: Galcanezumab European Drug Utilisation and Safety Outcomes Study

Purpose of the study:

The longer-term safety of galcanezumab (beyond 1 year) has not been established through the clinical trial programme. Migraine is a chronic condition; therefore, long-term galcanezumab use beyond 1 year is reasonably anticipated in routine clinical practice. Therefore, adverse effects which are infrequent, have a longer latency period such as malignancy, and/or are infrequent among migraine patients such as serious hypersensitivity could occur. Additionally, patients with recent acute cardiovascular events and/or serious cardiovascular risk, as well as patients over the age of 65, were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation.

The objective of this study is to evaluate the utilisation and long-term safety of galcanezumab, including cardiovascular safety, malignancy, and serious hypersensitivity events in routine clinical practice.

The secondary objective is to provide context for incidence rates of safety events seen in the galcanezumab cohort by describing the incidence rates observed in a comparator cohort and, as

feasible, to conduct comparative safety analyses of serious cardiovascular events, serious hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control.

Study short name: Galcanezumab US Drug Utilisation and Safety Outcomes Study

Purpose of the study:

The longer-term safety of galcanezumab (beyond 1 year) has not been established through the clinical trial programme. As migraine is a chronic condition, potential longer-term use beyond 1 year is anticipated in routine clinical practice. Therefore, adverse effects that have a longer latency period such as malignancy, and/or are infrequent among migraine patients such as serious hypersensitivity could occur. Additionally, patients with recent acute cardiovascular events and/or serious cardiovascular risk, as well as patients over the age of 65, were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation.

The objective of this study is to evaluate the utilisation and long-term safety of galcanezumab, including cardiovascular safety, malignancy, and serious hypersensitivity events in routine clinical practice.

The study also aims to understand the risk of specified safety events in patients receiving galcanezumab relative to adult patients who initiated treatment with another prophylactic migraine medication. Safety events observed in the primary objective will inform the design of comparative analyses.

Part VII: Annexes

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Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the Form
Form #1	Allergy
Form #2	Angioedema
Form #3	Anaphylaxis and similar events
Form #4	Cardiac disorders
Form #5	Cerebrovascular accident
Form #6	Pregnancy data collection maternal
Form #7	Pregnancy data collection paternal
Form #8	Pregnancy outcome maternal
Form #9	Pregnancy outcome paternal
Form #10	Breastfeeding
Form #11	Cancer-Neoplasm
Form #12	Peripheral vascular disease

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Allergy
Reaction Description (*include any relevant exposure and whether an allergist or dermatologist was consulted*)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Medical History/Risk Factors	
☐ Angioneurotic edema	☐ Drug allergy (please specify):
☐ Phototoxicity	☐ Family history of allergies (please specify):
☐ Skin disease	☐ Latex allergy (please specify):
☐ Vasculitis	☐ Other allergic disease (please specify):
☐ Atopy	

Medications at Time of Event (*Please include prescription, OTC, and herbal preparations*)	
☐ Aspirin	☐ NSAIDS
☐ ACE Inhibitors/ARBs	☐ Beta-blockers
☐ Contrast Agents	☐ Other (please specify):

Diagnostic Test	**Results** (include units of measurement)		
Blood Pressure (mmHg)			
Pulse (beats per minute)			
Anti APC antibody test	Base line:	Nadir:	Current:
Autoimmune screening (specify)			
WBC Total:	Neutrophils:	Eosinophils:	Lymphocytes:
ECG			
Biopsy (provide pathology report)			
Sensitivity testing (describe)			
Other (specify)			

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Possible Angioedema (AE)
Primary Diagnosis for the reported event(s):

