20 September 2018
EMA/708631/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Emgality

International non-proprietary name: galcanezumab

Procedure No. EMEA/H/C/004648/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AAN	American Academy of Neurology
ADAs	anti-drug antibodies
AE	adverse event
ART-01	I5Q-AR-ART1
AUC	area under the plasma concentration time curve
BMI	body mass index
BW	body weight
CGAA	I5Q-MC-CGAA
CGAB	I5Q-MC-CGAB
CGAE	I5Q-MC-CGAE
CGAS	I5Q-MC-CGAS
CGAT	I5Q-MC-CGAT
CGRP	calcitonin gene-related peptide
CHAMP	Childhood and Adolescent Migraine Prevention
C-SSRS	Columbia-Suicide Severity Rating-Scale
CV	cardiovascular
DCAE	discontinuations due to adverse event
DBF	dermal blood flow
ECG	electrocardiogram
EFNS	European Federation of Neurological Societies
FC	food consumption
GBD	Global Burden of Disease study
GRAS	Generally Regarded As Safe
ICHD-3	International Classification of Headache Disorders, Third Edition, beta version
IHS	International Headache Society
IV	intravenous
IVRS	interactive voice response system
LDI	Laser Doppler Imaging
LY120-mg	galcanezumab 120 mg
LY240-mg	galcanezumab 240 mg
LY2951742	galcanezumab
MHD	Migraine headache day
MSQ	Migraine Specific Quality of Life Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment Questionnaire
MMRM	mixed model repeated measures
MSQ	Migraine-specific Quality of Life Questionnaire
MSQ-EF	Migraine-specific Quality of Life Questionnaire – Emotional Function
MSQ-RFP	Migraine-specific Quality of Life Questionnaire – Role Function Preventive
MSQ-RFR	Migraine-specific Quality of Life Questionnaire – Role Function Restrictive
NOAEL	no-observed-adverse-effect-level
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PedMIDAS	Pediatric MIgraine Disability ASsessment
PGI-I	Patient Global Impression of Improvement
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PWA	pulse wave analysis
Q4W	every 4 weeks
QTcB	Bazett's corrected QT interval
QTcF	Fridericia corrected QT interval
SAE	serious adverse events
SC	subcutaneous
SMQ	standardized MedDRA query
TEAE	treatment-emergent adverse event
TK	toxicokinetic

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 30 October 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Emgality, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2016.

The applicant applied for the following indication: Emgality is indicated for the prophylaxis of migraine in adults.

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0341/2016 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0341/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

New active Substance status

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

Scientific advice

The applicant received Scientific advice from the CHMP on 18 December 2014. The Scientific advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Daniela Melchiorri Co-Rapporteur: Kristina Dunder

The application was received by the EMA on	30 October 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	04 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	2 July 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 July 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 July 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	05 September 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Emgality on	20 September 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Among primary headaches, defined as independent disorders not caused by another disease or trauma (ICHD, 2nd ed., 2004) and that include also tension-type headache, trigeminal autonomic cephalalgias and other primary headache disorders, migraine is very common and has two major subtypes based on specific features and symptoms that accompany each attack: migraine without aura (the most frequent form) and migraine with aura, in which transient focal neurological symptoms usually precede or sometimes accompany the headache. There are trigger factors that include hypo-hyper activity, hunger, sleep deprivation, exposure to intense or pulsatile light, depressed mood, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain which migraineurs experience hours or even days before the headache, or during its resolution. Migraine without aura is the commonest form of primary headaches. Headache typically is recurrent and lasts 4 to 72 hours, has unilateral location, pulsating quality, moderate to severe intensity and aggravated with routine activity, associated or not to nausea, phono- or photophobia. Migraine with aura needs the coexistence of fully reversible aura symptoms spreading over at least 5 minutes with 5 to 60 minutes duration and followed by headache. In the early stage of an attack, the accompanying premonitory symptoms may be associated with hypothalamic involvement (Maniyar FH, 2014).

Migraine is a complex and multifaceted brain disorder and two main categories can be identified, based mainly on the frequency of attacks: episodic migraine (EM), defined as less than 15 headache days per month and chronic migraine (CM), defined as the patient having 15 or more headache days per month, with at least five attacks fulfilling criteria for EM with or without aura. However, there is a substantial overlap in terms of symptoms between the two forms, as well as pathophysiology and burden of disability, which make preventive treatment one of the key strategies for migraine management.

2.1.2. Epidemiology

Including both EM and CM, migraine has a one-year prevalence of 15-18% worldwide, with extensive financial yearly burden on global economies, ranging from $19.6 in the United States to €27 billion in the European Union. It was ranked as the third most prevalent disorder and sixth-highest specific cause of disability worldwide by the WHO (Global Burden of Disease Study, 2013).

Migraine predominantly affects females with a 3:1 ratio, with a peak of incidence between the ages of 25 to 55 years, thus it may profoundly impact upon quality of life and productivity. In fact, due to the neurological deficits experienced in the acute phase (such as nausea, vomiting, light and/or sound sensitivity, need to be isolated from the outer world including workplace and school), as well as the aftermath following an attack that lasts for hours or days, subjects experience a condition of true restrictive lifestyle. The vast majority (approximately 90%) of migraine sufferers have a reduced ability to function, and one-third require bed rest during migraine attacks (Lipton et al. 2007).

Migraine has a significant impact on the population, as each year, about 2.5 % of patients with EM develop new-onset CM (Manack et al., 2011). Demographic and comorbidity data outline some clinical differences among subjects with CM and EM, being EM patients more frequently overweight and younger,

unemployed and with and anxious-depressed mood (Blumenfield et al 2010), whereas in several CM patients there are risk factors like medications abuse as well as different response to treatments, both preventive and abortive.

Comorbidities of migraines include, but are not limited to, psychiatric and medical conditions such as depression and vascular disorders (Buse et al, 2010; Bigal et al, 2009).

2.1.3. Biologic features

Over the past two decades, new theories apart from the classical neurovascular theory, have tried to elucidate the pathogenesis of migraine while focusing on activation of the trigeminovascular system (Goadsby et al., 2002), cortical hyperexcitability (Coppola wt al., 2002), and dysregulation of brainstem regions involved in antinociception and vascular control. The so called trigeminal durovascular afferent pathway has undergone in-depth analyses through immunohistochemistry and functional brain imaging, starting from the knowledge that pain-sensitive structures such as the intracranial blood vessels and the meninges, especially the dura mater, are supplied with sensory nerve fibres (Pietrobon & Striessnig, 2003) by the ophthalmic ramus of the first branch of the trigeminal nerve. They arise from pseudounipolar neurons located in the trigeminal ganglion (Link et al., 2008) projecting onto second order sensory neurons in the trigeminal nucleus caudalis in the brain stem and its related extensions down to the C2-level called the trigeminocervical complex (Goadsby, 2007).

In light of this, several experiments have tried to elucidate the details behind each of the four phases in which a migraine attack is classically subdivided: the premonitory, aura, headache, and postdrome phases. There is wide consensus over the notion that migraine attacks are the results of a cyclic disorder of brain sensory processing, which is influenced by genetic and environmental factors. The premonitory phase involves brain stem and diencephalic systems that modulate afferent signals and explain photophobia or phonophobia, followed by pain up to the resolution or postdromal phase. A dysfunction of central pain processing in the interictal state has been gathered from the hypometabolism of central pain processing areas including bilateral insula, bilateral anterior and posterior cingulate cortex, left premotor and prefrontal cortex, and left primary somatosensory cortex as revealed by 18F-FDG and BOLD-fMRI imaging studies.

The major classes of medicines identified thus far, such as triptans, serotonin 5-HT1B/1D receptor agonists, calcitonin gene-related peptide (CGRP) modulators, including receptor antagonists and monoclonal antibodies, gepants, ditans, 5-HT1F receptor agonists glurants, mGlu5 modulators would exert their main effect at this stage of the whole process.

With regard to CGRP, this neuropeptide is abundant in perivascular trigeminal nerve fibres by which is activated, especially during migraine attacks, and shows the capability of dilating intracranial and extracranial blood vessels while modulating vascular nociception at central level. As such, CGRP may play an important role in the pathophysiology of migraine and, conversely, blockade of CGRP receptors as well as its own peripheral circulation may contribute to abort migraine.

Elevated blood concentrations of CGRP have been associated with migraine (Edvinsson and Goadsby 1994; Bigal et al. 2013). In addition, CGRP infusions can induce migraine-like attacks in individuals with a history of migraine (Lassen et al. 2002; Hansen et al. 2010).

CGRP peptide can directly exert excitatory effects on nociceptive neurons leading to sensitisation or activation of neurons in pain signalling pathways, suggesting that can it can drive maladaptive processes in peripheral nerves that induce peripheral sensitisation and ultimately pain. It can also facilitate the effects of other pain transmitters including glutamate and substance P (Ma et al. 2010).

The rationale in using CGRP mAbs stands behind the possibility to target smooth muscle cells on blood vessels and neurons and glial cells outside the blood–brain barrier, contributing to halt vasodilation, mast cell degranulation, neurogenic inflammation, and possibly peripheral pain sensitization in migraine (Russel FA et al, 2014).

2.1.4. Clinical presentation, diagnosis

Migraine is a chronic condition, albeit prolonged remissions are frequently observed. The diagnosis of migraine is based on patient history and follows the International Headache Society (IHS) diagnostic criteria

According to the definition of common migraine (migraine without aura or hemicrania simplex, coded with 1.1 in the ICHD-3 beta) patients must have at least 5 recurrent attacks lasting 4-72 hours (untreated or unsuccessfully treated) and the headache must have at least 2 of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs). In addition, during the headache the patient must have had at least 1 between nausea and/or vomiting, photophobia and phonophobia. These features must not have been attributable to another disorder.

With regard to prognosis, migraine is a rather benign condition and is not associated with an increased risk of death. The natural history of migraine may slightly change according to the exact type of headache and usually ranges from complete resolution, to symptoms continuation with gradually less or even worsening intensity and frequency over time. Generally Episodic Migraine tend to convert to chronic migraine provided that medication overuse has taken place in the meantime.

The presence of aura may double the risk for ischemic stroke (Kurth et al., 2012). Increase risk for migraine has been linked to young adult age, female gender, use of hormonal birth control, and smoking, whereas the absence of aura do not appear to be constitute a risk factor for specific conditions. Generally, the severity and frequency of migraine attacks tend to diminish with increasing age.

2.1.5. Management

In the management of migraine, among the first steps to be taken there is the reduction or, if possible, the elimination of the exposure to triggers. This can be done through several ways that include diet and physical exercise. If control of these stimuli is ineffective in preventing the onset of the migraine crisis, and if intense pain prevents normal daily activities, it is possible to resort to drug therapy.

Migraine medications can relieve pain and symptoms during the acute phase of headache or prevent further attacks. The most appropriate therapeutic approach should be formulated in relation to the extent of the disorder, the symptoms and the personal needs of the patient. In case of comorbid conditions, care should be taken when prescribing specific medications and considering drug interactions as well as the patient's individual metabolic characteristics. The excessive and prolonged use of these drugs can, in fact, cause resistance to treatment and generate a particular form of secondary headache due to drug overuse.

About the product

Galcanezumab is a humanised immunoglobulin (subclass) G4 (IgG4) monoclonal antibody that binds CGRP, preventing its biological activity without blockade of CGRP receptor. Galcanezumab targets CGRP and binds with high affinity (KD = 31 pM) and high specificity (>10,000-fold vs. related peptides adrenomedullin, amylin, calcitonin and intermedin).

Type of Application and aspects on development

Scientific Advice was received from the CHMP for galcanezumab on 18 December 2014 related to the pre-clinical and clinical development plan

2.2. Quality aspects

2.2.1. Introduction

Galcanezumab is a recombinant humanised monoclonal antibody produced in Chinese hamster ovary (CHO) cells.

Emgality is presented as a solution for subcutaneous injection containing 120 mg of galcanezumab as active substance (also referred to as AS) formulated with L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sodium chloride and water for injections (WFI).

The finished product (also referred to as FP) is available in pre-filled pen and pre-filled syringe (packs of 1 and 3 each).

Although this dossier is not considered a Quality by Design (QbD) application, certain elements of an enhanced approach were applied.

2.2.2. Active Substance

General information

Galcanezumab is a humanised monoclonal antibody of IgG4 that binds calcitonin gene-related peptide (CGRP) thus preventing its biological activity. Elevated blood concentrations of CGRP have been associated with migraine.

Galcanezumab is comprised of two identical heavy chains and two identical light chains. Each heavy chain contains a single N-linked glycosylation site at Asn296. The N-linked glycosylation structure is predominantly a fucosylated, complex biantennary glycan with O-galactose residues (G0F) on either arm.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Information about the manufacturing, storage and control facilities for the active substance (AS) has been provided. GMP compliance for the manufacturers has been demonstrated.

Manufacturing of the active substance is performed at Imclone Systems LLC (Branchburg), USA (part of Eli Lilly and Company). Galcanezumab is manufactured using a Chinese hamster ovary (CHO) cells fed batch process in bioreactors. The purification process includes a series of chromatography, viral inactivation and filtration steps. The process has been described in sufficient detail.

Galcanezumab AS is filled into a gamma-irradiated high-density polyethylene (HDPE) container closed with a polypropylene screw-cap closure. Extractable and leachables studies have been presented adequately. Furthermore an acceptable specification for the HDPE container has been provided. The container closure for active substance is considered acceptable.

Control of materials

Raw materials are sufficiently described and controlled. The history and generation of the cell substrate are described in detail. The Master Cell Bank (MCB)/WCB manufacturing, characterisation and viral testing have been executed in accordance to ICH Q5A and Q5D. An adequate protocol for preparation of future WCBs has been provided.

Control of critical steps and intermediates

Critical process parameters (CPP), in-process controls (IPC) and operational performance parameters (OPP) are described. It is noted that few operational parameters are classified as critical; however the process is well controlled. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process.

Process validation

The process validation was performed and acceptable results from both critical and non-critical parameters and controls are presented. Furthermore, results from all production bioreactor CPPs are provided. The release results from the active substance validation batches are provided, together with information about additional data on in-process impurities. All acceptance criteria were met. Process validation demonstrated that the process is robust. Clearance of process-related impurities (host cell proteins (HCP), DNA, Protein A and Triton-X) was demonstrated to acceptable low levels (below limit of quantitation in several cases) during process validation.

Manufacturing process development

Three AS processes are described in the dossier. Two comprehensive comparative exercises were performed to demonstrate comparability between processes.

The comparability assessments include comparison of specifications, comparison to historical data and head-to-head comparison among AS batches. The quality attributes evaluated were based on a risk assessment of the potential impact of the manufacturing process change. Overall, data from seven active substance batches were evaluated within the comparability assessment. This provides an assurance of similarity between the different processes. The strategy for determination of critical quality attributes (CQA) is well elaborated. With respect to process characterisation, each unit operation is described separately. The purpose of the step, process parameter risk assessment, description of small scale model, study plan and results from design of experiments (DoE) studies are adequately described with sufficient amount of details. The results support the ranges chosen for process parameters.

Characterisation

Physicochemical and biological characterisation of galcanezumab has been performed using a battery of state-of-the–art methods

The product-related and process-related impurities in galcanezumab were characterised throughout development.

Specification

The specification of the AS includes control of identity, purity and impurities, potency and other general tests.

The proposed release specification for AS is found acceptable with respect to test methods chosen. The release specification ranges are considered acceptable.

Consistent removal of process-related impurities has been demonstrated during process validation.

Analytical methods

The descriptions of the analytical procedures used for release and stability testing of AS contain a sufficient level of detail and are found acceptable. All non-compendial methods have been validated in accordance with ICH Q2 and are considered acceptable. These validations also include finished product. Compendial methods have been appropriately verified for their intended use.

Batch analysis

Batch analysis from process validation and commercial-scale, primary stability studies and clinical trial, development and toxicology studies are provided. The release results from the commercial AS process support a consistent manufacturing of active substance.

Reference materials

A two-tiered system is applied for the reference standard (RS). The current primary (PRS) and working reference standards (WRS) were manufactured from galcanezumab active substance batch selected as a representative Phase 3 clinical batch. The historical RS, qualification protocol for current PRS/WRS as well as qualification and requalification protocols for future WRS have been described.

Stability

A shelf life of 36 months at not more than -65°C for the storage of the active substance is considered acceptable.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is filled in a semi-finished syringe (SFS), which is further assembled into one of two different delivery devices. The proposed presentations are a pre-filled syringe and a pre-filled pen. Each pre-filled pen and each pre-filled syringe contains 120 mg of galcanezumab in 1 mL.

All excipients are of compendial quality and comply with the corresponding Ph. Eur. monographs. The primary container closure system for galcanezumab solution for injection is a 1-mL-long, Type I borosilicate glass syringe barrel with laminated bromobutyl elastomeric plunger. The container closure system filled with finished product is referred to as the SFS. Compliance with relevant Ph. Eur. requirements in monographs has been confirmed for the materials of construction.

The information provided for the delivery devices is comprehensive, and in general confirms the suitability of the chosen devices. The combination of the SFS and the pre-filled syringe, and the SFS and the pre-filled pen (auto-injector) forms two separate integral products, and are not considered as separate medical devices.

Pharmaceutical development

An acceptable overview of the development of the formulation has been provided, including data supporting the proposed composition of the commercial finished product. The commercial finished product manufacturing process was developed using a science- and risk-based approach, in line with ICH Q8. DoE/QbD principles have been implemented during development of the manufacturing process as well as the formulation for finished product. Extensive documentation has been presented and the results

are clearly summarised. The manufacturing process development is described in sufficient detail. The development of the control strategy is generally well explained and acceptable justification has been provided. The development of the primary container closure system is sufficiently described in the dossier. The safety of the materials of construction was established in accordance with the relevant standards. Comprehensive profiles for extractables for the container closure system have been provided. Container closure integrity has been evaluated. Compatibility has been confirmed and is considered appropriate

Manufacture of the product and process controls

Manufacture

The process involves five unit operations: buffer excipient solution compounding, finished product formulation compounding, sterile filtration, aseptic syringe filling and plunger insertion, and inspection. Limits for process parameters and process controls have been provided. The assembly process for the pre-filled syringe and the pre-filled pen is described. The information provided regarding the manufacturing process is considered sufficiently detailed.

Process controls

Operating ranges for process parameters and acceptance criteria for controls are provided for the parameters/controls that have been determined to be critical to ensuring that the CQAs are met (CPPs, critical IPCs, and in-process specifications). Parameters and controls (critical and non-critical) are managed via the internal quality system, including change control management, deviation management, and routine process and product performance monitoring.

Process validation

The process validation studies described in the dossier comprise FP process validation, sterilisation process validation, and shipping validation.

Three consecutive commercial-scale process verification batches (also referred to as process performance qualification (PPQ) batches) were manufactured. All validation batches complied with the established in-process and release specifications, and all parameters were within operating ranges and met protocol acceptance criteria.

Product specification

The specifications for the galcanezumab finished product are presented and include control of identity, purity and impurities, potency and other general tests.

The proposed FP release and end of shelf-life specifications are found acceptable.

Analytical methods

Several of the analytical procedures used for release and stability testing of FP are also used for release and stability testing of the AS. The analytical procedures applicable only for testing of FP have been described in sufficient detail. The non-compendial procedures specific to the control of FP have been appropriately validated. Compendial methods have been appropriately verified for their intended use.

Reference materials

The reference standard for testing of finished product is the same as described for active substance.

Batch analysis

Batch analyses data has been provided for the PPQ batches and the primary stability batches, manufactured using the proposed commercial process and at commercial scale. All data complies with the proposed finished product specifications. In addition, batch analyses data is also included for early development batches. In conclusion, the batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for galcanezumab finished product.

Stability of the product

The provided real time and supportive stability data confirmed the acceptable shelf-life for FP of 24 months at 2-8°C, in the original package in order to protect from light.

Results from patient in-use stability study at end of shelf life support the proposed patient in-use period of 7 days up to 30°C.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Adventitious agents

Raw material of animal origin used early in the cell line generation process has been listed and adequately addressed. The information provided in relation to adventitious agents for these materials together with the viral testing on MCB and end-of-production (EOP) cells (limit of *in vitro* cell age) is found adequate to address the adventitious agent safety of these materials.

The risk of TSE contamination is considered adequately addressed.

With regards to virus safety, satisfactory information has been provided regarding test of MCB, WCB and end-of-production cell bank (ECB).

The viral clearance studies were performed in accordance with the CHMP Note for Guidance on Virus Validation Studies (CPMP/BWP/268/95) and ICH Q5A and demonstrate effective reduction of both enveloped and non-enveloped viruses. The down-scale of the process steps has also been sufficiently described to justify the applicability of the virus clearance results to the full-scale process.

Post approval change management protocol(s)

Four post-approval change management protocols (PACMPs) were proposed. They are considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Emgality dossier was of good quality and no major issues were identified in the documentation submitted. There were however some "other concerns" identified, partly due to lack of detail, and also related to lack of justification for some proposals and statements made by the applicant. All these issues are now resolved.

The AS and FP manufacturing process description and process controls were described with sufficient amount of detail and were considered acceptable. The cell bank system was properly tested and qualified. CPPs were identified and the process is appropriately validated.

Extended characterisation of galcanezumab was performed. Multiple orthogonal analytical methods were applied to assess galcanezumab molecular properties, such as primary structure, post-translational and other modifications, higher order structure and biological activity.

The information provided for the delivery devices, the pre-filled syringe and pre-filled pen, is comprehensive, and confirms the suitability of the chosen devices. Design verification was performed as per ISO 11608-1. Compliance with Medical Device Directive Essential Requirements has been demonstrated.

The concern raised during the procedure related to the justification of specification for FP was satisfactorily addressed. Furthermore, additional data from the ongoing stability studies were requested to further support the proposed shelf-life for AS which is now considered acceptable.

The applicant's proposal for Established Conditions was removed from the dossier due to the draft status of ICH Q12 guideline on lifecycle management.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Emgality is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Emgality is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant has conducted a comprehensive battery of tests to characterise pharmacology and toxicology of galcanezumab.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies have shown that galcanezumab was able to bind with relatively high (picomolar) affinity human αCGRP with association rate (kon) of 7.4 x 106 M-1 s-1, dissociation rate (koff) of 2.2 x 10-4 s-1 and average KD of 31 pM.

LY2951742 was shown to be a potent inhibitor of cAMP production induced by both human and rabbit CGRPs on the human CGRP-receptor expressed in neuroepithelioma cell line SK-N-MC, with IC50 values of 0.23 nM (human) and 0.06 nM (rabbit): this result supports the choice of rabbit as second species in the embryo-fetal development study.

In vivo activity was demonstrated in male rat and in female cynomolgus models of capsaicin-induced increase of dermal blood flow (DBF). Galcanezumab (4 mg/Kg SC and 5 mg/Kg IV in rat and cynomolgus, respectively) potently reduced 2 mg capsaicin-induced increases in dermal blood flow by 80.5% at 5 days post-administration of galcanezumab in rats, and by 87%, 71%, 63% at 1, 15 and 29 days respectively, post-administration of galcanezumab in monkeys. The higher dose needed in rat vs cynomolgus to achieve a similar effect in reducing the dermal blood flow, indicates that the rat is less relevant species.

Secondary pharmacodynamic studies

The applicant has provided an overview on possible secondary pharmacology effects following galcanezumab treatment with focus on potential effects on glucose metabolism, gastrointestinal system, reducing defence from pathogens, delaying wound healing and effects on bone.

Glucose metabolism

CGRP was shown to inhibit glucose-stimulated insulin secretion in normal and alphaCGRP knockout animals. Possible implication of CGRP inhibitors in the treatment of metabolic disorders (e.g. diabetes and obesity) is to be further studied. Interestingly, biological association between migraine and obesity has been postulated based on epidemiological evidence (i.e. common biomarkers that are elevated in both conditions, elevated plasma levels of CGRP found in obese individuals) (Recober and Goadsby, 2010).

Gastrointestinal system

It is well known that CGRP is widely distributed in the mesenteric neurons along gastrointestinal tract. Biological effects of CGRP on gastrointestinal tract include increase in the intestinal blood flow, relaxation of the smooth muscle, anti-inflammatory and immunesuppressive effects. In CGRP knockout mice, the ulcer healing process elicited by acetic acid was significantly delayed and CGRP was able to prevent gastric mucosal injury elicited by ethanol. In the same study, a proangiogenic activity of CGRP was demonstrated *in vitro* (Ohno et al., 2008).

Adaptive and innate immunity

Recent studies on CGRP's role in innate immune responses have shown that CGRP may inhibit the proinflammatory response and neutrophil function, while blocking CGRP signaling in prophylaxis or treatment modes resulted in improved survival in a mouse model of bacterial pneumonitis. Therefore, blocking of CGRP signalling may hypothetically improve clinical outcomes to bacterial infections. However, there are currently no signals from any of the non-clinical or clinical studies with galcanezumab in relation to immune function and susceptibility to infection or on mast cell mediated host defence.

Wound healing

The role of CGRP in facilitating wound healing is thought to be mediated through its ability to promote keratinocytes proliferation, enhance revascularization (angiogenetic effect), reduce expression of tumor necrosis factor-α and attenuate macrophage infiltration (Deen et al., 2017). Therefore, blocking of CGRP signalling may lead to alterations in wound healing and increased inflammatory responses in skin injuries at the site of injection. Non-clinical studies in rodents suggest that CGRP may play an important role in wound healing. The non-clinical toxicity studies conducted with galcanezumab in rats or monkeys show no significant effect of CGRP blockade on wound healing, which may, according to the Applicant, be partly explained by the redundancy in promoting angiogenesis at the site of injury. In addition, there is no direct evidence for alterations in wound healing observed in the clinical program of galcanezumab, nor have there been any reports on adverse effects on wound healing in the literature with other CGRP blocking antibodies used in migraine patients.

Bone

In the literature CGRP has been recognized as a neurotransmitter involved in the regulation of bone formation and bone remodeling. Experimental bone studies in vitro using a transfected osteoblastic MG-63 human cell line have an osteogenic (bone producing) phenotype when exposed to CGRP, which favor osteoblast formation and the subsequent activation of bone formation. In vivo, transgenic mice overexpressing CGRP in differentiated osteoblasts display a bone phenotype characterized by an increased bone volume caused by an increased rate of bone formation, while knockout mice deficient for alpha-CGRP are osteopenic due to a decrease in bone formation. Large animal studies evaluating the effects of CGRP on bone growth or maintenance of bone mass were not found in the literature. Based on human genetics it's known that individuals with familial dysautonomia, who suffer from a progressive dysfunction of the autonomic, sensory, and motor nervous systems, show low levels of circulating CGRP and reduced bone mineral density. Collectively, these findings suggest that CGRP is an anabolic factor for bone acting directly on osteoblasts. The potential risk of adverse galcanezumab effects on bone growth and/or remodelling cannot be ruled out.

Galcanezumab did not produce any effects on respiration rate and no galcanezumab-related neurological observations or changes in body temperature were noted in monkey.

Safety pharmacology programme

No dedicated safety pharmacology studies were performed with galcanezumab. The safety pharmacology core battery to identify undesirable pharmacodynamic properties of galcanezumab to vital functions such

as cardiovascular, respiratory and central nervous system was included in the repeated-toxicity studies in monkey. This approach was considered acceptable by the EMA EMA/CHMP/SAWP/767666/2014) and provided a full description of the endpoints investigated according to ICH S7A guideline. The applicant provided additional safety data on potential effects of CGRP antagonism on coronary vasospasm and myocardial ischemia based on published experimental data which, however, does not include any clinical information on the potentially galcanezumab cardiovascular risks on treated patients as requested by ICH S7 guideline.

Safety pharmacology endpoints on the cardiovascular, respiratory, or central nervous systems galcanezumab effect have been evaluated in the 6-week and 6-month repeated-dose toxicity studied in monkey (see toxicological section). In both studies, the cardiac effects of galcanezumab were evaluated through Electrocardiographic (ECG) evaluation and measurements using jacketed non-surgical telemetry on anesthetized animals. ECG waveforms collected has been analyzed to determine PR and QT intervals, and QRS duration. The corrected QT (QTc) interval was determined using an individual animal correction factor. The RR interval has been used to derive heart rate and used in QT interval correction. No galcanezumab-related effects on cardiovascular parameters measured were identified in the 6-month monkey study: i.e. no rhythm abnormalities or qualitative ECG changes and no effect on heart rate, RR or QTc interval were observed following galcanezumab SC administration at any dose group. The applicant clarifies that the cardiovascular (mainly QT/QTc interval) and neurovascular risk assessments, integrated in repeated-dose 6-week and 6-month toxicity studies, were performed at relevant exposure timepoints for toxicological extrapolation to clinical setting since monkeys exposure levels were sufficiently high up to 24 hours postdose on Day 29 [the last EEG recording time], and 16 hours postdose on Day 169 [the last EEG recording time], in the 6-week and 6-month studies, respectively. It is also noted that galcanezumab has a long half-life (in monkey single dosed IV= 7.6 days). The reduced galcanezumab serum concentrations due to suspected ADAs observed in 1 female exposed to the highest dose level (100 mg/Kg) in the 6-week study, and in a number of female monkeys in the 6-month study in the lowest dose level (2 mg/kg), were recorded after Days 36 and 176, respectively, outside the cardiovascular/neurovascular timepoints assessment.

Pharmacodynamic drug interactions

Due to the high target specificity of galcanezumab, no pharmacodynamic drug interaction studies were performed.

2.3.3. Pharmacokinetics

No standard ADME studies were performed with galcanezumab according to ICH S6(R1) guideline. The only PK study on galcanezumab was a non-GLP study performed in male cynomolgus monkey using only one single dose (2 mg/kg) administered IV (8214340LO); thus, it is not possible to draw any conclusion on gender effect or any dose-response relationship. The applicant did not provide any justification about the rationale behind the large dose intervals used for the monkey dose-repeated toxicity studies (i.e. 1.5-15-100 mg/kg; 15-100 mg/kg; 2-100 mg/kg). Following IV administration, the volume of distribution of galcanezumab was similar to total plasma volume in monkeys, as is typical for IgG4 monoclonal antibodies, which indicate galcanezumab is mainly confined in plasma compartment with limited extravasation within tissues.

In an *in vivo* study (study PM120) aimed at exploring galcanezumab distribution in rat Central and Peripheral nervous tissues, SC radiolabelled galcanezumab distribution in peripheral and CNS tissues was limited with respect to plasma concentrations (in peripheral tissues -dura mater, spleen, and trigeminal ganglia- ranging from 5% to 11%; in hypothalamus, prefrontal cortex, cerebellum, and spinal cord ranging from 0.10% to 0.35%; in the CSF ranging from 0.10% to 0.13%). The Cmax of galcanezumab was seen at 72 hrs and persisted for at least 7 days. Tissue binding was persistent across 7 days post dose. Results indicate that antibody distribution into the central nervous system including the cerebrospinal fluid is relatively low compared to peripheral tissues. The distribution of galcanezumab into the dura mater and the trigeminal ganglia is more similar to that of a highly innervated peripheral tissue, such as spleen, than central nervous system tissues, confirming that these two tissues are outside of the blood brain barrier and are potential target tissues for galcanezumab.

No studies on protein binding have been conducted since specific or non-specific interactions with plasma proteins were not expected to occur for galcanezumab.

Galcanezumab is a monoclonal antibody that is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous IgG. As such, there is no metabolic inhibition or induction of enzymatic pathways.

The physical size of galcanezumab (144.084 kDa) excludes it from efficient glomerular filtration and, therefore, elimination of intact galcanezumab via urine is not expected. Biliary secretion is not an important route of elimination of IgG antibodies. Therefore, rather than being excreted, galcanezumab will be eliminated by degradation to smaller peptides and amino acids by a variety of proteolytic processes in the cells following receptor-mediated endocytosis that is saturable because of the finite number of targets.

Galcanezumab is not anticipated to be metabolised by CYP450 enzymes, and is unlikely to have any effect on transporters or drug-metabolising enzymes because it has high specificity for the target ligand CGRP. Pharmacokinetic interactions with other drugs that rely on renal or hepatic mechanisms for their clearance are not expected, and no drug-drug interaction studies were conducted. PD interaction studies with drugs that are potentially going to be co- administered in the clinical situation would be more relevant.

2.3.4. Toxicology

Repeat dose toxicity

Repeat-dose toxicity studies conducted in monkeys and rats were 6 weeks, 3 months, and 6 months in duration. Fertility, embryo-fetal development, and pre- and postnatal development studies were conducted in rats. Embryo-fetal development studies were also conducted in rabbits. Additionally, a juvenile toxicity study in rats was conducted to assess potential effects on growth and development to support paediatric development. In all toxicity studies, galcanezumab was administered by SC route, which is the clinical route.

Overall, galcanezumab was well tolerated in rat. Deaths observed during and after dosing phase in female and male animals, were registered only in the 6-month repeated-dose rat toxicity study (8297946) at the highest dose level of 250 mg. The Applicant considered these deaths not related to galcanezumab due to the lack of any notable pathology findings in these animals.

Across all toxicology studies, the most frequent observed finding was minimal to slight perivascular mononuclear cell infiltrates, chronic inflammation, and pigment at injection sites (SC) that was generally dose-dependent with no evident gender effect and reversed at the end of the recovery period in 15 and 100 mg/kg dose levels.

Reproduction Toxicity

Studies in rats were conducted to assess the potential effects of galcanezumab on male and female fertility, embryo-fetal development (also in rabbits), and prenatal and postnatal development.

No effects on fertility parameters such as oestrous cycle, sperm analysis, or mating and reproductive performance were observed in rats that were administered galcanezumab (exposures approximately 4 to 20 times the human exposure at 240 mg). In male fertility study, right testis weight was significantly reduced at exposures to 4 times the human exposure at 240 mg.

At Gestational Day 20, an increase in the number of foetuses and litters with short ribs and a decrease in the mean number of ossified caudal vertebrae occurred in the rat embryo-foetal toxicity development study at an exposure approximately 20 times the human exposure at 240 mg. These findings were noted at no maternal toxicity and were considered to be related to galcanezumab but non-adverse.

At Gestational Day 29, in rabbit embryo-foetal development toxicity study skull anomaly was found in one male foetus from mother treated with galcanezumab at an exposure approximately 33 times the human exposure at 240 mg.

In a juvenile toxicology study in which rats were administered galcanezumab twice weekly from Postnatal Day 21 through 90, systemic effects were limited to reversible, minimal, nonadverse decreases in total bone mineral content and bone mineral density at exposures approximately 50 times the human exposure at 240

2.3.5. Ecotoxicity/environmental risk assessment

The active substance galcanezumab is a protein, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, galcanezumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

CGRP is widely expressed in both central and peripheral nervous systems and maternal and foetal tissues with a wide-range control functions. Consequently, the Applicant has provided an overview on possible secondary pharmacology effects following galcanezumab treatment with focus on potential effects of galcanezumab on glucose metabolism, gastrointestinal system, reducing defence from pathogens, delaying wound healing and effects on bone.

Inhibition of CGRP pathway could result in diarrhea or constipation and could evoke gastric ulcerative events. Events of gastric and peptic ulcers were found in clinical trials even if no clear causal relationship with galcanezumab treatment has been determined. In the monkey 6-month study, dose-dependent fecal abnormalities (liquid and/or non-formed) related to galcanezumab, were observed but not considered adverse because did not result in changes in body weight or clinical condition. In clinical studies cases of

constipation (even persistent) have been observed more frequently in galcanezumab treated patients compared to placebo.

The role of CGRP in facilitating wound healing is thought to be mediated through its ability to promote keratinocytes proliferation, enhance revascularization (angiogenetic effect), reduce expression of tumor necrosis factor-α and attenuate macrophage infiltration (Deen et al., 2017). Therefore, blocking of CGRP signalling may lead to alterations in wound healing and increased inflammatory responses in skin injuries at the site of injection. The non-clinical toxicity studies conducted with galcanezumab in rats or monkeys show no significant effect of CGRP blockade on wound healing, which may, according to the applicant, be partly explained by the redundancy in promoting angiogenesis at the site of injury. In addition, there is no direct evidence for alterations in wound healing observed in the clinical program of galcanezumab, nor have there been any reports on adverse effects on wound healing in the literature with other CGRP blocking antibodies used in migraine patients.

The applicant did not provide any discussion on the implication of CGRP in the respiratory system. However, in the 6-week and 6-month repeated-dose toxicity studies in cynomolgus monkeys there were no effects of galcanezumab on respiration function with exposure margins exceeding 100-fold compared to clinical C_{max}.

No non-clinical studies were conducted to fully investigate the vascular effects of galcanezumab to evaluate its vasoconstriction potential such as test in isolated arteries (e.g. aorta, coronary artery); any additional mechanistic/safety non-clinical studies to address the role of this specific target in human ischemic diseases would be poorly informative given the lack of validated and predictive animal (rodent) models.

Although no direct measurement of hemodynamic parameters was carried out in animal studies, "Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events" is now included among the important potential risk. In addition, cardiovascular safety will be considered in the "Observational Cohort Study of Galcanezumab Utilisation and Long-Term Safety" as required additional pharmacovigilance activities.

According to Walter et al. (2014) it has been suggested that CGRP in the CNS is associated with regulation of various hemodynamic parameters, while peripheral inhibition of CGRP does not induce any hemodynamic changes, likely due to the number of overlapping compensatory mechanisms that are involved in the modulation of blood pressure.

No non-clinical studies were conducted to fully investigate the vascular effects of galcanezumab to evaluate its vasoconstriction potential such as test in isolated arteries (e.g. aorta, coronary artery).

In vitro galcanezumab was able to prevent activation of the AMY-R also found in human coronary arteries: thus, respect to CGRP-R antagonist, galcanezumab shows a potential additional risk for cardiovascular and neurovascular risk. CGRP administration in vivo rat models of cerebral ischemia significantly reduced ischemic brain injury volume by improving blood flow in the penumbra region via its action of vasodilation and playing in this way an indirect cerebral neuroprotection (Jeremy P et al 1994 - Zhen Liu et al 2011 vol. 171).

Consistently with ICH S6(R1) guidance, genotoxicity studies were not conducted because galcanezumab is a monoclonal antibody. Standard carcinogenicity bioassays of galcanezumab were not conducted, as well. On the basis of evidence gathered so far, further *in vivo* or *in vitro* (e.g. cellular proliferation) studies aimed at better characterizing the galcanezumab carcinogenic potential, are not envisaged.

In the literature CGRP has been recognized as a neurotransmitter involved in the regulation of bone formation and bone remodeling. Large animal studies evaluating the effects of CGRP on bone growth or maintenance of bone mass were not found in the literature. Based on human genetics it's known that individuals with familial dysautonomia, who suffer from a progressive dysfunction of the autonomic, sensory, and motor nervous systems, show low levels of circulating CGRP and reduced bone mineral density. Collectively, these findings suggest that CGRP is an anabolic factor for bone acting directly on osteoblasts. The potential risk of adverse galcanezumab effects on bone growth and/or remodelling cannot be ruled out.

Bone effect of galcanezumab was specifically investigated only in juvenile rat study in which treatment with galcanezumab 250 mg/kg reduced bone content and density in both female and male metaphysis, but however adverse effects in bone development (i.e. short ribs -right, left, or bilateral 13th-, reduction in the mean number of ossified caudal vertebrae) were also observed in foetuses and litters from female rats dosed 250 mg/kg (study 20096436).

Considering the CGRP role in supporting bone metabolism, adverse effect in children growth is of particular concern, considering the chronic intended treatment. Although the applicant clarified that no alteration of bone parameters, assessed as gross examination, was observed in adults monkey in repeated-dose toxicity studies up to 100 mg/kg treatment, signs of potential impact on bone metabolism have been shown in toxicity studies in juvenile rats and in embryo-foetal development toxicity studies in rat and rabbits, up to galcanezumab 250 mg/kg.

In the additional rat embryo-foetal development toxicity study, increases in the foetal and litter incidences of short ribs, as well as a reduction in the mean number of ossified caudal vertebrae (which reached statistically significance vs control group), occurred at the only dose tested of 250 mg/kg (corresponding to 20-fold the clinical exposure reached with 240 mg) and were considered to be related to galcanezumab but non-adverse. These findings were noted at no maternal toxicity. Although signs in bone metabolism were observed in both embryo-foetal development toxicity studies at high multiple of clinical exposure, results have been reflected in the section 5.3 of the SmPC.

Moreover, the potential negative impact of galcanezumab on maintenance of bone mass might be particular relevant in the elderly and in post-menopausal women with underlying osteoporosis. No imbalance was observed in the frequency of bone fractures between galcanezumab treated patients and PBO Phase 3 trials. However, based on the physiological role of CGRP and on data coming from animal studies, it could not be ruled out that long term use of CGRP inhibitors may adversely impact migraine patients with more fragile bone metabolism (e.g., post-menopausal women, osteoporotic patients) and young growing patients.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted in support of galcanezumab are considered adequate for the marketing authorisation in the prophylaxis of migraine in adults.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Tabular overview of clinical studies

Brief description of Study	Trial Alias	Population	SC Dosing Regimen
Phase 1 Studies			
Single and multiple dose safety, PK, PD	CGAA	Healthy subjects	1, 5, 25, 75, 200, or 600 mg single dose. 150 mg Q2W for a total of 4 doses.
Single and multiple dose safety, tolerability, PK, PD	CGAE	Healthy Japanese and Caucasian subjects	5, 50, 120, or 300 mg single dose. 300 mg Q4W.
PK, PD, and tolerability of the lyophilized formulation compared to the solution formulation using a prefilled syringe	CGAO	Healthy subjects	Part A: galcanezumab 240-mg single dose as a solution versus placebo. Part B: galcanezumab 300-mg single dose reconstituted lyophilized versus 300-mg single-dose solution.
PK and PD of galcanezumab administered via a prefilled syringe compared to an autoinjector	CGAQ	Healthy subjects	240-mg single dose as a solution.
Phase 2 Studies			
Efficacy, safety, tolerability, PK, PD	CGAB	Patients with episodic migraine	5, 50, 120, or 300 mg Q4W.
Phase 3 Studies			
Efficacy, safety, tolerability, PK, PD	CGAG	Patients with episodic migraine	240-mg loading dose followed by 120 mg monthly, or 240 mg monthly.
Efficacy, safety, tolerability, PK, PD	CGAH	Patients with episodic migraine	240-mg loading dose followed by 120 mg monthly, or 240 mg monthly.
Efficacy, safety, tolerability, PK, PD	CGAI	Patients with chronic migraine	240-mg loading dose followed by 120 mg monthly, or 240 mg monthly.
Safety, tolerability, PK, PD	CGAJ	Patients with migraine, with or without aura	240-mg loading dose followed by 120 mg monthly, or 240 mg monthly.

2.4.2. Pharmacokinetics

Absorption

Based on the population PK analysis, mean peak serum concentrations of galcanezumab are expected to be achieved by 5 to 7 days after receiving a subcutaneous dose of 120- or 240-mg galcanezumab. Slow absorption observed following subcutaneous administration is consistent with the PK properties of an immunoglobulin (Ig)G monoclonal antibody. The time to peak serum concentration is similar in healthy subjects and patients, and after a single administration or multiple administration.

Distribution

The apparent volume of distribution (V/F) of galcanezumab was 7.3 L (34% Inter Individual Variability [IIV]).

Elimination

Galcanezumab is not expected to be metabolised by the cytochrome P450 (CYP450) families of drug-metabolising enzymes responsible for metabolism and elimination of small molecules and would, therefore, not produce any active metabolites.

The physical size of galcanezumab (144.084 kDa) excludes it from efficient glomerular filtration and, therefore, elimination of intact galcanezumab via urine is not expected.

Biliary secretion is not a predominant route of elimination of IgG antibodies. Therefore, galcanezumab is not expected to be excreted in bile. IgG is catabolised to small peptides and amino acids by proteolytic processes in cells following endocytosis. Galcanezumab is expected to be catabolised in the same manner as IgG.

The apparent clearance is low (0.00785 L/h) and this is consistent with the long half-life (about 27 days).

2.4.3. Pharmacodynamics

Mechanism of action

Galcanezumab is a humanized IgG4 monoclonal antibody that binds calcitonin gene-related peptide (CGRP) and prevents its biological activity without blocking the CGRP receptor. Elevated blood concentrations of CGRP have been associated with migraine. In addition, CGRP infusions can induce migraine-like attacks in some individuals with a history of migraine. Galcanezumab targets CGRP and binds with high affinity (KD = 31 pM) and high specificity (>10,000-fold vs related peptides adrenomedullin, amylin, calcitonin and intermedin).

Primary and Secondary pharmacology

Pharmacodynamic evaluations were conducted mainly on the basis of total concentrations of CGRP (ligand that binds to the galcanezumab antibody), immunogenicity, and migraine headache days

(primary efficacy outcome). In patients with migraine, the total CGRP plasma concentrations increased following galcanezumab treatment, and then declined after galcanezumab treatment was stopped. These data indicate that the disposition of CGRP is governed by the disposition characteristics of galcanezumab because most CGRP is bound to galcanezumab at the galcanezumab concentrations achieved after 120-mg and 240-mg doses. At 240 mg, mean CGRP plasma concentrations were slightly higher than at 120 mg.

A dose of 120 and 240 mg is estimated to achieve an average concentration of galcanezumab at steady-state during multiple dosing (Cav,ss) of 22100 and 42300 ng/mL, respectively. At these concentrations, CGRP is estimated to be greater than 99.9% bound to galcanezumab and indicates extensive target engagement.

2.4.4. Discussion on clinical pharmacology

Galcanezumab is a humanized IgG4 monoclonal antibody that binds calcitonin gene-related peptide (CGRP) and prevents its biological activity without blocking the CGRP receptor. The clinical pharmacology of galcanezumab has been studied in healthy subjects, and in patients with episodic and chronic migraine. Moreover, the relative bioavailabilty of galcanezumab lyophilised formulation and solution formulation has been investigated.

Based on the population PK analysis, Cmax,ss, Cmin,ss, and AUCtau,ss increased dose proportionally after receiving a subcutaneous dose of 120- or 240-mg galcanezumab. Body weight was identified as a significant covariate on CL/F and its effect on galcanezumab concentration has been investigated. No PK interaction with other drugs is expected considering that galcanezumab is a monoclonal antibody.

According to ICH E14 guidance R3, a thorough QT/QTc study was not conducted. However, in order to better investigate QT interval prolongation, the Applicant was requested to provide an exposure-safety analysis. The exposure-safety analysis to investigate QT interval prolongation has been provided. Galcanezumab concentration-ΔQTcF modelling seams to support the conclusion that galcanezumab does not prolong QTcF interval at the doses evaluated in the Phase 3 migraine program.