Eli Lilly and Company - Global Patient Safety **Case Number:**

Hospitalization for this event? ☐ No ☐ Yes	
Pre-Existing History (*Please specify type and date of diagnosis*):	
☐ Angioedema (Angioneurotic edema)	If Hereditary AE:
Reaction to:	☐ Type 1: Deficiency of C1 INH protein
☐ Idiopathic recurrent AE	☐ Type 2: Dysfunction of C1 INH protein
☐ Allergic AE (IgE mediated)	☐ Type 3: Coagulation factor XII mutation
☐ Medication-Induced AE (e.g. ACE inhibitors)	If Acquired AE:
☐ Physically Induced AE (cold, heat, vibration, trauma, emotional stress, ultraviolet light)	☐ Type 1: Associated lymphoproliferative disease
☐ Cytokine Mediated AE syndrome (Gleich's syndrome)	☐ Type 2 Autoimmune (anti-C1 INH antibody)
☐ Thyroid autoimmune disease-associated AE	☐ Food allergies
☐ Other allergic disease	☐ Family history of angioedema
☐ Anaphylactic Reactions	☐ Familial allergies
☐ Allergies to medications:	☐ Other relevant history:
If yes, reaction to what (if known)?	
Medications at Time of Event: (*Please include prescription, OTC and Herbal Preparations)*	
☐ Aspirin	☐ NSAIDS
☐ ACE Inhibitors/ARBs	☐ Beta-blockers
☐ Contrast Agents	☐ Other:
Presenting Signs and Symptoms:	
Edema? Location/description:	Rash? ☐ No ☐ Yes – Location:
Was edema pitting? ☐ No ☐ Yes ☐ Other:	
Laboratory Tests/Diagnostic Testing (*Please include results, if available*):	
☐ IgE:	☐ C4:
☐ IgG:	☐ C1q:
☐ IgM:	☐ Platelet count:
☐ C1-INH:	☐ Other:
CBC with Differential:	
☐ Red Blood Cell Count:	☐ Hematocrit:
	☐ Hemoglobin:
White Blood Cell Differential:	
☐ Neutrophils:	☐ Eosinophils:
☐ Lymphocytes:	☐ Basophils:
☐ Monocytes:	
Treatment:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

What treatment was provided?	
Was an immunologist consulted?	Was another specialist consulted?
☐ Yes	☐ Yes – specify:
☐ No	☐ No

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Anaphylaxis and Similar Events

Presenting Signs and Symptoms

☐ Acute Onset (within 30 minutes of suspected drug)	☐ Dyspnea
☐ Urticaria/Hives	☐ Bronchospasm/Wheezing
☐ Cutaneous Erythema	☐ Syncope
☐ Rash	☐ Hypotension (Blood Pressure):
☐ Pruritis	☐ Shock
☐ Angioedema (location):	☐ Gastrointestinal Symptoms (vomiting/diarrhea)
☐ Anxiety	☐ Other (please specify):

Pre-Existing History (*Please specify type and date of diagnosis*):

☐ Anaphylaxis reaction to:	☐ Asthma
☐ Anaphylactoid reaction to:	☐ Urticaria/hives
☐ Angioedema after:	☐ Atopy

Prior Allergies:

☐ None

☐ Please list all prior allergies:

☐ Other:

Medications at Time of Event (*Please include prescription, OTC, and herbal preparations*):

☐ Aspirin	☐ NSAIDS
☐ ACE Inhibitors/ARBs	☐ Beta-blockers
☐ Contrast Agents	☐ Other (please specify):

Laboratory Tests/Diagnostic Testing:

☐ O2 saturation:	☐ Histamine:
☐ Eosinophil count:	☐ Tryptase:
☐ IgE:	☐ Complement studies:
☐ Skin testing (List positive results):	☐ Other (please specify):

Treatment:

☐ Antihistamines	☐ Oxygen
☐ Corticosteroids	☐ Intubation
☐ Epinephrine	☐ Vasopressors

Final Diagnosis:

☐ Anaphylaxis	☐ Angioedema

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Anaphylactoid reaction	☐ Urticaria
☐ Other (please specify):	

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Cardiac Disorders			
Primary Diagnosis for the reported event(s):			
☐ Chest Pain/Angina	☐ Myocardial Infarction	☐ Arrhythmia	☐ Other – please describe:
Hospitalization for this event? ☐ No ☐ Yes			
Presenting Signs/Symptoms			
☐ Heart Rate:		☐ Blood Pressure:	
☐ Palpitations		☐ Shortness of Breath	
☐ Syncope		☐ Chest Pain (please specify):	
☐ Cardiac Exam:			
☐ Pulmonary Exam:			
☐ Other (please specify):			
Relevant Medical History (please specify if needed)			
☐ Atrial Arrhythmia		☐ Ventricular Arrhythmia	
☐ Conduction Disorders		☐ Congenital Heart Abnormalities	
☐ Cardiovascular Disease		☐ Hypertension	
☐ Cardiovascular Infection		☐ Cardiac Surgeries	
☐ Pulmonary Disease		☐ Pulmonary Embolism	
☐ Metabolic Disorders		☐ Psychiatric/Emotional Disorders	
☐ Pericarditis		☐ Syncope	
☐ Poor compliance with BP/Cardiac Meds		☐ Dizziness	
☐ Family History of cardiac disease, congenital QT prolongation, premature cardiac death		☐ Substance Abuse	
☐ Other (please specify):			
Historic Drugs (please specify)			
☐ Antiarrhythmics:		☐ Antihypertensives:	
☐ Psychiatric Medications:		☐ Antibiotics:	
☐ Others:			
Concomitant Meds (include prescription, substance, OTC, and herbal)			
☐ Nitrates/Nitrites		☐ Alpha Blocker	
☐ ED Medication (please specify):		☐ Others:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Cardiac Enzyme (please specify):				
Serum Potassium				
Serum Calcium				
pO2				
O2 Saturation				

Other Diagnostic Tests	Results		
EKG (Q Waves)/EKG (QTC Interval)			
Myocardial Scan			
Echocardiogram (ECHO)			
Coronary Angiography			
Exercise Stress Test			
QT Interval (milliseconds)			
QTc (Corrected Value)			
How was QT Interval measured?	☐ Machine	☐ Manually	☐ Other
QT Correction Formula	☐ Bazett	☐ Fridericia	☐ Other
Other:			

Treatment	
☐ Cardioversion/Defibrillation	☐ Treatment not required
☐ Medication (please specify):	☐ Ablation
☐ Other (please specify):	

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Cerebrovascular Accident
Primary Diagnosis for the reported event(s):

Eli Lilly and Company - Global Patient Safety **Case Number:**

Hospitalization for this event? ☐ No ☐ Yes		
Concomitant Medications/Substances (please include prescription, OTC and herbal)		
Presenting Signs/Symptoms		
Onset Date:	End Date:	
Impairments:		
☐ Paralysis (specify):	☐ Dysarthria	☐ Impaired consciousness
☐ Weakness (specify):	☐ Visual field defect	☐ Seizure
☐ Dysphagia	☐ Aphasia	☐ Other findings:
Severity		
☐ No/Mild	☐ Moderate	☐ Severe
Relevant Medical History		
☐ Diabetes	☐ Artrial fibrillation	☐ Head trauma
☐ Smoking	☐ Hypertension	☐ Prior stroke
☐ Myocardial infarction	☐ Hyperlipidemia	☐ Other (please specify):

Relevant Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelet Count				
Glucose				
INR				
aPTT				
Thrombin Time				
Fibrinogen				
Other:				

Other Tests	Results
CT	
MRI	
Angiography	
EEG	
Other:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment		
☐ Support and organization	☐ Thrombolytic agent	☐ Ablation
☐ Antiplatelet agent	☐ Anticoagulant	Other:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Pregnancy Data Collection – Maternal

Pregnancy Details	
Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)					
Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring patient's pregnancy:	Medical professional responsible for monitoring the infant:
Name:	Name:
Address:	Address:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy Data Collection – Paternal

Patient (Father) Details

Name or initials:	Date of Birth or Age:

Father's medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the father:	Medical professional responsible for monitoring the mother:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy Outcome Maternal

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance (please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Breast Feeding Information

Date the breast feeding started Date the breast feeding stopped

Breast feeding continued ? ☐ No ☐ Yes

Was the breast-feeding experience 3 months or longer while on Lilly drug ☐ No ☐ Yes

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy/Fetal Outcome	
☐ Live birth/full term	☐ Premature birth (less than 37 weeks)
☐ Spontaneous/missed abortion	☐ Fetal death in utero/stillbirth
☐ Live birth with neonatal death	☐ Post natal death
☐ Elective termination (provide below the reason and the gestational age at termination):	
Were congenital or chromosomal abnormalities detected? ☐ No ☐ Yes Please define:	
Did the infant experience perinatal or post-perinatal complications? ☐ No ☐ Yes Please define:	
Was the infant admitted to the neonatal intensive care unit (NICU) at birth? ☐ No ☐ Yes Please define:	
Did the infant experience an increased incidence or severity of infection? ☐ No ☐ Yes Please define:	

Neonatal/Infant Data		
Infant name or initials:	EDC (Due Date):	Date of Delivery:
Gestational age:	Gender: ☐ Undetermined/unknown ☐ Male ☐ Female	
Apgar scores: at 1 minute at 5 minutes		
Weight: ☐ grams ☐ pounds		Length: ☐ cm ☐ inches
Infant's overall health status?		