2.4.5. Conclusions on clinical pharmacology

The CHMP concluded that galcanezumab PK and PD profiles have been characterised sufficiently.

2.5. Clinical efficacy

The efficacy of galcanezumab in migraine prophylaxis in adults was tested through three pivotal, phase 3, randomized, double-blind, placebo-controlled, multinational clinical studies, of which two identically designed in episodic migraine (Studies I5Q-MC-CGAG [CGAG] and I5Q-MC-CGAH [CGAH]) and one in chronic migraine (Study I5Q-MC-CGAI [CGAI]). Supportive data come from 1 open-label Phase 3 study in patients with either episodic or chronic migraine up to 1 year (Study I5Q-MC-CGAJ [CGAJ]), and 2 Phase 2 studies: a proof-of concept study (Study I5QAR-ART1 [ART-01] and a dose-ranging study (Study I5Q-MC-CGAB [CGAB]).

2.6. Dose response study

Study CGAB in episodic migraine (with or without aura)

This was a phase 2b, randomized, dose-ranging, multicenter, double-blind, placebo-controlled study of LY2951742 in patients with *episodic migraine*, conducted in 37 study centers in 1 country (United States) to evaluate the efficacy and safety of LY2951742 in the prevention of migraine headache and to determine the optimal LY2951742 dose(s) for future Phase 3 development.

This study included 5 treatment groups: galcanezumab at 5 mg, 50 mg, 120 mg, 300 mg or placebo. The study comprised 4 study periods: I) screening and washout period, II) a prospective 4-week baseline period for assessment of the type, frequency, and severity of headaches, III) a 12-week treatment period, and IV) a 12-week post-treatment, follow-up period.

The primary efficacy objective was to assess whether at least one dose of galcanezumab was superior to placebo in the prevention of migraine headache.

A total of 414 patients entered the study, and 410 received at least one dose of study drug (LY2951742, N=273; placebo, N=137). Overall, 375 patients (91.5%) completed the study's double-blind treatment period (Study Period III), with 249 patients (91.2 %) in the LY_All doses group completing treatment and 126 patients (92%) in the placebo group completing treatment. Overall, the patient population was predominantly female (83%) and White (75%), with a mean age of approximately 40 years. Significant differences at baseline were observed between the overall galcanezumab and placebo groups for weight (p=.033), BMI (p=.005), multiple race (p=.046), and the number of patients who declared Black or African American as their race (p=.003). The number of baseline MHDs (overall mean: 6.7 days), probable and migraine headache days (overall mean: 8.3 days), or migraine attacks (overall mean: 4.7 attacks) were not different among treatment groups, nor were there any significant differences in the mean severity of migraine, mean severity of migraine for patients who had experienced at least 1 headache, and the number of days with migraine headache medication use.

At Week 12, the only dose regimen to satisfy the primary objective and meet the critical success factor in the last 28-day period (Month 3) was the 120 mg dose, which also showed a statistically significant overall effect (Month 1 to Month 3) (see Table below).

The totality of presented data including analysis of relationship of galcanezumab serum concentration and mean change from baseline of number of MHDs, suggest that both highest – 120 mg and 300 mg, - tested doses are having similar efficacy supporting dose selection for phase 3 pivotal studies.

Table 9 - Mean Change from Baseline in Migraine Headache Days Repeated Measures Analysis Study CGAB LSMean

			LSMean Change in MHD (Not Including Probable Migraine)			
Galcanezumab Dose Regimen	Treatment Weeks	Treatment Month	PBO	GMB	Difference From Placebo	p-Value
5 mg Q4W	0 - 4	1	-3.05	-3.77	-0.73	0.074
	4 - 8	2	-3.61	-3.77	-0.16	0.708
	8 - 12	3	-3.58	-4.28	-0.70	0.126
	0 - 12	1-3	-3.41	-3.94	-0.53	0.151
50 mg Q4W	**0 - 4**	**1**	**-3.05**	**-4.00**	**-0.95**	**0.017**
	4 - 8	2	-3.61	-4.11	-0.50	0.222
	8 - 12	3	-3.58	-3.73	-0.15	0.744
	0 - 12	1-3	-3.41	-3.95	-0.53	0.140
120 mg Q4W	0 - 4	1	-3.05	-3.74	-0.69	0.082
	4 - 8	2	-3.61	-4.17	-0.56	0.169
	8 - 12	**3**	**-3.58**	**-4.90**	**-1.32**	**0.004**
	0 - 12	**1-3**	**-3.41**	**-4.27**	**-0.86**	**0.018**
300 mg Q4W	**0 - 4**	**1**	**-3.05**	**-4.18**	**-1.13**	**0.005**
	4 - 8	**2**	**-3.61**	**-4.51**	**-0.90**	**0.030**
	8 - 12	3	-3.58	-4.16	-0.58	0.206
	0 - 12	**1-3**	**-3.41**	**-4.28**	**-0.87**	**0.018**

Abbreviations: GMB = galcanezumab; LSMean = Least Squares Mean; MHD = migraine headache day; PBO = placebo; Q4W = every 4 weeks.
Source: \lillyce\prd\ly2951742\i5q_mc_cgab\intrm1\output\shared\rmmhdp11.rtf

2.6.1. Main studies

Studies I5Q-MC-CGAG (CGAG, the EVOLVE-1 study) and I5Q-MC-CGAH (CGAH, the EVOLVE-2 study) for episodic migraine (with or without aura)

Studies CGAG and CGAH were two identically designed Phase 3, randomized, double-blind, placebo-controlled studies of galcanezumab administered as monthly subcutaneous injection in patients suffering from episodic migraine. Two doses of galcanezumab were evaluated, 120 mg/month and 240 mg/month, to assess whether at least 1 dose would be superior to placebo in the prevention of migraine headache in during a 6-month double-blind treatment phase. Due to the identical design, both studies are described together in this report.

Methods

Each study comprised 4 study periods (SP):

SP I: Screening. Full clinical assessment, including a comprehensive medical evaluation documenting medical history, and a physical and neurological examination at Visit 1. Patients were required to discontinue all migraine prevention treatments at least 30 days prior to Visit 2. Botulinum toxin A or B in the head or neck area should have been discontinued at least 4 months prior to Visit 2.

SP II: Baseline. A prospective 30-40 day baseline phase to determine the final eligibility to the study of qualified patients. Beginning at Visit 2, patients logged in daily to the electronic patient-reported outcomes (ePRO) system to answer questions about the occurrence of headaches, headache duration, headache features, severity of headache, and use of headache medication. This prospective baseline

period was to confirm that the patient had between 4 and 14 MHDs and at least 2 migraine attacks between Visits 2 and 3, and to establish baseline data for comparison of endpoints during the treatment phase.

SP III: Treatment (6-month double-blind treatment phase). Patients were randomized to 1 of 3 treatment groups in a 2:1:1 ratio to receive placebo, 120 mg/month galcanezumab (with a loading dose of 240 mg at V3 only, i.e. 2 injections of 120 mg each), or 240 mg/month galcanezumab, respectively.

Patients continued to log in and complete the ePRO diary each day. Patients could continue to take their allowed acute migraine headache medications during the treatment phase, but opioid- and barbiturate containing medications were limited to 3 days per month, with only 1 corticosteroid injection allowed at any time during the trial, and no oral corticosteroids.

SP IV: Follow-up (4-month FU, ongoing). All randomized patients were to enter this 4-month post-treatment phase (washout), including patients who discontinued treatment early in SP III. Patients did not receive galcanezumab or placebo in SP IV. One month after Visit 12, if clinically warranted due to a worsening of symptoms, patients could start migraine prevention medications at the discretion of the investigator. Blind was maintained to site personnel and patients regarding previous treatment assignments.

Study Participants

Main inclusion criteria

1- Patients are male and female 18 to ≤65 years of age at the time of screening.

2- Diagnosis of migraine as defined by HIS ICHD-3 beta guidelines (1.1 or 1.2) (ICHD-3 2013), with a history of migraine headaches of at least 1 year prior to Visit 1, and migraine onset prior to age 50.

3- Prior to visit 1, a history of 4 to 14 MHDs occurring during at least 2 migraine attacks per month on average over the past 3 months.

4- From Visit 2 to Visit 3 (prospective baseline period), have a frequency of 4 to 14 MHDs occurring during at least 2 migraine attacks (patients must be unaware regarding the number of migraine headache days on which study qualification is based, to avoid biased reporting).

5- From Visit 2 to Visit 3 (prospective baseline period), must achieve sufficient compliance with ePRO daily headache entries as demonstrated by completion of at least 80% of daily diary entries.

Treatments

Patients received galcanezumab (120 or 240 mg) or placebo administered once monthly by subcutaneous injection at dosing visits. Patients randomized to the 120-mg dose received a loading dose of 240 mg (2 injections of 120 mg each at Visit 3 only). All treatment groups received two 1-ml injections of IMP at each dosing visit to maintain the blind (two placebo injections, two 120-mg galcanezumab injections, or one placebo injection and one 120-mg injection) for a total of 6 administrations during the 6-month treatment phase. Subcutaneous injection sites included the abdomen, thigh, upper arm, or buttocks.

Objectives

The primary objective was to test the hypothesis that at least 1 dose of galcanezumab (120 or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with episodic migraine.

Key secondary objectives were as follows:

-To compare LY2951742 with placebo with respect to 50%-75%-100% response rate (during the 6-month double-blind treatment phase);

-To compare LY2951742 with placebo with respect to change in functioning (as assessed through the mean change from baseline in the Role Function-Restrictive domain score of the MSQ Questionnaire ver. 2.1 (average of Months 4, 5, and 6);

Outcomes/endpoints

The primary endpoint was the overall mean change from baseline in the number of monthly MHDs during the 6-month double-blind treatment phase.

- Key secondary endpoints were: 50%, 75%, and 100% response rates in terms of monthly MHDs
- Mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score (average of Months 4, 5, and 6)
- Overall mean change from baseline in the number of monthly MHDs with acute medication use for treatment of migraine or headache
- Mean change from baseline in the PGI-S (average of Months 4, 5, and 6)

Sample size

Approximately 1557 patients had to be screened to ensure randomization of 825 patients at each phase 3 study on EM (CGAG and CGAH), with an estimated 611 completers. Eligible patients had to be randomized in blinded fashion in a 2:1:1 ratio to placebo (target of 413 patients), LY2951742 120 mg/month (target of 206 patients), or 240 mg/month (target of 206 patients), estimated to provide approximately 95% power with the assumption of a 26% discontinuation rate and an effect size of 0.33, and that at least 1 dose of LY2951742 would separate from placebo at a two-sided significance level of 0.05 based on simulations using Dunnett (Dunnett 1955) test.

Randomisation

After enrolment, patients were randomized to double-blind treatment at Visit 3 with an assignment of each patient to a treatment group determined by a computer-generated random sequence using an interactive web-response system (IWRS), which also allowed the personnel to double-check the correct assignment package by entering the confirmation number found on the package into the IWRS (which in turn also allowed Emergency unblinding for AEs).

A stratification by '*region*' (the eastern half of the US, the western half of the US, Puerto Rico and Canada for study CGAG, whereas it was unspecified for study CGAH) and '*baseline migraine frequency*' (<8 vs. ≥8 MHDs/month in both studies) was carried out, in order to achieve between-group comparability. To

ensure an appropriate balance of low- and high-frequency migraine headache day patients, the sponsor had planned to stop enrolment of low-frequency patients if the number exceeded an estimated 578.

Blinding (masking)

Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. A minimum number of Lilly personnel was allowed to have access to the randomization table and treatment assignments before database lock for the double-blind treatment phase.

Statistical methods

Statistical analyses was to be conducted on the intent-to-treat (ITT) population, including all randomized patients who received at least one dose of investigational product, each analyzed according to the randomized treatment group. When change from baseline was assessed, the patient was included in the analysis only if he/she had a baseline and a postbaseline measurement.

The primary efficacy *measure is the overall mean change from the baseline period in the number of monthly migraine headache day during the 6-month double-blind treatment phase, and the primary analysis will evaluate the efficacy of LY2951742 (120 or 240 mg/month) compared with placebo.* The primary analysis was to be performed using a restricted maximum likelihood-based mixed models repeated measures (MMRM) technique with prespecified model terms and unstructured covariance matrix . The analysis had to include the *fixed categorical effects* of treatment, region, month, and *treatment-by-month interaction*, as well as the *continuous fixed covariates* of baseline number of migraine headache days and *baseline number of migraine headache days-by-month interaction*.

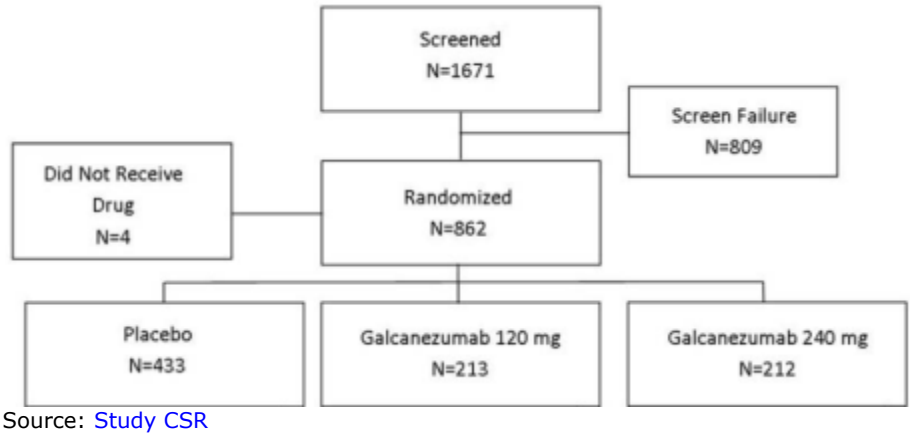
In addition to the MMRM approach, analysis of covariance (ANCOVA) model or analysis of variance (ANOVA) with the last observation carried forward (LOCF) had to be implemented. The ANCOVA model included the main effects of treatment and region, as well as the continuous fixed covariates of baseline, while the ANOVA model used the same terms except the continuous fixed covariate of baseline.

Results

Results for Study CGAG

- **Participant flow**

Patient disposition through the DB phase (ITT population):



Source: Study CSR

A total of 1671 patients were screened and 862 patients were randomized. The most common reason for screen failure was patients not meeting criteria for study enrolment based on migraine headache information collected in the ePRO diary during the prospective baseline phase. A total of 858 randomized patients received at least 1 dose of IP and were included in the ITT population (n=433 patients randomized to placebo, n=213 patients randomized to galcanezumab 120 mg, and n=212 patients randomized to galcanezumab 240 mg).

Overall, 703 patients (81.9%) completed the double-blind treatment phase (n=351 patients in the placebo arm, n=177 patients in the galcanezumab 120 mg arm, and n=175 patients in the galcanezumab 240 mg).

The overall discontinuation rate from the double-blind treatment phase due to any reason was 18.9% (n=82) in the placebo group, 16.9% and 17.4% in the galcanezumab 120mg and 240mg groups, respectively, totalling 155 patients (18.1%), with 113 of those patients also discontinuing from study and the remaining 42 patients discontinuing treatment while continuing in the post-treatment phase. The most frequent reason for discontinuation from the double-blind treatment phase was withdrawal by patient in similar percentage across treatment groups. Seven patients discontinued from the treatment phase of the study due to pregnancy and for one of them (Patient assigned to the placebo group) it resulted as physician decision.

- **Recruitment**

This study was conducted at 90 study centers in 2 countries.

Of the 858 subjects in the ITT population (i.e., who were randomized and received at least 1 dose of IP), 843 patients with nonmissing change in MHDs were analyzed for the primary efficacy measure. Efficacy analyses were performed on the ITT population.

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

- **Conduct of the study**

Important Protocol deviations

An overview of the important protocol deviations that occurred during baseline and DB Treatment Phase is shown in the table below:

Table CGAG.10.2. Overview of Important Protocol Deviations During Baseline and Double-Blind Treatment Phase

Deviation	Placebo (N=433) n (%)	LY 120 mg (N=213) n (%)	LY 240 mg (N=212) n (%)	LY_All (N=425) n (%)	Total (N=858) n (%)
Patients with ≥1 Important Protocol Deviation	69 (15.94)	35 (16.43)	46 (21.70)	81 (19.06)	150 (17.48)
Dosing Interval Outside Specified Limits	22 (5.08)	15 (7.04)	17 (8.02)	32 (7.53)	54 (6.29)
Missing Data	22 (5.08)	7 (3.29)	9 (4.25)	16 (3.76)	38 (4.43)
Took Excluded Concomitant Medications	19 (4.39)	4 (1.88)	12 (5.66)	16 (3.76)	35 (4.08)
Inclusion/Exclusion Criteria Not Met	12 (2.77)	10 (4.69)	11 (5.19)	21 (4.94)	33 (3.85)
Stratification Error	0	1 (0.47)	2 (0.94)	3 (0.71)	3 (0.35)
Administrative: PI Oversight	0	1 (0.47)	1 (0.47)	2 (0.47)	2 (0.23)
Informed Consent	0	1 (0.47)	1 (0.47)	2 (0.47)	2 (0.23)
Dosing Error (Other Significant Violation of Dosing)	1 (0.23)	0	1 (0.47)	1 (0.24)	2 (0.23)
Not Observed for 30 Minutes after First Dose	1 (0.23)	0	0	0	1 (0.12)

Abbreviations: LY = LY2951742/galcanezumab; N = number of patients in the intent-to-treat population; n = number of patients in the specified category; PI = principal investigator.

- **Baseline data**

Table CGAG.11.1. Summary of Patient Demographics ITT Population

Characteristic	Placebo N=433	LY 120 mg[a] N=213	LY 240 mg[a] N=212	LY_All[a] N=425
Age (years)				
Mean (±SD)	41.33 (±11.40)	40.93 (±11.87)	39.07 (±11.52)*	40.00 (±11.72)
Sex, n (%)				
Male	71 (16.40)	32 (15.02)	37 (17.45)	69 (16.24)
Female	362 (83.60)	181 (84.98)	175 (82.55)	356 (83.76)
Race, n (%)				
American Indian or Alaska Native	0	0	3 (1.42)	3 (0.71)
Asian	13 (3.00)	7 (3.29)	4 (1.89)	11 (2.59)
Black or African American	42 (9.70)	29 (13.62)	23 (10.85)	52 (12.24)
Native Hawaiian or Other Pacific Islander	1 (0.23)	0	2 (0.94)	2 (0.47)
White	356 (82.22)	169 (79.34)	165 (77.83)	334 (78.59)
Multiple	21 (4.85)	8 (3.76)	15 (7.08)	23 (5.41)
Body Mass Index (kg/m^2)				
Mean (±SD)	28.60 (±5.52)	27.77 (±5.34)	28.60 (±5.68)	28.18 (±5.52)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; N = number of patients in the intent-to-treat population; n = number of patients within each specific category; SD = standard deviation.

[a] Asterisk (*) denotes p-value comparison vs. placebo <.05.

Table CGAG.11.2. Summary of Disease Characteristics ITT Population

Characteristic	Placebo N=433	LY 120 mg[a] N=213	LY 240 mg[a] N=212	LY_All[a] N=425
Duration of migraine illness, years, mean (±SD)	19.89 (±12.30)	21.12 (±12.97)	19.30 (±11.88)	20.22 (±12.46)
Number of comorbidities, mean (±SD)	4.81 (±3.57)	4.67 (±3.79)	4.44 (±3.63)	4.56 (±3.71)
MHDs per month, mean (±SD)	9.08 (±2.97)	9.21 (±3.05)	9.14 (±2.91)	9.17 (±2.98)
Migraine attacks per month, mean (±SD)	5.79 (±1.72)	5.61 (±1.70)	5.74 (±1.81)	5.67 (±1.76)
MHD category ≥8, n (%)	285 (65.82)	140 (65.73)	139 (65.57)	279 (65.65)
Mean severity of migraine headaches per month, mean (±SD)[b]	2.09 (±0.36)	2.07 (±0.37)	2.09 (±0.39)	2.08 (±0.38)
MHD with acute medication use per month, mean (±SD)	7.38 (±3.48)	7.42 (±3.68)	7.34 (±3.30)	7.38 (±3.49)
Prior preventive treatment, n (%)	257 (59.35)	133 (62.44)	125 (58.96)	258 (60.71)
MIDAS total score, mean (±SD)	31.84 (±27.31)	32.93 (±28.18)	36.09 (±27.76)	34.50 (±27.98)
MSQ Role Function-Restrictive, mean (±SD)	52.92 (±15.41)	51.39 (±16.20)	48.76 (±16.82)*	50.09 (±16.54)*
PGI-S, mean (±SD)	4.21 (±1.12)	4.35 (±1.08)	4.51 (±1.12)*	4.43 (±1.11)*

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; MHD(s) = migraine headache day(s); MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of patients in the intent-to-treat population; n = number of patients within each specific category; PGI-S = Patient Global Impression of Severity; SD = standard deviation.

a Asterisk (*) denotes p-value comparison vs. placebo <.05.

b Severity ratings were 1 = mild, 2 = moderate, and 3 = severe.

Concomitant Medications

The vast majority of patients (92.8%) used a concomitant therapy during the double-blind treatment period, the most commonly used (≥5%) concomitant medications (i.e., taken during the study and recorded via eCRF) were generally not significantly differently distributed among groups (in order, ibuprofen, paracetamol, thomapyrin N, sumatriptan, vitamins, naproxen sodium, vitamin D NOS, cetirizine hydrochloride, salbutamol, diphenhydramine hydrochloride, and loratadine and many others).

The concomitant medications used for the acute treatment of migraine as recorded by patients in the ePRO diary were accounted for as an efficacy measure and patients were allowed to start migraine prevention medications not before one month after the last visit of the treatment phase (Visit 12) at the discretion of the investigator if clinically warranted due to a worsening of symptoms. However, statistically significant differences between treatment groups were seen in the use of some concomitant medications: thomapyrin N (24.06% in LY-240mg vs 15.02% in LY-120mg [p=.020]), cetirizine hydrochloride (5.3% in placebo vs 12.7% galcanezumab 120 mg [p=.002]) and naproxen sodium (9.5% placebo vs 4.25% LY-240mg [p=.02]).

Concomitant therapies frequently used during the DB period were comparable with the ones used during the post-treatment phase, with the addition of fish oil and vitamin B12.

- **Outcomes and estimation**

ePRO compliance

Given the crucial role played by the ePRO diary compliance for the assessment of key primary and secondary efficacy measure, it was observed that the average compliance in the ITT population across month 1 to 6 was 89.8% in placebo, 91.9% and 90.8% in the LY-120mg and LY-240mg, respectively, without significant differences among treatment groups.

Primary Efficacy Endpoint

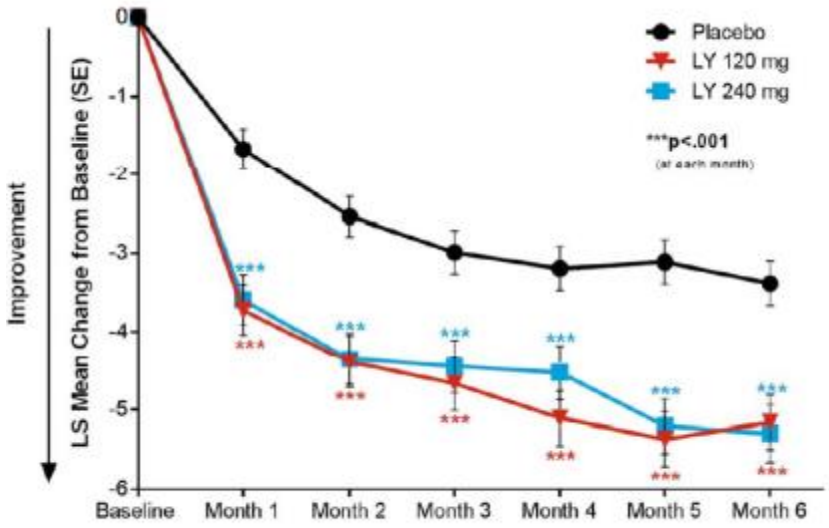
The results of primary endpoint analysis are presented in the Table below.

Table CGAG.11.3. Change from Baseline in the number of MHDs, Repeated Measures Analysis (ITT population), Study Period III:

						vs 1)		
Period	Treatment	N	LS Mean Change from Baseline (SE)	95% CI	Within group p-Value	LS Mean Change Difference (SE)	95% CI	p-Value
Month 1	1)Placebo	422	-1.67 (0.26)	(-2.17, -1.16)	<.001			
	2)LY120mg	210	-3.72 (0.32)	(-4.35, -3.09)	<.001	-2.05 (0.32)	(-2.69, -1.41)	<.001
	3)LY240mg	208	-3.59 (0.32)	(-4.22, -2.95)	<.001	-1.92 (0.33)	(-2.56, -1.28)	<.001
Month 2	1)Placebo	403	-2.54 (0.26)	(-3.05, -2.02)	<.001			
	2)LY120mg	199	-4.39 (0.33)	(-5.03, -3.75)	<.001	-1.85 (0.33)	(-2.51, -1.20)	<.001
	3)LY240mg	199	-4.35 (0.33)	(-4.99, -3.70)	<.001	-1.81 (0.33)	(-2.47, -1.15)	<.001
Month 3	1)Placebo	381	-2.99 (0.27)	(-3.52, -2.46)	<.001			
	2)LY120mg	194	-4.67 (0.34)	(-5.34, -4.01)	<.001	-1.68 (0.35)	(-2.37, -1.00)	<.001
	3)LY240mg	191	-4.45 (0.34)	(-5.12, -3.78)	<.001	-1.46 (0.35)	(-2.15, -0.77)	<.001
Month 4	1)Placebo	369	-3.19 (0.28)	(-3.73, -2.64)	<.001			
	2)LY120mg	189	-5.11 (0.35)	(-5.79, -4.42)	<.001	-1.92 (0.37)	(-2.64, -1.19)	<.001
	3)LY240mg	185	-4.53 (0.35)	(-5.23, -3.84)	<.001	-1.34 (0.37)	(-2.07, -0.61)	<.001
Month 5	1)Placebo	358	-3.11 (0.28)	(-3.65, -2.57)	<.001			
	2)LY120mg	180	-5.37 (0.35)	(-6.05, -4.68)	<.001	-2.26 (0.37)	(-2.98, -1.54)	<.001
	3)LY240mg	176	-5.21 (0.35)	(-5.90, -4.52)	<.001	-2.10 (0.37)	(-2.83, -1.38)	<.001
Month 6	1)Placebo	342	-3.38 (0.28)	(-3.93, -2.83)	<.001			
	2)LY120mg	177	-5.16 (0.35)	(-5.85, -4.46)	<.001	-1.77 (0.37)	(-2.50, -1.04)	<.001
	3)LY240mg	171	-5.30 (0.36)	(-6.00, -4.60)	<.001	-1.92 (0.38)	(-2.66, -1.18)	<.001
Overall	1)Placebo	425	-2.81 (0.24)	(-3.28, -2.34)	<.001			
	2)LY120mg	210	-4.73 (0.29)	(-5.31, -4.16)	<.001	-1.92 (0.28)	(-2.48, -1.37)	<.001
	3)LY240mg	208	-4.57 (0.29)	(-5.15, -3.99)	<.001	-1.76 (0.28)	(-2.31, -1.20)	<.001

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value; CI = confidence interval; LS = least square; SE = standard error.
MMRM Model: Change = treatment, pooled region 1/country, month, and treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Source: Table CGAG.11.3 of Study Report

A statistically significant improvement for both doses of galcanezumab compared with placebo was observed as early as at Month 1 for both the galcanezumab 120-mg and 240-mg treatment groups (to be noted that patients in the 120-mg treatment group received a loading dose of 240 mg at the first injection, the initial treatment effect observed at Month 1 was based on a 240-mg dose). Such a difference was maintained for all subsequent months during the double-blind treatment phase.



Abbreviations: LS = Least Squares; LY = LY2951742/galcanezumab; SE = standard error.
Note: not statistically significant between LY doses at any month.

- *Sensitivity Analysis for the Primary Objective*:

Missing Data Assumptions

In total, 9 sets of delta were used. The results of this sensitivity analysis were consistent with the primary efficacy analysis :

Table CGAG.14.16. Change from Baseline in the Number of MHDs. Sensitivity Analysis for Missing Data Assumptions - Delta Method for Overall Across Month 1 to 6 (ITT Population; Study Period III)

Delta for Placebo	Delta for LY120mg	Delta for LY240mg	Treatment	N	LS Mean Change (SE)	95% CI	vs Placebo: LS Mean Change difference	vs Placebo: 95%CI	vs Placebo: p-Value
0.00	0.00	0.00	1)Placebo	425	-2.80(0.24)	(-3.27,-2.34)			
			2)LY120mg	210	-4.76(0.29)	(-5.33,-4.19)	-1.96	(-2.51,-1.41)	<.001
			3)LY240mg	208	-4.57(0.29)	(-5.14,-3.99)	-1.77	(-2.32,-1.21)	<.001
	0.96	0.96	1)Placebo	425	-2.80(0.24)	(-3.27,-2.33)			
			2)LY120mg	210	-4.68(0.29)	(-5.25,-4.11)	-1.87	(-2.43,-1.32)	<.001
			3)LY240mg	208	-4.48(0.29)	(-5.05,-3.90)	-1.67	(-2.24,-1.11)	<.001
	1.92	1.92	1)Placebo	425	-2.80(0.24)	(-3.27,-2.33)			
			2)LY120mg	210	-4.59(0.29)	(-5.16,-4.02)	-1.79	(-2.35,-1.23)	<.001
			3)LY240mg	208	-4.39(0.30)	(-4.97,-3.80)	-1.58	(-2.15,-1.02)	<.001
2.81	2.81	2.81	1)Placebo	425	-2.50(0.25)	(-2.98,-2.02)			
			2)LY120mg	210	-4.51(0.30)	(-5.10,-3.92)	-2.01	(-2.59,-1.44)	<.001
			3)LY240mg	208	-4.30(0.30)	(-4.90,-3.71)	-1.80	(-2.38,-1.22)	<.001
	3.77	3.77	1)Placebo	425	-2.50(0.25)	(-2.99,-2.01)			
			2)LY120mg	210	-4.43(0.30)	(-5.02,-3.83)	-1.93	(-2.51,-1.35)	<.001
			3)LY240mg	208	-4.21(0.31)	(-4.81,-3.61)	-1.71	(-2.30,-1.13)	<.001
	4.73	4.73	1)Placebo	425	-2.50(0.25)	(-2.99,-2.00)			
			2)LY120mg	210	-4.34(0.31)	(-4.94,-3.74)	-1.84	(-2.43,-1.26)	<.001
			3)LY240mg	208	-4.12(0.31)	(-4.72,-3.51)	-1.62	(-2.21,-1.03)	<.001
5.62	5.62	5.62	1)Placebo	425	-2.19(0.26)	(-2.70,-1.68)			
			2)LY120mg	210	-4.26(0.32)	(-4.88,-3.64)	-2.07	(-2.68,-1.45)	<.001
			3)LY240mg	208	-4.03(0.32)	(-4.66,-3.40)	-1.84	(-2.46,-1.22)	<.001
	6.58	6.58	1)Placebo	425	-2.19(0.26)	(-2.70,-1.68)			
			2)LY120mg	210	-4.17(0.32)	(-4.80,-3.54)	-1.98	(-2.60,-1.36)	<.001
			3)LY240mg	208	-3.94(0.32)	(-4.57,-3.30)	-1.75	(-2.38,-1.12)	<.001
	7.54	7.54	1)Placebo	425	-2.19(0.26)	(-2.71,-1.67)			
			2)LY120mg	210	-4.09(0.32)	(-4.72,-3.45)	-1.90	(-2.53,-1.27)	<.001
			3)LY240mg	208	-3.85(0.33)	(-4.49,-3.20)	-1.66	(-2.29,-1.02)	<.001

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value.
For each set of Delta value: MMRM Model: Change = treatment, pooled region 1/country, month, and treatment*month, baseline, and baseline*month.
For each set of Delta value, the following steps were conducted
1) Predict the missing outcomes for each treatment via multiple imputation based on observed primary endpoint and baseline values. Such imputation will be carried out using a Markov Chain Monte Carlo method with a Jeffreys prior via SAS PROC MI. 30 imputations will be created.
2) Add the corresponding delta to the imputed values based on the patient treatment group.
3) Conduct the primary analysis separately for each of the 30 imputations.
4) Combine the results of these analyses using Rubin's combining rules, as implemented in SAS PROC MI ANALYZE.

Source: Table CGAG.14.16 of Report Body

Normality Assumption

The validity of the primary MMRM results with respect to deviations from normality assumption was conducted with a repeated measures negative binomial regression analysis fitted with SAS PROC GLIMMIX:

Period	Treatment	N	Estimated Number of MH D per 30 Day Period (SE)	95% CI	Within-group p-value	vs 1) Rate Ratio per 30 day period	95% CI	P Value	vs 2) Rate Ratio per 30 day period	95% CI	P Value
Overall*a	1) Placebo	425	6.04 (0.25)	(5.56,6.55)	<.001						
	2) LY120mg	210	4.09 (0.26)	(3.61,4.64)	<.001	0.68	(0.60,0.77)	<.001			
	3) LY240mg	208	4.31 (0.28)	(3.79,4.89)	<.001	0.71	(0.63,0.80)	<.001	1.05	(0.90,1.23)	.514

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value.
Negative Binomial Model: raw number of MHDs = offset, treatment, pooled region 1/country, month, and treatment*month, baseline, and baseline*month. Source: Table CGAG.14.17 of Report Body

The outcomes of the primary analyses remained unmodified also after performing another form of sensitivity analysis on patients with outlier residuals identified as those who had absolute value of studentized residual less than 2 at any month of the double-blind treatment phase. The results remained consistent before and after removing outlier patients (N=46 for placebo, N=24 for galcanezumab 120 mg, and N=31 for galcanezumab 240 mg):

Population	Time Frame	Treatment	N	LS Mean Change (SE)	95% CI	vs Placebo LS Mean Change difference	95%CI	p-Value
All Patients	Month 1 to 6	1) Placebo	425	-2.81 (0.24)	(-3.28, -2.34)			
		2) LY120mg	210	-4.73 (0.29)	(-5.31, -4.16)	-1.92 (0.28)	(-2.48, -1.37)	<.001
		3) LY240mg	208	-4.57 (0.29)	(-5.15, -3.99)	-1.76 (0.28)	(-2.31, -1.20)	<.001
Drop Placebo and LY Patients with Extreme Studentized Residuals	Month 1 to 6	1) Placebo	379	-3.45 (0.19)	(-3.81, -3.09)			
		2) LY120mg	186	-5.39 (0.23)	(-5.83, -4.94)	-1.94 (0.22)	(-2.36, -1.51)	<.001
		3) LY240mg	177	-5.43 (0.23)	(-5.89, -4.98)	-1.98 (0.22)	(-2.41, -1.55)	<.001

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value; CI = confidence interval; LS = least square; SE = standard error. The values obtained are from separate repeated measures analyses of 2 patient populations: All patients, Placebo and LY120mg and LY240mg patients with a Studentized Residual >=2 or <= -2 at any month are dropped.
Each MMRM Model: Change = treatment, pooled region 1/country, month, and treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Source: Table CGAG.14.18 of Report Body

Secondary Efficacy Analyses

After ensuring that the primary objective was met, the set of key secondary objectives were tested according to the predefined multiple testing procedure, implemented to provide strong control of the type I error rate, with results summarized in the following table for continuous measures:

Multiplicity Testing Results Primary and Key Secondary Objectives (ITT Population, Study Period III):

Endpoint	Time Frame	Treatment	N	Comparison with Placebo			
				LSMean Change Difference/Odds Ratio[a]	P-value	Adjusted Significance Level[b]	Significance
Monthly Migraine Headache Days	Month 1 to 6	Placebo	425				
		LY 120 mg	210	-1.92	<.001	0.026	S
		LY 240 mg	208	-1.76	<.001	0.026	S
Monthly Migraine Headache Days with Acute Medication Use	Month 1 to 6	Placebo	425				
		LY 120 mg	210	-1.81	<.001	0.0125	S
		LY 240 mg	208	-1.61	<.001	0.0125	S
MSQ Role Function-Restrictive	Month 4 to 6	Placebo	377				
		LY 120 mg	189	7.74	<.001	0.025	S
		LY 240 mg	184	7.40	<.001	0.025	S
Patient Global Impression of Severity Rating	Month 4 to 6	Placebo	377				
		LY 120 mg	189	-0.32	0.002	0.025	S
		LY 240 mg	184	-0.28	0.008	0.025	S
50% Response	Month 1 to 6	Placebo	425				
		LY 120 mg	210	2.628	<.001	0.025	S
		LY 240 mg	208	2.480	<.001	0.025	S
75% Response	Month 1 to 6	Placebo	425				
		LY 120 mg	210	2.654	<.001	0.025	S
		LY 240 mg	208	2.619	<.001	0.025	S
100% Response	Month 1 to 6	Placebo	425				
		LY 120 mg	210	2.804	<.001	0.025	S
		LY 240 mg	208	2.605	<.001	0.025	S

Abbreviations: LSMean = Least Squares Mean; LY = LY2951742/galcanezumab; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of intent-to-treat patients who had nonmissing baseline and at least one postbaseline value; S = significant.
[a] Odds ratio is provided for response measures. For the other measures, LSMean change difference is provided.
[b] If p-value is less than or equal to the adjusted significance level, then the results are statistically significant after adjustment for multiplicity

The response rates (categorical measures) for the mean percentage of patients with ≥30%, ≥50%, ≥75%, and 100% reduction from baseline (MHDs) during the 6-month treatment phase are summarized below, for the ITT Population, with comparisons across various prespecified thresholds:

Response Rate	Placebo N=425	LY 120 mg N=210			LY 240 mg N=208		
	Model Estimated Rate, % (SE)	Model Estimated Rate, % (SE)	Odds Ratio vs. Placebo	95% CI for Odds Ratio	Model Estimated Rate, % (SE)	Odds Ratio vs. Placebo	95% CI for Odds Ratio
≥30%	56.8 (1.8)	77.1 (2.1)	2.56	1.94, 3.37	74.3 (2.2)	2.20	1.68, 2.88
≥50%	38.6 (1.7)	62.3 (2.4)	2.63	2.05, 3.37	60.9 (2.5)	2.48	1.94, 3.18
≥75%	19.3 (1.4)	38.8 (2.4)	2.65	2.04, 3.45	38.5 (2.4)	2.62	2.01, 3.41
100%	6.2 (0.8)	15.6 (1.6)	2.80	1.96, 4.01	14.6 (1.6)	2.61	1.81, 3.75

Abbreviations: CI = confidence interval; ITT = intent-to-treat; LY = LY2951742/galcanezumab; N = number of intent-to-treat patients who had nonmissing baseline and at least one postbaseline value; SE = standard error; vs. = versus. Source: Table CGAG.11.6 of the Body report

Additional Secondary Efficacy Analyses:

The endpoints supporting the secondary objectives across the DB phase were not adjusted for multiplicity and were based on changes across 1 to 6 or 4 to 6 months of double-blind treatment. Results for continuous measures are shown in the table below:

Summary of Overall Results (Average of All 6 Months) - ITT

Population

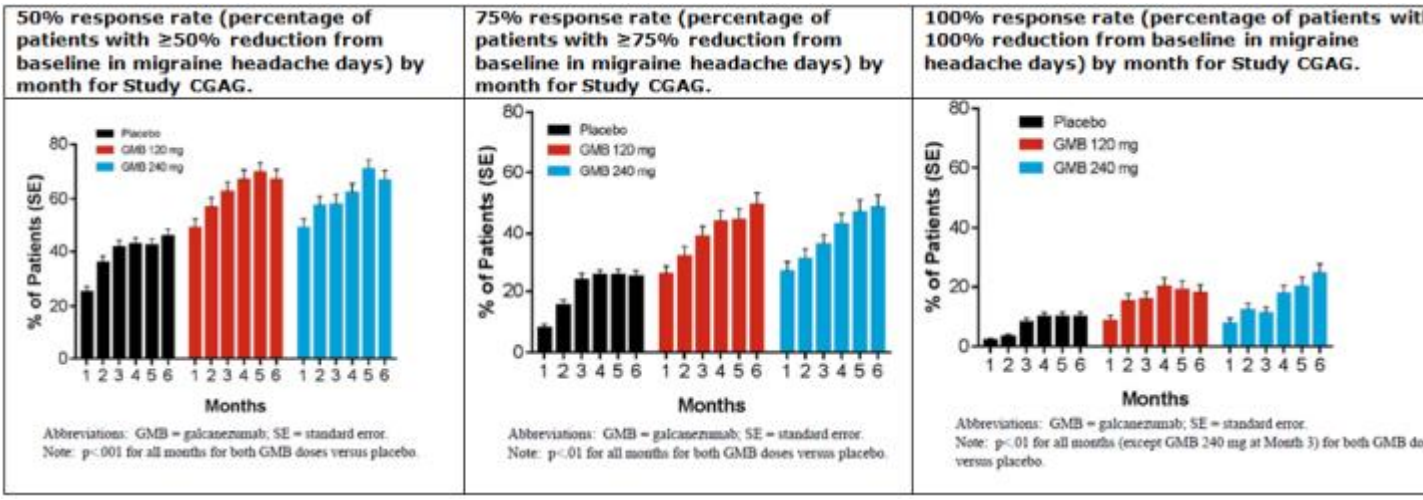
	Placebo N=425	LY 120 mg N=210	LY 240 mg N=208
Change from Baseline in Number of Monthly Headache Days			
LSMean Change (SE)	-3.03 (0.26)	-4.69 (0.32)	-4.79 (0.32)
Diff. vs. Placebo (SE)		-1.66 (0.30)	-1.77 (0.30)
95% CI on Difference		-2.25, -1.07	-2.36, -1.17
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Moderate to Severe Headache Days			
LSMean Change (SE)	-2.89 (0.21)	-4.24 (0.25)	-4.15 (0.25)
Diff. vs. Placebo (SE)		-1.35 (0.23)	-1.26 (0.24)
95% CI on Difference		-1.81, -0.89	-1.72, -0.80
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly ICHD Migraine Headache Days (ie, Excluding Probable Migraine)			
LSMean Change (SE)	-2.15 (0.22)	-3.68 (0.26)	-3.71 (0.27)
Diff. vs. Placebo (SE)		-1.53 (0.25)	-1.56 (0.25)
95% CI on Difference		-2.02, -1.04	-2.05, -1.06
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Attacks			
LSMean Change (SE)	-2.35 (0.12)	-3.17 (0.14)	-3.12 (0.14)
Diff. vs. Placebo (SE)		-0.82 (0.14)	-0.77 (0.14)
95% CI on Difference		-1.09, -0.55	-1.04, -0.50
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Hours			
LSMean Change (SE)	-14.75 (2.13)	-29.08 (2.56)	-27.02 (2.59)
Diff. vs. Placebo (SE)		-14.33 (2.42)	-12.27 (2.43)
95% CI on Difference		-19.08, -9.57	-17.04, -7.50
p-value vs. placebo		<.001	<.001

	Placebo N=425	LY 120 mg N=210	LY 240 mg N=208
Change from Baseline in Number of Monthly Headache Hours			
LSMean Change (SE)	-15.67 (2.24)	-29.65 (2.70)	-29.31 (2.72)
Diff. vs. Placebo (SE)		-13.98 (2.55)	-13.64 (2.57)
95% CI on Difference		-18.99, -8.97	-18.68, -8.60
p-value vs. placebo		<.001	<.001
Change from Baseline in Mean Severity of Remaining Migraine Headache Days			
LSMean Change (SE)	-0.17 (0.02)	-0.19 (0.03)	-0.22 (0.03)
Diff. vs. Placebo (SE)		-0.02 (0.03)	-0.05 (0.03)
95% CI on Difference		-0.07, 0.03	-0.10, 0.01
p-value vs. placebo		.447	.086
Patient Global Impression of Improvement Rating			
LSMean (SE)	2.65 (0.07)	2.09 (0.08)	2.11 (0.08)
Diff. vs. Placebo (SE)		-0.57 (0.08)	-0.54 (0.08)
95% CI on Difference		-0.72, -0.42	-0.70, -0.39
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of Triptans (additional analysis to support secondary objectives)			
LSMean Change (SE)	-0.60 (0.16)	-2.12 (0.19)	-1.74 (0.19)
Diff. vs. Placebo (SE)		-1.51 (0.18)	-1.14 (0.19)
95% CI on Difference		-1.88, -1.15	-1.50, -0.78
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of NSAIDs/Aspirin (additional analysis to support secondary objectives)			
LSMean Change (SE)	-1.78 (0.19)	-3.22 (0.23)	-3.13 (0.24)
Diff. vs. Placebo (SE)		-1.44 (0.22)	-1.35 (0.22)
95% CI on Difference		-1.87, -1.00	-1.79, -0.91
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of Acetaminophen/Paracetamol (additional analysis to support secondary objectives)			
LSMean Change (SE)	-1.23 (0.18)	-2.38 (0.22)	-2.27 (0.22)
Diff. vs. Placebo (SE)		-1.15 (0.21)	-1.04 (0.21)
95% CI on Difference		-1.56, -0.74	-1.45, -0.63
p-value vs. placebo		<.001	<.001

Abbreviations: CI = confidence interval; diff = difference; ICHD = International Classification of Headache Disorders; ITT = intent-to-treat; LS = Least Squares; LY = LY2951742/galcanezumab; N = number of patients in the analysis population for the primary measure; NSAIDs = nonsteroidal anti-inflammatory drug; SE = standard error; vs. = versus

Further Response Analyses Based on Reduction in Monthly MHDs

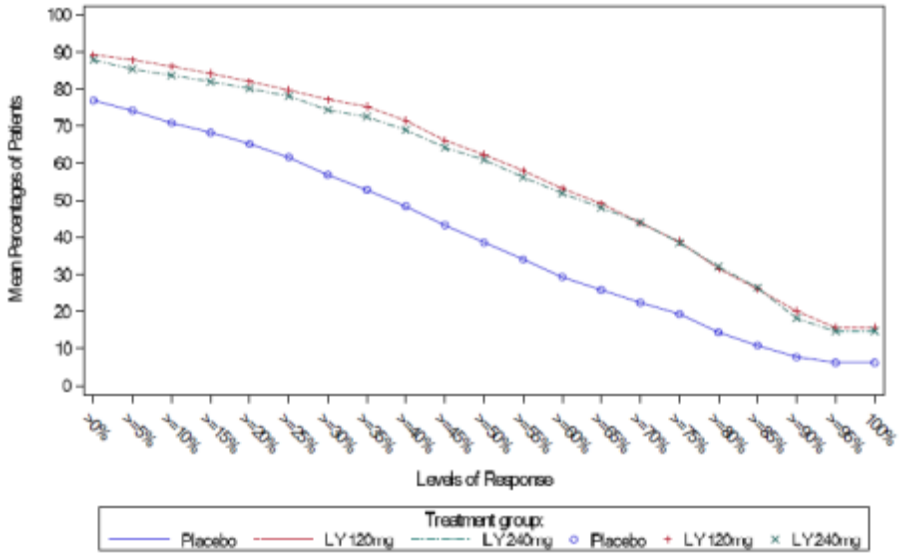
Percentages of patients who had a ≥50%, ≥75%, and 100% reduction in MHD:



Source: Fig. 2.7.3.5; 2.7.3.6; 2.7.3.7 of the Summary of clinical efficacy

At each month, the percentages of patients with ≥50% or ≥75% reduction from baseline in MHDs were statistically significantly greater in both the galcanezumab 120 mg and 240 mg treatment groups compared with placebo. Similar results were obtained for 100% reduction from baseline in MHDs, except for one time point that was not statistically significantly different between galcanezumab 240 mg and placebo (Month 3).