Infant Adverse Events/Complications
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes
Please describe:
Treatment:
Continuing? ☐ No ☐ Yes
Infant's overall health status:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown	

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring patient's pregnancy:	Medical professional responsible for monitoring the infant:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number**

Pregnancy Outcome Paternal

Patient (Father) Details

Name or initials:	Date of Birth or Age:
Father's medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)	

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Eli Lilly and Company - Global Patient Safety **Case Number**

Pregnancy/Fetal Outcome	
☐ Live birth/full term	☐ Premature birth (less than 37 weeks)
☐ Spontaneous/missed abortion	☐ Fetal death in utero/stillbirth
☐ Live birth with neonatal death	☐ Post natal death
☐ Elective termination (provide below the reason and the gestational age at termination):	
Were congenital or chromosomal abnormalities detected? ☐ No ☐ Yes Please define:	
Did the infant experience perinatal or post-perinatal complications? ☐ No ☐ Yes Please define:	
Was the infant admitted to the neonatal intensive care unit (NICU) at birth? ☐ No ☐ Yes Please define:	
Did the infant experience an increased incidence or severity of infection? ☐ No ☐ Yes Please define:	

Neonatal/Infant Data		
Infant name or initials:	EDC (Due Date):	Date of Delivery:
Gestational age:	Gender: ☐ Undetermined/unknown ☐ Male ☐ Female	
Apgar scores: at 1 minute at 5 minutes		
Weight: ☐ grams ☐ pounds	Length: ☐ cm ☐ inches	
Infant's overall health status?		

Infant Adverse Events/Complications
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes
Please describe:
Treatment:
Continuing? ☐ No ☐ Yes
Infant's overall health status:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome:	

Eli Lilly and Company - Global Patient Safety **Case Number**

☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the father:	Medical professional responsible for monitoring the mother:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Breast Feeding	
Pregnancy Details	
Name or initials:	Date of Birth or Age:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Due Date:			Last menstrual period:		
Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)					
Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				
Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)					
Contraceptive method:					
Maternal Lilly Drug Information					
Drug name:					
Infant's age at first use:			Date of first use:		
Infant's age at last use:			Date of last use:		
Maternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)					
Breast Feeding Information					
Date the breast feeding started:			Date the breast feeding stopped:		
Breast feeding continued? ☐ No ☐ Yes					
Was the breast feeding experience 3 months or longer while on Lilly drug? ☐ No ☐ Yes					
Infant Adverse Events/Complications					
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes Please describe:					
Treatment:					
Continuing? ☐ No ☐ Yes					
Infant's overall health status:					

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the mother:	Medical professional responsible for monitoring the infant:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide brief explanation:

Cancer/Neoplasm

Primary Diagnosis for the reported event(s):	
Hospitalization for this event? ☐ No ☐ Yes	
☐ Please specify primary site:	
☐ Neoplasm (benign mass/lesions)	☐ Possible malignant tumor – not yet confirmed
☐ Malignant tumor (please attach copy of pathology report or provide the information of Stage/Grade, Staging classification and tissue source):	
Concomitant Medications/Substances (please include prescription, OTC, and herbal)	
Relevant Tests/Studies (please attach copy of pathology report, if available)	
Study	**Result**
Histopathology (please indicate stage/grade, staging classification and tissue source)	
Ultrasound	
CAT Scan	
MRI	
Other:	
Medical History/Risk Factors	
☐ Cancer:	☐ Family history of cancer:
☐ Chemotherapy:	☐ Radiation therapy
☐ Estrogen use: years	☐ Tobacco use
☐ Diabetes mellitus	☐ Obesity
☐ Alcohol	☐ No known predisposing factors
☐ Immunosuppression:	☐ Environmental risk:
☐ Other (please describe):	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment provided (please describe):

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ F ☐ M ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb. ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Peripheral Vascular Disease

Primary Diagnosis for the reported event(s):

Hospitalization for this event? ☐ Yes ☐ No

Concomitant Medications/Substances (please include prescription, OTC, and herbal)

Clinical Course

Onset date (mm/dd/yyyy):	Resolution date:
☐ Pain on exercise (intermittent claudication)	☐ Pain on rest
☐ Critical limb ischemia	☐ Other (specify)

A brief description of the event (include the affected body parts and extent of ischemia):

Medical History/Risk Factors

Smoking: please specify number of cigarettes per day and years.

Stop date (mm/dd/yyyy): (if applicable)

☐ Raynaud's disease/peripheral vascular disease	☐ Diabetes
☐ Cardiovascular disease (for example, DVT)	☐ Thromboangitis
☐ Occlusive vascular disease	☐ Connective tissue disease
☐ Atherosclerosis	☐ Intermittent claudication
☐ Other (specify):	

Diagnostic Test	Results
Ankle brachial pressure index	
Doppler ultrasound	
Angiography	
CT scan	
Other:	

Was Surgery required? ☐ No ☐ yes (please describe):

Treatment provided (please describe)

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:

☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown

☐ Recovered with Sequella (Please provide details):

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide rationale for relatedness assessment:

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.