The distribution of response rates (i.e., the mean percentage of patients with different levels of reduction from baseline in monthly MHDs during the 6-month double-blind treatment phase), took into account 21 levels of monthly MHD reduction in 5% increments starting from ≥0%, up to 100% response. The following figure shows the response rates based on estimates from the GLIMMIX model, over the ITT population:



Abbreviation: LY = LY2951742.
All data points in the plot are estimated from GLIMMIX: Responder indicator = treatment, month, treatment*month, and baseline MHD.
Mean Percentages of Patients are estimated percentages over months 1 to 6 from the GLIMMIX model.

Source: Figure CGAG.11.2.

Onset of treatment effect and Maintenance of effect

Based on results from the primary analysis model for change from baseline in number of monthly MHDs during the double-blind treatment phases of each study, the earliest month in which a statistically significant improvement for both doses of galcanezumab compared with placebo was observed and maintained for all subsequent months during the double-blind treatment phase was considered the month of onset of effect. For study CGAG, onset of treatment effect was observed at Month 1 for both galcanezumab treatment groups.

A statistically significantly higher percentage of patients in each galcanezumab treatment group maintained the ≥50% response for both at least 3 and 6 consecutive months during the DB treatment phase compared with placebo:

Table CGAG.11.7. Maintenance of 50% Response for 3 Months or 6 Months
Logistic Regression
Intent-to-Treat Population
Study Period III

Treatment Group	N	n(%)	vs 1) Odds Ratio	vs 1) 95% CI for Odds Ratio	vs 1) P-value*a	vs 2) Odds Ratio	vs 2) 95% CI for Odds Ratio	vs 2) P-value*a
50% Response maintained for >=3 consecutive months until patient's endpoint in SP III								
1)Placebo	425	93 (21.88)						
2)LY120mg	210	94 (44.76)	2.89	(2.03,4.14)	<.001			
3)LY240mg	208	92 (44.23)	2.83	(1.98,4.05)	<.001	0.98	(0.66,1.44)	.914
50% Response maintained from Month 1 to Month 6								
1)Placebo	425	38 (8.94)						
2)LY120mg	210	43 (20.48)	2.62	(1.63,4.21)	<.001			
3)LY240mg	208	40 (19.23)	2.44	(1.51,3.94)	<.001	0.93	(0.57,1.50)	.764

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value.
*a: p-values from logistic regression: x-month sustained 50% responder indicator = treatment, pooled region1/country, and baseline. X is either 3 or 6, defined below: *3-month sustained 50% responders* are defined as patients meeting 50% response criteria for their last three months in the treatment phase; everyone else are non-responders, including those discontinued early within 3 months and those continued after 3 months but did not meet 50% response criteria for their last three months. *6-month sustained 50% responders* are defined as patients meeting 50% response criteria for all 6 months during the treatment phase; everyone else are non-responders, including those who discontinued early and those who completed 6-month treatment phase but did not meet 50% response criteria for one or more of the 6 months.

Secondary Analyses on Health Outcomes

The Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) was administered at baseline and monthly post-baseline visits, while the Migraine Disability Assessment (MIDAS) was administered at baseline, Month 3, and Month 6.

Table CGAG.11.8. Secondary Health Outcomes Analyses: Summary of Results ITT Population

	Placebo N=425	LY 120 mg N=210	LY 240 mg N=208
Change from Baseline in MSQ Total Score (average of Months 4 to 6)			
LSMean Change (SE)	21.51 (1.02)	28.85 (1.25)	28.22 (1.26)
Diff. vs. Placebo (SE)		7.34 (1.24)	6.70 (1.25)
95% CI on Difference		4.91, 9.77	4.25, 9.16
p-value vs. placebo		<.001	<.001
Change from Baseline in MSQ Role Function-Preventive Domain Score (average of Months 4 to 6)			
LSMean Change (SE)	17.13 (0.94)	22.69 (1.15)	21.81 (1.16)
Diff. vs. Placebo (SE)		5.56 (1.14)	4.68 (1.15)
95% CI on Difference		3.31, 7.80	2.42, 6.95
p-value vs. placebo		<.001	<.001
Change from Baseline in MSQ Emotional Function Domain Score (average of Months 4 to 6)			
LSMean Change (SE)	20.73 (1.26)	29.03 (1.54)	27.90 (1.56)
Diff. vs. Placebo (SE)		8.29 (1.52)	7.16 (1.54)
95% CI on Difference		5.30, 11.28	4.14, 10.19
p-value vs. placebo		<.001	<.001
Change from Baseline in MIDAS Total Score (Month 6)			
LSMean Change (SE)	-14.87 (1.37)	-21.16 (1.65)	-20.06 (1.68)
Diff. vs. Placebo (SE)		-6.29 (1.61)	-5.19 (1.63)
95% CI on Difference		-9.45, -3.13	-8.39, -1.98
p-value vs. placebo		<.001	.002

Abbreviations: CI = confidence interval; diff = difference; ITT = intent-to-treat; LS = Least Squares; LY = LY2951742/galcanezumab; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of patients in the analysis population for the primary measure; SE = standard error; vs. = versus.

Migraine symptoms

Further exploratory analyses were conducted at each month and overall over the mean reductions from baseline in number of monthly MHDs with nausea and/or vomiting, as well as photophobia and phonophobia, which resulted statistically significantly greater in both galcanezumab dose treatment groups compared with placebo.

Migraine with aura

Exploratory analyses were also conducted on the overall mean reductions from baseline in number of monthly MHDs with aura as well as prodromal symptoms other than aura, the vast majority of which were statistically significantly greater at each month in both the galcanezumab dose groups compared with placebo.

- **Ancillary analyses**

Subgroup analyses for the primary efficacy measure

There were no differential treatment effects based on sex, race, ethnicity, or presence of aura or not at baseline. Statistically significant subgroup-by-treatment interactions at a 2-sided 0.1 significance level were present for baseline MHD category (<8 vs. ≥ 8) and baseline treatment resistance status (failed ≥ 2 prior preventive treatments or not). For baseline MHD category, there was a greater treatment effect with galcanezumab 240 mg compared to placebo in patients with ≥ 8 MHDs at baseline. For baseline treatment resistance status, there was a greater treatment effect with galcanezumab 240 mg compared

with placebo and compared with galcanezumab 120 mg in the patients who had failed at least 2 treatments.

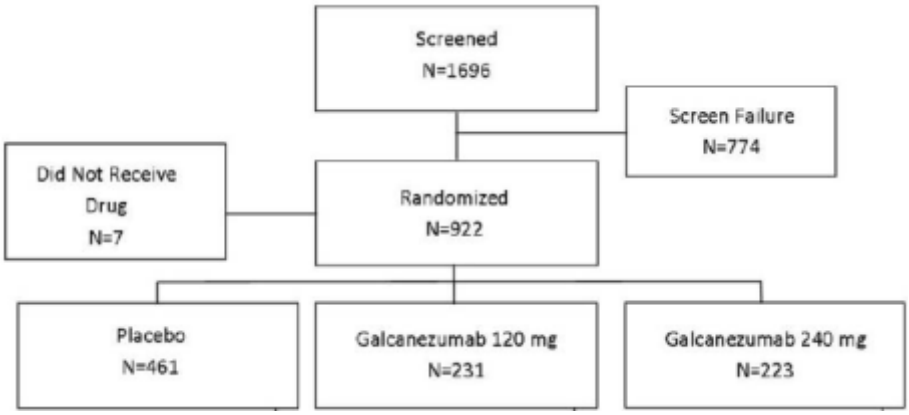
Exploratory responder analyses were conducted on the MSQ Role Function-Restrictive domain and MIDAS total score.

- For the MSQ Role Function-Restrictive domain, response was defined as change from baseline to average of Months 4 to 6 ≥ 25. The percentages of patients meeting this definition of response was statistically significantly greater in both the galcanezumab 120-mg and 240-mg treatment groups (63.5% and 69.6%) compared with placebo (47.2%)
- For the MIDAS total score, a patient was a responder for the specific visit if his/her percent change from baseline was ≥ 50% at the specific visit. The model estimated percentage of patients meeting this definition of response at Month 6 (where the questions were asked for the previous 3 months of double-blind treatment) was statistically significantly greater in both the galcanezumab 120-mg and 240-mg treatment groups (80.3% and 76.2%) compared with placebo (54.8%)

Results for Study CGAH

- **Participant flow**

Patient disposition through the DB phase (ITT population):



Source: Study CSR

A total of 1696 patients were screened, 922 patients were randomized and there were 774 screen failures. The most common reason for screen failure was patients not meeting criteria for study enrolment based on migraine headache information collected in the ePRO diary during the prospective baseline phase. A total of 915 randomized patients received at least 1 dose of galcanezumab and were included in the ITT population (n=461 patients randomized to placebo, n=231 patients randomized to galcanezumab 120 mg, and n=223 patients randomized to galcanezumab 240 mg). Overall, 785 patients (85.8%) completed the double-blind treatment phase (n=387 patients in the placebo arm, n=203 patients in the galcanezumab 120 mg arm, and n=195 patients in the galcanezumab 240 mg).

Table CGAH.10.1. Disposition of Patients from Double-Blind Treatment Phase ITT Population

Patient Disposition	Placebo (N=461) n (%)	LY 120 mg[a] (N=231) n (%)	LY 240 mg[a] (N=223) n (%)	LY_All[a] (N=454) n (%)
Completed Double-Blind Treatment Phase	387 (83.95)	203 (87.88)	195 (87.44)	398 (87.67)
Discontinued Double-Blind Treatment Phase Due to Any Reason	74 (16.05)	28 (12.12)	27 (12.11)[b]	55 (12.11)
Adverse Event	8 (1.74)	5 (2.16)	9 (4.04)	14 (3.08)
Lack of Efficacy	6 (1.30)	1 (0.43)	1 (0.45)	2 (0.44)
Lost to Follow Up	10 (2.17)	7 (3.03)	0*	7 (1.54)
Physician Decision	4 (0.87)	0	2 (0.90)	2 (0.44)
Pregnancy	1 (0.22)	2 (0.87)	0	2 (0.44)
Protocol Deviation	5 (1.08)	2 (0.87)	1 (0.45)	3 (0.66)
Terminated by Sponsor	1 (0.22)	0	0	0
Withdrawal by Patient	39 (8.46)	11 (4.76)	14 (6.28)	25 (5.51)
Completed Double-Blind Treatment Phase and Did Not Enter Post-Treatment Phase Due to Any Reason:	5 (1.08)	1 (0.43)	4 (1.79)	5 (1.10)
Lack of Efficacy	1 (0.22)	0	0	0
Lost to Follow Up	0	0	1 (0.45)	1 (0.22)
Withdrawal by Patient	4 (0.87)	1 (0.43)	3 (1.35)	4 (0.88)
Entered Post-Treatment Phase	292 (63.34)	156 (67.53)	155 (69.51)	311 (68.50)
Completed Post-Treatment Phase[c]	136 (46.58)	71 (45.51)	71 (45.81)	142 (45.66)
Ongoing in Post-Treatment Phase[c]	142 (48.63)	82 (52.56)	79 (50.97)	161 (51.77)
Discontinued Post-Treatment Phase Due to Any Reason[c]	15 (5.14)	3 (1.92)	5 (3.23)	8 (2.57)
Lost to Follow Up	5 (1.71)	1 (0.64)	1 (0.65)	2 (0.64)
Pregnancy	1 (0.34)	0	0	0
Protocol Deviation	0	1 (0.64)	0	1 (0.32)
Withdrawal by Patient	9 (3.08)	1 (0.64)	4 (2.58)	5 (1.61)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; N = number of patients in the intent-to-treat population.

- **Recruitment**

This study was conducted at 109 study centers in 11 countries. Due to investigator changes during the study, the number of principal investigators is higher than the number of study centers.

The first patient was enrolled on 29 January 2016, the last patient completed double-blind phase on 29 March 2017.

- **Conduct of the study**

Important Protocol deviations

An overview of the important protocol deviations that occurred during baseline and DB Treatment Phase is shown in the table below:

Table CGAH.10.2. Overview of Important Protocol Deviations During Baseline and Double-Blind Treatment Phase

Deviation	Placebo (N=461) n (%)	LY 120 mg (N=231) n (%)	LY 240 mg (N=223) n (%)	LY_All (N=454) n (%)	Total (N=915) n (%)
Patients with ≥1 Important Protocol Deviation	111 (24.08)	40 (17.32)	40 (17.94)	80 (17.62)	191 (20.87)
Dosing Interval Outside Specified Limits	48 (10.41)	17 (7.36)	17 (7.62)	34 (7.49)	82 (8.96)
Missing Data	28 (6.07)	9 (3.90)	12 (5.38)	21 (4.63)	49 (5.36)
Inclusion/Exclusion Criteria Not Met	23 (4.99)	10 (4.33)	6 (2.69)	16 (3.52)	39 (4.26)
Took Excluded Concomitant Medications	19 (4.12)	7 (3.03)	6 (2.69)	13 (2.86)	32 (3.50)
Missed Procedure	2 (0.43)	1 (0.43)	3 (1.35)	4 (0.88)	6 (0.66)
Informed Consent	1 (0.22)	1 (0.43)	1 (0.45)	2 (0.44)	3 (0.33)
Safety (Other)	1 (0.22)	1 (0.43)	0	1 (0.22)	2 (0.22)
Administrative/Oversight	1 (0.22)	1 (0.43)	0	1 (0.22)	2 (0.22)
Stratification Error	1 (0.22)	1 (0.43)	0	1 (0.22)	2 (0.22)
Not Observed for 30 Minutes after First Dose	1 (0.22)	0	0	0	1 (0.11)
Dosing Error (Other Significant Violation of Dosing)	1 (0.22)	0	0	0	1 (0.11)

Abbreviations: LY = LY2951742/galcanezumab; N = number of patients in the intent-to-treat population; n = number of patients in the specified category.

- **Baseline data**

Table CGAH.11.1. Summary of Patient Demographics ITT Population

Characteristic	Placebo N=461	LY 120 mg[a] N=231	LY 240 mg[a] N=223	LY_All[a] N=454
Age (years)				
Mean (±SD)	42.33 (±11.30)	40.91 (±11.15)	41.91 (±10.77)	41.40 (±10.97)
Sex, n (%)				
Male	68 (14.75)	34 (14.72)	32 (14.35)	66 (14.54)
Female	393 (85.25)	197 (85.28)	191 (85.65)	388 (85.46)
Race, n (%)				
American Indian or Alaska Native	20 (4.34)	8 (3.46)	13 (5.83)	21 (4.63)
Asian	50 (10.85)	28 (12.12)	24 (10.76)	52 (11.45)
Black or African American	36 (7.81)	11 (4.76)	16 (7.17)	27 (5.95)
Native Hawaiian or Other Pacific Islander	0	0	2 (0.90)	2 (0.44)
White	325 (70.50)	166 (71.86)	152 (68.16)	318 (70.04)
Multiple	30 (6.51)	18 (7.79)	16 (7.17)	34 (7.49)
Geographic Region, n (%)				
North America	224 (48.59)	112 (48.48)	110 (49.33)	222 (48.90)
Europe	122 (26.46)	60 (25.97)	59 (26.46)	119 (26.21)
Other	115 (24.95)	59 (25.54)	54 (24.22)	113 (24.89)
Body Mass Index (kg/m^2)				
Mean (±SD)	26.71 (±5.35)	26.83 (±5.27)	27.15 (±5.48)	26.99 (±5.37)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; N = number of patients in the intent-to-treat population; n = number of patients within each specific category; SD = standard deviation.

[a] None of the treatment group comparisons versus placebo were statistically significant.

Similarly to CGAG study and in line with known epidemiological data according to which the post-pubertal female-to-male ratio of migraine is of 4:1, the overall patient population was predominately female (85.4%) and White (70.3%) with a mean age of 41.9 years. Nearly half the patients were from North America. Across treatment groups the demographic characteristics of sex, age, race, geographic region, and BMI were similarly distributed.

Table CGAH.11.2. Summary of Disease Characteristics ITT Population

Characteristic	Placebo N=461	LY 120 mg[a] N=231	LY 240 mg[a] N=223	LY_All[a] N=454
Duration of migraine illness, years, mean (±SD)	21.15 (±12.75)	19.93 (±11.73)	20.01 (±12.12)	19.97 (±11.91)
Number of comorbidities, mean (±SD)	3.66 (±3.08)	3.64 (±3.41)	3.26 (±2.75)	3.46 (±3.11)
MHDs per month, mean (±SD)	9.19 (±2.99)	9.07 (±2.87)	9.06 (±2.92)	9.06 (±2.89)
Migraine attacks per month, mean (±SD)	5.67 (±1.82)	5.54 (±1.76)	5.66 (±1.80)	5.60 (±1.78)
MHD category ≥8, n (%)	307 (66.59)	154 (66.67)	151 (67.71)	305 (67.18)
Mean severity of migraine headaches per month, mean (±SD)[b]	2.08 (±0.38)	2.08 (±0.37)	2.11 (±0.38)	2.10 (±0.38)
MHD with acute medication use per month, mean (±SD)	7.62 (±3.40)	7.47 (±3.34)	7.47 (±3.25)	7.47 (±3.29)
Prior preventive treatment, n (%)	298 (64.64)	157 (67.97)	144 (64.57)	301 (66.30)
MIDAS total score, mean (±SD)	34.25 (±31.03)	30.87 (±27.90)	32.75 (±28.84)	31.79 (±28.35)
MSQ Role Function-Restrictive, mean (±SD)	51.35 (±15.73)	52.47 (±14.76)	51.71 (±16.31)	52.10 (±15.53)
PGI-S, mean (±SD)	4.29 (±1.22)	4.14 (±1.19)	4.18 (±1.17)	4.16 (±1.18)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; MHD(s) = migraine headache day(s); MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of patients in the intent-to-treat population; n = number of patients within each specific category; PGI-S = Patient Global Impression of Severity; SD = standard deviation.

[a] None of the treatment group comparisons versus placebo were statistically significant.

[b] Severity ratings were 1 = mild, 2 = moderate, and 3 = severe.

Prior and Concomitant Medications

The use of preventives was not allowed during the double-blind phase, whereas at least one prior migraine preventive treatment was reported by 65.5% of subjects overall (64.6% in the PBO treatment group vs 68% and 64.6% of LY120mg and LY240mg groups, respectively, without statistically significant differences). Overall, the previous most frequently used medications were topiramate (23%), ibuprofen (13%), paracetamol (9%), sumatriptan (10%), amitriptyline hydrochloride and amitriptyline (about 5% each), propranolol (7.1%) thomapyrin N (6.9%), botulinum toxin type A (4.9%). Statistically significant treatment group differences concerned topiramate (LY120mg [28.6%] vs LY240mg [18.4%], p=.01), paracetamol (LY120mg [13.4%] vs placebo [8.2%], p=.04 and vs LY240mg [5.8%], p=.007), and amitriptyline hydrochloride (placebo [2.3%] vs. LY120mg [9.1%], p <.001, and vs LY240mg [6.7%], p= 0.009). Within this medicines category, the overall most frequently reported reasons for discontinuation was inadequate response for topiramate (11.5%), amitriptyline hydrochloride, propranolol (2.6% each) and amitriptyline (1.9%).

Patients were allowed to start migraine prevention medications not before one month after the last visit of the treatment phase (Visit 12), at the discretion of the investigator if clinically warranted due to a worsening of symptoms. However, concomitant medications (recorded via eCRF) were used during the DB treatment period by the majority of subjects overall (89.8%), with the most frequent being ibuprofen, paracetamol, sumatriptan, Thomapyrin N, acetylsalicylic acid, ketorolac, naproxen, vitamins NOS, levothyroxine sodium. The most relevant statistically significant group differences regarded sumatriptan (placebo [13.8%] vs LY240mg [8.5%], p =.046) and salbutamol (placebo [1.74%] vs LY120mg [5.2%], p =.015). There was sufficient consistency between the concomitant therapies most frequently used during the DB treatment and those in the post-treatment periods.

- **Outcomes and estimation**

ePRO compliance

Compliance with the ePRO diary is an important consideration in interpreting efficacy results derived from the diary. At each month during the double-blind treatment phase, a majority of patients (>80%) completed at least 80% of their daily diary entries. Mean compliance with the ePRO diary averaged over the 6-month treatment phase was similar across treatment groups (91.3% placebo, 90.9% galcanezumab 120 mg, 92.7% galcanezumab 240 mg).

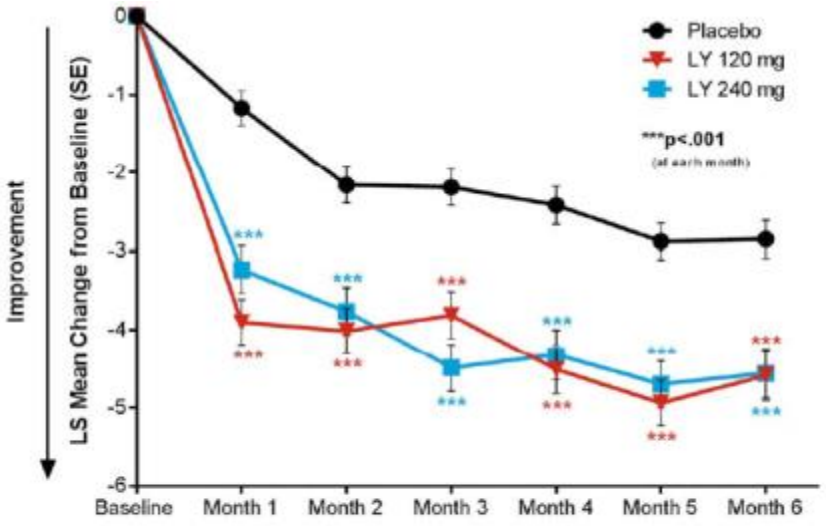
Primary Efficacy Endpoint:

Table CGAH.11.3. Change from Baseline in the Number of Migraine Headache Days
Repeated Measures Analysis
Intent-to-Treat Population
Study Period III

					Within group	vs 1)		
Period	Treatment	N	LS Mean Change from Baseline (SE)	95% CI	P-value	LS Mean Change Difference (SE)	95% CI	P-value
Month 1	1) Placebo	450	-1.17 (0.22)	(-1.60, -0.73)	<.001			
	2) LY120mg	225	-3.90 (0.29)	(-4.47, -3.33)	<.001	-2.74 (0.32)	(-3.37, -2.10)	<.001
	3) LY240mg	219	-3.23 (0.30)	(-3.81, -2.65)	<.001	-2.06 (0.33)	(-2.70, -1.42)	<.001
Month 2	1) Placebo	424	-2.16 (0.23)	(-2.60, -1.71)	<.001			
	2) LY120mg	217	-4.01 (0.29)	(-4.59, -3.44)	<.001	-1.86 (0.33)	(-2.51, -1.21)	<.001
	3) LY240mg	217	-3.76 (0.30)	(-4.34, -3.18)	<.001	-1.60 (0.33)	(-2.25, -0.96)	<.001
Month 3	1) Placebo	402	-2.19 (0.23)	(-2.64, -1.73)	<.001			
	2) LY120mg	213	-3.81 (0.30)	(-4.40, -3.22)	<.001	-1.62 (0.34)	(-2.28, -0.95)	<.001
	3) LY240mg	216	-4.49 (0.30)	(-5.08, -3.89)	<.001	-2.30 (0.34)	(-2.96, -1.63)	<.001
Month 4	1) Placebo	397	-2.42 (0.24)	(-2.90, -1.95)	<.001			
	2) LY120mg	208	-4.51 (0.31)	(-5.13, -3.90)	<.001	-2.09 (0.36)	(-2.79, -1.39)	<.001
	3) LY240mg	208	-4.32 (0.32)	(-4.94, -3.70)	<.001	-1.90 (0.36)	(-2.60, -1.19)	<.001
Month 5	1) Placebo	384	-2.88 (0.23)	(-3.33, -2.43)	<.001			
	2) LY120mg	199	-4.94 (0.29)	(-5.52, -4.36)	<.001	-2.06 (0.33)	(-2.71, -1.41)	<.001
	3) LY240mg	198	-4.70 (0.30)	(-5.28, -4.12)	<.001	-1.82 (0.33)	(-2.48, -1.17)	<.001
Month 6	1) Placebo	382	-2.85 (0.24)	(-3.33, -2.37)	<.001			
	2) LY120mg	196	-4.59 (0.32)	(-5.21, -3.96)	<.001	-1.73 (0.36)	(-2.44, -1.03)	<.001
	3) LY240mg	192	-4.56 (0.32)	(-5.19, -3.93)	<.001	-1.71 (0.36)	(-2.42, -1.00)	<.001
Overall	1) Placebo	450	-2.28 (0.20)	(-2.67, -1.88)	<.001			
	2) LY120mg	226	-4.29 (0.25)	(-4.79, -3.80)	<.001	-2.02 (0.27)	(-2.55, -1.48)	<.001
	3) LY240mg	220	-4.18 (0.26)	(-4.68, -3.67)	<.001	-1.90 (0.27)	(-2.44, -1.36)	<.001

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value; CI = confidence interval; LS = least square; SE = standard error. MMRM Model: Change = treatment, pooled region 1/country, month, and treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Source: Table CGAG.11.3 of Study Report

The overall LSMean reduction from baseline in the number of monthly MHDs during the double-blind treatment phase was -2.3 days for placebo, -4.3 days for LY-120mg and -4.2 days for LY-240mg (LSMean change difference from placebo: -2.0 and -1.9; p<.001 for each dose group versus placebo:



Abbreviations: LS = Least Squares; LY = LY2951742/galcanezumab; SE = standard error.
Note: not statistically significant between LY doses at any month.

Figure CGAH.11.1. Change from baseline in the number of migraine headache days.

The effect sizes were -0.61 and -0.57 for LY-120mg and LY-240mg dose groups versus placebo, respectively:

Table CGAH.14.14. Effect Size for Change in Migraine Headache Days and Number Needed to Treat for 50%, 75% and 100% Response Rate
Intent-to-Treat Population
Study Period III

					Comparison vs Placebo			
Measure	Time Frame	Treatment	N	LS Mean Change	LS Mean Change Difference	Standard Deviation	Effect Size	95% CI for Effect Size
Change from Baseline in Migraine Headache Days	Month 6	1)Placebo	382	-2.85				
		2)LY120mg	196	-4.59	-1.73	4.23	-0.41	(-0.58, -0.24)
		3)LY240mg	192	-4.56	-1.71	4.23	-0.40	(-0.58, -0.23)
	Overall	1)Placebo	450	-2.28				
		2)LY120mg	226	-4.29	-2.02	3.30	-0.61	(-0.77, -0.45)
		3)LY240mg	220	-4.18	-1.90	3.30	-0.57	(-0.74, -0.41)

***- Sensitivity Analysis for the Primary Objective*:**

Missing Data Assumptions

Table CGAH.14.15. Change from Baseline in the Number of Migraine Headache Days Sensitivity Analysis for Missing Data Assumptions - Delta Method for Overall Across Month 1 to 6 Intent-to-Treat Population Study Period III

Delta for Placebo	Delta for LY120mg	Delta for LY240mg	Treatment	N	LS Mean Change (SE)	95% CI	vs Placebo: LS Mean Change difference	vs Placebo: 95%CI	vs Placebo: p-Value
0.00	0.00	0.00	1) Placebo	450	-2.29 (0.20)	(-2.68,-1.90)			
			2) LY120mg	226	-4.29 (0.25)	(-4.79,-3.80)	-2.00	(-2.54,-1.47)	<.001
			3) LY240mg	220	-4.18 (0.26)	(-4.68,-3.68)	-1.89	(-2.43,-1.35)	<.001
	1.01	1.01	1) Placebo	450	-2.30 (0.20)	(-2.69,-1.91)			
			2) LY120mg	226	-4.23 (0.25)	(-4.72,-3.73)	-1.93	(-2.46,-1.39)	<.001
			3) LY240mg	220	-4.13 (0.26)	(-4.64,-3.63)	-1.83	(-2.38,-1.29)	<.001
	2.02	2.02	1) Placebo	450	-2.31 (0.20)	(-2.70,-1.92)			
			2) LY120mg	226	-4.16 (0.25)	(-4.66,-3.67)	-1.85	(-2.39,-1.32)	<.001
			3) LY240mg	220	-4.09 (0.26)	(-4.60,-3.58)	-1.78	(-2.32,-1.24)	<.001
2.28	2.28	2.28	1) Placebo	450	-2.08 (0.20)	(-2.48,-1.68)			
			2) LY120mg	226	-4.14 (0.26)	(-4.64,-3.64)	-2.06	(-2.60,-1.51)	<.001
			3) LY240mg	220	-4.07 (0.26)	(-4.58,-3.56)	-1.99	(-2.54,-1.44)	<.001
	3.29	3.29	1) Placebo	450	-2.09 (0.20)	(-2.49,-1.69)			
			2) LY120mg	226	-4.07 (0.26)	(-4.58,-3.57)	-1.98	(-2.53,-1.44)	<.001
			3) LY240mg	220	-4.02 (0.26)	(-4.54,-3.51)	-1.93	(-2.49,-1.38)	<.001
	4.30	4.30	1) Placebo	450	-2.10 (0.20)	(-2.50,-1.70)			
			2) LY120mg	226	-4.01 (0.26)	(-4.52,-3.50)	-1.91	(-2.46,-1.36)	<.001
			3) LY240mg	220	-3.98 (0.26)	(-4.49,-3.46)	-1.88	(-2.43,-1.32)	<.001
4.56	4.56	4.56	1) Placebo	450	-1.88 (0.21)	(-2.29,-1.47)			
			2) LY120mg	226	-3.99 (0.26)	(-4.51,-3.47)	-2.11	(-2.67,-1.55)	<.001
			3) LY240mg	220	-3.96 (0.27)	(-4.49,-3.44)	-2.09	(-2.65,-1.52)	<.001
	5.57	5.57	1) Placebo	450	-1.89 (0.21)	(-2.30,-1.48)			
			2) LY120mg	226	-3.93 (0.27)	(-4.45,-3.41)	-2.04	(-2.60,-1.47)	<.001
			3) LY240mg	220	-3.92 (0.27)	(-4.45,-3.39)	-2.03	(-2.60,-1.46)	<.001
	6.58	6.58	1) Placebo	450	-1.90 (0.21)	(-2.31,-1.48)			
			2) LY120mg	226	-3.86 (0.27)	(-4.38,-3.34)	-1.96	(-2.53,-1.40)	<.001
			3) LY240mg	220	-3.87 (0.27)	(-4.41,-3.34)	-1.98	(-2.55,-1.40)	<.001

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value.
For each set of Delta value: MMRM Model: Change = treatment, pooled region 1/country, month, and treatment*month, baseline, and baseline*month.
For each set of Delta value, the following steps were conducted
1) Predict the missing outcomes for each treatment via multiple imputation based on observed primary endpoint and baseline values.
Such imputation will be carried out using a Markov Chain Monte Carlo method with a Jeffery's prior via SAS PROC MI. 30 imputations will be created.
2) Add the corresponding delta to the imputed values based on the patient treatment group.
3) Conduct the primary analysis separately for each of the 30 imputations.
4) Combine the results of these analyses using Rubin's combining rules, as implemented in SAS PROC MI ANALYZE.

Normality Assumptions

The sensitivity analysis for the raw number of MHDs (ie, the total number of MHDs for each interval without normalization to 30-day period) performed to assess the validity of the primary MMRM results with respect to deviations from normality, showed the following results:

Table CGAH.14.16. Number of Migraine Headache Days
Sensitivity Analysis for Normality Assumption - Negative Binomial Distribution
Intent-to-Treat Population
Study Period III

						vs 1)			vs 2)		
Period	Treatment	N	Estimated Number of MHD per 30 day period (SE)	95% CI	Within-group P-value	Rate Ratio per 30 day period	95% CI	P-value	Rate Ratio per 30 day period	95% CI	P-value
Month 1	1)Placebo	450	7.69 (0.25)	(7.21, 8.20)	<.001						
	2)LY120mg	225	4.96 (0.24)	(4.51, 5.47)	<.001	0.65	(0.58, 0.71)	<.001			
	3)LY240mg	219	5.66 (0.32)	(5.06, 6.32)	<.001	0.74	(0.65, 0.83)	<.001	1.14	(0.99, 1.31)	.064
Month 2	1)Placebo	424	6.65 (0.24)	(6.19, 7.15)	<.001						
	2)LY120mg	217	4.86 (0.27)	(4.35, 5.42)	<.001	0.73	(0.65, 0.82)	<.001			
	3)LY240mg	217	5.13 (0.32)	(4.54, 5.80)	<.001	0.77	(0.68, 0.88)	<.001	1.06	(0.90, 1.24)	.488
Month 3	1)Placebo	402	6.63 (0.25)	(6.15, 7.13)	<.001						
	2)LY120mg	213	5.09 (0.31)	(4.53, 5.73)	<.001	0.77	(0.68, 0.87)	<.001			
	3)LY240mg	216	4.40 (0.27)	(3.91, 4.96)	<.001	0.66	(0.59, 0.75)	<.001	0.86	(0.74, 1.01)	.070
Month 4	1)Placebo	397	6.41 (0.27)	(5.91, 6.95)	<.001						
	2)LY120mg	208	4.43 (0.30)	(3.89, 5.06)	<.001	0.69	(0.60, 0.80)	<.001			
	3)LY240mg	208	4.56 (0.30)	(4.00, 5.19)	<.001	0.71	(0.62, 0.82)	<.001	1.03	(0.86, 1.23)	.767
Month 5	1)Placebo	384	5.99 (0.25)	(5.52, 6.51)	<.001						
	2)LY120mg	199	4.01 (0.25)	(3.55, 4.55)	<.001	0.67	(0.58, 0.77)	<.001			
	3)LY240mg	198	4.22 (0.30)	(3.67, 4.85)	<.001	0.70	(0.60, 0.82)	<.001	1.05	(0.88, 1.26)	.587
Month 6	1)Placebo	382	6.01 (0.26)	(5.52, 6.55)	<.001						
	2)LY120mg	196	4.35 (0.30)	(3.79, 4.98)	<.001	0.72	(0.62, 0.84)	<.001			
	3)LY240mg	192	4.38 (0.31)	(3.81, 5.03)	<.001	0.73	(0.62, 0.85)	<.001	1.01	(0.83, 1.21)	.941
Overall	1)Placebo	450	6.54 (0.22)	(6.12, 6.99)	<.001						
	2)LY120mg	226	4.60 (0.23)	(4.18, 5.07)	<.001	0.70	(0.63, 0.78)	<.001			
	3)LY240mg	220	4.70 (0.26)	(4.22, 5.24)	<.001	0.72	(0.64, 0.81)	<.001	1.02	(0.89, 1.17)	.765

As a further sensitivity analysis for primary efficacy, outlier patients identified as having studentized residuals less than 2 at any month of the DB treatment phase were identified and excluded (n=66 for placebo, n=25 for LY120mg, and n=29 for LY240mg), without changing the primary efficacy results:

						vs Placebo		
Population	Time Frame	Treatment	N	LS Mean Change (SE)	95% CI	LS Mean Change Difference (SE)	95% CI	P-value
Drop Placebo and LY Patients with Extreme Studentized Residuals	Month 1 to 6	1)Placebo	384	-2.86 (0.16)	(-3.17, -2.54)			
		2)LY120mg	201	-4.77 (0.20)	(-5.15, -4.38)	-1.91 (0.21)	(-2.33, -1.49)	<.001
		3)LY240mg	191	-4.95 (0.20)	(-5.36, -4.55)	-2.10 (0.22)	(-2.52, -1.67)	<.001

Source

Secondary Efficacy Analyses

The set of key secondary objectives tested after ensuring that the primary objective was met, followed the predefined multiple testing procedure, implemented to provide strong control of the type I error rate, with results summarized in the following table for continuous measures:

Table CGAH.11.4. Multiplicity Testing Results
Primary and Key Secondary Objectives
Intent-to-Treat Population
Study Period III

Endpoint	Time Frame	Treatment	N	Comparison with Placebo			
				LSMean Change Difference/Odds Ratio[a]	P-Value	Adjusted Significance Level[b]	Significance
Monthly Migraine Headache Days	Month 1 to 6	Placebo	450				
		LY 120 mg	226	-2.02	<.001	0.026	S
		LY 240 mg	220	-1.90	<.001	0.026	S
Monthly Migraine Headache Days with Acute Medication Use	Month 1 to 6	Placebo	450				
		LY 120 mg	226	-1.82	<.001	0.0125	S
		LY 240 mg	220	-1.78	<.001	0.0125	S
MSQ Role Function-Restrictive	Month 4 to 6	Placebo	396				
		LY 120 mg	213	8.82	<.001	0.025	S
		LY 240 mg	210	7.39	<.001	0.025	S
Patient Global Impression of Severity Rating	Month 4 to 6	Placebo	396				
		LY 120 mg	213	-0.29	0.002	0.025	S
		LY 240 mg	210	-0.23	0.012	0.025	S
50% Response	Month 1 to 6	Placebo	450				
		LY 120 mg	226	2.597	<.001	0.025	S
		LY 240 mg	220	2.314	<.001	0.025	S
75% Response	Month 1 to 6	Placebo	450				
		LY 120 mg	226	2.335	<.001	0.025	S
		LY 240 mg	220	2.416	<.001	0.025	S
100% Response	Month 1 to 6	Placebo	450				
		LY 120 mg	226	2.160	<.001	0.025	S
		LY 240 mg	220	2.667	<.001	0.025	S

Abbreviations: LSMean = Least Squares Mean; LY = LY2951742/galcanezumab; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of intent-to-treat patients who had nonmissing baseline and at least one postbaseline value; S = significant.
[a] Odds ratio is provided for response measures. For the other measures, LSMean change difference is provided.
[b] If p-value is less than or equal to the adjusted significance level, then the results are statistically significant after adjustment for multiplicity.

The response rates (categorical measures) for the mean percentage of patients with ≥30%, ≥50%, ≥75%, and 100% reduction from baseline in MHDs (ITT Population) during the 6-month treatment phase are summarized below:

Table CGAH.11.6. Mean Percentage of Patients with ≥30%, ≥50%, ≥75%, and 100% Reduction from Baseline in Monthly Migraine Headache Days ITT Population

Response Rate	Placebo N=450	LY 120 mg N=226			LY 240 mg N=220		
	Model Estimated Rate, % (SE)	Model Estimated Rate, % (SE)	Odds Ratio vs. Placebo	95% CI for Odds Ratio	Model Estimated Rate, % (SE)	Odds Ratio vs. Placebo	95% CI for Odds Ratio
≥30%	52.7 (1.8)	73.4 (2.2)	2.49	1.92, 3.22	72.6 (2.2)	2.38	1.84, 3.08
≥50%	36.0 (1.7)	59.3 (2.4)	2.60	2.03, 3.32	56.5 (2.5)	2.31	1.81, 2.96
≥75%	17.8 (1.3)	33.5 (2.3)	2.34	1.78, 3.06	34.3 (2.3)	2.42	1.84, 3.17
100%	5.7 (0.7)	11.5 (1.4)	2.16	1.50, 3.12	13.8 (1.5)	2.67	1.87, 3.81

Abbreviations: CI = confidence interval; ITT = intent-to-treat; LY = LY2951742/galcanezumab; N = number of intent-to-treat patients who had nonmissing baseline and at least one postbaseline value; SE = standard error; vs. = versus.

Exploratory responder analyses

Exploratory responder analyses were conducted on the MSQ Role Function-Restrictive domain.

Response was defined as change from baseline to average of Months 4 to 6 $\geq$ 25. The percentages of patients meeting this definition of response was statistically significantly greater in both the galcanezumab 120-mg and 240-mg treatment groups (58.2% and 60.0%) compared with placebo (43.4%).

A post hoc exploratory responder analysis was conducted on the PGI-S.

Response at each visit was defined as having a severity decrease from baseline of at least 2 points on the 7-point scale at the specific visit. The model estimated mean percentages of patients meeting this definition of response over the final 3 months of double-blind treatment (average of Months 4 to 6) was statistically significantly greater in both the galcanezumab 120-mg and 240-mg treatment groups (38% and 37%) compared with placebo (29%)

Secondary endpoints

Several endpoints as part of the additional secondary efficacy analyses in support of the key secondary objectives across the DB phase were tested, which all showed significant differences in favour of both galcanezumab dose groups compared to placebo. No adjustment for sensitivity was considered in this case:

Table CGAH.11.5. Additional Secondary Efficacy Analyses: Summary of Overall Results (Average of All 6 Months)
ITT Population

	Placebo N=450	LY 120 mg N=226	LY 240 mg N=220
Change from Baseline in Number of Monthly Headache Days			
LSMean Change (SE)	-2.30 (0.22)	-4.31 (0.28)	-4.30 (0.28)
Diff. vs. Placebo (SE)		-2.00 (0.30)	-2.00 (0.30)
95% CI on Difference		-2.58, -1.42	-2.58, -1.41
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Moderate to Severe Headache Days			
LSMean Change (SE)	-2.31 (0.18)	-3.90 (0.22)	-3.78 (0.22)
Diff. vs. Placebo (SE)		-1.59 (0.23)	-1.47 (0.24)
95% CI on Difference		-2.05, -1.13	-1.93, -1.01
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly ICHD Migraine Headache Days (ie, Excluding Probable Migraine)			
LSMean Change (SE)	-1.67 (0.18)	-3.44 (0.23)	-3.22 (0.23)
Diff. vs. Placebo (SE)		-1.78 (0.24)	-1.55 (0.24)
95% CI on Difference		-2.25, -1.30	-2.03, -1.07
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Attacks			
LSMean Change (SE)	-1.98 (0.10)	-2.76 (0.12)	-2.80 (0.13)
Diff. vs. Placebo (SE)		-0.78 (0.13)	-0.82 (0.13)
95% CI on Difference		-1.04, -0.52	-1.08, -0.56
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Hours			
LSMean Change (SE)	-11.32 (1.81)	-26.33 (2.28)	-24.22 (2.32)
Diff. vs. Placebo (SE)		-15.01 (2.46)	-12.90 (2.47)
95% CI on Difference		-19.83, -10.18	-17.75, -8.05
p-value vs. placebo		<.001	<.001

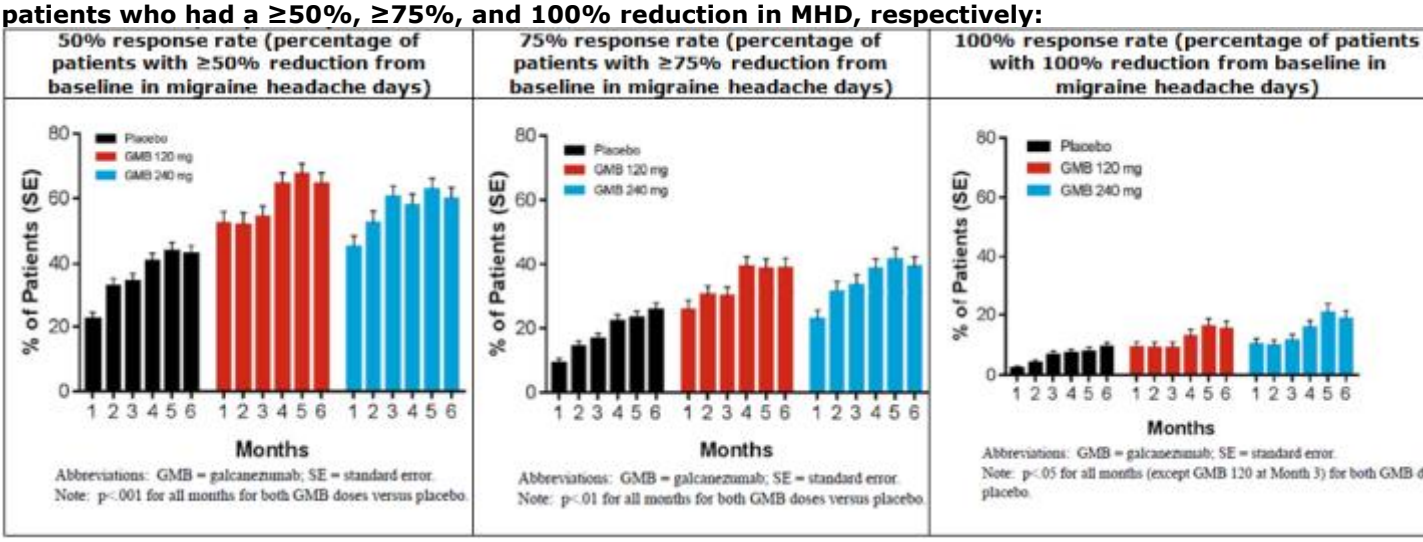
Additional Secondary Efficacy Analyses: Summary of Overall Results (Average of All 6 Months), ITT Population

	Placebo N=450	LY 120 mg N=226	LY 240 mg N=220
Change from Baseline in Number of Monthly Headache Hours			
LSMean Change (SE)	-10.89 (1.92)	-26.07 (2.41)	-24.44 (2.44)
Diff. vs. Placebo (SE)		-15.19 (2.59)	-13.56 (2.60)
95% CI on Difference		-20.27, -10.11	-18.67, -8.44
p-value vs. placebo		<.001	<.001
Change from Baseline in Mean Severity of Remaining Migraine Headache Days			
LSMean Change (SE)	-0.15 (0.02)	-0.20 (0.03)	-0.22 (0.03)
Diff. vs. Placebo (SE)		-0.06 (0.03)	-0.08 (0.03)
95% CI on Difference		-0.11, -0.01	-0.13, -0.03
p-value vs. placebo		.031	.004
Patient Global Impression of Improvement Rating			
LSMean (SE)	2.95 (0.06)	2.28 (0.07)	2.36 (0.07)
Diff. vs. Placebo (SE)		-0.67 (0.07)	-0.59 (0.08)
95% CI on Difference		-0.82, -0.52	-0.74, -0.45
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of Triptans (additional analysis to support secondary objectives)			
LSMean Change (SE)	-0.63 (0.15)	-2.10 (0.19)	-2.21 (0.19)
Diff. vs. Placebo (SE)		-1.47 (0.20)	-1.58 (0.21)
95% CI on Difference		-1.87, -1.07	-1.98, -1.18
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of NSAIDs/Aspirin (additional analysis to support secondary objectives)			
LSMean Change (SE)	-1.37 (0.16)	-2.64 (0.20)	-2.48 (0.21)
Diff. vs. Placebo (SE)		-1.27 (0.22)	-1.10 (0.22)
95% CI on Difference		-1.70, -0.84	-1.54, -0.67
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of Acetaminophen/Paracetamol (additional analysis to support secondary objectives)			
LSMean Change (SE)	-0.77 (0.12)	-1.43 (0.16)	-1.40 (0.16)
Diff. vs. Placebo (SE)		-0.66 (0.17)	-0.63 (0.17)
95% CI on Difference		-0.99, -0.33	-0.96, -0.30
p-value vs. placebo		<.001	<.001

Abbreviations: CI = confidence interval; diff = difference; ICHD = International Classification of Headache Disorders; ITT = intent-to-treat; LSMean = Least Squares Mean; LY = LY2951742/galcanezumab; N = number of patients in the analysis population for the primary measure; NSAIDs = nonsteroidal anti-inflammatory drug; SE = standard error; vs. = versus.

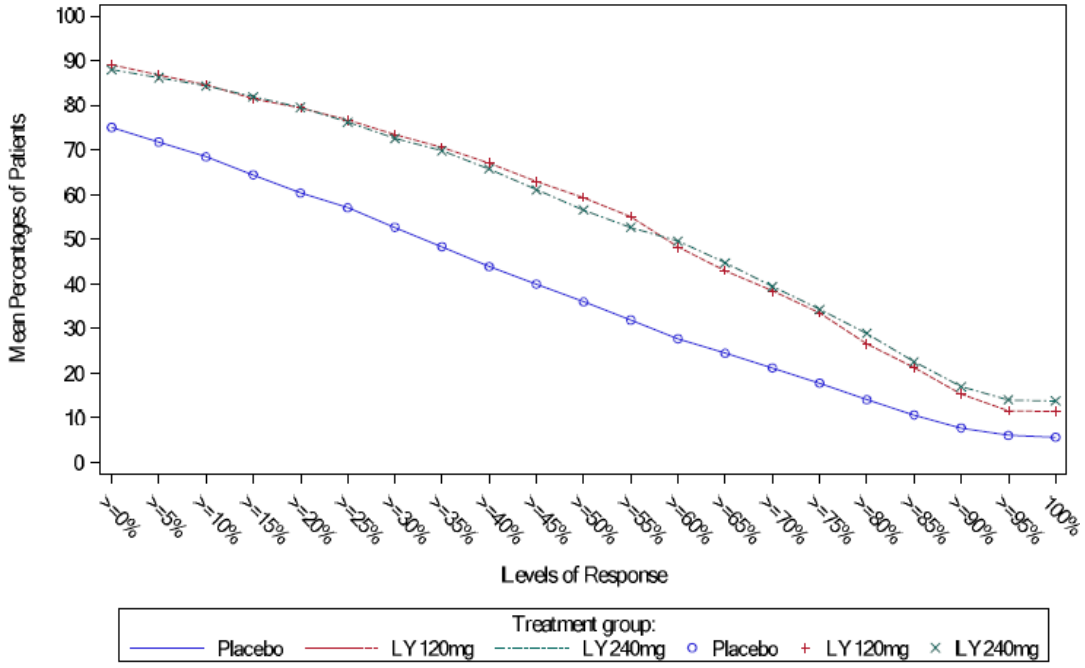
Further Response Analyses Based on Reduction in Monthly MHDs

Study CGAH (Additional secondary analyses): summary, by month, of the percentages of patients who had a ≥50%, ≥75%, and 100% reduction in MHD, respectively:



Source: Figure 2.7.3.9; 2.7.3.10; 2.7.3.11. of the Summary of clinical Efficacy

At each month, the percentages of patients with ≥50% or ≥75% reduction from baseline in MHDs were statistically significantly greater in both the LY120 mg and LY240mg groups compared with placebo. Similar results were obtained for 100% reduction from baseline in MHDs, with the exception of 1 time point that was not statistically significantly different between galcanezumab 120 mg and placebo (Month 3).



Abbreviation: LY = LY2951742.
All data points in the plot are estimated from GLIMMIX: Responder indicator = treatment, month, treatment* month, and baseline MHD.
Mean Percentages of Patients are estimated percentages over months 1 to 6 from the GLIMMIX model.

Onset and Maintenance of effect

The earliest month where the statistical significance was observed and maintained for all the subsequent months during DB treatment phase was considered as the onset of ≥50% sustained response (key secondary measure of ≥50% response rate that was statistically significant), and was observed at Month 1 for both galcanezumab treatment groups.

A statistically significantly higher percentage of patients in each galcanezumab treatment group maintained the ≥50% response either for at least 3 and 6 consecutive months to the patient's endpoint during the double-blind treatment phase compared with placebo:

Table CGAH.11.7. Maintenance of 50% Response for 3 Months or 6 Months
Logistic Regression
Intent-to-Treat Population
Study Period III

				vs 1)			vs 2)		
Sustained Response	Treatment Group	N	n(%)	Odds Ratio	95% CI for Odds Ratio	P-values*a	Odds Ratio	95% CI for Odds Ratio	P-values*a
50% Response maintained for >=3 consecutive months until patient's endpoint in SP III	1)Placebo	450	94 (20.89)						
	2)LY120mg	226	87 (38.50)	2.45	(1.72, 3.51)	<.001			
	3)LY240mg	220	84 (38.18)	2.42	(1.69, 3.46)	<.001	0.98	(0.67, 1.45)	.938
50% Response maintained from Month 1 to Month 6	1)Placebo	450	32 (7.11)						
	2)LY120mg	226	40 (17.70)	2.85	(1.73, 4.68)	<.001			
	3)LY240mg	220	49 (22.27)	3.80	(2.35, 6.16)	<.001	1.34	(0.84, 2.14)	.226

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have non-missing baseline value and at least one post-baseline value.
*a: p-values from logistic regression: x-month sustained 50% responder indicator = treatment, pooled region1/country, and baseline.
X is either 3 or 6, defined below:
3-month sustained 50% responders are defined as patients meeting 50% response criteria for their last three months in the treatment phase; everyone else are non-responders, including those discontinued early within 3 months and those continued after 3 months but did not meet 50% response criteria for their last three months.
6-month sustained 50% responders are defined as patients meeting 50% response criteria for all 6 months during the treatment phase; everyone else are non-responders, including those who discontinued early and those who completed 6-month treatment phase but did not meet 50% response criteria for one or more of the 6 months.

Secondary Analyses on Health Outcomes:

Table CGAH.11.8. Secondary Health Outcomes Analyses: Summary of Results ITT Population

	Placebo N=450	LY 120 mg N=226	LY 240 mg N=220
Change from Baseline in MSQ Total Score (average of Months 4 to 6)			
LSMean Change (SE)	16.58 (0.86)	25.03 (1.08)	23.88 (1.09)
Diff. vs. Placebo (SE)		8.45 (1.19)	7.30 (1.19)
95% CI on Difference		6.13, 10.78	4.95, 9.64
p-value vs. placebo		<.001	<.001
Change from Baseline in MSQ Role Function-Preventive Domain Score (average of Months 4 to 6)			
LSMean Change (SE)	12.25 (0.82)	20.09 (1.03)	18.91 (1.05)
Diff. vs. Placebo (SE)		7.83 (1.13)	6.66 (1.14)
95% CI on Difference		5.61, 10.06	4.41, 8.90
p-value vs. placebo		<.001	<.001
Change from Baseline in MSQ Emotional Function Domain Score (average of Months 4 to 6)			
LSMean Change (SE)	15.60 (1.00)	24.10 (1.26)	23.43 (1.28)
Diff. vs. Placebo (SE)		8.50 (1.38)	7.83 (1.39)
95% CI on Difference		5.78, 11.22	5.09, 10.57
p-value vs. placebo		<.001	<.001
Change from Baseline in MIDAS Total Score (Month 6)			
LSMean Change (SE)	-12.02 (1.27)	-21.17 (1.58)	-20.24 (1.62)
Diff. vs. Placebo (SE)		-9.15 (1.76)	-8.22 (1.78)
95% CI on Difference		-12.61, -5.69	-11.71, -4.72
p-value vs. placebo		<.001	<.001

Abbreviations: CI = confidence interval; diff = difference; ITT = intent-to-treat; LSMean = Least Squares Mean; LY = LY2951742/galcanezumab; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of patients in the analysis population for the primary measure; SE = standard error; vs. = versus.

Exploratory responder analyses were conducted on MIDAS total score.

For the MIDAS total score, a patient was a responder for the specific visit if his/her percent change from baseline was ≥ 50% at the specific visit. The model estimated percentage of patients meeting this definition of response at Month 6 (where the questions were asked for the previous 3 months of double-blind treatment) was statistically significantly greater in both the galcanezumab 120-mg and 240-mg treatment groups (73.0% and 77.1%) compared with placebo (55.6%).

Migraine symptoms

Further exploratory analyses were conducted at each month and overall over the mean reductions from baseline in number of monthly MHDs with nausea and/or vomiting, as well as photophobia and phonophobia, which resulted statistically significantly greater in both galcanezumab dose treatment groups compared with placebo.

Migraine with aura

Exploratory analyses were also conducted on the overall mean reductions from baseline in number of monthly MHDs with aura as well as prodromal symptoms other than aura, the vast majority of which were statistically significantly greater at each month in both the galcanezumab dose groups compared with placebo.

- **Ancillary analyses**

Subgroup analyses for the primary efficacy measure

Subgroup analyses for the primary efficacy measure of change from baseline in the number of

monthly MHDs included the following subgroup variables:

sex, race, ethnicity, geographic region, baseline monthly MHD category, baseline treatment resistance status, and presence of aura (or not) at baseline.

The statistical significance of the subgroup-by-treatment interaction was assessed at a 2-sided with 0.1 significance level.

Statistically significant subgroup-by-treatment interactions pertained the following subgroups variables:

- *race*, p=.07 for galcanezumab 240 mg compared with placebo, due to a greater difference of LY240 mg versus placebo in the Asian group (-2.4 days) and White group (-2.1 days) as compared with the Other subgroup (-0.4 days). The applicant explains such interaction as not clinically meaningful given the higher placebo response observed in the Other race group, despite comparable magnitudes of change observed in galcanezumab treated groups at all races.

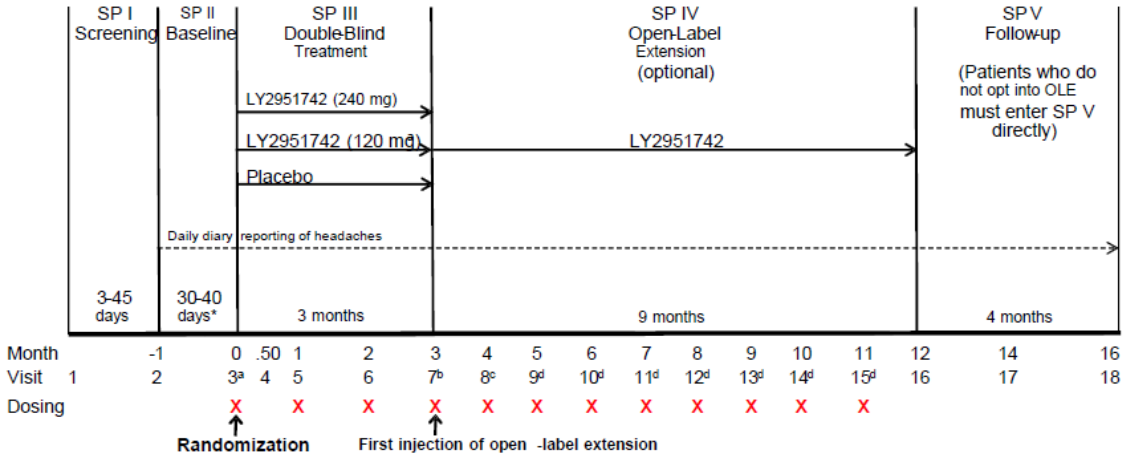
- *geographic region*, p=.003 for galcanezumab 240mg compared with placebo (p=.003), due to significantly greater difference observed in European subgroup (-3.4 days) compared to North American (-1.2 days) and Other (-1.7 days). The applicant considered these results as clinically not meaningful given the low placebo response in the European subgroup.

- *presence of aura (or not) at baseline,* p=.037 and p=.026 for galcanezumab 120mg and galcanezumab LY240mg, respectively, due to significantly greater difference observed in the subgroup without aura at baseline (-2.7 days and -2.6 days for LY120mg and LY240mg versus placebo) compared with the subgroup with aura at baseline (-1.5 days and -1.4 days). The applicant considered these results as not clinically meaningful given the similarity in the magnitude of change for galcanezumab-treated patients in patients with and without aura, that varied for placebo-treated patients in the 2 subgroups.

There were no other statistically significant subgroup-by-treatment interactions for either galcanezumab dose group compared with placebo for any other subgroup variables in change from baseline in the number of monthly MHDs.

Study I5Q-MC-CGAI (CGAI, the REGAIN study) for chronic migraine (with or without aura)

Methods



Abbreviations: LY2951742 = galcanezumab; OLE = open-label extension; SP = study period.

* Eligibility period determined between a minimum of 30 days and a maximum of 40 days. Investigators had up to 5 additional days (beyond the 40 days) if needed to schedule a patient's Visit 3 appointment.

[a] Patients randomized to the 120-mg dose received a loading dose of 240 mg at the first injection only (Visit 3).

[b] At Visit 7, all patients who entered the open-label extension received galcanezumab at a dose of 240 mg.

[c] At Visit 8, all patients received galcanezumab at a dose of 120 mg.

[d] Starting at Visit 9, dosing was flexible (galcanezumab 120 or 240 mg) at the discretion of the investigator.

Study Participants

Inclusion Criteria

Patient and Disease Characteristics

[1] Patients are 18 to 65 years of age (inclusive) at the time of screening.
[2] Have a diagnosis of chronic migraine as defined by the IHS ICHD-3 beta guidelines (1.3) (ICHD-3 2013):

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On ≥8 days per month for >3 months, fulfilling any of the following:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

[3] Migraine onset prior to age 50.
[4] Prior to Visit 1, a history of at least 1 headache-free day per month for the past 3 months.
[5] From Visit 2 to Visit 3 (prospective baseline period), have a frequency of at least 15 headache days, of which at least 8 must have the features of migraine headache. To avoid biased reporting, patients must not be told the number of migraine headache days on which study qualification is based.
[6] From Visit 2 to Visit 3 (prospective baseline period), have at least one headache-free day.

[7] From Visit 2 to Visit 3 (prospective baseline period), must achieve sufficient compliance with ePRO daily headache entries as demonstrated by completion of at least 80% of daily diary entries.
Patients also had to agree to use an acceptable contraceptive method during the study and for at least 5 months after last dose of IMP.

Treatments

During the DB treatment phase, patients received galcanezumab (120 or 240 mg) or placebo administered once monthly by subcutaneous injection at dosing visits. Patients randomized to the 120-mg dose received a *loading dose of 240 mg* (2 injections of 120 mg each at V3 only). All treatment groups received two 1-ml injections of IP at each dosing visit to maintain the blind (two placebo injections; two 120-mg galcanezumab injections; or one placebo injection and one 120-mg galcanezumab injection) for a total of 3 administrations during the 3-month DB treatment phase.

During the open-label extension (ongoing) galcanezumab dosing was comprised of monthly injections at 9 office visits. Doses administered during this phase were 240 mg at V7, 120 mg at V8, and either 120 or 240 mg/month, thereafter, at the discretion of the investigator. Dosing and dose changes could only occur at regular once-monthly visits. Subcutaneous injection sites included the abdomen, thigh, upper arm, or buttocks.

Objectives

Primary, secondary and tertiary objectives with endpoints tested during the DB period of Study CGAI were the same as the Studies CGAG and CGAH, but tested on the shorter **3-month time period** (overall mean change from baseline over Months 1 to 3 for most efficacy measures or mean change from baseline at Month 3 for measures of functioning and disability and the PGI-S).

During the open-label period, mean changes in MHDs, functioning, disability, and rates of response and sustained response were evaluated. As in Studies CGAG and CGAH, an MHD was defined as a calendar day on which a migraine headache or probable migraine headache occurred.

Outcomes/endpoints

The primary endpoint was the overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind treatment phase.

Sample size

The sample size derived from an initially planned re-estimation procedure due to uncertainties in the effect size of galcanezumab in chronic migraine, ranged between a minimum of 825 patients to a maximum of 1140 patients. The minimum estimated sample size was based on the assumption of an effect size of 0.33 and a dropout rate of approximately 15%, expected to provide more than 90% power that at least 1 dose of LY2951742 would separate from placebo at a two-sided significance level of 0.05 based on simulations Dunnett test. The maximum estimate was based on the same dropout rate with an effect size of 0.30 in the last month of the 3-month DB phase, to provide approximately 95% power that at least 1 dose of galcanezumab would separate from placebo at a 1-sided 0.025 significance level.

Randomisation

Patients who met all criteria for enrolment were randomly assigned to DB treatment group at V3 by an interactive web-response system (IWRS). The stratification factors considered to achieve between-group comparability, were country, acute headache medication overuse (yes/no), and use of concurrent migraine prophylactic medication (yes/no). Acute headache medication overuse was determined during the prospective baseline period with diagnostic criteria adapted from Section 8.2 of the ICHD-3 beta guidelines (ICHD-3 2013), while taking into consideration the following drug-related thresholds specifications, in terms of total days of use per 30-day period of the prospective baseline as reported in the ePRO diary.

Blinding (masking)

In this double-blind study, a minimum number of the sponsor's personnel saw the randomization table and treatment assignments before the study was complete. This was explained as a measure to preserve the blinding of the study. Emergency unblinding for AEs could be performed through the IWRS, in which all the unblinding events were to be recorded and reported.

Statistical methods

The primary efficacy measure was the overall mean change from the baseline period in the number of monthly migraine headache days during the 3-month double-blind treatment phase, and the primary analysis evaluated the efficacy of galcanezumab (LY120 or LY240 mg/month) compared with placebo. The primary analysis was performed using a restricted maximum likelihood-based mixed models repeated measures (MMRM) technique and includes the fixed categorical effects of treatment, pooled country, medication overuse (yes/no), concomitant prophylaxis use (yes/no), month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of migraine headache days and baseline number of migraine headache days-by-month interaction. Visitwise binary efficacy variables were analyzed using a generalized linear mixed model (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis.

Results

DOUBLE-BLIND treatment phase

- **Participant flow**

Patient disposition through the DB phase (ITT population):

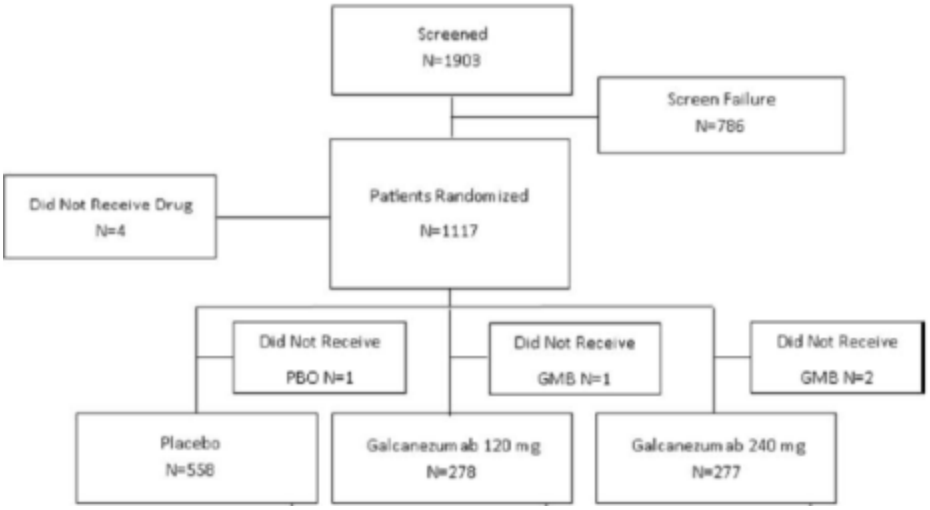


Table CGAI.10.1. Disposition of Patients from Double-Blind Treatment Phase ITT Population

Double-Blind Patient Disposition	Placebo (N=558) n (%)	LY 120 mg[a] (N=278) n (%)	LY 240 mg[a] (N=277) n (%)	LY_All[a] (N=555) n (%)
Completed Double-Blind Treatment Phase	508 (91.04)	263 (94.60)	266 (96.03)**	529 (95.32)**
And Entered Open-Label Treatment Phase	501 (89.78)	259 (93.17)	261 (94.22)	520 (93.69)
Discontinued Double-Blind Treatment Phase Due to Any Reason	49 (8.78)[b]	15 (5.40)	11 (3.97)*	26 (4.68)**
Discontinued Double-Blind Treatment Phase Due to:				
Adverse Event	6 (1.08)	3 (1.08)	2 (0.72)	5 (0.90)
Lack of Efficacy	4 (0.72)	0 (0.00)	0 (0.00)	0 (0.0)*
Lost to Follow Up	10 (1.79)	4 (1.44)	1 (0.36)	5 (0.90)
Physician Decision	2 (0.36)	1 (0.36)	1 (0.36)	2 (0.36)
Pregnancy	2 (0.36)	2 (0.72)	0 (0.00)	2 (0.36)
Protocol Deviation	6 (1.08)	1 (0.36)	0 (0.00)	1 (0.18)
Withdrawal by Subject	19 (3.41)	4 (1.44)	7 (2.53)	11 (1.98)
Reasons for Withdrawal by Subject:				
Concern about Study Procedures/Perceived Risks	2 (0.36)	0 (0.00)	0 (0.00)	0 (0.00)
Scheduling Conflicts	9 (1.61)	2 (0.72)	4 (1.44)	6 (1.08)
Subject is Moving or Has Moved	1 (0.18)	1 (0.36)	3 (1.08)	4 (0.72)
Other[c]	7 (1.25)	1 (0.36)	0 (0.00)	1 (0.18)*
Completed Double-Blind Treatment but Did Not Enter Open-Label Phase	7 (1.25)	4 (1.44)	5 (1.81)	9 (1.62)
And Entered Post-treatment Phase	1 (0.18)	0 (0.00)	1 (0.36)	1 (0.18)
And Discontinued Study	6 (1.08)	4 (1.44)	4 (1.44)	8 (1.44)
Reasons for Discontinuing Study:				
Lack of Efficacy	1 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)
Lost to Follow Up	2 (0.36)	0 (0.00)	2 (0.72)	2 (0.36)
Physician Decision	2 (0.36)	0 (0.00)	0 (0.0)	0 (0.0)
Withdrawal by Subject	1 (0.18)	4 (1.44)*	2 (0.72)	6 (1.08)
Reasons for Withdrawal by Subject:				
Concern about Study Procedures/Perceived Risks	0 (0.00)	0 (0.00)	1 (0.36)	1 (0.18)
Scheduling Conflicts	0 (0.00)	2 (0.72)*	1 (0.36)	3 (0.54)
Other[d]	1 (0.18)	2 (0.72)	0 (0.00)	2 (0.36)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; N = number of patients in the ITT population.

[a] Asterisk (*) denotes p-value comparison vs. placebo <.05 and (**) denotes p-value comparison vs. placebo <.01.

[b] 1 patient randomized to placebo discontinued early (withdrawal by subject) but because the discontinuation date was listed after the data cut-off date, the patient is not counted among the 49 discontinuations.

[c] Sub-reasons for Other: Placebo group: withdrew consent (2), family emergency (1), injection too painful (1), adverse event (1), visit not done (1); traveling abroad (1); LY 120-mg group: moving (1).

[d] Sub-reasons for Other: Placebo group: death in family (1); LY 120-mg group: lost to follow-up (1), started prohibited medication (1).

:

- **Conduct of the study**

A total of 203 patients (18.2%) had ≥1 important protocol deviation during the baseline and double-blind periods (n=103 [18.5%] of placebo; n=53 [19.1%] and n=47 [17%] of LY120-mg and LY240-mg treatment groups, respectively):

Table CGAI.10.4. Overview of Important Protocol Deviations During Baseline and Double-Blind Treatment Phase

Double-Blind Treatment Phase	Placebo (N=558) n (%)	LY 120 mg (N=278) n (%)	LY 24 0mg (N=277) n (%)	LY_All (N=555) n (%)	Total (N=1113) n (%)
Patients with ≥1 Important Protocol Deviation	103 (18.5)	53 (19.1)	47 (17.0)	100 (18.0)	203 (18.2)
Stratification Error	34 (6.1)	13 (4.7)	18 (6.5)	31 (5.6)	65 (5.8)
Dosing Interval Outside Specified Limits	24 (4.3)	19 (6.8)	10 (3.6)	29 (5.2)	53 (4.8)
Took Excluded Concomitant Medications	27 (4.8)	7 (2.5)	11 (4.0)	18 (3.2)	45 (4.0)
Inclusion/Exclusion Criteria Not Met	15 (2.7)	13 (4.7)	8 (2.9)	21 (3.8)	36 (3.2)
Missing Data	16 (2.9)	4 (1.4)	1 (0.4)	5 (0.9)	21 (1.9)
Dose Error (received IP not fit for use)	1 (0.2)	2 (0.7)	1 (0.4)	3 (0.5)	4 (0.4)
Administrative: Unqualified C-SSRS Rater	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.2)
Missed Procedure	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Not Observed for 30 Minutes after First Dose	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.2)
Improper Informed Consent	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	1 (0.1)

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; IP = investigational product;

Table CGAI.10.5 Overview of Important Protocol Deviations During Open-Label Treatment Phase

Open-Label Phase	Total (N=1021) n (%)
Patients with ≥1 Important Protocol Deviation	142 (13.9)
Dosing Interval Outside Specified Limits	72 (7.1)
Took Excluded Concomitant Medications	47 (4.6)
Missing Data	23 (2.3)
Not Observed for 30 Minutes after First Open-Label Dose	8 (0.8)
Site Did Not Appropriately Report SAE	2 (0.2)
Missed Procedure	1 (0.1)

Abbreviations: LY = LY2951742/galcanezumab; N = number of patients in the open-label treatment population; n = number of patients in the specified category; SAE = serious adverse event.

- **Baseline data**

Table CGAI.11.1. Summary of Patient Demographics ITT Population

Characteristic	Placebo N=558	LY 120 mg[a] N=278	LY 240 mg[a] N=277	LY_All[a] N=555
Age (years)				
Mean (±SD)	41.63 (±12.08)	39.66 (±11.88)*	41.05 (±12.40)	40.35 (±12.15)
Sex, n (%)				
Male	75 (13.44)	41 (14.75)	51 (18.41)	92 (16.58)
Female	483 (86.56)	237 (85.25)	226 (81.59)	463 (83.42)
Race, n (%)				
American Indian or Alaska Native	4 (0.72)	2 (0.72)	0 (0.00)	2 (0.36)
Asian	26 (4.66)	13 (4.68)	14 (5.07)	27 (4.87)
Black or African American	39 (6.99)	16 (5.76)	17 (6.16)	33 (5.96)
Native Hawaiian or Other Pacific Islander	1 (0.18)	0 (0.00)	0 (0.00)	0 (0.00)
White	432 (77.42)	223 (80.22)	224 (81.16)	447 (80.69)
Multiple	56 (10.04)	24 (8.63)	21 (7.61)	45 (8.12)
Region, n (%)				
North America	321 (57.53)	161 (57.91)	159 (57.40)	320 (57.66)
Europe	140 (25.09)	68 (24.46)	70 (25.27)	138 (24.86)
Other	97 (17.38)	49 (17.63)	48 (17.33)	97 (17.48)
Body Mass Index (kg/m^2)				
Mean (±SD)	26.87 (±5.55)	26.40 (±5.49)	26.67 (±5.24)	26.53 (±5.36)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; N = number of intent-to-treat patients with nonmissing demographic measures; n = number of patients with each specific category; SD = standard deviation.

[a] Asterisk (*) denotes p-value comparison vs. placebo <.05.

The patient population was predominantly female (85.0%), White (79.1%), and from North America (57.6%). The overall mean age was 41.0 years although the LY120-mg group was statistically significantly younger than the placebo group (39.7 vs. 41.6 years, p=.027). Sex, age, race, and BMI were generally similar across treatment groups.

Table CGAI.11.2. Summary of Disease Characteristics[a] ITT Population

Characteristic	Placebo N=558	LY 120 mg N=278	LY 240 mg N=277	LY_All N=555
Duration of migraine illness, years, mean (±SD)	21.94(±12.85)	20.37(±12.74)	20.06±(12.72)*	20.22 (±12.72)*
Had migraine with aura at baseline, n (%)	310 (55.56)	153 (55.04)	141 (50.90)	294 (52.97)
Number of comorbidities, mean (±SD)	4.39 (±3.70)	4.08 (±3.33)	4.21 (±3.19)	4.15 (±3.26)
Number of monthly MHDs, mean (±SD)	19.55 (±4.59)	19.36 (±4.27)	19.17 (±4.60)	19.27 (±4.44)
Number of monthly headache days, mean (±SD)	21.54 (±4.10)	21.24 (±3.97)	21.44 (±4.10)	21.34 (±4.03)
MHD with acute medication use, mean (±SD)	15.51 (±6.57)	15.12 (±6.25)	14.49 (±6.25)*	14.81 (±6.25)
Number of monthly migraine attacks, mean (±SD)	6.23 (±2.03)	6.48 (±1.95)	6.30 (±2.08)	6.39 (±2.02)
Mean severity of monthly migraine headaches[b], mean (±SD)	2.15 (0.36)	2.16 (0.36)	2.16 (0.37)	2.16 (0.36)
Prior migraine preventive treatment, n (%)				
No	123 (22.04)	67 (24.10)	57 (20.58)	124 (22.34)
Yes	435 (77.96)	211 (75.90)	220 (79.42)	431 (77.66)
Yes and did not fail	59 (10.57)	25 (8.99)	31 (11.19)	56 (10.09)
Yes and failed ≥1	274 (49.10)	130 (46.76)	145 (52.35)	275 (49.55)
Yes and failed ≥2	163 (29.21)	68 (24.46)	97 (35.02)	165 (29.73)
Baseline medication overuse[c], n (%)	353 (63.38)	178 (64.26)	177 (64.13)	355 (64.20)
Concurrent prophylaxis use, n (%)	82 (14.70)	37 (13.31)	43 (15.52)	80 (14.41)
Propranolol	23 (4.12)	11 (3.96)	14 (5.05)	25 (4.50)
Topiramate	59 (10.57)	26 (9.35)	30 (10.83)	56 (10.09)
MIDAS total score, mean (±SD)	68.66 (±57.36)	62.46 (±49.48)	69.17 (±64.08)	65.81 (±57.29)
MSQ Role Function-Restrictive domain, mean (±SD)	38.37 (±17.18)	39.29 (±17.30)	38.93 (±17.31)	39.11 (±17.29)
PGI-S, mean (±SD)	4.91 (±1.22)	4.79 (±1.24)	4.87 (±1.31)	4.83 (±1.28)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; MHD = migraine headache day; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of intent-to-treat patients with nonmissing demographic measures; n = number of patients with each specific category; PGI-S = Patient Global Impression of Severity; SD = standard deviation.

[a] Asterisk (*) denotes p-value comparison vs. placebo <.05.

[b] Severity ratings were 1 = mild, 2 = moderate, and 3 = severe.

[c] Baseline medication overuse was based on use of acute headache medication reported in the ePRO diary.

With regard to disease characteristics, out of an average of 21.4 headache days per month, the overall mean number of MHDs was 19.4, with comparable distributions among groups. Average number of migraine headache hours per month was 136.0 and average number of migraine attacks per month was 6.3. Within the ITT population, the proportion of patients reporting migraine with or without aura at baseline **(as measured in the last 7 days)** was slightly in favour of the former type (54.2% vs 45.7% overall, without significant differences among treatment groups).

An average of 15.2 MHDs per month included any acute headache medication use and, of these, an average of 9.4 MHDs per month included triptan use (ranging from 0 to 29 MHDs per month). Criteria for medication overuse regarded 63.8% of patients overall, and the majority of patients (77.8%) reported using prior migraine preventive treatment, with 29.5% having failed 2 or more such treatments due to

lack of efficacy in the past 5 years, with higher proportions in the LY-240mg group (35.0%) with respect to placebo and LY-120mg group (29.2% and 24.5%, respectively). Although the protocol allowed for up to one-third of patients to continue on a stable dose of either topiramate or propranolol for concurrent migraine prophylaxis during the study, only 14.6% of patients elected to do so, with most of those on topiramate (10.3%) rather than propranolol (4.3%).

No statistically significant differences were observed regarding the overall mean of the number of migraine headache days with ergots use (n=0.67) , anti-nausea medication use (n=1.9), migraine headache hours (n=136.04 overall), migraine attacks (n=6.31), number of moderate-severe headache days (n=16.5), headache hours (n=145.17), ICHD migraine headache days (n=16.48), mean severity of migraine headaches (2.16), number of migraine days with aura (n=5.03).

However, statistically significant differences were observed for the following baseline characteristics:

- *years since migraine diagnosis*, higher in the placebo group with respect to LY240mg (mean values 22 years vs 20.1 years, respectively, p=.046) and LY_overall (mean 20.2 years, p=.024);

-*number of migraine headache days with abortive medication use* (15.51 for placebo, 14.5 for LY240mg, p=.031);

- *number of migraine headache days with:*

  - NSAIDS/Aspirin Use (12.24 for placebo, 11.32 and 10.88 for LY240mg and LY120mg, respectively, p=.028);

  - Acetaminophen/Paracetamol Use (7.83 for placebo vs 6.34 for LY240mg, p=.022 and LY120mg (8.19) vs LY240mg, p=.013);

- *number of migraine headache days with nausea or vomiting* in the placebo vs LY240mg groups (9.21 vs 8.13, p=.028, respectively)

- *number of migraine headache days with photophobia or phonophobia* in the placebo vs LY240mg groups (15.18 vs 13.98, p=.025, respectively).

The mean overall values of the measures of functioning, disability, and migraine disease state severity at baseline, including respectively MSQ Role-Function Restrictive score (38.7), total MIDAS score (67.2) and Mean PGI-S (4.9) were consistent with a chronic migraine population, without statistically significant differences observed among treatment groups

The most common preexisting conditions (≥10%) were seasonal allergy, drug hypersensitivity, insomnia, depression, anxiety, and back pain.

At least one **prior migraine preventive treatment** was reported by 77.8% of subjects overall (77.9% in the PBO treatment group vs 75.9% and 79.4% of LY120mg and 240mg groups, respectively, without statistically significant differences), with 29.5% having failed 2 or more such treatments due to lack of efficacy in the past 5 years. Among such treatments, the overall most commonly reported were topiramate (34.7%), amitriptyline (14.9%), propranolol (14.6%), ibuprofen (14.0%), botulinum toxin type A (12.9%), sumatriptan (10.3%), paracetamol (7.7%), thomapyrin N (7.2%), valproate sodium (5.8%), amitriptyline hydrochloride (5.9%), and nortriptyline (5.0%) without significant differences among treatment groups except for topiramate (placebo [35.8%] vs LY120mg [28.4%], p=.036). The most commonly reported reason for their discontinuation was inadequate response, followed by no response and medical history event, without statistically significant intergroup differences.

Concomitant Medication

The vast majority of all subjects reported at least one **concomitant medications** (89.8%, without statistically significant treatment group differences), the most commonly overall reported being ibuprofen (23.6%), paracetamol (16.0%), sumatriptan (11.9%), topiramate (10.3%), thomapyrin N (8.5%), without relevant significant differences even with other medications at much lower subject proportions. The above medications were also among the most frequently reported in the OL treatment phase (study period IV).

The concomitant medications used for the acute treatment of migraine as recorded by patients in the ePRO diary were accounted for as an efficacy measure (see later on for details).

With regard to the open-label treatment phase, as of the cutoff date 87.4% of patients used a concomitant therapy, with the most frequently used concomitant medications being ibuprofen (25.1%), paracetamol (15.6%), sumatriptan (12.6%), topiramate (10.2%), thomapyrin N (8.1%), with the exception of diphenhydramine hydrochloride and vitamin D NOS that were more frequently used (5.8% 5.0% overall, respectively.

- **Numbers analysed**

Of the 1113 patients in the ITT population, 1085 patients with nonmissing change in MHDs were analyzed for the primary efficacy measure.

In addition to presenting efficacy analyses from the completed 3-month double-blind treatment phase, some efficacy analyses containing up to 6 months of OL (ie, up to Month 9) were included by the Applicant.

- **Outcomes and estimation**

ePRO Diary Compliance

Table CGAI.14.14. ePRO Diary Compliance
Intent-to-Treat Population
Study Period III

Period	Treatment Group	N	Mean(SD)	Median	(Min, Max)	Subjects with >=80% Compliance n(%)	Subjects with <=50% Compliance n(%)	P-value *a vs 1)	P-value *a vs 2)
Baseline	1)Placebo	558	97.64 (4.74)	100.00	(77.50, 100.00)	557 (99.82)	0 (0.00)		
	2)LY120mg	278	97.52 (4.84)	100.00	(80.00, 100.00)	278 (100.00)	0 (0.00)	.759	
	3)LY240mg	277	98.09 (4.27)	100.00	(80.00, 100.00)	277 (100.00)	0 (0.00)	.190	.162
Month 1	1)Placebo	557	92.71 (15.98)	100.00	(3.33, 100.00)	496 (89.05)	22 (3.95)		
	2)LY120mg	278	94.66 (12.34)	100.00	(17.71, 100.00)	259 (93.17)	5 (1.80)	.057	
	3)LY240mg	277	95.31 (12.81)	100.00	(3.23, 100.00)	261 (94.22)	7 (2.53)	.014	.635
Month 2	1)Placebo	528	93.36 (13.58)	100.00	(4.26, 100.00)	474 (89.77)	14 (2.65)		
	2)LY120mg	273	91.59 (16.48)	100.00	(3.33, 100.00)	233 (85.35)	9 (3.30)	.100	
	3)LY240mg	272	94.31 (11.59)	100.00	(13.33, 100.00)	249 (91.54)	4 (1.47)	.351	.025
Month 3	1)Placebo	511	92.18 (13.77)	97.06	(3.33, 100.00)	447 (87.48)	13 (2.54)		
	2)LY120mg	263	92.51 (13.36)	100.00	(13.33, 100.00)	229 (87.07)	7 (2.66)	.667	
	3)LY240mg	267	92.51 (13.75)	100.00	(6.67, 100.00)	237 (88.76)	5 (1.87)	.703	.965
Average across month 1 to 3	1)Placebo	557	90.97 (16.32)	97.70	(3.33, 100.00)	481 (86.36)	22 (3.95)		
	2)LY120mg	278	91.82 (14.29)	98.81	(17.71, 100.00)	242 (87.05)	7 (2.52)	.398	
	3)LY240mg	277	93.46 (11.75)	98.77	(3.85, 100.00)	248 (89.53)	4 (1.44)	.022	.209

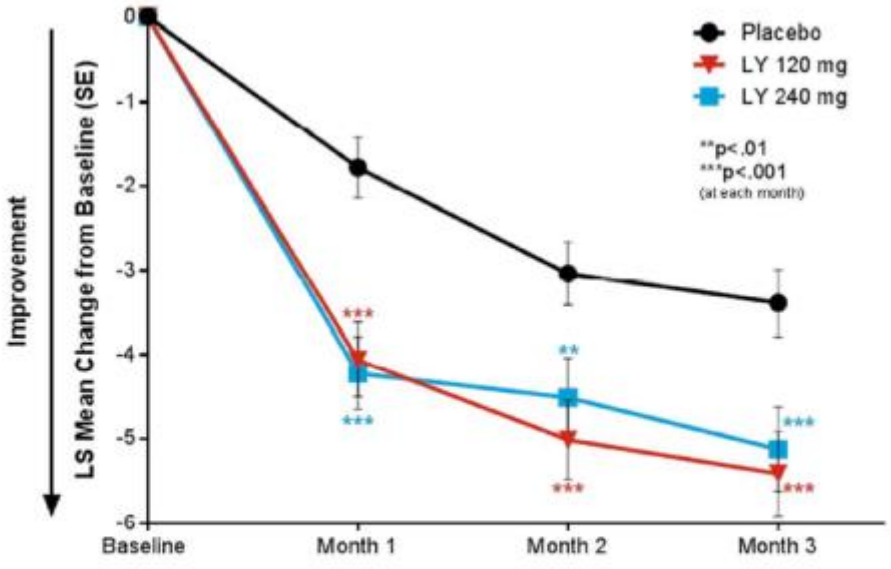
Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects with nonmissing ePRO diary compliance rate.
*a, ANOVA with treatment, pooled country, baseline medication overuse, and concurrent prophylaxis use.

Primary efficacy endpoint

Table CGAI.11.3. Change from Baseline in the Number of Migraine Headache Days
Repeated Measures Analysis
Intent-to-Treat Population
Study Period III

Period	Treatment	N	LS Mean Change from Baseline (SE)	95% CI	Within group P-value	vs 1) LS Mean Change Difference (SE)	95% CI	P-value
Month 1	1) Placebo	535	-1.78 (0.36)	(-2.49, -1.07)	<.001			
	2) LY120mg	273	-4.06 (0.44)	(-4.92, -3.20)	<.001	-2.28 (0.42)	(-3.10, -1.45)	<.001
	3) LY240mg	270	-4.22 (0.43)	(-5.07, -3.37)	<.001	-2.44 (0.42)	(-3.27, -1.61)	<.001
Month 2	1) Placebo	514	-3.04 (0.38)	(-3.79, -2.29)	<.001			
	2) LY120mg	264	-5.01 (0.47)	(-5.93, -4.09)	<.001	-1.97 (0.47)	(-2.90, -1.04)	<.001
	3) LY240mg	268	-4.51 (0.47)	(-5.42, -3.59)	<.001	-1.47 (0.47)	(-2.39, -0.54)	.002
Month 3	1) Placebo	498	-3.39 (0.40)	(-4.18, -2.59)	<.001			
	2) LY120mg	256	-5.41 (0.50)	(-6.40, -4.42)	<.001	-2.03 (0.52)	(-3.05, -1.00)	<.001
	3) LY240mg	262	-5.12 (0.50)	(-6.10, -4.14)	<.001	-1.73 (0.52)	(-2.76, -0.71)	<.001
Overall	1) Placebo	538	-2.74 (0.36)	(-3.45, -2.03)	<.001			
	2) LY120mg	273	-4.83 (0.44)	(-5.69, -3.97)	<.001	-2.09 (0.42)	(-2.92, -1.26)	<.001
	3) LY240mg	274	-4.62 (0.43)	(-5.47, -3.76)	<.001	-1.88 (0.42)	(-2.71, -1.05)	<.001

Abbreviations: LY = LY2951742; For a specific month, N = number of intent-to-treat subjects with nonmissing baseline value and nonmissing value for that month; For 'Overall', N = number of intent-to-treat subjects with nonmissing baseline value and at least one nonmissing postbaseline value; CI = confidence interval; LS = least square; SE = standard error.
MMRM model: Change = treatment, pooled country, baseline medication overuse, concurrent prophylaxis use, month, treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure.
The Kenward-Roger approximation was used to estimate denominator degrees of freedom.



Abbreviations: LS = Least Squares; LY = LY2951742/galcanezumab; SE = standard error.
Note: not statistically significant between LY doses at any month.

Figure CGAI.11.1. Change from baseline in the number of migraine headache days.

Effect size for change in migraine headache days:

					Comparison vs Placebo			
Measure	Time Frame	Treatment	N	LS Mean Change	LS Mean Change Difference	Standard Deviation	Effect Size	95% CI for Effect Size
Change from Baseline in Migraine Headache Days	Month 3	1)Placebo	498	-3.39				
		2)LY120mg	256	-5.41	-2.03	6.91	-0.29	(-0.44, -0.14)
		3)LY240mg	262	-5.12	-1.73	6.91	-0.25	(-0.40, -0.10)
	Overall	1)Placebo	538	-2.74				
		2)LY120mg	273	-4.83	-2.09	5.65	-0.37	(-0.52, -0.22)
		3)LY240mg	274	-4.62	-1.88	5.65	-0.33	(-0.48, -0.19)

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have nonmissing baseline value and at least one postbaseline value; CI = confidence interval; INF = infinity; NNT = Number Needed to Treat; SE = standard error.
Notes: (1) For change in monthly migraine headache days, MMRM model: Change = treatment, pooled country, baseline medication overuse, concurrent prophylaxis use, month, treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure.
(2) For response rate in migraine headache days: Categorical pseudo likelihood-based repeated measures model for binary outcome: Responder indicator = treatment, baseline medication overuse, concurrent prophylaxis use, month, treatment*month, and baseline. Confidence limits are computed by applying the inverse link transformation to the confidence limits on the logit scale and may be asymmetric. Estimates were obtained using chol covariance structure.
(3) The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Fisher's scoring algorithm was used.

Sensitivity analyses for the primary objective

- Sensitivity analysis for missing data assumptions

The potential impact of missing data assumptions was assessed by a series of worst-case scenarios analyses around the distribution of missing outcome data (missing outcome values imputed to be worse than expected, with no treatment benefit at all seen in missing outcomes data, i.e. delta method). In total, 9 sets of delta were used and the results were consistent with the primary efficacy analysis.

-Sensitivity analysis for normality assumption

To assess the validity of the primary MMRM results with respect to deviations from normality assumption, a sensitivity analysis for the raw number of MHDs (ie, the total number of MHDs for each interval without normalization to 30-day period) was conducted with a repeated measures negative binomial regression analysis. The results of this sensitivity analysis were consistent with the primary efficacy analysis ($p<.001$ at all comparisons of placebo vs both galcanezumab treated groups at each month).

A further sensitivity analysis was conducted on the studentized residuals from the primary analysis model, i.e. patients with outlier residuals removed. The outlier patients were 43 for placebo, 21 for LY120-mg, and 36 for LY240-mg. The results were consistent before and after removing patients with outlier residuals ($p<.001$ in the difference among both galcanezumab treated groups vs placebo).

- Post-hoc sensitivity analysis excluding patients with an eligibility related important protocol deviation

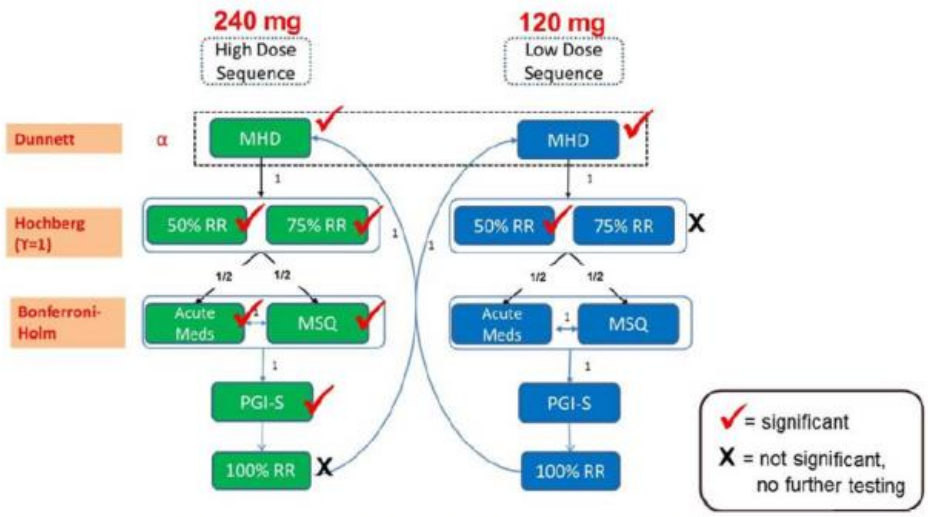
There were 36 ITT patients who were inadvertently enrolled and identified as having an important protocol deviation of inclusion/exclusion criteria not being met. Their exclusion did not modify the primary efficacy analysis.

- Post hoc sensitivity analysis using IWRS stratification factors for baseline medication overuse and concurrent prophylaxis use

There were 65 ITT patients with stratification errors for either baseline medication overuse or concurrent prophylaxis use, identified as having an important protocol deviation. After removing those subjects, the results of were consistent with the primary efficacy analysis.

Key Secondary Efficacy Analyses

After ensuring that the primary objective was met, the key secondary objectives were tested according to the predefined multiple testing procedure in order to provide strong control of the type I error rate, which resulted in the main points showed in the following picture:



Abbreviations: Acute Meds = MHD with the use of acute (abortive) treatment; MHD = the number of monthly migraine headache days (mean change from baseline); MSQ = Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive domain; PGI-S = Patient Global Impression of Severity; RR = response rate.

The results of the multiple testing procedure, including those gathered from each individual test with significance p levels before and after corrections, are provided in the tables below:

Table CGAI.11.4. Multiplicity testing results for primary and key secondary objectives (ITT Population, Study Period III)

Endpoint	Time Frame	Treatment	N	Comparison with Placebo			
				LSMean Change Difference/ Odds Ratio[a]	P-value	Adjusted Significance Level[b]	Significance
Monthly MHDs	Month 1 to 3	Placebo LY 120 mg LY 240 mg	538 273 274	 -2.09 -1.88	 <.001 <.001	 0.026 0.026	 S S
Monthly MHDs with Acute Medication Use	Month 1 to 3	Placebo LY 120 mg LY 240 mg	538 273 274	 -2.51 -2.01	 <.001 <.001	 0 0.0125	 Not Tested S
MSQ Role Function-Restrictive	Month 3	Placebo LY 120 mg LY 240 mg	494 252 253	 5.06 6.29	 <.001 <.001	 0 0.025	 Not Tested S
PGI-S Rating	Month 3	Placebo LY 120 mg LY 240 mg	494 252 253	 -0.14 -0.28	 0.181 0.006	 0 0.025	 Not Tested S
≥50% Response	Month 1 to 3	Placebo LY 120 mg LY 240 mg	538 273 274	 2.091 2.080	 <.001 <.001	 0.0125 0.025	 S S
≥75% Response	Month 1 to 3	Placebo LY 120 mg LY 240 mg	538 273 274	 1.604 2.039	 0.031 <.001	 0.025 0.025	 NS S

100% Response	Month 1 to 3	Placebo LY 120 mg LY 240 mg	538 273 274	1.367 2.612	0.597 0.058	0 0.025	Not Tested S

Abbreviations: LSMean = Least Squares Mean; LY = LY2951742/galcanezumab; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of intent-to-treat patients who had nonmissing baseline and at least one postbaseline value; NS = not significant; S = significant.
[a]Odds ratio is provided for response measures. For the other measures, LSMean change difference is provided.
[b]If p-value is less than or equal to the adjusted significance level, then the results are statistically significant after adjustment for multiplicity.

50%, 75%, and 100% Response Rate and NNT. ITT population

	Placebo N=538	LY 120 mg N=273				LY 240 mg N=274				
Response Rate	Model Estimated Rate, % (SE)	Model Estimated Rate, % (SE)	Odds Ratio vs. Placebo	NNT	95% C.I. for NNT	Model Estimated Rate, % (SE)	Odds Ratio vs. Placebo	95% CI for Odds Ratio	NNT	95% C.I. for NNT
≥30%	32.3 (2.1)	44.8 (2.9)	1.70			46.4 (2.9)	1.82	1.41, 2.34		
≥50%	15.4 (1.6)	27.6 (2.7)	2.09	8.2	5.4,16	27.5 (2.6)	2.08	1.55, 2.78	8.27	5.5,16
≥75%	4.5 (0.9)	7.0 (1.4)	1.60	39.5	(-INF,-166.6)U(16,INF)	8.8 (1.7)	2.04	1.36, 3.06	23.4	11.8, 119.8
100%	0.5 (0.3)	0.7 (0.4)	1.37			1.3 (0.6)	2.61	0.97, 7.04		

Exploratory responder analyses of MSQ Role function-restrictive domain

Response for the MSQ Role Function-Restrictive domain was defined as a change from baseline to Month 3 ≥17.14 points on the transformed 100-point scale, corresponding to a change of 6 points on the raw scale. There were statistically significantly greater percentages of patients meeting this definition of response in both the galcanezumab 120-mg and 240-mg treatment groups (64.3% and 64.8%, p=.003 and p=.002, respectively) compared with placebo (54.1%).

PGI-S

The overall mean reduction (improvement across Months 1 to 3) from baseline in PGI-S was significantly greater only in the LY240-mg treatment group compared with placebo (LS Mean change from baseline -0.48 for placebo vs -0.73 for LY-240mg treatment groups, p=.002), as well as at each month for such a dose. No statistically significant differences between the lower galcanezumab dose and placebo in the mean change in PGI-S rating were found at any month or overall.

Post hoc exploratory responder analysis for PGI-S

The analysis was conducted through a model estimating, at Month 3 of the DB treatment period, the percentages of patients meeting the definition of PGI-S response (i.e., those who at the specific visit had a severity decrease from baseline of at least 2 points on the 7-point scale) were not statistically significantly different between the two galcanezumab dose treatment groups (23.8% and 25.1%, for LY120-mg and LY240-mg, respectively) compared to placebo (19.5%), with p=.15 and p=.062, respectively. Statistically significant differences were found overall 3 months in both the galcanezumab 120-mg and 240-mg treatment groups (p=.048 and p=.014, respectively) compared to placebo.

Other Secondary Efficacy Analyses

Table CGAI.11.5. Additional Secondary Efficacy Analyses: Summary of Overall Results (Average of All 3 Months) ITT Population

	Placebo N=538	LY 120 mg N=273	LY 240 mg N=274
Change from Baseline in Number of Monthly Headache Days			
LSMean Change (SE)	-3.01 (0.35)	-4.84 (0.43)	-4.61 (0.43)
Diff. vs. Placebo (SE)		-1.84 (0.42)	-1.60 (0.42)
95% CI on Difference		-2.65, -1.02	-2.41, -0.78
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Moderate to Severe Headache Days			
LSMean Change (SE)	-2.92 (0.33)	-4.90 (0.40)	-4.64 (0.39)
Diff. vs. Placebo (SE)		-1.98 (0.38)	-1.72 (0.38)
95% CI on Difference		-2.73, -1.23	-2.47, -0.97
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly ICHD Migraine Headache Days (ie, Excluding Probable Migraine)			
LSMean Change (SE)	-2.27 (0.35)	-4.56 (0.43)	-4.06 (0.43)
Diff. vs. Placebo (SE)		-2.29 (0.41)	-1.79 (0.41)
95% CI on Difference		-3.10, -1.48	-2.60, -0.98
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Attacks			
LSMean Change (SE)	-1.47 (0.12)	-1.26 (0.14)	-1.63 (0.14)
Diff. vs. Placebo (SE)		0.21 (0.13)	-0.16 (0.13)
95% CI on Difference		-0.05, 0.48	-0.42, 0.11
p-value vs. placebo		.111	.243
Change from Baseline in Number of Monthly Migraine Headache Hours			
LSMean Change (SE)	-14.10 (3.83)	-36.20 (4.63)	-32.12 (4.59)
Diff. vs. Placebo (SE)		-22.10 (4.48)	-18.02 (4.46)
95% CI on Difference		-30.88,-13.32	-26.78, -9.26
p-value vs. placebo		<.001	<.001

Table CGAI.11.5. Additional Secondary Efficacy Analyses: Summary of Overall Results (continued)

Change from Baseline in Number of Monthly Headache Hours			
LSMean Change (SE)	-13.44 (3.91)	-36.15 (4.74)	-31.53 (4.70)
Diff. vs. Placebo (SE)		-22.71 (4.60)	-18.09 (4.58)
95% CI on Difference		-31.74, -13.69	-27.09, -9.09
p-value vs. placebo		<.001	<.001
Change from Baseline in Mean Severity of Remaining Migraine Headache Days[a]			
LSMean Change (SE)	-0.12 (0.02)	-0.19 (0.02)	-0.19 (0.02)
Diff. vs. Placebo (SE)		-0.07 (0.02)	-0.07 (0.02)
95% CI on Difference		-0.11, -0.03	-0.11, -0.03
p-value vs. placebo		<.001	<.001
Patient Global Impression of Improvement Rating[b]			
LSMean (SE)	3.43 (0.06)	3.05 (0.07)	2.99 (0.07)
Diff. vs. Placebo (SE)		-0.38 (0.07)	-0.44 (0.07)
95% CI on Difference		-0.52, -0.24	-0.58, -0.30
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of Triptans (additional analysis to support secondary objectives)			
LS Mean Change (SE)	-1.21 (0.27)	-3.20 (0.32)	-2.49 (0.32)
Diff. vs. Placebo (SE)		-1.99 (0.31)	-1.28 (0.13)
95% CI on Difference		-2.59, -1.38	-1.88, -0.67
p-value vs. placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of NSAIDs/Aspirin (additional analysis to support secondary objectives)			
LS Mean Change (SE)	-1.33 (0.32)	-3.33 (0.39)	-3.51 (0.39)
Diff. vs Placebo (SE)		-2.00 (0.37)	-2.18 (0.37)
95% CI on Difference		-2.74, -1.27	-2.91, -1.45
p-value vs placebo		<.001	<.001
Change from Baseline in Number of Monthly Migraine Headache Days with Use of Acetaminophen/Paracetamol (additional analysis to support secondary objectives)			
LS Mean Change (SE)	-1.04 (0.26)	-1.89 (0.32)	-1.65 (0.32)
Diff. vs. Placebo (SE)		-0.86 (0.31)	-0.61 (0.31)
95% CI on Difference		-1.46, -0.25	-1.21, -0.01
p-value vs. placebo		.005	.047

Abbreviations: CI = confidence interval; Diff. = difference; ICHD = International Classification of Headache Disorders; ITT = intent-to-treat; LS = Least Squares; LY = LY2951742/galcanezumab; N = number of intent-to-treat subjects with nonmissing baseline value and at least one nonmissing postbaseline value; NSAIDs = nonsteroidal anti-inflammatory drug; SE = standard error; vs. = versus.

[a] For Mean Severity of Remaining Migraine Headache Days, N=537 (placebo), N=273 (LY 120 mg), and N=274 (LY 240 mg)

[b] For Patient Global Impression of Improvement Rating, N=524 (placebo), N=269 (LY 120 mg), and N=267 (LY 240 mg)

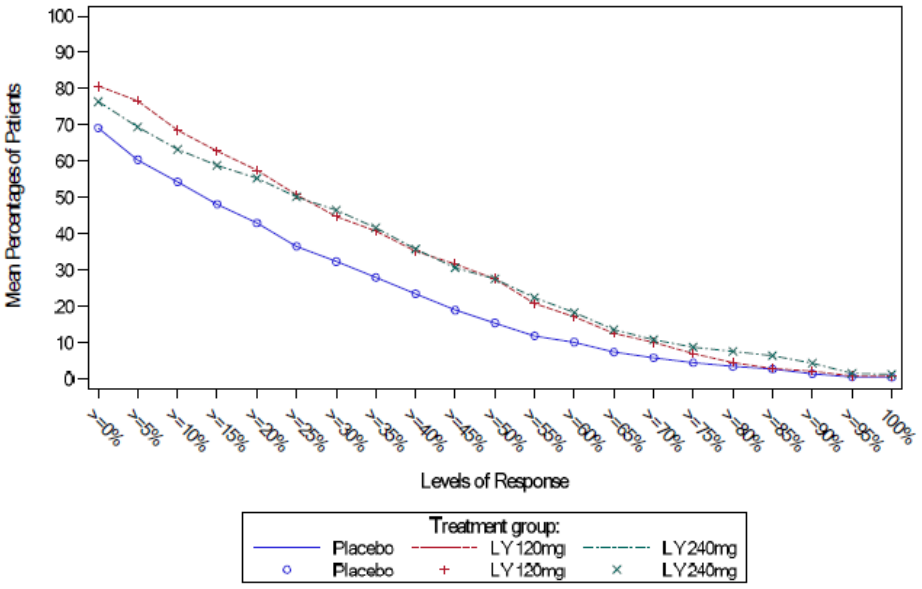
and for categorical measures:

Onset and maintenance of treatment effect

Both galcanezumab dose treatment groups reported significantly higher proportions compared to placebo at each month (p<.001) and at month 3 in the proportion of patients with 50% reduction from baseline, (with proportions 22.4%, 31.9%, and 34.0% for placebo, galcanezumab 120-mg and galcanezumab 240-mg treatment groups, respectively), and as such onset of treatment effect for the assessment of maintenance of efficacy was set at month 1.

When evaluated across all patients in the ITT population, a statistically significantly higher percentage of patients who maintained ≥50% response for all 3 months of the DB treatment phase was observed in each galcanezumab treatment group (16.9% and 14.6% for those on 120-mg and 240-mg, respectively) vs placebo (6.3%, p<.001 at both comparisons).

The distribution of response rates (i.e., the mean percentage of patients with different levels of reduction from baseline in monthly MHDs but over the 3-month double-blind treatment phase, based on estimates from a GLMM) is depicted in the graph below.



Abbreviation: LY = LY2951742.
Notes, (1) All data points in the table are estimated from GLIMMIX: Responder indicator = treatment, month, treatment* month, baseline MHD, baseline medication overuse, and concurrent prophylaxis use. (2) Mean Percentages of Patients are estimated percentages over months 1 to 3 from the GLIMMIX model.

Health outcomes measures (MSQ v2.1, MIDAS, HCRU and Employment Status)

- The MSQ, Healthcare resource utilization (HCRU), and employment status assessments were administered at baseline and monthly postbaseline visits, while the MIDAS was administered at baseline and Month 3 (the results from the multiple testing procedure for the MSQ Role Function-Restrictive are indicate in the above section on key secondaries).

- MSQ and MIDAS

Table CGAI.11.7 Summary of mean change results in health outcomes measures at Month 3 (ITT Population)

	Placebo	LY 120 mg	LY 240 mg
Change from Baseline in MSQ Total Score			
N	535	273	270
LSMean Change (SE)	14.55 (1.21)	20.51 (1.49)	20.49 (1.49)
Diff. vs. Placebo (SE)		5.96 (1.51)	5.93 (1.51)
95% CI on Difference		2.99, 8.93	2.96, 8.90
p-value vs. placebo		<.001	<.001
Change from Baseline in MSQ Role Function-Preventive Domain Score			
N	535	273	270
LSMean Change (SE)	10.98 (1.15)	17.98 (1.42)	16.07 (1.41)
Diff. vs. Placebo (SE)		7.00 (1.44)	5.09 (1.44)
95% CI on Difference		4.17, 9.83	2.26, 7.92
p-value vs. placebo		<.001	<.001

Change from Baseline in MSQ Emotional Function Domain Score			
N	535	273	270
LSMean Change (SE)	14.07 (1.55)	21.03 (1.91)	20.70 (1.90)
Diff. vs. Placebo (SE)		6.96 (1.94)	6.62 (1.93)
95% CI on Difference		3.16, 10.76	2.83, 10.42
p-value vs. placebo		<.001	<.001
Change from Baseline in MIDAS Total Score			
N	504	254	258
LSMean Change (SE)	-11.53 (3.38)	-20.27 (4.07)	-17.02 (4.05)
Diff. vs. Placebo (SE)		-8.74 (3.90)	-5.49 (3.88)
95% CI on Difference		-16.39, -1.08	-13.10, 2.12
p-value vs. placebo		.025	.157

Abbreviations: CI = confidence interval; Diff. = difference; ITT = intent-to-treat; LS = Least Squares; LY = LY2951742/galcanezumab; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of intent-to-treat patients with nonmissing baseline value and nonmissing value for Month 3 (MIDAS) or at least one postbaseline value (MSQ) ; SE = standard error; vs. = versus.

An overall greater mean improvement in patients' perception of their level of disability due to migraine as suggested by the MIDAS total score was statistically significantly different superior only for Galcanezumab 120 mg group (p=.025).

- Looking at the individual items of the MIDAS at the Month 3 assessment, a statistically significantly greater mean improvement from baseline for galcanezumab 120-mg and 240-mg treatment groups compared with placebo was observed on Q3 (number of days of missed household work [p=.019 and p=.036, respectively]), Q-A (number of days with headache [p=<.001 and p=.001, respectively]), and Q-B (pain score of headache, [both p<.001 versus placebo]).

- With regard to HRCU during the DB period (including change from baseline of the following: number of emergency room visits, number of times admitted to hospital, number of overnight hospital stays, number of other healthcare professional visits, number of healthcare professional visits related to migraine, number of other healthcare professional visits related to migraine), there were neither statistically significant differences between either galcanezumab treatment group and placebo for any of the above measures, nor significant changes in employment status during the pre-baseline to post-baseline period.

Exploratory responder analyses were conducted on MIDAS total score.

For the MIDAS total score, response was defined as having ⩾50% improvement from baseline to Month 3. The model estimated percentages of patients meeting this definition of response at Month 3 was statistically significantly greater in both the galcanezumab 120-mg and 240-mg treatment groups (48.8% and 45.0%) compared with placebo (35.8%).

Table CGAI.11.9. Summary of Migraine-Related Healthcare Resource Utilization Rates per 100 Patient-Years

Event	Placebo N=533		LY 120 mg N=269		LY 240 mg N=270	
	Baseline[a]	Treatment[a]	Baseline[a]	Treatment[a]	Baseline[a]	Treatment[a]
Healthcare Professional Visits	110.69	44.64	102.60	29.04	142.96	36.00
Emergency Room Visits	21.01	13.86	18.59	13.76	25.19	15.00
Admissions to Hospital	1.50	0	1.49	0	0.74	0
Overnight Hospital Stays	4.88	0	2.97	0	2.96	0

Abbreviations: LY = LY2951742/galcanezumab; N = number of intent-to-treat patients who have nonmissing baseline value and at least one postbaseline value.

[a] Refers to events per 100 patient-years based on data from the 6-months prior to randomization (Baseline) and the 3-month double-blind treatment period (Treatment).

- **Ancillary analyses**

Exploratory efficacy analyses

- Changes in migraine symptoms

At each month and overall, the mean reductions from baseline in number of monthly MHDs with nausea and/or vomiting, as well as photophobia and phonophobia, were statistically significantly greater in both the galcanezumab 120-mg and 240-mg treatment groups compared with placebo.

-Migraine with aura

At each month and overall, the mean reductions from baseline in number of monthly MHDs with aura were not statistically significantly different in either of the galcanezumab treatment groups compared with placebo. The mean reduction from baseline in number of monthly MHDs with prodromal symptoms other than aura was statistically significantly greater in both of the galcanezumab treatment groups compared with placebo overall and at each month except for Months 1 and 2 for the LY120-mg treatment group.

- Patients who failed previous prophylactic treatments

In patients who failed one or more prophylactic treatments for efficacy reasons, the treatment difference for the reduction of mean monthly MHDs observed between galcanezumab 120 mg and placebo was -3.54 days ($p < 0.001$) and between galcanezumab 240 mg and placebo -1.37 days ($p < 0.05$). In patients failing two or more prophylactic treatments, the treatment difference was -4.48 days ($p < 0.001$) between 120 mg and placebo and -1.86 days ($p < 0.01$) between 240 mg and placebo.

OPEN-LABEL treatment phase

- **Numbers analysed and ePRO Compliance**

As of the data cutoff date of 16 March 2017, a total of 795 patients had evaluable ePRO diary data at Month 6 (397 placebo/LY; 194 LY120mg/LY; 204 LY240mg/LY), 447 had such data at Month 9 (228 placebo/LY; 108 LY120mg/LY; 111 LY240mg/LY), and 145 had such data at Month 12 (77 placebo/LY; 34 LY120mg/LY; 34 LY240mg/LY). On average, 84% of all patients in the three treatment groups had daily diary compliance ≥80% through Month 10, and approximately 81% of them were ≥80% compliant at Months 12.

As of the cutoff date 16 Mar 2017, according to the Table CGAI.14.79 neither the overall proportions of patients with evaluable ePRO diary data at each assigned group nor the proportions of compliant subjects at month level correspond to the figures indicated in the body text of study CGAI. The applicant should provide explanations for such a discrepancy, indicating which are the figures to be considered and if any potential implication for the interpretation of study data is derived from this apparent confusion **(OC)**.

Primary and key secondary endpoints of change in MHDs

- Reduction in Number of Migraine Headache Days

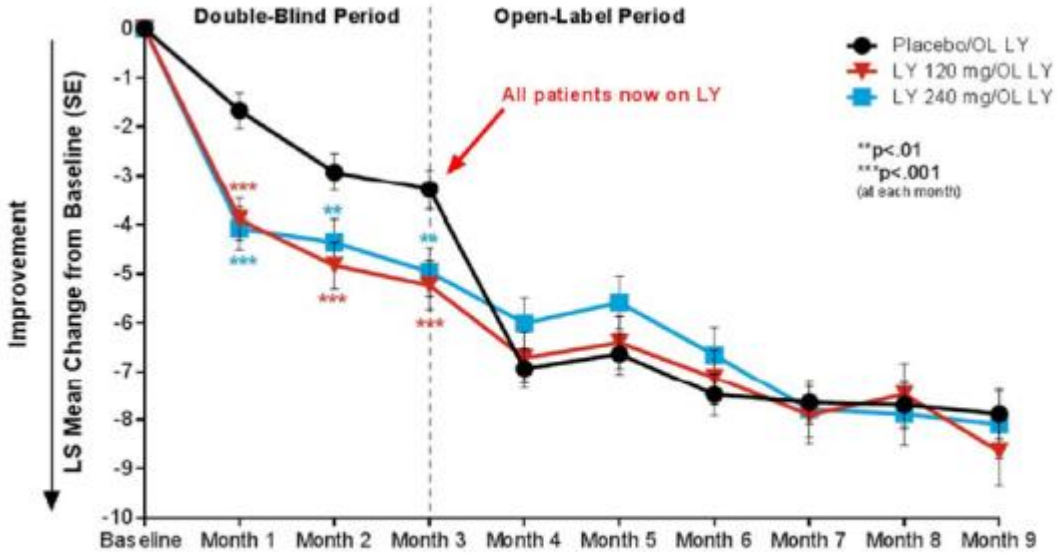
The repeated measures analysis of change in the number of monthly MHDs on the full 9 months period (i.e., data from the 3 months DB and ongoing 6 months OL) showed the following results:

Table CGAI.14.80. Change from Baseline in the Number of Migraine Headache Days – up to Month 9
Repeated Measures Analysis
Intent-to-Treat Population
Study Period III/IV

Period	Treatment Group in DB Phase	N	LS Mean Change from Baseline (SE)	95% CI	Within group P-value	vs 1) LS Mean Change Difference (SE)	vs 1) 95% CI	vs 1) P-value
Month 1	1)Placebo	535	-1.67 (0.36)	(-2.38, -0.97)	<.001			
	2)LY120mg	273	-3.90 (0.43)	(-4.75, -3.05)	<.001	-2.23 (0.42)	(-3.06, -1.40)	<.001
	3)LY240mg	270	-4.08 (0.43)	(-4.93, -3.23)	<.001	-2.40 (0.42)	(-3.23, -1.57)	<.001
Month 2	1)Placebo	514	-2.93 (0.38)	(-3.68, -2.19)	<.001			
	2)LY120mg	264	-4.83 (0.47)	(-5.75, -3.92)	<.001	-1.90 (0.47)	(-2.83, -0.97)	<.001
	3)LY240mg	268	-4.36 (0.46)	(-5.27, -3.45)	<.001	-1.42 (0.47)	(-2.35, -0.50)	.003
Month 3	1)Placebo	498	-3.29 (0.40)	(-4.08, -2.51)	<.001			
	2)LY120mg	256	-5.23 (0.50)	(-6.22, -4.25)	<.001	-1.94 (0.52)	(-2.97, -0.92)	<.001
	3)LY240mg	262	-4.96 (0.50)	(-5.93, -3.98)	<.001	-1.67 (0.52)	(-2.69, -0.65)	.001
Month 4	1)Placebo	483	-6.93 (0.41)	(-7.74, -6.12)	<.001			
	2)LY120mg	253	-6.71 (0.52)	(-7.73, -5.69)	<.001	0.22 (0.55)	(-0.86, 1.30)	.691
	3)LY240mg	254	-6.00 (0.52)	(-7.02, -4.99)	<.001	0.93 (0.55)	(-0.15, 2.00)	.092
Month 5	1)Placebo	455	-6.63 (0.42)	(-7.46, -5.80)	<.001			
	2)LY120mg	230	-6.40 (0.54)	(-7.45, -5.34)	<.001	0.24 (0.57)	(-0.89, 1.36)	.680
	3)LY240mg	230	-5.58 (0.54)	(-6.63, -4.53)	<.001	1.05 (0.57)	(-0.07, 2.18)	.067
Month 6	1)Placebo	397	-7.48 (0.44)	(-8.33, -6.62)	<.001			
	2)LY120mg	194	-7.12 (0.56)	(-8.22, -6.01)	<.001	0.36 (0.61)	(-0.83, 1.55)	.554
	3)LY240mg	204	-6.65 (0.56)	(-7.74, -5.56)	<.001	0.83 (0.60)	(-0.35, 2.01)	.169
Month 7	1)Placebo	349	-7.64 (0.45)	(-8.52, -6.75)	<.001			
	2)LY120mg	163	-7.90 (0.59)	(-9.06, -6.75)	<.001	-0.26 (0.64)	(-1.52, 1.00)	.682
	3)LY240mg	172	-7.79 (0.58)	(-8.93, -6.65)	<.001	-0.15 (0.64)	(-1.40, 1.09)	.809
Month 8	1)Placebo	287	-7.69 (0.49)	(-8.65, -6.73)	<.001			
	2)LY120mg	137	-7.48 (0.65)	(-8.76, -6.21)	<.001	0.21 (0.72)	(-1.21, 1.63)	.775
	3)LY240mg	145	-7.88 (0.64)	(-9.13, -6.63)	<.001	-0.19 (0.71)	(-1.60, 1.21)	.787
Month 9	1)Placebo	228	-7.88 (0.52)	(-8.90, -6.85)	<.001			
	2)LY120mg	108	-8.65 (0.70)	(-10.02, -7.27)	<.001	-0.77 (0.79)	(-2.32, 0.78)	.330
	3)LY240mg	111	-8.10 (0.69)	(-9.46, -6.74)	<.001	-0.22 (0.78)	(-1.76, 1.32)	.780

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have nonmissing baseline value and nonmissing value for a specific month; CI = confidence interval; DB = double-blind; LS = least square; SE = standard error.
MMRM model: Change = treatment, pooled country, baseline medication overuse, concurrent prophylaxis use, month, treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure.
The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Figure CGAI.11.4. Change from baseline in the number of migraine headache days including data from the ongoing open-label phase (up to Month 9) (MMRM analysis)



Abbreviations: LS=Least Squares; LY=LY2951742/galcanezumab; MMRM = mixed model repeated measures; OL=open-label; SE=standard error.
Note: MMRM model same as primary outcome, but out to 9 months.

According to the dosing scheme adopted in the OL phase and to maintain the blinding to previous treatment group, at the last visit of DB period (V7, Month 3) all patients received a LY240-mg loading dose (2 injections), and then **all patients were started on the 120-mg maintenance dose** (1 injection) at the first visit of OL period (V8, Month 4) to encourage use of the lower dose. Starting at V9 (Month 5), patients were flexibly dosed (1 or 2 injections) at the investigator's discretion, resulting in 64.3% of patients switched to the LY240-mg dose, and up to 75.8% of patients receiving the 240-mg dose thereafter.

- Response Analyses Based on Reduction in Migraine Headache Days

Proportion of patients with ≥50% reduction from baseline in monthly MHDs was analyzed using repeated measures methodology on the data from the completed double-blind and ongoing openlabel phases combined up to Month 9.

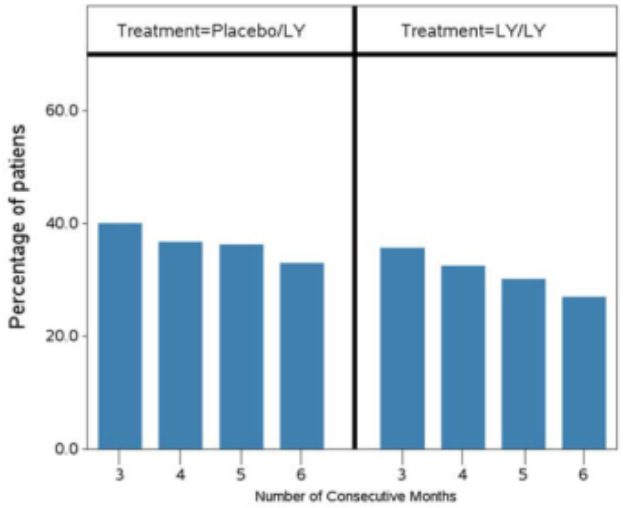
Table CGAI.14.82. Estimated Proportion of 50% Responders for Migraine Headache Days – Up to Month 9
Repeated Measures Analysis
Intent-to-Treat Population
Study Period III/IV

Period	Treatment Group in DB Phase	N	n (Raw Rate)	Model Estimated Rate (SE)	95% CI of Estimated Rate	vs 1) Odds Ratio	vs 1) 95% CI for Odds Ratio	vs 1) P-value	vs 2) Odds Ratio	vs 2) 95% CI for Odds Ratio	vs 2) P-value
Month 1	1)Placebo	535	59 (0.110)	0.098 (0.013)	(0.075, 0.126)						
	2)LY120mg	273	72 (0.264)	0.232 (0.027)	(0.184, 0.289)	2.790	(1.903, 4.091)	<.001			
	3)LY240mg	270	64 (0.237)	0.208 (0.025)	(0.163, 0.263)	2.429	(1.645, 3.587)	<.001	0.871	(0.588, 1.289)	.488
Month 2	1)Placebo	514	91 (0.177)	0.159 (0.017)	(0.128, 0.196)						
	2)LY120mg	264	81 (0.307)	0.272 (0.029)	(0.218, 0.332)	1.970	(1.389, 2.794)	<.001			
	3)LY240mg	268	84 (0.313)	0.279 (0.029)	(0.226, 0.340)	2.047	(1.447, 2.897)	<.001	1.039	(0.715, 1.511)	.840
Month 3	1)Placebo	498	123 (0.247)	0.221 (0.020)	(0.184, 0.263)						
	2)LY120mg	256	90 (0.352)	0.312 (0.031)	(0.255, 0.376)	1.599	(1.151, 2.223)	.005			
	3)LY240mg	262	97 (0.370)	0.335 (0.031)	(0.277, 0.399)	1.776	(1.284, 2.458)	<.001	1.111	(0.774, 1.595)	.569
Month 4	1)Placebo	483	233 (0.482)	0.454 (0.026)	(0.403, 0.506)						
	2)LY120mg	253	107 (0.423)	0.380 (0.033)	(0.318, 0.447)	0.737	(0.541, 1.005)	.054			
	3)LY240mg	254	107 (0.421)	0.391 (0.033)	(0.329, 0.458)	0.773	(0.568, 1.052)	.102	1.048	(0.734, 1.496)	.796
Month 5	1)Placebo	455	191 (0.420)	0.393 (0.026)	(0.344, 0.445)						
	2)LY120mg	230	101 (0.439)	0.396 (0.034)	(0.331, 0.464)	1.012	(0.737, 1.389)	.943			
	3)LY240mg	230	100 (0.435)	0.395 (0.034)	(0.331, 0.463)	1.009	(0.735, 1.384)	.958	0.997	(0.693, 1.435)	.987
Month 6	1)Placebo	397	192 (0.484)	0.461 (0.028)	(0.407, 0.516)						
	2)LY120mg	194	93 (0.479)	0.421 (0.037)	(0.351, 0.495)	0.851	(0.609, 1.190)	.345			
	3)LY240mg	204	96 (0.471)	0.446 (0.036)	(0.376, 0.518)	0.939	(0.675, 1.308)	.711	1.104	(0.752, 1.620)	.614
Month 7	1)Placebo	349	182 (0.521)	0.498 (0.029)	(0.442, 0.555)						
	2)LY120mg	163	85 (0.521)	0.455 (0.039)	(0.380, 0.533)	0.842	(0.590, 1.201)	.342			
	3)LY240mg	172	92 (0.535)	0.523 (0.039)	(0.447, 0.599)	1.105	(0.777, 1.573)	.578	1.313	(0.871, 1.979)	.193
Month 8	1)Placebo	287	148 (0.516)	0.492 (0.030)	(0.434, 0.551)						
	2)LY120mg	137	72 (0.526)	0.458 (0.041)	(0.379, 0.539)	0.871	(0.600, 1.265)	.469			
	3)LY240mg	145	75 (0.517)	0.504 (0.041)	(0.425, 0.583)	1.048	(0.725, 1.515)	.802	1.203	(0.784, 1.847)	.398
Month 9	1)Placebo	228	123 (0.539)	0.510 (0.033)	(0.447, 0.574)						
	2)LY120mg	108	61 (0.565)	0.518 (0.045)	(0.430, 0.606)	1.033	(0.683, 1.560)	.879			
	3)LY240mg	111	60 (0.541)	0.503 (0.045)	(0.416, 0.590)	0.970	(0.645, 1.459)	.884	0.939	(0.583, 1.513)	.797

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects with nonmissing baseline value and nonmissing value for a specific month; n = number of responders among N; CI = confidence interval; SE = standard error.
Categorical pseudo likelihood-based repeated measures model for binary outcome: Responder indicator = treatment, baseline medication overuse, concurrent prophylaxis use, month, and treatment*month, and baseline.
Confidence limits are computed by applying the inverse link transformation to the confidence limits on the logit scale and may be asymmetric. Estimates were obtained using unstructured covariance structure.
The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Maintenance of response during the open-label treatment phase was evaluated using different definitions and subsets of patients. An analysis for maintenance of response defined by meeting ≥50% response at any time and subsequently maintaining ≥40% response until each patient's endpoint was conducted through 6 months of open-label treatment:

Figure CGAI.11.5 Percentages of patients who met ≥50% response at any time and subsequently maintained ≥40% response for ≥3, 4, 5, or 6 consecutive months until the patient's endpoint during open-label treatment.



Abbreviations: LY = galcanezumab; OL = open-label treatment phase.
Note: Denominator is number of intent-to-treat subjects who entered OL with nonmissing baseline before randomization and with at least 1 postbaseline value for migraine headache days during the OL treatment phase. On y axis, 3, 4, 5, and 6 represents ≥3, 4, 5, or 6 consecutive months.

- *PGI-S*

A repeated measures analysis of change in PGI-S rating was conducted using data from the double-blind and ongoing open-label phases combined up to Month 9

Table CGAI.14.86. Change from Baseline in Patient Global Impression of Severity – Up to Month 9
Repeated Measures Analysis
Intent-to-Treat Population
Study Period III/IV

Period	Treatment Group in DB Phase	N	LS Mean Change from Baseline (SE)	95% CI	Within group P-value	vs 1) LS Mean Change Difference (SE)	vs 1) 95% CI	vs 1) P-value
Month 1	1)Placebo	510	-0.23 (0.07)	(-0.38, -0.09)	.002			
	2)LY120mg	267	-0.39 (0.09)	(-0.57, -0.21)	<.001	-0.16 (0.09)	(-0.34, 0.02)	.089
	3)LY240mg	263	-0.47 (0.09)	(-0.65, -0.30)	<.001	-0.24 (0.09)	(-0.42, -0.06)	.009
Month 2	1)Placebo	508	-0.53 (0.08)	(-0.68, -0.38)	<.001			
	2)LY120mg	256	-0.62 (0.09)	(-0.80, -0.43)	<.001	-0.08 (0.10)	(-0.27, 0.11)	.396
	3)LY240mg	263	-0.80 (0.09)	(-0.98, -0.61)	<.001	-0.26 (0.10)	(-0.45, -0.08)	.006
Month 3	1)Placebo	494	-0.61 (0.08)	(-0.76, -0.45)	<.001			
	2)LY120mg	252	-0.75 (0.10)	(-0.94, -0.55)	<.001	-0.14 (0.10)	(-0.34, 0.06)	.169
	3)LY240mg	255	-0.91 (0.10)	(-1.10, -0.71)	<.001	-0.30 (0.10)	(-0.50, -0.10)	.003
Month 4	1)Placebo	457	-1.10 (0.08)	(-1.26, -0.94)	<.001			
	2)LY120mg	232	-0.94 (0.10)	(-1.14, -0.73)	<.001	0.16 (0.11)	(-0.05, 0.38)	.143
	3)LY240mg	242	-1.10 (0.10)	(-1.30, -0.89)	<.001	0.01 (0.11)	(-0.21, 0.22)	.960
Month 5	1)Placebo	408	-1.18 (0.09)	(-1.34, -1.01)	<.001			
	2)LY120mg	201	-0.97 (0.11)	(-1.19, -0.76)	<.001	0.20 (0.12)	(-0.03, 0.43)	.082
	3)LY240mg	212	-1.11 (0.11)	(-1.32, -0.90)	<.001	0.07 (0.12)	(-0.16, 0.29)	.566

Month 6	1)Placebo	356	-1.33 (0.09)	(-1.50, -1.16)	<.001			
	2)LY120mg	174	-1.14 (0.11)	(-1.36, -0.93)	<.001	0.18 (0.12)	(-0.05, 0.42)	.123
	3)LY240mg	183	-1.16 (0.11)	(-1.38, -0.95)	<.001	0.17 (0.12)	(-0.07, 0.40)	.159
Month 7	1)Placebo	294	-1.36 (0.09)	(-1.54, -1.19)	<.001			
	2)LY120mg	137	-1.15 (0.12)	(-1.37, -0.92)	<.001	0.22 (0.13)	(-0.03, 0.47)	.082
	3)LY240mg	147	-1.30 (0.11)	(-1.53, -1.08)	<.001	0.06 (0.12)	(-0.18, 0.30)	.629
Month 8	1)Placebo	230	-1.50 (0.09)	(-1.68, -1.32)	<.001			
	2)LY120mg	110	-1.11 (0.12)	(-1.35, -0.87)	<.001	0.39 (0.13)	(0.13, 0.65)	.004
	3)LY240mg	113	-1.48 (0.12)	(-1.71, -1.24)	<.001	0.02 (0.13)	(-0.24, 0.28)	.857
Month 9	1)Placebo	177	-1.37 (0.10)	(-1.56, -1.17)	<.001			
	2)LY120mg	85	-1.40 (0.13)	(-1.66, -1.14)	<.001	-0.03 (0.15)	(-0.32, 0.26)	.827
	3)LY240mg	87	-1.43 (0.13)	(-1.68, -1.17)	<.001	-0.06 (0.15)	(-0.34, 0.23)	.690

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have nonmissing baseline value and nonmissing value for a specific month; CI = confidence interval; DB = double-blind; LS = least square; SE = standard error.
MMRM model: Change = treatment, pooled country, baseline medication overuse, concurrent prophylaxis use, month, treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure.
The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

- MSQ Role Function-Restrictive Domain

A repeated measures analysis of change from baseline in the MSQ Role Function-Restrictive domain score was conducted using data from the double-blind and ongoing open-label phases combined up to Month 9.

Table CGAI.14.87. Change from Baseline in Quality of Life Measures: MSQ Role Function-Restrictive – Up to Month 9
Repeated Measures Analysis
Intent-to-Treat Population
Study Period III/IV

						vs 1)		
Period	Treatment Group in DB Phase	N	LS Mean Change from Baseline (SE)	95% CI	Within group P-value	LS Mean Change Difference (SE)	95% CI	P-value
Month 1	1)Placebo	510	11.96 (1.18)	(9.65, 14.28)	<.001			
	2)LY120mg	267	17.54 (1.45)	(14.70, 20.39)	<.001	5.58 (1.47)	(2.70, 8.46)	<.001
	3)LY240mg	263	19.49 (1.45)	(16.65, 22.33)	<.001	7.52 (1.47)	(4.63, 10.42)	<.001
Month 2	1)Placebo	508	15.20 (1.22)	(12.80, 17.60)	<.001			
	2)LY120mg	256	20.09 (1.53)	(17.09, 23.08)	<.001	4.89 (1.58)	(1.79, 7.99)	.002
	3)LY240mg	263	22.69 (1.52)	(19.71, 25.66)	<.001	7.49 (1.57)	(4.40, 10.58)	<.001
Month 3	1)Placebo	494	16.18 (1.23)	(13.77, 18.60)	<.001			
	2)LY120mg	252	21.23 (1.54)	(18.21, 24.24)	<.001	5.04 (1.60)	(1.91, 8.18)	.002
	3)LY240mg	255	22.61 (1.53)	(19.62, 25.61)	<.001	6.43 (1.59)	(3.31, 9.55)	<.001
Month 4	1)Placebo	457	29.31 (1.29)	(26.77, 31.85)	<.001			
	2)LY120mg	232	25.35 (1.63)	(22.14, 28.55)	<.001	-3.96 (1.73)	(-7.36, -0.57)	.022
	3)LY240mg	242	25.47 (1.61)	(22.31, 28.63)	<.001	-3.84 (1.72)	(-7.21, -0.47)	.025
Month 5	1)Placebo	408	26.03 (1.33)	(23.43, 28.63)	<.001			
	2)LY120mg	201	25.19 (1.70)	(21.86, 28.52)	<.001	-0.84 (1.81)	(-4.39, 2.71)	.642
	3)LY240mg	212	21.38 (1.66)	(18.12, 24.64)	<.001	-4.65 (1.78)	(-8.15, -1.15)	.009
Month 6	1)Placebo	356	30.29 (1.31)	(27.73, 32.85)	<.001			
	2)LY120mg	174	31.07 (1.67)	(27.80, 34.34)	<.001	0.78 (1.76)	(-2.68, 4.23)	.660
	3)LY240mg	183	27.16 (1.63)	(23.96, 30.37)	<.001	-3.13 (1.74)	(-6.54, 0.28)	.072
Month 7	1)Placebo	293	29.30 (1.38)	(26.59, 32.00)	<.001			
	2)LY120mg	137	28.44 (1.81)	(24.90, 31.99)	<.001	-0.85 (1.95)	(-4.68, 2.97)	.661
	3)LY240mg	147	27.56 (1.76)	(24.11, 31.01)	<.001	-1.74 (1.91)	(-5.49, 2.01)	.363
Month 8	1)Placebo	230	29.31 (1.46)	(26.44, 32.18)	<.001			
	2)LY120mg	110	28.63 (1.93)	(24.85, 32.42)	<.001	-0.68 (2.12)	(-4.84, 3.48)	.748
	3)LY240mg	113	28.54 (1.90)	(24.81, 32.26)	<.001	-0.78 (2.10)	(-4.90, 3.35)	.712
Month 9	1)Placebo	177	31.14 (1.49)	(28.22, 34.06)	<.001			
	2)LY120mg	85	32.70 (1.97)	(28.84, 36.56)	<.001	1.56 (2.16)	(-2.69, 5.81)	.471
	3)LY240mg	87	29.80 (1.95)	(25.98, 33.62)	<.001	-1.34 (2.15)	(-5.57, 2.89)	.535

Abbreviations: LY = LY2951742; N = number of intent-to-treat subjects who have nonmissing baseline value and nonmissing value for a specific month; CI = confidence interval; DB = double-blind; LS = least square; SE = standard error.
MMRM model: Change = treatment, pooled country, baseline medication overuse, concurrent prophylaxis use, month, treatment*month, baseline, and baseline*month. Estimates were obtained using unstructured covariance structure.
The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well

as the benefit risk assessment (see later sections).

Table 10 - **Summary of efficacy for trial I5Q-MC-CGAG**

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Migraine – the EVOLVE-1 Study				
Study identifier	**I5Q-MC-CGAG**			
Design	*Phase 3, multicentre, randomised, double-blind, placebo-controlled study to compare the efficacy and safety of 2 doses of galcanezumab (120 or 240 mg/month) with placebo in the prevention of migraine headache in patients with episodic migraine (with or without aura). The study consisted of 4 periods, including a 6-month treatment phase and a 4-month post- treatment follow-up phase (washout).*			
	Duration of run-in phase: Duration of main phase: Duration of extension phase (washout):			30-40 days 6 months 4 months
Hypothesis	Superiority			
Treatment groups (randomised patients with at least one injection)	Galcanezumab 120 mg s.c., once monthly (with a 240-mg loading dose)			213
	Galcanezumab 240 mg subcutaneous, once monthly			212
	Placebo subcutaneous, once monthly			433
Endpoints and definitions	Primary endpoint	Migraine headache days (MHDs)	Overall mean change from baseline in the number of monthly MHDs during the 6-month	
	Key secondary endpoints	≥50%,≥75%, and 100% response rates	Mean percentages of patients with reduction from baseline ≥50%, ≥75%, and 100% in monthly MHDs during the 6-month double-blind	
		MHDs with acute medication use	Overall mean change from baseline in the number of monthly MHDs with acute medication use for treatment of migraine or headache during the 6- month double-blind period	
		Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1 Role Function-Restrictive Score	Mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score (average of Months 4, 5, and 6)	
		Patient Global Impression of Severity (PGI-S)	Mean change from baseline in the PGI-S rating (average of Months 4, 5, and 6)	
	Other secondary endpoints	≥30% response rate	Mean percentages of patients with reduction from baseline ≥30% in monthly MHDs during the 6-month double-blind period	
Database lock: 28 April 2017				
Results and Analysis				
Primary Analysis				

Overall mean change in monthly MHDs across Months 1 to 6	Treatment group (number of subjects)	PBO N=425	GMB 120 mg N=210	GMB 240 mg N=208
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-2.81 (0.24)	-4.73 (0.29) -1.92 (0.28) -2.48, -1.37 <.001	-4.57 (0.29) -1.76 (0.28) -2.31, -1.20 <.001
Key secondary endpoint:				
Mean percentage of ≥50% responders for migraine headache days over 6 months	Treatment group	PBO	GMB 120 mg	GMB 240 mg
	number of subjects)	N=425	N=210	N=208

	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	38.6 (1.7)	62.3 (2.4) 2.63 2.05, 3.37 <.001	60.9 (2.5) 2.48 1.94, 3.18 <.001
Mean percentage of ≥75% responders for migraine headache days over 6 months	Treatment group (number of subjects)	PBO N=425	GMB 120 mg N=210	GMB 240 mg N=208
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	19.3 (1.4)	38.8 (2.4) 2.65 2.04, 3.45 <.001	38.5 (2.4) 2.62 2.01, 3.41 <.001
Mean percentage of 100% responders for migraine headache days over 6 months	Treatment group (number of subjects)	PBO N=425	GMB 120 mg N=210	GMB 240 mg N=208
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	6.2 (0.8)	15.6 (1.6) 2.80 1.96, 4.01 <.001	14.6 (1.6) 2.61 1.81, 3.75 <.001
Overall mean change in monthly MHDs with acute medication use across Months 1 to 6	Treatment group (number of subjects)	PBO N=425	GMB 120 mg N=210	GMB 240 mg N=208
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-2.15 (0.21)	-3.96 (0.25) -1.81 (0.24) -2.28, -1.33 <.001	-3.76 (0.26) -1.61 (0.24) -2.09, -1.14 <.001
Mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score (average of Months 4, 5, and 6)	Treatment group (number of subjects)	PBO N=377	GMB 120 mg N=189	GMB 240 mg N=184
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	24.69 (1.07)	32.43 (1.31) 7.74 (1.29) 5.20, 10.28 <.001	32.09 (1.32) 7.40 (1.31) 4.83, 9.97 <.001
Mean change from baseline in the PGI-S rating (average of Months 4, 5, and 6)	Treatment group (number of subjects)	PBO N=377	GMB 120 mg N=189	GMB 240 mg N=184
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-1.27 (0.08)	-1.59 (0.10) -0.32 (0.10) -0.52, -0.12 .002	-1.55 (0.10) -0.28 (0.10) -0.48, -0.07 .008
Additional secondary endpoint:				
Mean percentage of ≥30% responders for migraine headache days over 6 months	Treatment group (number of subjects)	PBO N=425	GMB 120 mg N=210	GMB 240 mg N=208
	Estimated Rate, % (SE) Odds ratio vs PBO 95% CI on odds ratio P-value vs placebo	56.8 (1.8)	77.1 (2.1) 2.56 1.94, 3.37 <.001	74.3 (2.2) 2.20 1.68, 2.88 <.001

Table 11 - Summary of efficacy for trial I5Q-MC-CGAH

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Migraine – the EVOLVE-2 Study	
Study identifier	**I5Q-MC-CGAH**
Design	*Study I5Q-MC-CGAH was a Phase 3, multicentre, randomised, double-blind, placebo-controlled study to compare the efficacy and safety of 2 doses of galcanezumab (120 or 240 mg/month) with placebo in the prevention of migraine headache in patients with episodic migraine (with or without aura). The study consisted of 4 periods, including a 6-month treatment phase and a 4-month post- treatment follow-up phase (washout).*

	Duration of main phase: Duration of run-in phase: Duration of extension phase:	6 months not applicable not applicable	
Hypothesis	Superiority		
Treatment groups and number of randomised patients with at least one injection	Galcanezumab 120 mg s.c., once monthly (with a 240-mg loading dose)		226
	Galcanezumab 240 mg s.c., once monthly		220
	Placebo s.c., once monthly		450
Endpoints and definitions	Primary endpoint	Migraine headache days (MHDs)	Overall mean change from baseline in the number of monthly MHDs during the 6-month
	Key secondary endpoints	≥50%,≥75%, and 100% response rates	Mean percentages of patients with reduction from baseline ≥50%, ≥75%, and 100% in monthly MHDs during the 6-month double-blind
		MHDs with acute medication use	Overall mean change from baseline in the number of monthly MHDs with acute medication use for treatment of migraine or headache during the 6- month double-blind period
		Migraine-Specific Quality of Life Questionnaire (MSQ) version 2.1 Role Function-Restrictive Score	Mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score (average of Months 4, 5, and 6)
		Patient Global Impression of Severity (PGI-S)	Mean change from baseline in the PGI-S rating (average of Months 4, 5, and 6)
Endpoints and definitions, continued	Other secondary endpoints	≥30% response rate	Mean percentages of patients with reduction from baseline ≥30% in monthly MHDs during the 6-month double-blind period
Database lock	05 May 2017		

Results and Analysis

Primary Analysis:

Overall mean change in monthly MHDs across Months 1 to 6	Treatment group (number of subjects)	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-2.28 (0.20)	-4.29 (0.25) -2.02 (0.27) -2.55, -1.48 <.001	-4.18 (0.26) -1.90 (0.27) -2.44, -1.36 <.001

Key secondary endpoints

Mean percentage of ≥50% responders for migraine headache days over 6 months	Treatment group (number of subjects)	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	36.0 (1.7)	59.3 (2.4) 2.60 2.03, 3.32 <.001	56.5 (2.5) 2.31 1.81, 2.96 <.001
Mean percentage of ≥75% responders for migraine headache days over 6 months	Treatment group (number of subjects)	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	17.8 (1.3)	33.5 (2.3) 2.34 1.78, 3.06 <.001	34.3 (2.3) 2.42 1.84, 3.17 <.001
Mean percentage of 100% responders for migraine headache days over 6 months	Treatment group (number of subjects)	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	5.7 (0.7)	11.5 (1.4) 2.16 1.50, 3.12 <.001	13.8 (1.5) 2.67 1.87, 3.81 <.001

Overall mean change in monthly MHDs with acute medication use across Months 1 to 6	Treatment group (number of subjects)	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-1.85 (0.18)	-3.67 (0.22) -1.82 (0.24) -2.29, -1.36 <.001	-3.63 (0.23) -1.78 (0.24) -2.25, -1.31 <.001
Mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score (average of Months 4, 5, and 6)	Treatment group (number of subjects)	PBO N=396	GMB 120 mg N=213	GMB 240 mg N=210
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	19.65 (0.92)	28.47 (1.15) 8.82 (1.27) 6.33, 11.31 <.001	27.04 (1.17) 7.39 (1.28) 4.88, 9.90 <.001
Mean change from baseline in the PGI-S rating (average of Months 4, 5, and 6)	Treatment group (number of subjects)	PBO N=396	GMB 120 mg N=213	GMB 240 mg N=210
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-0.94 (0.07)	-1.22 (0.08) -0.29 (0.09) -0.47, -0.11 .002	-1.17 (0.08) -0.23 (0.09) -0.41, -0.05 .012
Additional secondary endpoint				
Mean percentage of ≥30% responders for migraine headache days over 6 months	Treatment group (number of subjects)	PBO N=450	GMB 120 mg N=226	GMB 240 mg N=220
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	52.7 (1.8)	73.4 (2.2) 2.49 1.92, 3.22 <.001	72.6 (2.2) 2.38 1.84, 3.08 <.001

Table 12 - Summary of efficacy for trial I5Q-MC-CGAI

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study			
Study identifier	**I5Q-MC-CGAI**		
Design	*Study I5Q-MC-CGAI was a Phase 3, multicentre, randomised, double-blind, placebo-controlled study to compare the efficacy and safety of 2 doses of galcanezumab (120 or 240 mg/month) in the prevention of migraine headache in patients with chronic migraine. The study consisted of 5 periods, including a 3-month double-blind treatment phase, an optional 9-month open-label extension, and a 4-month post-treatment*		
	Duration of main phase: Duration of run-in phase: Duration of open-label extension phase:		3 months not applicable 9 months
Hypothesis	Superiority		
Treatment groups and number of randomised patients with at least one injection	Galcanezumab 120 mg subcutaneous, once monthly (with a 240-mg loading dose)		278
	Galcanezumab 240 mg subcutaneous, once monthly		277
	Placebo subcutaneous, once monthly		558
Endpoints and definitions	Primary endpoint	Migraine headache days (MHDs)	Overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind period
	Key secondary endpoints	≥50%,≥75%, and 100% response rates	Mean percentages of patients with reduction from baseline ≥50%, ≥75%, and 100% in monthly MHDs during the 3-month

		MHDs with acute medication use	Overall mean change from baseline in the number of monthly MHDs with acute medication use for treatment of migraine or headache during the 3- month double-blind period
		Migraine-Specific Quality of Life Questionnaire (MSQ) ver. 2.1. Role Function-Restrictive Score	Mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Month 3
		Patient Global Impression of Severity (PGI-S)	Mean change from baseline in the PGI-S rating at Month 3
Endpoints and definitions, continued	Other secondary endpoints	≥30% response rate	Mean percentages of patients with reduction from baseline ≥30% in monthly MHDs during the 3-month double-blind period
Database lock	05 May 2017		

Results and Analysis

Primary Analysis (ITT population):

Overall mean change in monthly MHDs across Months 1 to 3	Treatment group (number of subjects)	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-2.74 (0.36)	-4.83 (0.44) -2.09 (0.42) -2.92, -1.26 <.001	-4.62 (0.43) -1.88 (0.42) -2.71, -1.05 <.001

Key secondary endpoint (ITT population/ across Months 1 to 3)

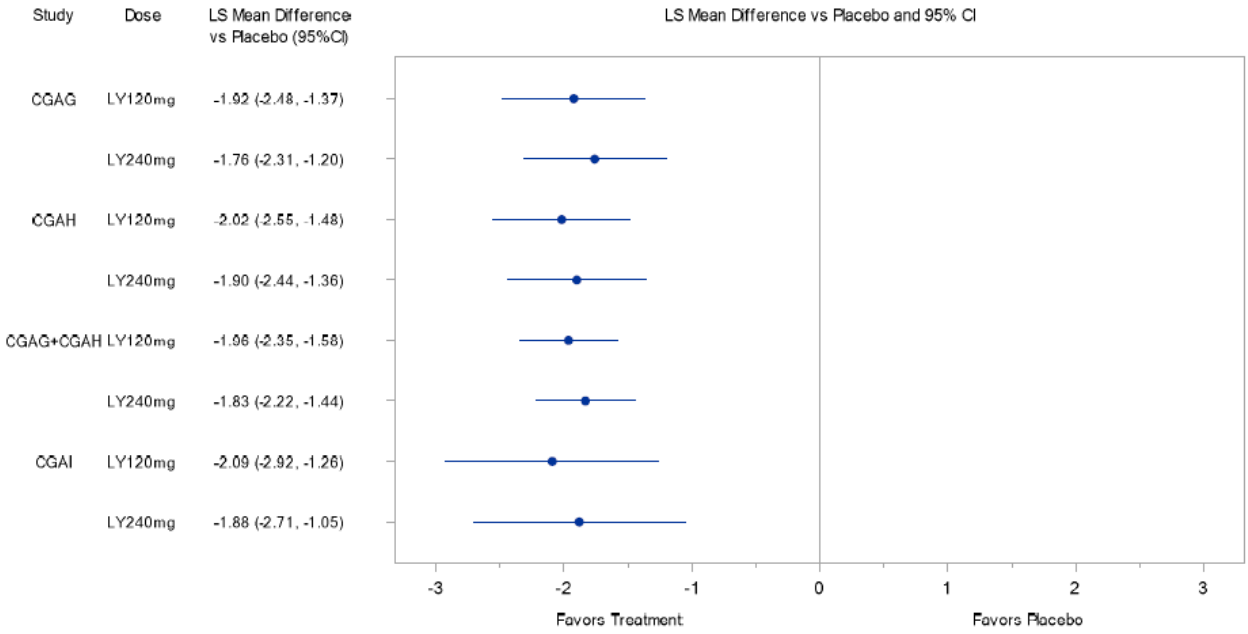
Mean percentage of ≥50% responders for migraine headache days over 3 months	Treatment group (number of subjects)	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	15.4 (1.6)	27.6 (2.7) 2.09 1.56, 2.80 <.001	27.5 (2.6) 2.08 1.55, 2.78 <.001
Mean percentage of ≥75% responders for migraine headache days over 3 months	Treatment group (number of subjects)	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	4.5 (0.9)	7.0 (1.4) 1.60 1.04, 2.46 .031	8.8 (1.7) 2.04 1.36, 3.06 <.001
Mean percentage of 100% responders for migraine headache days over 3 months	Treatment group (number of subjects)	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	0.5 (0.3)	0.7 (0.4) 1.37 0.43, 4.37 .597	1.3 (0.6) 2.61 0.97, 7.04 .058
Overall mean change in monthly MHD with acute medication use across Months 1 to 3	Treatment group (number of subjects)	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-2.23 (0.33)	-4.74 (0.40) -2.51 (0.38) -3.27, -1.76 <.001	-4.25 (0.40) -2.01 (0.38) -2.77, -1.26 <.001
Mean change from baseline in the MSQ	Treatment group (number of subjects)	PBO N=494	GMB 120 mg N=252	GMB 240 mg N=253

v2.1 Role Function-Restrictive domain score (at Month 3)	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	16.76 (1.18)	21.81 (1.41) 5.06 (1.50) 2.12, 7.99 <.001	23.05 (1.63) 6.29 (1.66) 3.03, 9.55 <.001
Mean change from baseline in the PGI-S rating (at Month 3)	Treatment group (number of subjects)	PBO N=494	GMB 120 mg N=252	GMB 240 mg N=253
	LSMean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-0.62 (0.08)	-0.76 (0.10) -0.14 (0.10) -0.34, 0.06 .181	-0.91 (0.10) -0.28 (0.10) -0.48, -0.08 .006
Additional secondary endpoint				
Mean percentage of ≥30% responders for migraine headache days across Months 1 to 3	Treatment group (number of subjects)	PBO N=538	GMB 120 mg N=273	GMB 240 mg N=274
	Estimated Rate, % (SE) Odds ratio vs Placebo 95% CI on odds ratio P-value vs placebo	32.3 (2.1)	44.8 (2.9) 1.70 1.32, 2.18 <.001	46.4 (2.9) 1.82 1.41, 2.34 <.001

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

The efficacy data from the two identical studies CGAG and CGAH on EM were integrated in an Episodic Migraine Integrated Analysis Set (also referred to as the Episodic Integrated Analysis Set), which included patient demographics and baseline characteristics, patient disposition, mean change from baseline in monthly MHDs, and number of weekly MHDs during first month of treatment, using the same methods as for each of the two parent studies.

After reviewing data from pivotal studies, dose regimens of galcanezumab were superior to placebo on the primary measure of overall mean reduction in monthly MHDs across Months 1 to 6 (for CGAG and CGAH) and Months 1 to 3 (for CGAI study on CM). Both doses also were superior to placebo on all key secondary and nearly all other secondary endpoints, with no statistically significant differences between the 2 dose regimens. The consistency of results observed at each of the two studies did not change the outcomes of the pooled analyses.



Note: For Study CGAG, Study CGAH, and Studies CGAG+CGAH combined, the LSMean difference vs placebo is the overall LSMean difference across Months 1 to 6; for Study CGAI, the LSMean difference vs placebo is the overall LSMean difference across Months 1 to 3.

Figure 2.7.3.18. Forest plot for least squares mean difference between galcanezumab and placebo in the number of monthly migraine headache days for Studies CGAG, CGAH, CGAG/H combined, and CGAI.

Table 2.7.3.7.16. Comparisons Between Galcanezumab 120 mg/month and Galcanezumab 240 mg/month Primary and Key Secondary Efficacy Analyses Studies CGAG, CGAH, and CGAI

Measure	Dose	CGAG				CGAH				CGAI			
Continuous Measures, LSMean Change		GMB	Diff from PBO	p-value vs PBO[a]	p-value vs 120 mg[a]	GMB	Diff from PBO	p-value vs PBO[a]	p-value vs 120 mg[a]	GMB	Diff from PBO	p-value vs PBO[a]	p-value vs 120 mg[a]
Number of monthly MHD	120 mg	-4.73	-1.92	<.001		-4.29	-2.02	<.001		-4.83	-2.09	<.001	
	240 mg	-4.57	-1.76	<.001	.615	-4.18	-1.90	<.001	.707	-4.62	-1.88	<.001	.664
Number of MHDs with acute medication use	120 mg	-3.96	-1.81	<.001		-3.67	-1.82	<.001		-4.74	-2.51	<.001	
	240 mg	-3.76	-1.61	<.001	.483	-3.63	-1.78	<.001	.875	-4.25	-2.01	<.001	.259
MSQ Role Function-Restrictive domain	120 mg	32.43	7.74	<.001		28.47	8.82	<.001		21.81	5.06	<.001	
	240 mg	32.09	7.40	<.001	.818	27.04	7.39	<.001	.328	23.05	6.29	<.001	.499
PGI-S	120 mg	-1.59	-0.32	.002		-1.22	-0.29	.002		-0.76	-0.14	.181	
	240 mg	-1.55	-0.28	.008	.710	-1.17	-0.23	.012	.609	-0.91	-0.28	.006	.221
Categorical Measures, Estimated Rate (%)		GMB	Odds Ratio vs PBO	p-value vs PBO[a]	p-value vs 120 mg[a]	GMB	Odds Ratio vs PBO	p-value vs PBO[a]	p-value vs 120 mg[a]	GMB	Odds Ratio vs PBO	p-value vs PBO[a]	p-value vs 120 mg[a]
≥50% response rate on MHD	120 mg	62.3	2.63	<.001		59.3	2.60	<.001		27.6	2.09	<.001	
	240 mg	60.9	2.48	<.001	.694	56.5	2.31	<.001	.418	27.5	2.08	<.001	.973
≥75% response rate on MHD	120 mg	38.8	2.65	<.001		33.5	2.34	<.001		7.0	1.60	.031	
	240 mg	38.5	2.62	<.001	.925	34.3	2.42	<.001	.816	8.8	2.04	<.001	.280
100% response rate on MHD	120 mg	15.6	2.80	<.001		11.5	2.16	<.001		0.7	1.37	.597	
	240 mg	14.6	2.61	<.001	.679	13.8	2.67	<.001	.247	1.3	2.61	.058	.238

Abbreviations: Diff = difference; GMB = galcanezumab; LSMean = Least Squares Mean; MHD = migraine headache day; MSQ = Migraine-Specific Quality of Life Questionnaire Version 2.1; PBO = placebo; PGI-S = Patient Global Impressionof Severity.

[a] P-values in this table provided without regard to adjustments for multiplicity. Results for continuous variables are from MMRM; results for response rates are from GLIMMIX. Results presented for PGI-S and MSQ Role Function-Restrictive for Studies CGAG and CGAH are for the average of Months 4 to 6 and for Study CGAI are at Month 3; results for presented all other measures are the overall result at the end of the study (average of all months).

The effects of various demographic and baseline characteristics on treatment outcome, planned subgroup analyses were presented for the Episodic Integrated Analysis Set (Studies CGAG and CGAH) and for Study CGAI.

Subgroup analyses were performed for mean change from baseline in the number of monthly MHDs for subgroups. Overall, these analyses did not show significant treatment-by-subgroup interactions by sex, racial group, ethnicity, number of MHDs at baseline, concurrent prophylaxis use, or baseline medication overuse. The significant treatment-by-subgroup interactions observed in the remaining analyses seemed to be driven more by variations in placebo response across subgroups than by variations in galcanezumab response across subgroups. Overall these analyses indicated that efficacy was not different in patients with a history of failure with multiple prophylactic treatment for their migraine.

Table 2.5.4.4. Mean Change from Baseline in Monthly Migraine Headache Days Patients with History of Failure of ≥1 or ≥2 Prophylactic Treatments Intent-to-Treat Population Studies CGAG and CGAH Pooled and Study CGAI

Patient Subgroup (dataset)	Trt	N	LSMean Change (SE)	LSMean Change Diff vs PBO (SE)	p-value vs PBO
Patients with history of:					
Failure of ≥1 prophylactic treatment (CGAG/CGAH Pooled)	PBO	214	-1.39 (0.40)		
	120 mg	124	-4.08 (0.46)	-2.69 (0.40)	<.001
	240 mg	110	-4.16 (0.48)	-2.78 (0.42)	<.001
Failure of ≥1 prophylactic treatment (CGAI)	PBO	268	-1.88 (0.51)		
	120 mg	126	-5.41 (0.62)	-3.54 (0.59)	<.001
	240 mg	141	-3.25 (0.59)	-1.37 (0.57)	.017
Failure of ≥2 prophylactic treatments (CGAG/CGAH Pooled)	PBO	85	-0.81 (0.61)		
	120 mg	43	-3.45 (0.73)	-2.64 (0.71)	<.001
	240 mg	44	-3.85 (0.77)	-3.04 (0.70)	<.001
Failure of ≥2 prophylactic treatments (CGAI)	PBO	161	-1.44 (0.62)		
	120 mg	66	-5.91 (0.79)	-4.48 (0.74)	<.001
	240 mg	96	-3.30 (0.71)	-1.86 (0.66)	.005

Abbreviations: LSMean = Least Squares Mean; PBO = placebo; N = total number of patients; SE = standard error; Trt = treatment.
Source: SCE Table 2.7.3.16

For patients in the Episodic Integrated Analysis Set both doses of galcanezumab were equally effective in mean change of the monthly MHD in patients with aura as well as in patients without aura. There was a statistically significant dose interaction in Study CGAI, in which patients with aura did better with the 240 mg dose while patients without aura did better with the 120 mg dose (p=0.016). Patients who did not take prior prophylactic treatment in the CGAI study responded better to the 240 mg dose (-7.57) compared to the 120 mg dose (-4.56) of galcanezumab.

In the Episodic Integrated Analysis Set the mean change from baseline in number of MHD for patients with <8 MHD at baseline overall was -0.96 for placebo, -2.76 for 120 mg dose and -2.28 for 240 mg dose with respective difference from placebo for 120 mg dose in 1.84 (p<0.001) and 1.36 MHD (p<0.001) for 240 mg dose. The mean change from baseline in number of MHD for patients with ≥8 MHD at baseline overall was -3.4 for placebo, -5.43 for 120 mg dose and -5.46 for 240 mg dose with difference from

placebo for 120 mg dose in 2.04 MHD (p<.001) and for 240 mg dose in 2.06 MHD (p<0.001) in the Episodic Integrated Analysis Set.

For the subset of patients who were using concurrent topiramate or propranolol, the overall mean reduction in the number of monthly MHDs across Months 1 to 3 was -1.41 for placebo (N=80) versus -2.27 for galcanezumab 120 mg (N=37) and -2.58 for galcanezumab 240 mg (N=41) with difference from placebo 0.86 for 120 mg (p=0.422) and 1.18 from 240 mg dose (p=0.242). Meanwhile, for patients who were not using concurrent topiramate or propranolol, the overall mean reduction in the number of monthly MHDs across Months 1 to 3 was -3.34 for placebo versus –5.66 for 120 mg and -5.42 for 240 mg dose with difference from placebo 2.32 for 120 mg (p<0.001) and 2.08 from 240 mg dose (p<0.001).

Supportive studies

Study ART-01

This was a phase 2a, proof-of-concept, randomized, multisite, double-blind, placebo-controlled study performed in U.S. and aimed at assessing the efficacy and safety of galcanezumab (LY2951742) in the prevention of episodic migraine in patients suffering from migraine headache with or without aura over a 3-month period.

This brief study lasted from 28 Jun 2013 (first subject first visit) to 15 Sep 2013 (last subject last visit).

Subjects received every 14 days 1 SC injections (in the abdominal region) of placebo or LY2951742 150 mg made up to 1.5mL with sterile water over a 12-week treatment period (totalling 900 mg of IMP or placebo), with the actual date and time of all dose administrations recorded in the subject's eCRF.

The study comprised 4 study periods, namely a screening and Washout (5–45 days), a baseline (28–38 days), a treatment (12 weeks) and a follow-up period (12 weeks).

Primary efficacy objectives was to evaluate the mean change from baseline in the number of migraine headache days in a 28-day period, being a migraine headache day defined as any calendar day with a headache lasting >30 minutes that met the criteria for migraine as defined by IHS ICHD–II (1.1 and 1.2) (ICHD–II, Cephalalgia 2004). Migraine headache should have started at least 1 year prior to enrollment, its onset prior to age 50, and a frequency of 4 to 14 migraine headache days per 28-day period as determined during the Baseline Period.

Secondary endpoints were the following: (i) the mean change from baseline in the number of headache days per 28-day period (being a headache day defined as any calendar day with a headache lasting ≥4 hours, to include migraine, probable migraine and non-migraine headaches); (ii) the mean change from baseline in number of migraine attacks per 28-day period (migraine attack defined as beginning on any day a migraine headache day was recorded and ending when a migraine headache-free day occurred); (iii) mean change from baseline in the number of probable migraine and migraine headache days (combined) in a 28-day period; (iv) proportion of responders (being a responder defined as a subject who had a >50% reduction in the number of migraine headache days in a 28-day period; (v) occurrence of AEs, and changes from baseline in vital signs, safety laboratory tests, and electrocardiograms (ECGs). In addition, the immunogenicity of LY2951742 was determined.

A total of 367 patients entered the study for the 4-week Baseline Period and 115 were not considered eligible. Migraine prevention medications had to be discontinued at least 30 days prior to entering the Baseline Period (the washout period was 120-day for botulinum toxin), during which the eligibility of patients enrollment was assessed. Overall, 149 patients were excluded after the Baseline Period, 218

were enrolled into the study (n=108 on IMP and n=110 on placebo) and randomly assigned on a 1:1 basis to either placebo or LY2951742 150 mg administered (at Visit 3 for the first time) on an out-patient basis as a SC injection once every 14 days for a 12-week period (6 SC totally injected doses per subject).

Results

In a 28-day cycle, the mean (±SD) number of migraine headache days recorded during the Baseline Period in subjects enrolled into the study (n=217) was 6.90 (±2.42). When compared with placebo, LY2951742 treatment significantly reduced the number of MHD over the 12-week treatment period in the ITT population (4.19 vs. 2.96 days for the LY2951742 and the placebo groups, respectively, p=0.003) as well as the PP population (4.22 vs. 2.95 days for the LY2951742 and the placebo groups, respectively, p=0.002). Similar results were obtained from the sensitivity analyses.

Subcutaneous administration of LY2951742 at a dose of 150 mg every 2 weeks was effective in reducing the number of migraine headache days, headache days, headache hours, and the number of migraine attacks in patients with frequent, episodic migraine.

In about one-third of subjects, LY2951742 treatment resulted in a total elimination of migraine headaches.

Odds ratio estimates confirmed that LY2951742 treatment was superior to placebo for 100%, 75% and 50% response rates in each treatment month of the Treatment Period.

The number of subjects that achieved a 100% or 75% reduction in migraine headaches was highest in the second month of LY2951742 treatment whereas the number of subjects that achieved a >50% response was highest in the third 065.

Study CGAJ

This was a Phase 3, long-term, randomized study designed to evaluate the safety and effectiveness of galcanezumab (120 mg/month and 240 mg/month) during a 12-month open-label treatment period in patients with EM or CM. The majority of patients in the study had episodic migraine (78.9%), with an overall mean of 10.6 monthly MHDs at baseline, with baseline means of 9.8 and 13.6 for the EM and CM subsets, respectively. The patient population was predominantly female (82.6%) and white (78.2%) with a mean age of 42.0 years. The mean MIDAS score at baseline for the entire population was 49.9, with means of 47.6 for the episodic migraine subset and 58.5 for the chronic migraine subset. In this study, 5.9% of patients were age 60 or higher at baseline.

A total of 270 patients participated, equally distributed among the two treatment groups. Overall, 210 patients (77.8%) completed the 12-month open-label treatment period (71.9% of patients in the 120 mg group and 83.7% of patients in the 240 mg group). The proportion of patients who discontinued due to lack of efficacy was 9.6% and 3.7% in the 120 mg and 240 mg treatment groups, respectively. The proportion of patients who discontinued due to an adverse event was 5.2% and 4.4% in the 120 mg and 240 mg treatment groups, respectively.

Baseline MIDAS scores were numerically higher for the 240-mg group compared to the 120-mg group (MIDAS total score 54.0 vs. 45.8)

Table 13 - Disease Characteristics by Migraine Diagnosis ITT Population

Characteristic	Episodic Migraine		Chronic Migraine	
	LY 120 mg N=109	LY 240 mg N=104	LY 120 mg N=26	LY 240 mg N=31
Duration of migraine illness, years, mean (±SD)	20.43 (±12.42)	21.91 (±12.31)	19.14 (±12.30)	19.16 (±12.95)
Number of comorbidities, mean (±SD)	4.34 (±3.23)	4.43 (±3.32)	4.08 (±2.89)	5.54 (±3.73)
MHDs per month, mean (±SD)	9.15 (±5.16)	10.38 (±5.74)	12.12 (±7.70)	14.81 (±8.46)
Prior preventive treatment, n (%)	66 (60.55)	63 (60.58)	15 (57.69)	25 (80.65)
MIDAS total score, mean (±SD)	44.55 (±41.85)	50.85 (±59.19)	51.08 (±43.41)	64.39 (±67.64)
MSQ Role Function-Restrictive, mean (±SD)	47.94 (±19.43)	48.82 (±18.54)	44.91 (±18.04)	43.78 (±17.56)
PGI-S, mean (±SD)	4.64 (±1.20)	4.59 (±1.21)	4.72 (±1.24)	4.87 (±1.15)

Abbreviations: ITT = intent-to-treat; LY = LY2951742/galcanezumab; MHD = migraine headache day; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of intent-to-treat patients with nonmissing demographic measures; n = number of patients within each specific category; PGI-S = Patient Global Impression of Severity; SD = standard deviation.

Source: /lillyce/prd/ly2951742/i5q_mc_cgaj/intrm1/output/shared/smdem21.rtf and fqdem21.rtf.

Efficacy measures were secondary in this study. The overall mean reduction from baseline in the number of monthly MHDs averaged over the 12-month open-label treatment phase was 5.6 days for galcanezumab 120 mg and 6.5 days for galcanezumab 240 mg. Compared to baseline, MHDs (120-mg treatment group = 9.7 days per month; 240-mg treatment group = 11.4 days per month), results in both groups showed statistically significant reductions in mean number of MHDs at each month during the 12-month open-label treatment phase.

Results of response rate analyses demonstrated that the mean percentage of patients in the galcanezumab 120-mg and 240-mg treatment groups with a ≥50% reduction in the number of monthly MHDs was 65.6% and 73.7%, respectively, during the 12-month open-label treatment phase. The mean percentage of patients in the galcanezumab 120-mg and 240-mg treatment groups, respectively, with ≥30% reduction in the number of monthly MHDs was 76.1% and 80.9%, with ≥75% reduction in the number of monthly MHDs was 44.5% and 52.5%, and with 100% reduction in the number of monthly MHDs was 21.4% and 21.8%.

The overall mean reduction in number of monthly days that patients took any acute medications for migraines or headaches was 5.1 days in both the galcanezumab 120-mg and 240-mg treatment groups. The high percentage of patients who received concomitant triptans during the trial (63% GMB 120 mg group and 72% in GMB 240 mg/ group), compared to around 26% of concomitant triptan use in GMB treated subjects in Analysis set A (who gathers all the placebo-controlled subjects of the phase 3 pivotal trials) was due to the different ways in which the information on acute medication use was collected (as prospective daily patient diary in the Analyses Set A, against a written track on daily basis taken by patients in study CGAJ and then enquired at each subsequent site visit along with the count of the number of MHD/headache days with/out acute medication in the past 30 days). Such a difference prevents to make a direct comparison.

Significant and clinically meaningful improvement was also demonstrated on the PGI-I, a global rating of how patients perceive improvement in their migraine disease. A majority of patients reported that their migraine headache condition felt "very much better" and "much better" beginning at Month 1.

Maintenance of Response

Maintenance of response was evaluated based on the definition of a patient meeting ≥ 50% response at a single month and subsequently maintaining ≥ 40% response until the patient's endpoint for at least 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 consecutive months (including initial month).

Notable percentages of patients treated with galcanezumab 120 mg or 240 mg maintained their response for at least 3 and up to 12 months (for patients treated with 240 mg and 120 mg, 59% and 55%, respectively, maintained ≥ 40% response for at least 4 months; and 35% and 24%, respectively, maintained this level of response for 12 months).

Immunogenicity

In the Phase 3 migraine clinical trials, the incidence of ADA and neutralizing antibodies (NAbs) at baseline ranged from 7.6% to 8.4% and 4.7% to 5.5%, respectively. The majority of patients with ADA present at baseline did not become TE ADA+ during treatment. Based on Phase 3 data, incidence of TE ADA while on galcanezumab treatment ranged from 2.6% in the 3-month double-blind treatment phase of Study CGAI (2.7% in 120 mg group; 2.6% in 240 mg group) to 9.5% in the 12-month open-label treatment phase of Study CGAJ (12.5% in 120 mg group; 6.6% in 240 mg group). The majority of patients who were TE ADA+ had NAb present.

2.6.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose finding study (CGAB)

Study CGAB, a double-blind, randomised, placebo-controlled study that tested galcanezumab at doses of 5, 50, 120, 300 mg given sc every 4 weeks, with the primary objective to assess whether at least 1 dose of galcanezumab was superior to placebo in the prophylaxis of migraine. The primary endpoint was the mean change from baseline in the number of MHDs in the last 28-day period of the 12-week treatment phase. CGAB enrolled patients who met criteria for episodic migraine, as defined by IHS ICHD-3 beta. Despite apparent similarity in reduction of MHDs during last 28 days between 5 mg and 300 mg dose, there was no statistically significant difference from placebo in reduction of MHDs at any timepoint for 5 mg dose group. However, the totality of presented data including analysis of relationship of galcanezumab serum concentration and mean change from baseline of number of MHDs, suggested that both 120 mg and 300 mg tested doses had similar efficacy, thus supporting dose selection for phase 3 pivotal studies. An earlier significantly higher response (at month 1) than placebo was shown for the 300 mg dose. This suggested to implement the 240-mg loading dose in Phase 3 trials in order to achieve steady-state galcanezumab concentrations by Month 1. The design and conduct of this study is considered adequate to support the selection of the galcanezumab doses for the 3 pivotal studies.

Pivotal Studies in EM (CGAG and CGAH)

The two studies in episodic migraine had identical design (including a screening period, a prospective 30-40 day baseline phase aimed at assessing the final eligibility to the study, and a double-blind period of 6 months). In addition, a 4-month post-treatment phase was also included.

The 2 studies did not include an active comparator. Response rates to placebo in migraine pts are known to be highly variable, and this is the reason why the CHMP Guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine (CPMP/EWP/788/01 Rev1.) recommends 3 treatment arms with an active comparator and placebo for internal validation. All patients had to have between 4 and 14 MHDs prior to visit 1 and at least 2 migraine attacks per month during prospective baseline period; however,

although the claimed indication included all migraine patients with no limits in terms of MHDs per month, the use of galcanezumab for the prophylaxis of migraine in adults should be limited to subjects who have at least 4 migraine days per month.

The primary endpoint was overall mean change from baseline in the number of monthly MHDs, which is acceptable as already used in other studies in migraine patients and may facilitate indirect comparison. The definition of MHD, as study endpoint and baseline criteria, included both migraine and probable migraine with a duration being considerably shorter than in the ICHD guideline, i.e. minimum 30 min untreated vs minimum 4 hours untreated. The reason for which being the need to not delay the use of acute medication for pain. The inclusion of probable migraine in the primary endpoint aims, according to the Applicant, at allowing the inclusion of episodes that do not become a full-blown migraine because of the use of acute medications. Although this may be acceptable, consistency of treatment effect in terms of both migraine and probable migraine headaches needs to be demonstrated, by separate analyses. In this regard, the Applicant's choice to have ICHD MHD (not including probable headache) among secondary endpoints is acknowledged. The results on the primary endpoint, as well as of the responder analysis, were confirmed by sensitivity analyses after using alternative definitions of migraine headache in terms of duration of the migraine episode, i.e. 2, 3 and 4 hours, being the 1-hour length included in the minimum 30 min definition of MHD. Secondary endpoints (key secondary and secondary) assessed mean change from baseline for numerous headache parameters, which are standard measurements of treatment effect for this pathology. Treatment effect on quality of life was also evaluated among key secondary endpoints, using a validated self-administered health status instrument, the Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ; Jhingran et al. 1998). The post-hoc change made on the threshold used for the responder analysis based on MSQ (from the initially planned cutoff ≥10.9 to the more restrictive ≥25 from baseline) which included both anchor and distribution-based methods was acceptable. It was confirmed that clinically meaningful changes in functioning were correlated with clinically meaningful improvements, also in the other relevant patient-reported measures used, like the Migraine Disability Assessment test (MIDAS) and the patient global impression of illness severity, PGI-S.

There was rather high screening failure observed in both CGAG and CGAH studies. Approximately 48% (n=809) patients failed screening in the CGAG study and 45% (n=774) failed screening in CGAH. The most common reason for screen failure was patients not meeting criteria for study enrolment based on migraine headache information collected in the ePRO diary during the prospective baseline phase.

Pivotal study in Chronic migraine, CGAI.

The CGAI study evaluated efficacy of galcanezumab in patients with chronic migraine defined by 15 or more headaches days per month (with at least 8 days having features of migraine) and at least 1 headache-free day per month for more than 3 months. The frequency of chronic migraine attacks had to be confirmed during the prospective baseline period of the study.

The design of the CGAI study is similar to that of Phase 3 episodic migraine Studies CGAG and CGAH. The key difference in study design is that the chronic migraine study had a shorter double-blind treatment period (3 months) to minimize the duration of exposure of this more severely ill patient population to placebo, and a flexibly dosed 9-month open-label extension to allow for assessment of durability of drug effect. The duration of the study is acceptable. However, the preventive treatment (topiramate and propranolol) allowed in the CGAI study, characterized by different route (per os) and frequency of administration (daily) prevented the applicant from running active comparator studies.

CM were stratified by country and acute headache medication overuse. It is noted that the exclusion criterion: past history of opioids or barbiturate containing analgesics >3 X per month for the treatment of pain in more than 2 of the past 6 months is far more restrictive than the definition of medication overuse

headache adopted in the ICHD-IIIβ (*"overuse of acute or symptomatic headache medication on 10 or more, or 15 or more days per month, depending on the medication, for more than 3 months")*, and harbors the risk of narrowing the chance to enroll patients with real CM, given the known high rate of use among them. The CHMP queried the percentage of patients in the ITT population with CM with previous use of opioids seems very low, raising doubts on the representativeness of the trial population in terms of the target population of the claimed indication.In this regard, it was clarified that the applicant's intention was to limit as much as possible the enrolment of habitual opioid/barbiturate users, as it is acknowledged that the use of these drug class is accompanied with a higher risk of addiction/withdrawal syndrome, rebound headache and difficulty to be discontinued once initiated. After reviewing the applicant's response, the CHMP agreed that the study population in CGAI was representative of the EU population.

The SAP initially included only the effect size, without details of the sample size and power calculation, or information on the expected treatment effect and relative SD for the three pivotal studies. The Applicant clarified that the assumptions for the determination of the sample size in the EM trials were a mean difference of 1.2 migraine headache days with a SD of 3.6 (corresponding to an effect size of 0.33). In study CGAI, a minimum sample size of 825 was planned based on results from Studies ART-01 and CGAB in episodic migraine, however, due to uncertainty of the effect size of galcanezumab in chronic migraine, an unblinded sample size re-estimation (SSR) approach was planned to appropriately size the study. In the end, a faster than expected enrolment rendered the application of such an approach unrealistic. Therefore, the Study CGAI team directly increased the study sample size to the predefined maximum sample size of 1140. In addition, the Applicant clarified that the choice to increase the sample size was also based on further external (though not provided) data from chronic migraine patients that indicated a smaller effect size than the one initially supposed. The applicant did not discuss the minimum detectable difference as requested, instead performed the primary analysis on the first 825 enrolled patient, in order to simulate what would have been resulted according the minimum estimated sample size. The provided "sensitivity" analysis further showed that, with selected sample size, highly statistically significant differences versus placebo could be observed even for very small (<1 MHD) improvements (as also reflected by negligible LS mean differences).

Efficacy data and additional analyses

Study CGAG

The demographic characteristics at baseline were comparable among treatment groups and showed that the patient population was predominately female (83.7%) and White (80.4%) with a mean age of 40.7 years. The mean duration of migraine illness was about 20 years in all groups. Approximately 66% of patients had migraine frequency at baseline of ≥8 MHDs per month. Mean MHDs per month (including both migraine and probable migraine HDs) were substantially similar in all treatment groups: roughly 9 MHDs per month. At least one prior migraine preventive treatment was reported by approximately 60% of subjects in all treatment groups. The proportions of subjects who failed 2 or more such treatments due to lack of efficacy in the previous 5 years were comparable among treatment groups (5.1% placebo and 4.7% each galcanezumab treatment group).

Based on monthly MHD, clinical history and mean severity of migraine, the patient population seems to be affected by a moderate to severe disease with an extreme variable impact on patients' functioning (mean MIDAS total score was 33, with high SD).

Overall, approximately half of patients in each treatment group had **migraine with aura at baseline**, without statistically significant intergroup differences.

Similar number of patients (17-19%) discontinued the double-blind phase of the study.

The primary endpoint was met with high statistical significance at both galcanezumab doses of 120 mg and 240 mg SC once monthly. This result remained consistent after running different sensitivity analyses.

After multiplicity adjustment, LS mean changes form baseline were -2.81 for placebo versus -4.73 for galcanezumab 120 mg [effect size -0.59] and -4.57 for galcanezumab 240 mg [effect size -0.54]). The LS mean difference from placebo for the 120 mg dose was 1.92 (SE 0.28), whereas that for the 240 mg dose was 1.76 (SE 0.28). The magnitude of treatment effect seems limited; however, it is acknowledged that there is no agreed minimal clinically relevant effect in terms of decrease in MHD in the literature or in the clinical practice. Thus, a sound assessment of the relevance of treatment effect in terms of the primary endpoint is difficult at present. The applicant has provided tabulated indirect comparison data with available treatments in order to contextualise treatment benefit. Overall, galcanezumab treatment effect seems comparable with that of other approved therapies in EM. However, although the Applicant's efforts are appreciated, the indirect comparison is not supported by a sound methodology, and its usefulness for the evaluation of treatment benefit is limited.

After multiplicity adjustment all key secondary objectives were met without significant differences between the 2 galcanezumab doses. They included the responder analysis for patients with ≥50% (61% vs 39% placebo), ≥75% (38.5% vs 19%), and 100% reduction (15% vs 6%), a stricter definition of MHD including any day with acute medication use, as well as PGI-S scores and MSQ function-restrictive.

As the change in MHDs with acute medication is considered irrespective of the total number of migraine days, the above data did not allow to infer if treatment effect induces a statistically significant reduction in acute medication use relative to total MHDs. The requested descriptive data of drug consumption for acute treatment totalled over the treatment period (i.e. migraine days with acute medication use on the total of migraine days), showed that at baseline, the proportions of MHDs with any acute medication use out of all MHDs were comparable among treatment groups in all pivotal studies (ranging from 76% to 83%), with the 75% to ≤100% subcategory having the highest percentages of patients at each timepoint (including baseline, each monthly interval and overall at the end of the DB period of both EM and CM studies). As per the two twin studies in EM, in study CGAG the mean reduction in the proportion of MHDs with acute medication use resulted statistically different for the LY-240mg group only, overall at the end of DB period (p=.029), a significant difference was also seen at month 2 (p=.002). In study CGAH the difference was statistically significant for both doses with respect to placebo (p≤.001). As per the change from baseline in the proportion of MHDs with triptan use, the difference vs placebo was significant for both galcanezumab doses in both EM studies (p≤.001). The absence of significant differences in the proportion of MHDs with acetaminophen/paracetamol use is not surprising, considering the increased shift from baseline towards the use of this medicine that was generally observed in all three pivotal studies for all treatment groups.

Although the vast majority of secondary endpoints were met with high statistical significance (p<0.001), overall, the treatment effect tends to be smaller, partially due to the smaller baseline number. Of note, the differences with placebo in changes in monthly moderate to severe MHDs were: 1.35 and 1.36 for the 120 mg and 240 mg galcanezumab doses. When the severity of remaining migraine days is taken into consideration, no difference with placebo is observed. The analysis of changes from baseline in MHDs according to the ICHD definition (with the exclusion of probable migraine days) substantially confirmed consistency of treatment effect independently of the definition of the primary endpoint, albeit with a lower gain over placebo (-1.53 and -1.56 for the low and high galcanezumab doses). When stricter definition of MHD including any day with acute medication use is applied (triptans, NSAIDS or paracetamol), the gain over placebo appears to fluctuate according to the type of acute medication used, reaching the minimum difference with paracetamol (-1.15 with the galcanezumab lower dose and -1.04 with the higher dose).

Study CGAH

The patient population recruited in this study was similar to that of the CGAG study. Similarly to study CGAG, also in study CGAH, the primary endpoint was met with high significance at both galcanezumab doses with comparable magnitude of effect between studies. The treatment effect for secondary endpoints was also similar to the one reported in the CGAG. Both doses of galcanezumab were equally effective.

Study CGAI

The discontinuation rate from the DB treatment phase due to any reason was 8.8%, 5.4% and 3.9% in the placebo, galcanezumab 120-mg and galcanezumab 240-mg treatment groups. No patients discontinued study due to lack of efficacy in both galcanezumab treatment groups, whereas 4 patients out of 558 discontinuations due to lack of efficacy in the placebo group during the DB phase of the study.

Overall 98.5% (n=1021) of patients who completed the DB treatment phase entered the optional OL treatment phase. At the cut-off date for the study report, the large majority of patients (79.4%) were still ongoing, and 125 patients (12.2%) discontinued early due to any reason. The rates of discontinuation from OL treatment due to adverse events were overall small (3.0%). Adverse event was the main reason to discontinue from OL treatment phase (3.0% overall).

Sex, age, race, and BMI were generally similar across treatment groups at baseline. Patients were predominantly female with mean age around 40 years, as expected on the basis of epidemiological data for the pathology. On average, MHDs per month were 19.4, most of which included acute headache medication use. The average number of migraine attacks per month was 6.3. Migraine severity was rated as moderate. The majority of patients (77.8%) had prior migraine preventive treatment, with 29.5% having failed 2 or more such treatments due to lack of efficacy in the past 5 years. More than 60% of patients met the criteria for medication overuse. The gain over placebo and the statistical soundness of the differences obtained in patients with medication overuse for both galcanezumab doses seem larger compared to what obtained in patients without medication overuse at baseline: 1.44 MHD for 120 mg dose in (p=0.037) and 1.30 MHD for 240 mg dose (p=0.056) (mean changes: -3.49 for placebo, -4.93 for 120 mg dose and -4.78 for 240 mg dose). The Applicant explained that the different response to galcanezumab treatment compared to placebo in patients with medication overuse headache at baseline and patients without medication overuse headache at baseline was mostly driven by the different placebo response in these two patients' groups.

Overall, treatment groups were balanced with respect to baseline disease characteristics. Both galcanezumab doses were statistically significantly superior to placebo for the primary endpoint. Overall LSMean mean reduction from baseline in the number of monthly MHDs during the DB treatment phase was 4.8 days and 4.6 days for galcanezumab 120-mg and galcanezumab 240-mg, respectively, compared with 2.7 days for placebo (LSMean change difference from placebo: -2.1 and -1.9; p<.001 for each dose group versus placebo). The magnitude of the effect appears limited, although a sound evaluation of its clinical relevance needs direct comparison with available treatments that is at present lacking. Although a reliable comparison with historical data from topiramate and Botox published studies is hampered by the diversity of study designs and endpoints, the treatment effect of Emgality shows similarities with those results.

All the sensitivity analyses performed were consistent with the primary analysis results. In all pivotal studies unusually high rates of subjects with at least one important protocol deviation in the baseline and DB treatment phase were observed (n=150 for study CGAG [17.5%], n=191 [21%] for study CGAH and

n=203 [18.2%]. The applicant provided 3 sets of data to verify if the results were influenced by specific deviations: i. the first set excluded patients with dosing intervals outside the specified limit (defined as intervals <21 or >37 days); ii. the second set excluded patients who used excluded concomitant medications (defined as taking prohibited migraine preventive medication for primary indication for >7 consecutive days, taking prohibited medication for any indication for >7 consecutive days, opioid/barbiturate use for >7 consecutive days, or use of botulinum toxin A and B for any indication, during Study Periods II or III). iii. the third set of analyses were per-protocol analyses that excluded all patients with any important protocol deviation. The results showed highly statistically significant differences in the overall LS Mean change from baseline of both galcanezumab doses vs placebo (p<.001 in all three studies). In some instances, however, the difference vs placebo resulted even somewhat higher than what observed in the ITT population (for example, in the first set, for study CGAG the mean difference (±SE) vs placebo was -2.10±0.29 days in the LY-120mg group compared to -1.92±0.28 in the ITT population and for study CGAI the mean difference (±SE) vs placebo was -2.19±0.44 days in the LY-120mg whereas it was -2.09±0.42 in the ITT population. The statistically significant differences were preserved also in the third set which was much more conservative by definition.

Only 14.6% of patients continued a stable dose of either topiramate or propranolol for concurrent migraine prophylaxis during the study. The additional treatment benefit of galcanezumab in patients with CM on treatment with either topiramate or propranolol seems relatively small, i.e. 1-day gain. Although no significant treatment-by-subgroup interaction was observed, the applicant discussed the benefit of galcanezumab treatment in add on to topiramate and propanol in CM patients as comparable to what observed from studies with fremanezumab, arguing that in add on setting the response to treatment might be less pronounced compared to monotherapy setting, while being more variable in individual patients. The proposed individualized approach, along with the initiations and evaluation of the treatment effect to be performed only by experienced physicians is endorsed.

For the 240-mg dose group, all key secondary objectives of the study were met after multiplicity adjustment except for 100% response rate.

For the 120-mg dose group, only the key secondary objective of ≥ 50% response rate remained statistically significant after multiplicity adjustment. Thus, all remaining items in the 120-mg testing sequence (MHD with acute medication use, MSQ Role Function-Restrictive, PGI-S, and 100% response rate) are considered not statistically significant after multiplicity adjustment regardless of p-value.

The estimated proportions of patients with ≥50% reduction from baseline in MHDs, were 15.4% (1.6), 27.6% (2.7) and 27.5% (2.6) for placebo galcanezumab 120 mg dose and galcanezumab 240 mg dose, respectively, with gains over placebo of 12%. The NNT to obtain a 50% reduction of monthly MHDs, was 8.2 (5.4,16) and 8.27 (5.5,16) for the low and high galcanezumab dose, respectively. About 50% of patients who were ≥50% responders maintained response to treatment for all 3 months of the DB period; when calculated as proportions of the ITT population these rates were 16.9% and 14.6% for patients on 120-mg and 240-mg galcanezumab, respectively, and 6.3% for placebo (p<.001). Again, the magnitude of treatment effect appears limited.

The threshold of ≥75% response was met by roughly 9% of patients treated with the high galcanezumab dose, albeit with a reduced gain over placebo of 4.3%. Although not statistically significant after multiplicity adjustment, a similar proportion (7%) of patients treated with the 120 mg dose met the ≥75% threshold. The NNT to obtain 75% reduction of monthly MHDs was, as expected, very high: 39.5 and 23.4 for the low and high galcanezumab doses, respectively.

Although the vast majority of secondary endpoints were met with high statistical significance (p<0.001), overall. Of note, the differences with placebo in changes in monthly moderate to severe MHDs were: 1.98

and 1.72 for the 120 mg and 240 mg galcanezumab doses. When the severity of remaining migraine days is taken into consideration, the difference with placebo, albeit statistical significant was very low: 0.007 and of difficult interpretation in terms of clinical significance. The analysis of changes from baseline in MHDs according to the ICHD definition (with the exclusion of probable migraine days) substantially confirmed consistency of treatment effect independently of the definition of the primary endpoint. The gain over placebo in reduction of MHDs, similarly to what observed in the EM studies, fluctuated according to the type of acute medication used.

The overall difference vs placebo of the mean reduction in the proportion of MHDs with acute medication use at the end of the 3-month DB period resulted statistically different for both doses in study CGAI (p<.001). As per the change from baseline in the proportion of MHDs with triptan use, the difference vs placebo was significant for both galcanezumab doses in CGAI study (p=.003 and .007 for the LY-120mg and LY-240mg dose groups, respectively). As observed above regarding the studies on episodic migraine, the absence of significant differences in the proportion of MHDs with acetaminophen/paracetamol use is not surprising, considering the increased shift from baseline towards the use of this medicine that was generally observed in all three pivotal studies for all treatment groups. It should be noted, that since patients could take multiple acute medications on the same day, their use ended up highly heterogeneously distributed among studies and among treated groups, giving unpredictable outcomes from a strictly clinical perspective. However, although it can be reasonably stated that this reflects the clinical reality, it would have been more reassuring to notice a clearer reduced use of acute medications relative to MHD.

In the OL phase of the study, all patients received equal doses in the first two timepoints (galcanezumab 240-mg at Visit 7, Month 3, as two injections, followed by the 120-mg maintenance dose at Visit 8, Month 4, as a single injection). This was done "*to encourage use of the lower dose 120 mg*", which is reasonable, although in contrast to the statement of the applicant who deemed natural that the 240 mg was generally preferred over the lower dose especially for responders at the higher galcanezumab dose in the DB phase, at risk of experiencing a "nocebo" effect once realizing the dose decrease in the OL phase after the first 240 mg dose. In fact, the physicians choose to shift the large majority of patients treated with the 120 mg dose to the 240 mg dose, during the OL phase, thus the maintenance of treatment effect for the 120 mg dose is not soundly assessable on the basis of the OL data. From the updated data provided up to month 12 it was clear that it remains at the clinician's discretion to opt for the most indicated dose according to the clinical need for each patient, with 120 mg being the default dose recommendation, after an initial 240 mg loading dose. Evidence of differences in response to treatment between the two galcanezumab dose is also derived from subgroup analyses.

Subgroup analyses

A statistically significant treatment-by-subgroup interaction suggested better results for patients without aura in both EM (Episodic Integrated Analysis Set) and CM studies. In addition, in the CM study CGAI, there was a statistically significant dose interaction suggesting that the 240 mg dose performed better in patients with aura, and the 120 mg did better in patients without (p=.016). However, when data were re-analysed after 12 months, both doses (120 mg and 240 mg) seem comparable in the subgroups of patients with aura vs without aura, failure of previous treatment or North America region vs Europe and Other regions. It is agreed that both – 120mg and 240mg - doses seem to have comparable efficacy and no obvious benefit in any of tested subgroups could be firmly established for the higher dose vs lower dose.

In both EM and CM study, both doses of galcanezumab were associated with statistically significantly higher reductions in mean MHD than placebo independently on prophylactic treatment failure (yes/no or $\geq$1 or $\geq$2), with the exception of patients who had not failed at least 1 treatment and received

galcanezumab 120 mg in Study CGAI, for whom difference from placebo was not statistically significant. There was also a statistically significant dose interaction in the CM study, such that the 120 mg dose performed better in patients who had failed at least 1 or at least 2 prophylactic treatment whereas the high dose did better in those patients who had not failed at least 1 or at least 2 prophylactic treatment ($p<.001$). The reason for this differential performance of the 2 galcanezumab doses in CM is not immediately explicable. It appears that placebo response was highest in North America (-4.39 – CGAI and -3.29 CGAH study) compared to Europe (-2.23 – CGAI and -1.26 CGAH) and Other regions (-1.98 – CGAI and -2.64 CGAH study).

Patients older than 65 years were not studied and efficacy in this group is not determined. The analyses of efficacy by age groups, e.g. in patients aged 18-40, 40-50, 50-55 and >55, requested to understand whether galcanezumab treatment in different age groups was equally effective and could be extrapolated to patients older than 65 years, demonstrated that up to that age no clear effect on galcanezumab efficacy could be envisaged, and numerically greater changes from baseline in MHDs were generally observed for older patients compared to younger subjects, without significant treatment-by-group interactions, except for the EM studies in which older subjects showed larger reductions from baseline in MHDs with acute medication use. Results of a subgroup analysis of primary outcome measure seem to indicate that the effect of galcanezumab occurs irrespectively of the baseline number of MHDs (<8 vs ≥8 in EM and <19 vs ≥19 in CM) also in patients aged ≥ 50 years. Therefore, the treatment effect of galcanezumab can be extrapolated to older patients (≥65 years). However, since the population of patients recruited to the pivotal studies was restricted to patients with 4 or more monthly MHD, the indication of galcanezumab for the prophylaxis of migraine is maintained for adults who have at least 4 migraine days per month.

2.6.3. Conclusions on the clinical efficacy

The CHMP concluded that the submitted data supports authorisation of galcanezumab in the prophylaxis of migraine. The indication has been modified to reflect the fact that the benefits are expected in patients who have at least 4 migraine days per month.

2.7. Clinical safety

Patient exposure

A total of 3156 patients were exposed to galcanezumab at any dose across the entire galcanezumab development program. At the dose range of 120 to 240 mg, 1647 patients were exposed to galcanezumab for ≥6 months (≥6 monthly doses), and 279 patients were exposed to galcanezumab for 1 year (12 monthly doses). A safety update included a total of 526 patients exposed to 12 monthly doses of galcanezumab and 1920 patients were exposed to galcanezumab for ≥6 months (≥6 monthly doses).

Adverse events

Injection site pain was the most common AE and was seen in 10.07% and 11.64% of GMB treated patients (120 mg and 240 mg respectively) and in 9.51% of placebo treated patients. Considering this small difference between GMB and placebo, the active compound itself does not seem to add much pain as opposed to other injection site reactions, eg erythema and pruritus. Injection site pain was considered

an ADR. Injection site pain was considered as severe in 9.6% of patients experiencing this AE; this should be reflected in the SmPC.

Injection site reaction (an unspecific term for all types of injection site reactions), injection site erythema, injection site pruritus and constipation were significantly more common in GMB treated patients than in placebo. The clinical phase 2/3 trials are not powered to find statistically significant differences for AEs, but dose response patterns were present for these four AEs, in particular injection site reaction. The injection site reactions may be due to immunogenicity and constipation has other biological plausibility. All of these were considered as ADR.

Time course analysis for common TEAEs

Injection site pain, injection site reaction, injection site erythema and injection site pruritus primarily occurred on the day of injection, but there was not a specific injection (for example, second dose, third dose, etc.) where it was most frequently observed. Most events were mild to moderate in severity and generally resolved on the same day. Constipation did not have a pattern of occurrence with regard to timing of injection. It was moderate in severity. Some patients reported persistent constipation (resolved in >30 days).

The frequencies of common TEAEs for the safety update were similar compared to the initial submission for the galcanezumab pooled dose group except for nasopharyngitis and viral upper respiratory tract infection that were due to the differences in mapping (MedDRA v 19.1 vs. 20.0) between the initial submission and safety update.

Table 5.3. EAIRs of Common Treatment-Emergent Adverse Events by Preferred Term GMB-Treated Time Analysis Set E

Preferred Term	GMB_All N=2586					
	Initial Submission			Safety Update		
	n	TPY	EAIR (95% CI)	n	TPY	EAIR (95% CI)
Nasopharyngitis[a]	218	1189.74	18.32 (15.97, 20.92)	9	1484.11	0.61 (0.28,1.15)
Viral upper respiratory tract infection[a]	20	1246.43	1.60 (0.98, 2.48)	248	1398.60	17.73 (15.59, 20.08)
Upper respiratory tract infection	189	1203.33	15.71 (13.55, 18.11)	198	1423.50	13.91 (12.04, 15.99)
Back pain[b]	97	1215.95	7.98 (6.47, 9.73)	111	1444.47	7.68 (6.32, 9.25)
Sinusitus	95	1223.01	7.77 (6.28, 9.50)	103	1449.79	7.10 (5.80, 8.62)
Urinary tract infection	78	1227.65	6.35 (5.02, 7.93)	96	1453.16	6.61 (5.35, 8.07)
Influenza	82	1226.06	6.69 (5.32, 8.30)	93	1451.71	6.41 (5.17, 7.85)
Nausea[b]	87	1214.75	7.16 (5.74, 8.83)	90	1443.09	6.24 (5.01, 7.67)
Dizziness	78	1216.03	6.41 (5.07, 8.01)	83	1447.18	5.74 (4.57, 7.11)
Arthralgia[b]	64	1228.82	5.21 (4.01, 6.65)	73	1458.50	5.01 (3.92, 6.29)
Fatigue	60	1223.35	4.90 (3.74, 6.31)	65	1452.99	4.47 (3.45, 5.70)
Bronchitis	53	1237.51	4.28 (3.21, 5.60)	63	1467.44	4.29 (3.30, 5.49)
Diarrhea[b]	54	1233.24	4.38 (3.29, 5.71)	63	1464.37	4.30 (3.31, 5.50)
Oropharyngeal pain	50	1233.68	4.05 (3.01, 5.34)	54	1465.37	3.69 (2.77, 4.81)
Cough	51	1235.22	4.13 (3.07, 5.43)	53	1465.79	3.62 (2.71, 4.73)
Rash[b]	49	1236.40	3.96 (2.93, 5.24)	53	1467.43	3.61 (2.71, 4.72)
Weight increased[b]	43	1237.86	3.47 (2.51, 4.68)	52	1468.85	3.54 (2.64, 4.64)
Neck pain	44	1234.71	3.56 (2.59, 4.78)	51	1466.10	3.48 (2.59, 4.57)
Pain in extremity[b]	43	1239.14	3.47 (2.51, 4.67)	49	1472.21	3.33 (2.46, 4.40)
Abdominal Pain	42	1236.05	3.40 (2.45, 4.59)	48	1468.52	3.27 (2.41, 4.33)
Myalgia[b]	40	1236.75	3.23 (2.31, 4.40)	43	1470.64	2.92 (2.12, 3.94)
Abdominal pain upper	37	1239.41	2.99 (2.10, 4.11)	42	1471.69	2.85 (2.06, 3.86)
Gastroenteritis	38	1239.07	3.07 (2.17, 4.21)	42	1471.79	2.85 (2.06, 3.86)

Preferred Term	GMB All N=2586					
	Initial Submission			Safety Update		
	n	TPY	EAIR (95% CI)	n	TPY	EAIR (95% CI)
Gastroenteritis viral	36	1238.08	2.91 (2.04, 4.03)	39	1472.88	2.65 (1.88, 3.62)
Headache	35	1239.66	2.82 (1.97, 3.93)	39	1472.06	2.65 (1.88, 3.62)
Insomnia	33	1239.43	2.66 (1.83, 3.74)	39	1470.38	2.65 (1.89, 3.63)
Anxiety	33	1240.58	2.66 (1.83, 3.74)	38	1472.93	2.58 (1.83, 3.54)
Vomiting[b]	32	1239.38	2.58 (1.77, 3.64)	36	1472.40	2.44 (1.71, 3.38)
Constipation	30	1239.72	2.42 (1.63, 3.45)	35	1472.04	2.38 (1.66, 3.31)
Pruritus[b]	31	1241.91	2.50 (1.70, 3.54)	34	1474.80	2.31 (1.60, 3.22)
Migraine	30	1241.94	2.42 (1.63, 3.45)	33	1474.97	2.24 (1.54, 3.14)
Influenza like illness	30	1240.04	2.42 (1.63, 3.45)	31	1471.82	2.11 (1.43, 2.99)

Abbreviations: CI = confidence interval; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; GMB_All = patients treated with any GMB dose in any duration; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients within each specific category; PT = Preferred Term; TPY = total patient-year-at-risk.

Note: Common adverse events related to injection sites are not included in EAIR analyses as they do not satisfy the constant hazard assumption of EAIR calculation; Shaded rows contain initial submission data provided here for ease of comparison; 'common' is defined as having ≥2% after rounding (ie, ≥1.5% before rounding) in any GMB-treated group; EAIR = 100 times the number of patients experiencing the event divided by event-specific total patient-year-at-risk

MedDRA versions 19.1 (initial submission) and 20.0 (safety update) were used.

[a] Due to MedDRA re-coding of this PT between initial submission and safety update, PTs of Nasopharyngitis and Viral upper respiratory tract infection are both included here.

[b] Exposure-adjusted PTs that meet unadjusted common threshold in Analysis Set E but not in Analysis Set A.

Sources: /lillyce/prd/ly2951742/migraine_120day/output/shared/fqteae_eair_e_ms.rtf (initial submission data) and /lillyce/prd/ly2951742/migraine_120day/output/shared/fqcomteae11.rtf, fqteae_eair_e_4m.rtf (safety update).

Uncommon important AEs

The event pruritus was reported in 0.28% in the placebo arm and 0.71% and 1.23% in the low and high GMB arm respectively. The difference was statistically significant for the high GMB group and placebo, as well as for the GMB pooled group and placebo. Vertigo was reported more frequently in the GMB_Pooled (n=14, 0.98%) and GMB 240 mg dose group (n=9, 1.23%) than in the placebo-treated group (n=3, 0.21%). Pruritus and vertigo show a dose response pattern. For both these AEs there is biological plausibility; pruritus belongs to the hypersensitivity reactions and for vertigo there is an association between the inhibition of CGRP and interference with vestibular function. Thus pruritus and vertigo were considered as ADRs. Overall among all galcanezumab-treated patients (Analysis Set E, all Galcanezumab exposure data set) 4/2586 events (0.15%) within HLT Hearing Losses (deafness unilateral/ sudden hearing loss/ hypoacusis) occurred during GMB 240 mg treatment, compared to no such event out of 1698 placebo treated patients. For two patients there were well-described confounders, such as ear infections or cerumen impaction. None of the events coded as hearing loss were SAE and no patient discontinued treatment due to a hearing loss event.

The Applicant identified 10 MedDRA high level terms (HLT) potentially correlated to ulcer healing. In the placebo controlled Analysis Set A, the incidence of patients reporting these events in galcanezumab treated patients (n=6; 0.4%; EIAR 1.12 PY; PTs: gastric ulcer 3, aphtous ulcer 2, skin ulcer 1) was similar to placebo (n=4; 0.3%; EIAR 0.75/ 100 PY. PTs: aphtous ulcer 1, peptic ulcer 2, stomatitis 1). In Analysis Set E (all GMB exposures) a total of 12 cases were identified (GMB treated time 0.5%; EIAR 0.81/ 100 PY). None of these events were serious.

The Applicant also conducted a search for events of wound by searching "wound" in all MedDRA PTs, lower-level terms, and reported terms, plus any PT in the HLT of Healing Abnormal NEC. In the placebo-controlled Analysis Set A, the incidence of patients reporting these events in galcanezumab-treated patients (n=4; 0.3%; EAIR 0.75/100 PY) was similar to placebo (n=3; 0.2%; EAIR 0.56/100 PY). In Analysis Set E (all galcanezumab exposures), a total of 6 wound-related cases were identified (GMB-treated time 0.2%; EAIR 0.40/100 PY). There was only one case reported as impaired healing. Nineteen days after the 5th monthly dose, the patient reported mild impaired healing ("slow wound healing") which resolved in 10 days. The patient said he noticed an ant bite or cut which appeared

to be healing slower than bites or cuts received prior to investigational drug being taken. The investigator considered the event related to study drug. The patient continued treatment and completed the study. The event was confounded by concomitant use of corticosteroids which are known to impair healing.

Common AEs in analysis E of special interest

Of the additional AE occurring in ≥2% after rounding in analysis in the all Galcanezumab exposure data set but in the galcanezuamb placebo contolled data set, rash may be dose dependent Incidence proportions were 0.74%, 1.92%, 1.95% and 3.45% in dose groups <120mg, 120mg, 240mg and 300mg respectively. Exposure time was shorter for the lowest and the highest dose groups (3 months). This result may originate from imbalances in dose groups and exposure times.

Treatment Emergent Adverse Events by Maximum Severity

Primary Placebo-Controlled Integrated Analysis Set A

Among patients who reported TEAEs in Analysis Set A, severe TEAEs occurred in 6.9%, 6.7% and 6.6% in patients treated with GMB 120 mg, 240 mg and PBO, respectively; moderate TEAEs occurred in 31%, 28% and 27% of patients treated with GMB 120 mg, 240 mg and PBO, respectively.

Within the severe events for each of the galcanezumab dose groups, approximately one-third were TEAEs related to injection sites. The percentage of patients that reported injection site pain as severe was similar across both galcanezumab dose groups and placebo. However, there were more patients in the galcanezumab 240-mg dose group that reported a severe event of injection site reaction, injection site erythema, and injection site pruritus than either the galcanezumab 120-mg dose group or placebo.

Two events of gastric ulcer of moderate intensity occurred out of 730 patients treated with GMB 240 mg (0.3%), and one event of mild intensity occurred out of 705 patients treated with GMB 120 mg (0.1%), compared to no such events of any intensity out of 1451 patients treated with PBO. These two events of gastric ulcers were not considered drug related by the investigators. Combining the terms Gastric ulcer and Peptic ulcer, the following frequencies were observed: GMB 120 mg 1 patient 0.14%; GMB 240 mg 2 patients 0.27%; GMB Pooled 3 patients, 0.21%; PBO 2 patients 0.14%.

Two TEAEs of acute pancreatitis occurred in patients treated with GMB (0.14%) (one event of severe intensity in a patient treated with GMB 240 mg and one event of moderate intensity in a patients treated with GMB 120 mg, compared to no such event in PBO treated patients (see SAE section).

Adverse events of special interest

Evaluation of Cardiovascular Safety

There were two main reasons why cardiovascular safety was an important safety topic of interest in migraine patients. First, CGRP is a potent vasodilator thought to play a protective role in cardiovascular health and second, migraine patients have an increased risk of cardiovascular events.

Epidemiological studies have shown that for myocardial infarction, transient ischaemic attack, ischaemic stroke and angina, the incidence rate is approximately 1 per 1000 patient-years in migraine patients with somewhat higher incidence rates in men than women. New onset ischaemic heart disease has a higher incidence rate of approximately 4 per 1000 person-years. In safety analysis set A, total patients years were 533 for placebo and 536 for the pooled GMB exposed patients. To evaluate specific CV events in cardiovascular safety, even a longer follow up period to gain more patient-years may be needed. At present, pooled long term data can be informative.

Patients at high risk of cardiovascular events were excluded from the phase 3 clinical trials (exclusion criteria: recent acute cardiovascular events and/or serious cardiovascular risk within 6 months before

enrolment; in studies CGAH and CGAI: patients with lifetime history of stroke were excluded). Mean age of patients enrolled in Phase 3 studies was 41 years.

Despite these exclusion criteria, the Applicant tried to identify within the Phase 3 trial patient population patients having baseline cardiovascular disease risk if they had, at baseline, 1 or more defined conditions that were part of the patients' medical history or pre-existing conditions in the following SMQs: Ischaemic heart disease (Myocardial infarction (subSMQ, narrow terms only; Other ischaemic heart disease (subSMQ narrow terms only); Hypertension (SMQ narrow terms only); Cardiac failure (SMQ narrow terms only); Cardiomyopathy (SMQ narrow terms only); Ischaemic CNS vascular conditions (subSMQ under CNS vascular disorders, all terms are Narrow); Dyslipidaemia (SMQ, all terms are Narrow); Hyperglycaemia / new onset diabetes mellitus (SMQ, narrow terms only).

Approximately 17% to 19% of patients in the Phase 3 clinical trials had pre-existing cardiac risk factors such as: hypertension (GMB Pooled 8% vs PBO 7%), hypercholesterolemia (2.4% vs 4.3%), hyperlipidaemia (3% in both groups), Type 2 Diabetes Mellitus (1.4% vs 1.2%), dyslipidaemia (1.4% vs 0.8%). No patient reported a pre-existing condition or medical history of variant or microvascular angina at baseline.

Framingham risk score (FRS) is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual. Cardiovascular risk factors such as age, gender, smoking, systolic blood pressure and cholesterol are included. FRS scores were obtained for study subjects to further evaluate their CV risk. As expected the mean and median FRS were higher in patients with CV risk at baseline compared to those without risk.

Of female patients, 21%, 20% and 18% (placebo, GMB 120 mg and GMB 240 mg respectively) were classified as having baseline CV risk according to the Applicant's classification. In female patients, the mean and median FRS calculated CV risks were small, ≤ 1% per 10 years, regardless of CV risk class "yes" or "no". Comparing the 3rd quartile and the maximum risk shows that there may be female patients with somewhat higher CV risk in the "yes" group compared to the "no" group.

In male patients, 26%, 29% and 27% (placebo, GMB 120 mg and GMB 240 mg respectively) were classified as having baseline CV risk according to the applicant. The 10 years risk of CV disease based on FRS scores was similar in GMB and placebo treated patients. According to FRS classification, male patients in the upper quartile in the "yes" group have a moderate to high 10 year risk for CV disease and male study patients clearly had a higher baseline CV risk compared to female study subjects.

Migraine is more common in women than in men, and in young and middle aged people than in the elderly. This is reflected correctly in the study population. Patients ≥ 65 years of age and patients at risk for acute and/or serious cardiovascular risk were excluded from the trials. Consequently, the study population consisting of mainly middle aged women, in general a low risk population is not expected to provide much information about the impact of GMB in cardiovascular disease. Migraine, especially with a severity motivating prophylaxis, is uncommon in patients older than 65 years. The main concern for this age group is the generally increased cardiovascular risk and disease. Thus, it is more important to gain information about the interaction between GMB and CV disease than GMB and age > 65 years. Male migraine patients may be of special interest and young women with migraine aura.

In Analysis Set A, TEAEs in the Cardiac Disorders SOC occurred with a similar frequency in GMB Pooled group (11/1435, 0.8%) and PBO group (11/1451, 0.8%). Most events in the GMB treated group occurred in the GMB 240 mg group (9/11), with a statistically significant higher frequency in the GMB 240 mg group compared to the GMB 120 mg (1.23% vs 0.28%).

In order to identify TEAEs Likely cardiovascular in nature, the applicant used 9 MedDRA SMQs (specifically broad and narrow terms) and the list of events was then medically reviewed to determine if the terms identified represented likely cardiovascular events. The number of patients with at least 1 TEAE likely cardiovascular in nature (broad and narrow terms) were the following: PBO 42/1451 (2.89%), GMB 120 mg 18/705 (2.55%), GMB 240 mg 24/ 730 (3.29%), GMB Pooled 42/ 1435 (2.93%). No clinically relevant or statistically significant difference in the frequencies of TEAEs likely cardiovascular in nature was observed between placebo and any galcanezumab group or between the galcanezumab 120 mg and 240 mg dose groups.

Table 14. Patients with ≥ 1 Treatment-Emergent Adverse Events Likely Cardiovascular in Nature (9 MedDRA SMQs, broad and narrow terms)
Analysis Set A

			vs. PBO			vs. GMB 120 mg		
Treatment Group	**N**	**n(%)**	**ORa**	**95% CIa**	**P-value b**	**ORa**	**95% CIa**	**P-value b**
Placebo	1451	42 (2.89)						
GMB 120 mg	705	18 (2.55)	0.88	(0.50, 1.54)	.648			
GMB 240 mg	730	24 (3.29)	1.14	(0.69, 1.90)	.606	1.31	(0.71, 2.44)	.389
GMB_Pooled	1435	42 (2.93)	1.01	(0.66, 1.56)	.958			

Abbreviations: CI = confidence interval; CMH = Cochran–Mantel–Haenszel; GMB = galcanezumab; GMB_Pooled = GMB 120 mg and GMB 240 mg pooled; N = number of patients in the analysis population; n = number of patients within each specific category; OR = Mantel-Haenszel odds ratio; PBO = placebo.

a Mantel-Haenszel odds ratio stratified by study and 95% CI (CI calculated if ≥4 events in numerator and ≥1 event in denominator).

b p-values are from CMH test of general association stratified by study.

Table 15 TEAE Likely Cardiovascular in Nature Patients with at Least One Narrow Scope CV PT Analysis Set A Double-Blind Treatment Phase

SMQ	**Treatment Group**	**n/N (%)**	**Odds Ratio vs Placebo**	**p-value vs Placebo**
Unique patients reporting ≥1 TEAE CV in nature	Placebo	**27**/1451 (**1.86**)		
	GMB_Pooled	**25**/1435 (**1.74**)	**0.94**	**.81**
Cardiac arrhythmias	Placebo	6/1451 (0.41)		
	GMB_Pooled	5/1435 (0.35)	0.84	.78

Cardiac failure	Placebo	1/1451 (0.07)		
	GMB_Pooled	0/1435 (0.00)	0.00	.32
Cardiomyopathy	Placebo	0/1451 (0.00)		
	GMB_Pooled	0/1435 (0.00)	--	--
Central nervous system vascular disorders	Placebo	0/1451 (0.00)		
	GMB_Pooled	1/1435 (0.07)	--	.31
Embolic and thrombotic events	Placebo	4/1451 (0.28)		
	GMB_Pooled	4/1435 (0.28)	1.01	.99
Hypertension	Placebo	18/1451 (1.24)		
	GMB_Pooled	16/1435 (1.11)	0.90	.76
Ischaemic heart disease	Placebo	1/1451 (0.07)		
	GMB_Pooled	2/1435 (0.14)	2.02	.56
Pulmonary hypertension	Placebo	0/1451 (0.00)		
	GMB_Pooled	0/1435 (0.00)	--	--
Torsade de pointes/QT prolongation	Placebo	2/1451 (0.14)		
	GMB_Pooled	2/1435 (0.14)	1.01	.99

Abbreviations: CV = cardiovascular; GMB = galcanezumab; GMB_Pooled = GMB 120 mg and GMB 240 mg pooled; PT = Preferred Term; N = number of patients in the analysis population; n = number of patients within each specific category; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

For the nine standardised MedDRA queries analysed, there was one significant difference between GMB treated patients and placebo. With the incidence rates calculated for CV events based on epidemiological studies, statistically significant results are not necessarily expected with this number of patients and exposure time.

For the SMQ Pulmonary hypertension there was a significant difference between GMB treated patients and placebo when looking at broad and narrow scope preferred terms. Two of the three cases contributing to this result, were found unlikely to have pulmonary hypertension.

- For the Embolic and thrombotic events SMQ, four patients in the 240 mg GMB group and four placebo patients had treatment emergent CV AEs, (OR 1.99) were captured. Three of these events were SAE. For the GMB treated patients, FRS corresponded to a 10 year risk for CV disease of ≤1% and all belonged to the CV risk group "no". Two of the placebo patients had clear CV risk factors whereas all 4 events in the GMB-treated patients occurred unexpectedly in patients without CV risk factors.

Ischemic heart disease SMQ found 1 placebo patient with myocardial infarction and one 240 mg GMB patient also with myocardial infarction. These have already been described above in the thrombotic section. Two other GMB treated patients were captured by the Ischemic heart disease SMQ.

The other two TEAE in the SMQ ischemic heart disease that occurred in galcanezumab treated patients were: TEAE of ECG signs of ischemia (galcanezumab 120 mg to galcanezumab 240 mg), in a 49-year-old male, who smoked and had a pre-existing ECG ischemic finding at screening; and TEAE of ECG T wave abnormal (galcanezumab 120 mg), in a 55-year old female, without cardiovascular risk factors, which occurred on the same day of starting treatment with galcanezumab.

The table below shows severe CV AE in Analysis set A. All cases have been discussed above in the thromboembolic AE section.

Table 16 - **Severe cardiovascular events in analysis set A**

Preferred Term	1) Placebo (N=1451) n(%)		2) GMB120mg (N=705) n(%)		3) GMB240mg (N=730) n(%)		4) GMB_Pooled (N=1435) n(%)	
Patients with >= 1 SAE	3	(0.21)	0	(0.00)	3	(0.41)	3	(0.21)
Acute myocardial infarction	0	(0.00)	0	(0.00)	1	(0.14)	1	(0.07)
Pulmonary embolism	1	(0.07)	0	(0.00)	1	(0.14)	1	(0.07)
Transient ischaemic attack	0	(0.00)	0	(0.00)	1	(0.14)	1	(0.07)
Deep vein thrombosis	1	(0.07)	0	(0.00)	0	(0.00)	0	(0.00)
Myocardial infarction	1	(0.07)	0	(0.00)	0	(0.00)	0	(0.00)

- In addition to the SAEs noted for Analysis Set A, 4 SAEs were reported by 3 galcanezumab-treated patients in Analysis Set E: acute myocardial infarction and angina unstable in a patient with cardiovascular risk factors, cardiac failure congestive, in a patient with a final diagnosis of congenital cardiomyopathy, ruptured cerebral aneurysm in a patient with a final diagnosis of mycotic aneurysm and popliteal artery occlusion leading to knee amputation in a patient with multiple cardiovascular risk factors,including diabetes. Furthermore, a healthy subject in a phase 2 study experienced a SAE of atrial fibrillation, moderate in severity, 69 days after receiving a single dose of 300 mg lyophilized galcanezumab. The event was judged by the investigator to be possibly related to study treatment as no alternative causes were identified.

The proportion of patients reporting cardiovascular events did not vary based on the presence or absence of "cardiovascular risk" (as defined above) in the GMB 120 and 240 mg group.

Looking at CV AEs in patients with treatment emergent changes in blood pressure, pulse, quantitative and qualitative changes in ECG, this mostly didn't show any differences of interest between placebo and GMB treated patients. Of patients with TE quantitative changes in ECG, two patients in the placebo group (2.56%) and two patients in the GMB 240 mg group (5.26%) had TE cardiac arrhythmias. For pooled GMB patients, there is no difference in incidence compared to placebo and with this few cases no conclusions can be drawn. However the time period is short and the CV effect of example given hypertension, if not severe hypertension, may appear in a longer time span than 6 months.

Eight galcanezumab treated patients and 4 PBO treated patients reported a pre-existing condition or medical history of Raynaud's phenomenon. All patients, except 1, were females. One patient reported worsening of Raynaud's after the second dose (galcanezumab 150 mg/2 weeks), which resolved in 5 days. The study investigator considered the event related to treatment. The patient completed treatment (6 total doses) and the study with no reoccurrence. The limited available data do not allow to draw conclusions on galcanezumab's role in triggering a reoccurrence or worsening of Raynaud's phenomenon.

Cardiovascular findings in analysis set E (All Galcanezumab treated patients) and the long term studies CGAI and CGAJ

Severe AE, cardiovascular in nature in analysis set E not described in set A are discussed above. Among patients with categorical changes of interest in blood pressure, pulse, quantitative or qualitative changes in ECG, the proportion of patients in the galcanezumab pooled group reporting cardiovascular TEAEs was similar in set E to the proportions observed in Analysis Set A. The long-term safety of galcanezumab, including cardiovascular safety will be further followed in the planned Category 3 pharmacovigilance study.

Table 17 - Increase in cardiovascular medications in long term study CGAJ

		GMB-Treated Time*a					
				Cardiovascular Disease Risk Group			
		All Patients		Yes		No	
Medication Group	Treatment Group	N	n (%)	N	n (%)	N	n (%)
Anti-hypertensives	GMB120mg	129	3 (2.33)	22	1 (4.55)	107	2 (1.87)
	GMB240mg	141	8 (5.67)	28	5 (17.86)	113	3 (2.65)
	GMB_Pooled	270	11 (4.07)	50	6 (12.00)	220	5 (2.27)
Anti-arrhythmics	GMB120mg	129	0 (0.00)	22	0 (0.00)	107	0 (0.00)
	GMB240mg	141	2 (1.42)	28	2 (7.14)	113	0 (0.00)
	GMB_Pooled	270	2 (0.74)	50	2 (4.00)	220	0 (0.00)
Anti-anginals	GMB120mg	129	0 (0.00)	22	0 (0.00)	107	0 (0.00)
	GMB240mg	141	1 (0.71)	28	1 (3.57)	113	0 (0.00)
	GMB_Pooled	270	1 (0.37)	50	1 (2.00)	220	0 (0.00)
Anti-thrombotics	GMB120mg	129	3 (2.33)	22	1 (4.55)	107	2 (1.87)
	GMB240mg	141	5 (3.55)	28	4 (14.29)	113	1 (0.88)
	GMB_Pooled	270	8 (2.96)	50	5 (10.00)	220	3 (1.36)

Abbreviations: GMB = Galcanezumab; GMB_Pooled = GMB120mg and GMB240mg pooled; N = number of patients in the analysis population; n = number of patients within each specific category; Post-Trt = post-treatment phase.
*a, GMB-treated patients while receiving GMB treatment;
*b, GMB-treated patients while and after receiving GMB treatment;
Notes: (1) Increase in medication includes increase in dose or start of new medication.
(2) The following SMQs are used to identify patients in the Cardiovascular Disease Risk Group: Ischaemic heart disease (2 subSMQs following), Myocardial infarction (subSMQ, narrow terms only), Other ischaemic heart disease (subSMQ narrow terms only), Hypertension (SMQ narrow terms only), Cardiac failure (SMQ narrow terms only), Cardiomyopathy (SMQ narrow terms only), Ischaemic CNS vascular conditions (subSMQ under CNS vascular disorders, all terms are Narrow), Dyslipidaemia (SMQ, all terms are Narrow), Hyperglycaemia/new onset diabetes mellitus (SMQ, narrow terms only).
(3) Baseline is any time prior to first GMB treatment.
MedDRA version 19.1 was used.

In long term study CGAJ, the frequency of patients (GMB 120 mg and 240 mg pooled) with baseline CV risk ("yes "group) had a higher incidence of increase or a new start of CV medications compared to analysis set A. For study CGAJ incidence proportions were as follows: anti-hypertensives 12.0%,

anti-thrombotics 10.0 and anti-arrhythmics: 4.0%. The corresponding numbers for analysis set A were 4.1%, 1.2%, and 0.0%, respectively. The higher incidence proportions of CV medications for study CGAJ could partly be due to longer study duration, but the incidence proportions are about 3-8 times higher and the study duration about the double.

The greater proportion of patients with higher GMB doses needing anti-hypertensives in analysis set E and study CGAJ, is consistent with the increased proportions of patients meeting TE categories or levels for high blood pressure in the higher doses.

Table 4.48. Exposure-Adjusted Analyses for Increase in Cardiovascular Concomitant Medications Study CGAJ

Medication Group	Dose Group	n/TPY	EAIR (95% CI) All Patients N=270	n/TPY	EAIR (95% CI) CV Disease Risk Group-Yes N=50	n/TPY	EAIR (95% CI) CV Disease Risk Group-No N=220
Anti-hypertensives	GMB 120 mg	3/111.26	2.70 (0.56, 7.88)	1/19.97	5.01 (0.13, 27.90)	2/91.29	2.19 (0.27, 7.91)
	GMB 240 mg	8/115.77	6.91 (2.98, 13.62)	5/21.13	23.66 (7.68, 55.21)	3/94.64	3.17 (0.65, 9.26)
	GMB_Pooled	11/227.03	4.85 (2.42, 8.67)	6/41.10	14.60 (5.36, 31.77)	5/185.93	2.69 (0.87, 6.28)
Anti-arrhythmics	GMB 120 mg	0/112.48	0.00 (NA, 3.28)	0/20.10	0.00 (NA, 18.35)	0/92.38	0.00 (NA, 3.99)
	GMB 240 mg	2/119.10	1.68 (0.20, 6.07)	2/22.84	8.76 (1.06, 31.64)	0/96.26	0.00 (NA, 3.83)
	GMB_Pooled	2/231.58	0.86 (0.10, 3.12)	2/42.93	4.66 (0.56, 16.83)	0/188.64	0.00 (NA, 1.96)
Anti-anginals	GMB 120 mg	0/112.48	0.00 (NA, 3.28)	0/20.10	0.00 (NA, 18.35)	0/92.38	0.00 (NA, 3.99)
	GMB 240 mg	1/119.69	0.84 (0.02, 4.66)	1/23.43	4.27 (0.11, 23.78)	0/96.26	0.00 (NA, 3.83)
	GMB_Pooled	1/232.17	0.43 (0.01, 2.40)	1/43.52	2.30 (0.06, 12.80)	0/188.64	0.00 (NA, 1.96)
Anti-thrombotics	GMB 120 mg	3/111.61	0.69 (0.55, 7.86)	1/19.73	5.07 (0.13, 28.24)	2/91.88	2.18 (0.26, 7.86)
	GMB 240 mg	5/117.65	4.25 (1.38, 9.92)	4/22.35	17.90 (4.88, 45.83)	1/95.30	1.05 (0.03, 5.85)
	GMB_Pooled	8/229.26	3.49 (1.51, 6.88)	5/42.08	11.88 (3.86, 27.73)	3/187.18	1.60 (0.33, 4.68)

Abbreviations: CI = confidence interval; CV = cardiovascular; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; GMB_Pooled = GMB 120 mg and GMB 240 mg pooled; N = number of patients in the analysis population; n = number of patients within each specific category; N/A = not applicable; TPY = total patient-year-at-risk.

Source: /lillyce/prd/ly2951742/migraine_120day/output/shared/eu_submission/fqcvmed_eair_j.rtf.

Table 4.49. Exposure-Adjusted Analyses for Increase in Cardiovascular Concomitant Medications GMB-Treated Time Analysis Set E

Medication Group	Dose Group	n/TPY	EAIR (95% CI) All Patients N=2586	n/TPY	EAIR (95% CI) CV Disease Risk Group-Yes N=460	n/TPY	EAIR (95% CI) CV Disease Risk Group-No N=2126
Anti-hypertensives	GMB <120 mg	0/31.72	0.00 (NA, 11.63)	0/6.50	0.00 (NA, 56.78)	0/25.22	0.00 (NA, 14.63)
	GMB 120 mg	15/522.37	2.87 (1.61, 4.74)	8/86.84	9.21 (3.98, 18.15)	7/435.53	1.61 (0.65, 3.31)
	GMB 240 mg	30/878.12	3.42 (2.31, 4.88)	15/160.97	9.32 (5.22, 15.37)	15/717.14	2.09 (1.17, 3.45)
	GMB 300 mg	4/38.70	10.34 (2.82, 26.46)	3/6.56	45.73 (9.43, 133.65)	1/32.14	3.11 (0.08, 17.33)
	GMB_All	49/1470.91	3.33 (2.46, 4.40)	26/260.87	9.97 (6.51, 14.60)	23/1210.04	1.90 (1.20, 2.85)
Anti-arrhythmics	GMB <120 mg	0/31.72	0.00 (NA, 11.63)	0/6.50	0.00 (NA, 56.78)	0/25.22	0.00 (NA, 14.63)
	GMB 120 mg	0/528.09	0.00 (NA, 0.70)	0/89.80	0.00 (NA, 4.11)	0/438.29	0.00 (NA, 0.84)
	GMB 240 mg	6/887.16	0.68 (0.25, 1.47)	3/165.70	1.81 (0.37, 5.29)	3/721.46	0.42 (0.09, 1.22)
	GMB 300 mg	0/39.02	0.00 (NA, 9.45)	0/6.88	0.00 (NA, 53.64)	0/32.14	0.00 (NA, 11.48)
	GMB_All	6/1485.99	0.40 (0.15, 0.88)	3/268.87	1.12 (0.23, 3.26)	3/1217.11	0.25 (0.05, 0.72)
Anti-anginals	GMB <120 mg	0/31.72	0.00 (NA, 11.63)	0/6.50	0.00 (NA, 56.78)	0/25.22	0.00 (NA, 14.63)
	GMB 120 mg	0/528.09	0.00 (NA, 0.70)	0/89.80	0.00 (NA, 4.11)	0/438.29	0.00 (NA, 0.84)
	GMB 240 mg	5/887.40	0.56 (0.18, 1.31)	2/166.29	1.20 (0.15, 4.34)	3/721.11	0.42 (0.09, 1.22)
	GMB 300 mg	0/39.02	0.00 (NA, 9.45)	0/6.88	0.00 (NA, 53.64)	0/32.14	0.00 (NA, 11.48)
	GMB_All	5/1486.23	0.34 (0.11, 0.79)	2/269.46	0.74 (0.09, 2.68)	3/1216.77	0.25 (0.05, 0.72)
Anti-thrombotics	GMB <120 mg	0/31.72	0.00 (NA, 11.63)	0/6.50	0.00 (NA, 56.78)	0/25.22	0.00 (NA, 14.63)
	GMB 120 mg	11/525.03	2.10 (1.05, 3.75)	4/88.91	4.50 (1.23, 11.52)	7/436.11	1.61 (0.65, 3.31)
	GMB 240 mg	29/877.65	3.30 (2.21, 4.75)	7/164.30	4.26 (1.71, 8.78)	22/713.35	3.08 (1.93, 4.67)
	GMB 300 mg	0/39.02	0.00 (NA, 9.45)	0/6.88	0.00 (NA, 53.64)	0/32.14	0.00 (NA, 11.48)
	GMB_All	40/1473.42	2.71 (1.94, 3.70)	11/266.59	4.13 (2.06, 7.38)	29/1206.83	2.40 (1.61, 3.45)

Abbreviations: CI = confidence interval; CV = cardiovascular; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; GMB_All = patients treated with any GMB dose in any duration; N = number of patients in the analysis population; n = number of patients within each specific category; N/A = not applicable; TPY = total patient-year-at-risk.

Source: /lillyce/prd/ly2951742/migraine_120day/output/shared/eu_submission/fqcvmed_eair_e.rtf.

The Applicant provided exposure-adjusted analyses using time-at-risk-adjusted incidence rate (per 100 patient-years) for use of CV medications. The EAIRs for the 300 mg dose are numerically more unfavourable compared to the other dose groups for a range of events, including treatment-emergent systolic blood pressure, use of concomitant antihypertensives (increase in dose or start of new medication), rash of potential or likely hypersensitivity in nature, and treatment-emergent abnormally high hepatic enzyme values (ALP, ALAT, ASAT).

The EAIRs for the CV concomitant medications were higher for the galcanezumab 240 mg dose group compared to galcanezumab 120 mg for all 4 medication classes for the 'All Patients' group and CV Disease Risk Group-Yes.

Table 5.12. Exposure-Adjusted Treatment-Emergent Adverse Events Likely Cardiovascular in Nature Patients with at Least One Narrow Scope CV PT Analysis Set E GMB-Treated Time and Post-Treatment Phase

	Initial Submission GMB_All (N=2586)						Safety Update GMB_All (N=2586)					
	GMB-Treated Time[a]			GMB-Treated Time + Post-Treatment[b]			GMB-Treated Time[a]			GMB-Treated Time + Post-Treatment[b]		
SMQ	n	TPY	EAIR (95% CI)	n	TPY	EAIR (95% CI)	n	TPY	EAIR (95% CI)	n	TPY	EAIR (95% CI)
Cardiac arrhythmias	14	1246.69	1.12 (0.61, 1.88)	15	1581.14	0.95 (0.53, 1.56)	17	1481.77	1.15 (0.67, 1.84)	19	2024.92	0.94 (0.56, 1.47)
Cardiac failure	1	1250.58	0.08 (0.00, 0.45)	1	1587.36	0.06 (0.00, 0.35)	1	1487.20	0.07 (0.00, 0.37)	2	2034.15	0.10 (0.01, 0.36)
Cardiomyopathy	0	1250.64	0.00 (NA, 0.29)	0	1587.43	0.00 (NA, 0.23)	0	1487.26	0.00 (NA, 0.25)	1	2034.21	0.05 (0.00, 0.27)
CNS vascular disorders	1	1250.61	0.08 (0.00, 0.45)	2	1587.05	0.13 (0.02, 0.46)	2	1487.21	0.13 (0.02, 0.49)	3	2034.00	0.15 (0.03, 0.43)
Embolic and thromb. events	5	1249.67	0.40 (0.13, 0.93)	6	1585.64	0.38 (0.14, 0.82)	6	1485.88	0.40 (0.15, 0.88)	8	2031.61	0.39 (0.17, 0.78)
Hypertension	33	1241.20	2.66 (1.83, 3.73)	40	1572.47	2.54 (1.82, 3.46)	39	1474.78	2.64 (1.88, 3.62)	49	2011.76	2.44 (1.80, 3.22)
Ischaemic heart disease	3	1249.59	0.24 (0.05, 0.70)	3	1586.18	0.19 (0.04, 0.55)	3	1486.21	0.20 (0.04, 0.59)	4	2032.21	0.20 (0.05, 0.50)
Pulmonary hypertension	0	1250.64	0.00 (NA, 0.29)	0	1587.43	0.00 (NA, 0.23)	0	1487.26	0.00 (NA, 0.25)	0	2034.44	0.00 (NA, 0.18)
TdP/QT prolongation	4	1249.41	0.32 (0.09, 0.82)	4	1585.25	0.25 (0.07, 0.65)	5	1485.66	0.34 (0.11, 0.79)	5	2031.64	0.25 (0.08, 0.57)

Abbreviations: CI = confidence interval; CNS = central nervous system; CV = cardiovascular; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; GMB_All = patients treated with any GMB dose in any duration; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients in specific category; NA = not applicable; PT= Preferred Term; SMQ = Standardized MedDRA Query; TdP = Torsade de Point; thromb. = thrombotic; TPY = total patient-year-at-risk.

Note: (1) Shaded columns contain initial submission data provided here for ease of comparison. (2) The table includes likely cardiovascular events in nature identified by medical review; (3) EAIR = 100 times the number of patients experiencing the event divided by event-specific total patient-year-at-risk.

MedDRA versions 19.1 (initial submission) and 20.0 (safety update) were used.

[a] GMB-treated patients while receiving GMB treatment.

[b] GMB-treated patients while and after receiving GMB treatment.

Sources: EU SCS Table APP.1.245 (initial submission) and /lillyce/prd/ly2951742/migraine_120day/ output/shared/fqcveair_e_mr.rtf (safety update).

Blood pressure

In patients experiencing categorical changes of interest in blood pressure and pulse, the proportion of patients reporting TEAEs cardiovascular in nature in galcanezumab treated patients was equal or lower to the ones observed in PBO treated patients, apart from one serious event of TIA (classified both in the CNS vascular disorder SOC and in the thrombotic and embolic SOC) experienced by 1/177 (0.56%) of GMB treated patients compared to 0 events among the 165 placebo treated patients; and one event in the SOC pulmonary hypertension (Patients with at least one narrow or broad scope PT) experienced by 1/177 (0.56%) of GMB treated patients with Categorical Changes of Interest in Blood Pressure and Pulse compared to 0 events among the 165 placebo treated patients with Categorical Changes of Interest in Blood Pressure and Pulse.

Adverse Events related to injection sites

As discussed in the section about common adverse events, Injection site pain, injection site reaction (not further specified), injection site erythema and injection site pruritus were considered ADR. They mostly occur on the day of injection.

MAA includes GMB administration via prefilled syringe or prefilled pen (autoinjector). A randomized comparison of AEs in patients utilizing different injection devices shows that 12.5% of patients using the autoinjector experienced injection site pain versus 2.5% of patients using the syringe in the clinical

pharmacology study CGAQ in which healthy subject received 240 mg (2 doses) of galcanezumab either in pre-filled syringe or pre-filled pen one time. In the pivotal placebo controlled trial the prefilled syringe was used. During the long term study CGAJ, the prefilled pen (autoinjector) became available. Thus safety data are to a majority based on the device causing less pain. Based on the company's analysis for the limited group of patients who used both a prefilled syringe and an autoinjector at least 1 time (n= 179), one could conclude that injection site events tended to occur more frequently with the autoinjector.

Immunogenicity

"Injection site reactions", a composite term for all types of injection site reactions, were AEs statistically more common in ADA+ patients (11.1%) than in ADA negative patients (5.9%). "Injection site inflammation," was reported in 1.5% of treatment-emergent ADA+ patients compared to 0.1% of patients without treatment-emergent ADA (p-value<.001). The majority of those patients had the last "injection site reaction" event reported before the detection of TE ADA, after which no such AEs occurred.

Hypersensitivity events

In analysis set A, hypersensitivity reactions, both immediate and non-immediate, were significantly more common in GMB patients (0.98%, 3.83%) than in placebo (0.34%, 2.31%). Injection site reactions were the most common hypersensitivity AEs. One placebo treated patient and four GMB patients discontinued due to hypersensitivity reactions of which one was on the day of injection. There were no serious hypersensitivity reactions in placebo controlled studies. No case of immediate or non-immediate anaphylaxis was captured by the narrow PTs.

Urticaria has been identified as an ADR by the applicant. Overall, in the placebo-controlled studies of Analysis Set A, the incidence proportions for urticaria were 0.34% for placebo, 0.28% for galcanezumab 120 mg and 0.14% for galcanezumab 240 mg, respectively. None of the cases were deemed serious or severe in intensity. Two serious, but non-immediate cases of urticaria were reported later on, one in an open label phase and one post treatment. Of these, one case can possibly be related to galcanezumab treatment. The second case may be related, but other drugs (ciprofloxacin and norfloxacin) might also have contributed to the reaction. There were no serious (other) hypersensitivity reactions in placebo controlled studies.

Hypersensitivity treatment-emergent adverse events by treatment-emergent ADA status

Table 18 - Hypersensitivity reactions in relation to ADA status in studies CGAG, CGAH, CGAI and CGAJ, GMB treatment time

SMQ	TE ADA+ Status	N	n(%)	Odds Ratio[a]	p-value[a]
Anaphylactic reaction					
Patients with at least one Narrow scope PT	Y	135	0 (0.00)		
	N	1955	0 (0.00)		
Patients with at least one Narrow or Broad scope PT	Y	135	11 (8.15)	1.82	.066
	N	1955	88 (4.50)		
Angioedema					
Patients with at least one Narrow scope PT	Y	135	0 (0.00)	0	.332
	N	1955	13 (0.66)		
Patients with at least one Narrow or Broad scope PT	Y	135	1 (0.74)	0.58	.584
	N	1955	24 (1.23)		
Hypersensitivity					
Patients with at least one Narrow scope PT	Y	135	9 (6.67)	1.09	.813
	N	1955	119 (6.09)		
Patients with at least one Narrow or Broad scope PT	Y	135	15 (11.11)	1.45	.196
	N	1955	150 (7.67)		

Table 19 - Hypersensitivity reactions in relation to ADA status in studies CGAG, CGAH, CGAI and CGAJ, GMB treatment time + post treatment time

SMQ	TE ADA+ Status	N	n(%)	Odds Ratio[a]	p-value[a]
Anaphylactic reaction					
Patients with at least one Narrow scope PT	Y	183	0 (0.00)		
	N	1908	0 (0.00)		
Patients with at least one Narrow or Broad scope PT	Y	183	15 (8.20)	1.95	.019
	N	1908	87 (4.56)		
Angioedema					
Patients with at least one Narrow scope PT	Y	183	0 (0.00)	0	.249
	N	1908	16 (0.84)		
Patients with at least one Narrow or Broad scope PT	Y	183	1 (0.55)	0.40	.343
	N	1908	29 (1.52)		
Hypersensitivity					
Patients with at least one Narrow scope PT	Y	183	13 (7.10)	1.22	.514
	N	1908	118 (6.18)		
Patients with at least one Narrow or Broad scope PT	Y	183	21 (11.48)	1.59	.059
	N	1908	147 (7.70)		

The tables above show proportions of patients with different hypersensitivity reactions in relation to TE ADA status. The first table shows GMB treatment phase and the second GMB treatment + post treatment phase. The incidence proportion of broad scope anaphylactic reactions is almost double in patients with TE ADA, a difference that is significant (p=0.019) when the post treatment phase is included. Hypersensitivity reactions don't reach statistical significance, but there is a trend (p=0.059) when post treatment phases is added. The applicant was requested to further assess a possible association between immunogenicity and TEAEs. A patient level examination of TEAEs of interest in patients with treatment-emergent ADA was conducted. Overall, this review did not demonstrate a clear temporal association between these AEs and the presence of treatment-emergent ADA.

Upper Respiratory Tract Infections (URTI)

Preferred terms within the HLT of Upper respiratory tract infections were determined to be AEs of interest based on findings from the Phase 2 studies (ART-01 and CGAB), where a higher percentage of GMB treated patients presented Upper respiratory tract infection (PT) compared to PBO treated patients (Study ART-01, GMB 150 mg 24.3% vs PBO 10.9%; Study CGAB, GMB 120-mg 11.4% vs PBO 8.8%; GMB 300 mg 6.0%).

In analysis set A, the incidence of URTIs was comparable between the galcanezumab 120-mg dose group (15.3%), the galcanezumab 240 mg dose group (13.0%) and placebo (12.8%). Among the patients who reported treatment-emergent URTIs, the majority reported events of mild to moderate severity. Most cases resolved within a few days, but in some cases the events had a long duration.

Acute sinusitis occurred significantly more often in GMB treated patients (4/1435) than in placebo (0/1451), p=0.044. In analysis by SOC, pneumonia occurred significantly more in GMB treated patients (9/1435) than in placebo treated patients (2/1451) p=0.033 (GMB Pooled: 9/ 1435, 0.6%: 5 patients GMB 240, 4 patients GMB 120; PBO 2/1451 0.14%). In the investigator's opinion all of these events except one were not related to study drug. None of the cases of pneumonia resulted in discontinuation of treatment or were reported as SAEs. There was no apparent pattern in time to onset of the events, with the cases resolving, and all of the patients completed the treatment phases of the respective studies.

In Analysis Set E, exposure-adjusted incidence rates of URTI TEAEs (by event PTs) in Analysis Set A were comparable to Analysis Set E. The comparison with EAIRs in Study CGAI Galcanezumab-Treated Time and Long-Term Safety Study CGAJ did not suggest an association between increased URTIs and treatment duration. In Long-Term Safety Study CGAJ, the EAIR for sinusitis and pharyngitis was higher, but this was not consistent with Study CGAI Galcanezumab-Treated Time, which also includes patients treated up to 1 year. However in study CGAI, the EIAR for upper respiratory tract infection was higher than in Analysis Set A.

Hepatic safety

Hepatic safety investigated by MEDRA SMQ, showed TEAEs related to hepatic safety in less than 1% across treatment groups. A significant imbalance in the number of patients in the 240-mg dose group (n=6, 0.8%) as compared to placebo (n=3, 0.2%) reported a narrow scope PT for the Liver related investigations, signs and symptoms, p-value = 0.034. The Applicant provided an updated analysis due to the following revisions: an ascites event in one patient in the 240 mg group was removed in the updated analysis because the event was reported as due to pancreatitis and thus not an hepatic event; an additional event was included in the placebo group because the event reported (liver function test increased) changed from a broad scope search term to a narrow scope search term due to a change in the MedDRA version. Results of the updated analysis no longer show a statistically significant difference between these 2 treatment groups in frequency of TEAEs in the narrow scope SMQ "Liver related investigations, signs and symptoms."

Contradictory results were obtained for liver analytes, please see tables below, some data support increases ALT and AST with increased dose, i e consistent with the finding of increased liver investigations. However, no difference was seen between placebo and GMB in the randomized phases, nor from long term study CGAJ.

The AEs of high ALP, ALT and AST are shown for three different analysis sets in the tables below.

Table 20 The AEs of high ALP, ALT and AST in analysis set E

Table APP.1.44. Treatment-Emergent Abnormal Laboratory Measures at Any Time
GMB-Treated Population
Analysis Set E (Studies ART-01, CGAB, CGAG, CGAH, CGAI, and CGAJ)
GMB-Treated Time and Post-Treatment Phase

		GMB-Treated Time*a															
		<GMB120mg			GMB120mg			GMB240mg			GMB300mg			GMB_All			
Lab Category Lab test	Direction	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	
Chemistry																	
Albumin	Low	127	1	(0.79)	893	0	(0.00)	1188	0	(0.00)	168	0	(0.00)	2376	1	(0.04)	
	High	123	1	(0.81)	838	22	(2.63)	1136	24	(2.11)	167	1	(0.60)	2264	48	(2.12)	
Alkaline Phosphatase	Low	125	0	(0.00)	884	0	(0.00)	1176	1	(0.09)	168	0	(0.00)	2353	1	(0.04)	
	High	123	0	(0.00)	864	12	(1.39)	1144	20	(1.75)	165	4	(2.42)	2296	36	(1.57)	
Alanine Aminotransferase	Low	126	0	(0.00)	883	5	(0.57)	1188	3	(0.25)	168	0	(0.00)	2365	8	(0.34)	
	High	105	3	(2.86)	801	48	(5.99)	1044	70	(6.70)	141	9	(6.38)	2091	130	(6.22)	
Aspartate Aminotransferase	Low	126	0	(0.00)	886	3	(0.34)	1187	1	(0.08)	166	1	(0.60)	2365	5	(0.21)	
	High	108	2	(1.85)	843	29	(3.44)	1125	48	(4.27)	147	8	(5.44)	2223	87	(3.91)	
Direct Bilirubin	Low	125	0	(0.00)	357	84	(23.53)	410	112	(27.32)	63	0	(0.00)	955	196	(20.52)	
	High	125	0	(0.00)	887	0	(0.00)	1186	1	(0.08)	63	0	(0.00)	2261	1	(0.04)	

Table 21 - The AEs of high ALP, ALT and AST in study CGAI

Table APP.1.45. Treatment-Emergent Abnormal Laboratory Measures at Any Time
GMB-Treated Population
Study CGAI
GMB-Treated Time and Post-Treatment Phase

		GMB-Treated Time*a								
		GMB120mg			GMB240mg			GMB_Pooled		
Lab Category Lab test	Direction	N	n	(%)	N	n	(%)	N	n	(%)
Chemistry										
Albumin	Low	281	0	(0.00)	627	0	(0.00)	908	0	(0.00)
	High	262	5	(1.91)	594	14	(2.36)	856	19	(2.22)
Alkaline Phosphatase	Low	278	0	(0.00)	621	1	(0.16)	899	1	(0.11)
	High	271	2	(0.74)	598	14	(2.34)	869	16	(1.84)
Alanine Aminotransferase	Low	280	1	(0.36)	627	0	(0.00)	907	1	(0.11)
	High	259	12	(4.63)	541	41	(7.58)	800	53	(6.63)
Aspartate Aminotransferase	Low	279	1	(0.36)	626	0	(0.00)	905	1	(0.11)
	High	264	8	(3.03)	594	26	(4.38)	858	34	(3.96)
Direct Bilirubin	Low	80	18	(22.50)	195	51	(26.15)	275	69	(25.09)
	High	277	0	(0.00)	625	0	(0.00)	902	0	(0.00)

Abbreviations: GMB = Galcanezumab; GMB_Pooled = GMB120mg and GMB240mg pooled; for treatment-emergent Low, N = number of patients who have values greater than or equal to the low limit at all baseline visits and at least one nonmissing postbaseline value; for treatment-emergent High, N = number of patients who have values less than or equal to the high limit at all baseline visits and at least one nonmissing postbaseline value; for treatment-emergent abnormal, N = number of patients who have normal values at all baseline visits and at least one nonmissing postbaseline value; n = number of patients within each specific category; Post-Trt = post-treatment phase.
*a, GMB-treated patients while receiving GMB treatment;
*b, GMB-treated patients while and after receiving GMB treatment;
Note: Baseline is any time prior to first GMB treatment.

Table 22 - The AEs of high ALP, ALT and AST in study CGAJ

Table APP.1.46. Treatment-Emergent Abnormal Laboratory Measures at Any Time
Safety Population
Study CGAJ
GMB-Treated Time and Post-Treatment Phase

Lab Category / Lab test	Direction	GMB-Treated Time*a: GMB120mg N	GMB120mg n (%)	GMB240mg N	GMB240mg n (%)	GMB_Pooled N	GMB_Pooled n (%)
Chemistry							
Albumin	Low	127	0 (0.00)	135	0 (0.00)	262	0 (0.00)
	High	115	5 (4.35)	127	3 (2.36)	242	8 (3.31)
Alkaline Phosphatase	Low	124	0 (0.00)	134	0 (0.00)	258	0 (0.00)
	High	126	4 (3.17)	134	4 (2.99)	260	8 (3.08)
Alanine Aminotransferase	Low	124	1 (0.81)	135	0 (0.00)	259	1 (0.39)
	High	116	16 (13.79)	124	11 (8.87)	240	27 (11.25)
Aspartate Aminotransferase	Low	126	1 (0.79)	135	0 (0.00)	261	1 (0.38)
	High	120	10 (8.33)	132	7 (5.30)	252	17 (6.75)
Direct Bilirubin	Low	57	21 (36.84)	53	21 (39.62)	110	42 (38.18)
	High	127	0 (0.00)	135	0 (0.00)	262	0 (0.00)

Abbreviations: GMB = Galcanezumab; GMB_Pooled = GMB120mg and GMB240mg pooled; for treatment-emergent Low, N = number of patients who have values greater than or equal to the low limit at all baseline visits and at least one nonmissing postbaseline value; for treatment-emergent High, N = number of patients who have values less than or equal to the high limit at all baseline visits and at least one nonmissing postbaseline value; for treatment-emergent abnormal, N = number of patients who have normal values at all baseline visits and at least one nonmissing postbaseline value; n = number of patients within each specific category; Post-Trt = post-treatment phase.
*a, GMB-treated patients while receiving GMB treatment;
*b, GMB-treated patients while and after receiving GMB treatment;
Note: Baseline is any time prior to first GMB treatment.

In analysis set E, the AEs of high ALP, ALT and AST show slightly increasing proportions of patients with increased GMB dose, or at least in the 300 mg dose when considering the shorter observation time for this dose. Looking at study CGAI GMB treated time, there also seems to an increase of liver enzymes AE with increased GMB dose. However, more patients in the open label flex-dose phase were on the higher 240 mg dose, hence more long term data comes from the higher 240 mg dose group which can confound the proportion. Study CGAJ, a fixed dose open label study does not show increased AEs of liver analytes in the higher dose (240 mg). This strengthens the thought that longer observation time is a confounding factor when comparing dose groups in study CGAI and needs further investigation.

There was no SAE due to liver disease/injury. Two patients discontinued due to non-serious AEs. No patient met criteria for Hy's law.

Table 5.23. Exposure-Adjusted Treatment-Emergent Adverse Events for SMQs Related to Hepatic Injury and Function
GMB-Treated Population
GMB-Treated Time
Analysis Set E

	Initial Submission GMB All N=2586			Safety Update GMB All N=2586		
Narrow Scope Preferred Term	n	TPY	EAIR (95% CI)	n	TPY	EAIR (95% CI)
Alanine aminotransferase increased	8	1248.92	0.64 (0.28, 1.26)	11	1485.34	0.74 (0.37, 1.33)
Hepatic enzyme increased	8	1249.06	0.64 (0.28,1.26)	9	1485.03	0.61 (0.28, 1.15)
Aspartate aminotransferase increased	6	1248.92	0.48 (0.18, 1.05)	9	1485.34	0.61 (0.28, 1.15)
Liver function test increased	2	1250.28	0.16 (0.02, 0.58)	2	1486.90	0.13 (0.02, 0.49)
Blood alkaline phosphatase increased	2	1250.06	0.16 (0.02, 0.58)	2	1486.40	0.13 (0.02, 0.49)
Blood bilirubin increased	2	1250.26	0.16 (0.02, 0.58)	2	1486.88	0.13 (0.02, 0.49)
Hepatic steatosis	2	1250.38	0.16 (0.02, 0.58)	2	1486.58	0.13 (0.02, 0.49)
Ascites	1	1250.59	0.08 (0.00, 0.45)	1	1487.20	0.07 (0.00, 0.37)
International normalized ratio increased	1	1250.14	0.08 (0.00, 0.45)	1	1486.36	0.07 (0.00, 0.37)
Liver function test abnormal	1	1250.49	0.08 (0.00, 0.45)	1	1486.77	0.07 (0.00, 0.37)
Portal hypertensive gastropathy	1	1250.41	0.08 (0.00, 0.45)	1	1486.87	0.07 (0.00, 0.37)
Hepatic function abnormal	0	--	-	1	1486.90	0.07 (0.00, 0.37)

Abbreviations: CI = confidence interval; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; GMB_All = patients treated with any GMB dose in any duration; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients within each specific category; SMQ = Standardized MedDRA Query; TPY = total patient-year-at-risk.

Note: Shaded columns contain initial submission data provided here for ease of comparison. EAIR = 100 times the number of patients experiencing the event divided by event-specific total patient-year-at-risk; shaded columns contain initial submission data provided here for ease of comparison.

MedDRA versions 19.1 (initial submission) and 20.0 (safety update) were used.

Sources: lillyce/prd/ly2951742/migraine_submission/output/shared/fqteaehepsmq11.rtf; /lillyce/prd/ly2951742/migraine_120day/output/shared/fqteae_eair_e_ms.rtf (initial submission); lillyce/prd/ly2951742/migraine_120day/output/shared/fqteaehepsmq11.rtf, fqteae_eair_e_4m.rtf (safety update).

Serious Adverse Events Related to Hepatic Safety: Although no hepatic SAEs were identified by the SMQ searches, one patient ([galcanezumab 240 mg]) had ascites and hepatic cysts as symptoms of the SAE of pancreatitis acute.

Discontinuations due to Adverse Events Related to Hepatic Safety: Two patients discontinued due to AEs related to hepatic safety:

1 patient receiving galcanezumab 240 mg discontinued study treatment due to the non- serious AE of hepatic enzyme increase of moderate severity which occurred 64 days after beginning double-blind treatment with galcanezumab 240 mg and following 2 administrations of galcanezumab at this dose. Hepatic lab values remained elevated throughout course of post-treatment phase (washout), eventually returning to normal range after patient had completed the trial. The site investigator attributed the enzyme elevations to physical exertion playing sports.

1 patient receiving galcanezumab 240 mg discontinued study treatment due to non- serious AE of elevated liver enzyme of moderate severity which occurred 86 days after beginning double-blind treatment with galcanezumab 240 mg. Hepatic lab values were measured within normal range at Visit 14 of the post-treatment phase (washout), 106 days after hepatic enzyme elevation was noted. Concomitant medication included acetaminophen/paracetamol and naproxen.

Integrated Analysis set E: 11 additional patients in Analysis set E reported ALT≥3×ULN and AST≥3×ULN and in 5 of these patients ALT and AST elevations were reported as TEAEs. Thus the overall frequency of patients in Analysis set E reporting ALT≥3×ULN and AST≥3×ULN (24/2392) was similar to Analysis set A.

Treatment-Emergent Adverse Events Related to Hepatic Safety: In addition to the 10 galcanezumab-treated patients who had a TEAE related to hepatic lab values discussed above, there were 16 more galcanezumab- treated patients who had TEAEs related to hepatic lab values while on galcanezumab treatment.

An additional 4 patients reported TEAEs related to hepatic safety while not receiving galcanezumab treatment. Three patients reported TEAEs related to hepatic safety during the Post-Treatment Phase (washout) and a fourth patient receiving placebo in Phase 2 Study ART-01 reported an additional TEAE related to hepatic safety. There were no SAEs related to hepatic laboratory values.

Two further events of discontinuations due to AEs related to hepatic enzyme elevations occurred in the safety update period. In one case no definite explanation for the events of ALT increased and AST increased was found although the narrative reports that relevant medications taken prior to the event included ciprofloxacin and fluconazole, both for urinary tract infection. The second patient, discontinued the open-label treatment period due to the non-serious adverse event of hepatic enzyme increased (" elevated liver enzymes") of moderate severity. This was a previous placebo-treated patient with fatty liver infiltration who had elevated ALT and AST during the double-blind treatment period. ALT and AST continued to be elevated in the open-label treatment period.

Evaluation of Suicidal Ideation and Behaviour and Non- Suicidal Self-Injurious Behaviour

Patients with migraine headaches are at a greater risk for suicidality (Breslau et al. 2012); therefore, suicidal ideation and behaviour was assessed in all galcanezumab clinical trials using the Columbia Suicide Severity Rating Scale (Posner et al. 2011).

In Analysis set A, no imbalance was observed between GMB treated patients and PBO in the occurrence of Suicidal Ideation and Behaviour assessed using the Columbia Suicide Severity Rating Scale and Non-Suicidal Self-Injurious Behaviour (one patient in the GMB 240 mg group had preparatory behaviour and active suicidal thoughts and one PBO treated patient had a SAE of attempted suicide; two patient on PBO and one galcanezumab 240 mg treated patient reported a self-injurious behaviour without suicidal intent during the double-blind treatment phase).

Serious adverse event/deaths/other significant events

No deaths were reported in the migraine studies. Two deaths were reported across the entire galcanezumab development program: 1 death was reported in a cluster headache study (CGAM, patient with a history of prostate and laryngeal cancer with diffuse metastasis. The patient received 3 doses of galcanezumab 300 mg during the double-blind treatment phase and 1 dose of open-label galcanezumab treatment prior to study discontinuation. The patient died 17 days after study discontinuation.), and 1 death was reported in a clinical pharmacology study (CGAQ, accidental drowning in a study subject who received a single dose of galcanezumab 240 mg, 15 days prior to the death). Both deaths were considered non drug related by investigators.

Other SAEs

Of SAEs, there were two cases of pancreatitis in the GMB groups compared with none in placebo. In one of them, the diagnosis is uncertain and in the other the pancreatitis was associated with gallstones. Another case of SAE with cholelithiasis is noted in the GMB 120 mg group. Among less common (non-severe) AEs, upper abdominal pain was significantly more common in GMB treated patients (pooled 0.98%) than placebo (0.34%). CGRP has been stated to be a regulator of biliary flow (Rasmussen et al 1997) and to be involved in sphincter Oddi (Sand et al). In a more recently published clinical study, plasma levels of serotonin, calcitonin, and CGRP were followed in the course of acute pancreatitis in 60 patients and compared to matching healthy volunteers (Wahlstrøm KL, et al. Scand J Gastroenterol. 2017). CGRP levels in patients at admission did not differ from healthy volunteers, nor did CGRP change over time or show any relationship to severity, etiology or organ failure. However, stimulation of

endogenous release of CGRP was shown to improve pancreatic microcirculation and reduce inflammation in experimental acute pancreatitis in rats (Schneider L, et al. Pancreas. 2009). An overview of exposure adjusted treatment-emergent incidence rates for the PTs of pancreatitis, alcoholic pancreatitis, and pancreatitis acute does not indicate an imbalance between GMB and placebo or an increased rate over time. Overall, based on the study data and literature references, it cannot be excluded that inhibition of CGRP could play a role in the pathogenesis of pancreatitis and/or bile duct related disorders. However, the current data do not evoke a safety concern.A similar concern is put forward regarding urinary tract dysfunction. Among serious AEs in the GMB treated patients, there is one case of renal colic, one case of nephrolithiasis and one case of bladder dysfunction. Acute pyelonephritis was reported by more patients in the GMB 240-mg dose group (n=2, 0.27%) than in placebo (n=0, 0.00%). CGRP has been described to be an important ureter smooth muscle relaxant in guinea pig (Maggi et al) and other pre-clinical studies show CGRP actions in the bladder. The applicant has provided a discussion of the potential effects of CGRP on the urinary tract and whether inhibition of CGRP could lead to urinary tract related adverse events. Overall, based on the current data, there appears to be limited evidence for this. In Analysis Set A were 3 patients in the galcanezumab pooled dose group (0.21%) and 1 patient in the placebo group (0.07%) who reported pyelonephritis or acute pyelonephritis. While indicates a small imbalance, none of the events in the galcanezumab-treated patients was considered related to treatment by study investigator, none led to discontinuation, and none re-occurred. In addition, 1 case of nephritis was reported in a placebo-treated patient and none in galcanezumab-treated patients. Estimates of EAIRs related to these disorders did not indicate an increase in incidence rates by dose or continued exposure. Nephrolithiasis occurred more frequently in placebo-treated patients (0.41%) than in galcanezumab-treated patients (0.21%). Of interest, as stated by the Applicant, patients with migraine have been reported to have increased risk for developing urinary calculi. One of several possible explanations might be an inhibitory effect of CGRP on the motility of the human ureter, which may promote ureteral obstruction due to urine stasis and urinary calculi (Tsai et al, 2015). A presentation of other TEAEs (bladder dysfunction, renal colic, and hypertonic bladder) showed similar frequencies between the groups.Three serious cases of malignant neoplasms (adenocarcinoma of the cervix, colon cancer, tubular breast carcinoma) and 1 serious case of benign tumour (rectal polyp) were reported in the galcanezumab 120-mg dose group. Similar events were not reported by patients on placebo. When all types of neoplasms were lumped together, benign, malignant and unspecified (including cysts and polyps), neoplasms were more frequent among GMB exposed patients regardless of dose (0.71% and 0.68%) compared to placebo (0.28%). Almost all events were single cases. The EAIR for the Neoplasm SOC in Analysis Set E was similar to that of Set A. The EAIR in Study CGAJ was numerically higher for the galcanezumab 240 mg dose group (EAIR 4.25) compared to the other data sets. However, confidence intervals were overlapping. In Analysis Set E, a total of 32 patients (1.24%) presented benign or malignant events during GMB-treated time and the post-treatment phase. Overall, no particular trends were observed. A long term safety study has been proposed by the Applicant as a pharmacovigilance measure (Observational Cohort Study of Galcanezumab Utilisation and Long-Term Safety Including Cardiovascular Safety, Malignancy, and Serious Hypersensitivity). In this study, the incidence of malignancy among patients exposed to galcanezumab will be followed over a period of up to 5 years.

Laboratory findings

Laboratory abnormalities counted as adverse events mostly occurred to the same extent among GMB treated patients and placebo treated patients. Most of them seem disparate and do not consist of any clusters or patterns. More patients experienced TE low monocyte count in the GMB 240 mg group vs placebo, but there was no clinically relevant pattern. Reviewing data for analytes coupled to glucose and lipid metabolism, no differences of interest were found for GMB versus placebo.

ECG

No thorough QT/QTc study was performed and only ECG data from the clinical development program are available.

In Analysis set A, no patient presented QTcF >500 ms and a similar proportion of galcanezumab-treated patients and placebo had treatment-emergent changes (low and high) in heart rate, PR interval, and QTcF.

In Analysis set E, a trend towards higher frequency of QTcF prolongation with higher GMB dose was observed (>30 msec increase in QTcF: <120:1/130, 0.77%; 120 mg: 10/853, 1.2%, 240 mg: 26/1148, 2.3%; 300 mg: 9/165, 5.5%). Similarly stratification of QTcF according to cut off values of >450 ms, >480 and >500 ms showed that the highest frequency of cases with QTcF >450 ms occurred with increasing doses (<120:0; 120 mg: 25/853, 2.93%, 240 mg: 37/1148, 3.22%; 300 mg: 18/165, 10.91%). Four patients reached the >480 ms limit, one in the the 240 mg GMB dose group and 4 in the 300 mg dose group (n=3).However the limited number of patients exposed to GMB 300 mg compared with lower GMB doses (120 and 240 mg) does not allow to draw definitive conclusions. A comparison of Analysis set E with the pooled GMB group from analysis set A, shows a 3.5-4.4 times increase in incidence.

Safety in special populations

Concurrent prophylaxis other than GMB

Study CGAI, the only placebo-controlled study including patients with chronic migraine, allowed for up to approximately one-third of the patients to continue on topiramate or propranolol for migraine prevention if they had been on a stable dose for at least 2 months prior to the prospective baseline period. Of the 14.6% of patients on concurrent migraine prevention at the time of randomization, 10.1% of patients received topiramate and 4.5% received propranolol.

Subgroup analysis of common TEAEs by baseline concurrent prophylaxis use did not indicate any clinically meaningful differences in incidence of these AEs in patients with or without concurrent prophylaxis use. Analysis of vital signs and weight by concurrent prophylaxis subgroups (yes/no) found a statistically significant interaction between concurrent prophylaxis and treatment group on both systolic and diastolic blood pressure. For systolic blood pressure, the overall LSMean difference between the galcanezumab 240-mg dose group and placebo was -3.62 for the concurrent prophylaxis use 'yes' group, versus -0.03 for the 'no' group. Only 2 of the patients in the galcanezumab 240-mg dose group (1 receiving propranolol and the other on topiramate) had a treatment emergent decrease in either systolic or diastolic blood pressure.

There are possible differences in medical history, concomitant medications and co-morbidities between chronic migraine and episodic migraine patients. The Applicant provided a review of SAEs, discontinuation due to AEs, EAIRs of TEAEs, EAIRs of TEAEs likely CV in nature, and EAIRs of categorical changes in blood pressure. Overall, there were no signs of interaction by disease state (episodic or chronic migraine).

Patients with renal impairment

The migraine development program included patients with mild renal impairment (Analysis set B: PBO 365 patients, GMB: 353 patients; Analysis Set E: 569 patients), moderate renal impairment (Analysis set B: PBO 17 patients, GMB: 19 patients; Analysis Set E: 31 patients)and only one patient with severe renal impairment. In Analysis Set E, the frequency of SAEs and discontinuation due to AEs were similar for galcanezumab-treated patients with normal, mild, or moderate renal function. In Analysis Set B, the frequency of SAEs and discontinuation due to AEs in the moderate renal impairment group (5.26%) was higher compared with the normal and mild impaired renal function subgroup (SAEs: around 1%;

discontinuation due to AEs around 2%); this was due to 1 patient treated with galcanezumab in the moderate impairment group that reported an SAE and discontinued due to an AE of acute pancreatitis. The incidence of TEAEs was similar for galcanezumab treated patients with normal, mild or moderate renal function in Analysis set B and E. Incidence rates of categorical changes in blood pressure were similar across the renal function subgroup in Analysis Set E and in Analysis Set B, apart from the moderate impairment group in Analysis set B, were 2 patients that met the criteria for the high SBP resulted in a higher incidence (10.5%) in this group than in the galcanezumab treated patients in the normal (3.6%) and mild (2.6%) groups. No further patients with moderate renal impairment experienced high systolic blood pressure in Analysis set E.

Patients with hepatic impairment

Patients with hepatic impairment have been excluded from GMB clinical development program.

Use in pregnancy

Effects of galcanezumab on human foetal development are not known. Pregnant and lactating women were excluded from entering the clinical studies and pregnancy was a criterion for permanent discontinuation. Women in reproductive age are the main target subpopulation and pregnancy is included in the Safety specification as Missing information. Some studies have shown that CGRP is involved in the fetoplacental resistance and an important factor in blood pressure regulation during pregnancy and low CGRP levels have been associated with pre-eclampsia (Yallampalli et al 1998, Dong et al 2005 and Fei et al 2012). Experience in pregnancy is still very limited. Of 16 pregnancies, reported in total since the original submission, one pregnant patient has experienced pre-eclampsia (6.25% of pregnancies). On these grounds, hypertension during pregnancy and pre-eclampsia have been included in the safety specification as an important potential risk. The outcomes of the 16 pregnancies were the following: 6 normal outcomes; two pregnancy outcomes are pending. One premature baby (34 weeks) was delivered of a mother who experienced pre-eclampsia and underwent a caesarean section. The infant did not experience any complications, and the mother recovered the same day from pre-eclampsia. There was 1 elective termination and 2 spontaneous abortions. 4 patients were lost to follow-up despite multiple attempts to obtain outcome information.

Safety related to drug-drug interactions and other interactions

As a humanized Immunoglobulin (subclass) 4 (IgG4) monoclonal antibody, galcanezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Based on the pharmacokinetic characteristics of galcanezumab, drug interactions are not expected. Therefore, no drug interaction studies were conducted.

In Study CGAI 157 patients were using topiramate or propranolol as concurrent migraine prophylaxis at the time of randomisation (see previous section "Concurrent prophylaxis other than GMB").

Available safety data do not indicate a worse safety profile in GMB treated patients receiving concomitant oral contraceptives compared with galcanezumab treated patients not receiving oral contraceptives.

The very limited number of patients who received a PDE5 inhibitor in the galcanezumab clinical development program (4 patients randomized to placebo and 5 randomized to galcanezumab) do not allow to draw any conclusion on the possible PD interaction between PDE5 inhibitors and galcanezumab. This issue should be monitored in upcoming PSURs.

The Applicant provided safety data stratified by concomitant triptan use. Available data show a higher risk of EAIRs of TEAEs likely cardiovascular in nature among galcanezumab treated patients receiving concomitant triptans compared to placebo (5.54/ 4.43= 1.25) when receiving concomitant triptans compared to the corresponding treatment difference in triptan non users (3.95/ 5.83= 0.68), even though the treatment-by-triptan subgroup interaction was not statistically significant. Available data also show a higher risk of potentially clinically significant DBP increase among galcanezumab treated patients receiving concomitant triptans compared to placebo (2.76/ 1.11: 2.49) when receiving concomitant triptans compared to corresponding treatment difference in triptan non users (0.72/ 1.96: 0.37), with a statistically significant treatment-by-triptan subgroup interaction.

Discontinuation due to adverse events

In Analysis set A, a higher frequency of discontinuations due to TEAEs occurred in the GMB 240 mg dose group (3%), compared to GMB 120 mg (1.8%) and PBO (1.6%). Adverse events that led to discontinuation in ≥2 galcanezumab-treated patients were: migraine, injection site reaction, hepatic enzyme increased, nasopharyngitis, and weight increased.

From the limited available long term data it seems that there is no trend of an increase in discontinuations due to AEs with longer treatment duration when comparing Analysis Set A (up to 6 months treatment duration) with Analysis Set E (up to 12 months treatment duration), even though the limited long term data do not allow to draw definitive conclusions.

2.7.1. Discussion on clinical safety

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

A total of 3156 subjects (including 419 healthy subjects) were exposed to galcanezumab at any dose across the entire galcanezumab development program. At the dose range of 120 to 240 mg (Analysis set E, all migraine patients), 1920 migraine patients were exposed to galcanezumab for ≥6 months (≥6 monthly doses), and 526 patients were exposed to galcanezumab for 1 year (12 monthly doses). Thus the number of patients exposed long term is limited, even though the extent of exposure in the efficacious dose range of 120 to 240 mg in the galcanezumab safety database meets the exposure requirement consistent with International Conference on Harmonisation (ICH) guidance.

For evaluation of galcanezumab safety, 5 integrated analysis sets and 3 additional analysis sets were generated. All safety analyses used the safety population, which was defined as all randomized patients who received at least 1 dose of study treatment. Most important was Analysis Set A including data from the double-blind treatment phase for all Phase 3 placebo-controlled migraine prevention studies: CGAG and CGAH, 6 months double blind phase and CGAI, 3 months double blind phase. Analysis Set E included data from all galcanezumab-treated patients (placebo was not included), regardless of dose, from all Phase 2 and Phase 3 migraine prevention studies. Long-term study CGAJ was also informative due to fixed randomised doses and duration of 12 months.

Analysis Set A, which includes placebo-controlled, double-blind treatment phase data from Studies CGAG, CGAH, and CGAI was the dataset used as the basis for proposed labelling. However the duration of galcanezumab exposure in this dataset is only up to 6 months. In Integrated Analysis Set A, a total of 1435 migraine patients were exposed to galcanezumab, representing 536.3 patient-years of exposure, equally distributed between GMB 120 and 240 mg.

The **patient population** included in Phase 3 galcanezumab clinical trials is not entirely representative of the population in the sought indication, as it is well known from epidemiological studies that migraine patients are at higher risk of ischemic cardiovascular events and have increased cardiovascular morbidities compared to the non-migraine population. Patients at high risk of cardiovascular events were excluded from the phase 3 clinical trials. No patient reported a pre-existing condition or medical history of variant or microvascular angina at baseline. Thus no information is available as to whether treatment with galcanezumab could trigger a reoccurrence or worsening of variant or microvascular angina.

Mean age of enrolled patients was 41 years, with only 5.8% of patients aged between 60 and 65 years at baseline. No patients over 65 years were enrolled in GMB studies.

In Analysis set A, as expected, **TEAEs** occurred with higher frequency in GMB treated patients (62.5% GMB 120 mg, 64.7% GMB 240 mg) compared to 57% in PBO. Serious adverse events occurred in 1.7% and 1.5% patients respectively in GMB 120 mg and 240 mg dose, compared to 0.96% in PBO. No **deaths** were reported in the migraine studies. Two deaths were reported across the entire galcanezumab development program. Both subjects received galcanezumab treatment, but neither death was attributed by investigators to galcanezumab.

In Analysis set A, a higher frequency of **discontinuations** due to TEAEs occurred in the GMB 240 mg dose group (3%), compared to GMB 120 mg (1.8%) and PBO (1.6%). Adverse events that led to discontinuation in ≥2 galcanezumab-treated patients were: migraine, injection site reaction, hepatic enzyme increased, nasopharyngitis, and weight increased.

Significantly more patients discontinued due to AEs in the GMB 240 mg group (3.01%) compared to placebo (1.65%). Slightly higher incidence proportions are seen in set E, likely due to longer study duration.

Common TEAEs that occurred with higher frequency in GMB treated patients compared to PBO and that have been identified as ADR are injection site reactions (GMB 240 mg 22.8%, GMB 120 mg 18.2%, PBO 12.8%), constipation (GMB 240 mg 1.51%, GMB 120 mg 0.99%, PBO 0.55%), vertigo (GMB 240 mg 1.2%, GMB 120 mg 0.7% vs PBO 0.2%) and hypersensitivity TEAEs (those judged likely after medical review, up to 4.8% using the Hypersensitivity SMQ broad search vs PBO 3.3%).

The majority of injection site reactions occurred on the same day of treatment and resolved the same day or within ≤14 days, with no SAEs. Discontinuation due to any type of AE at the injection site occurred in 0.48% of patients (7/1435 GMB treated patients, mostly after reporting the event multiple times prior to discontinuation), compared with no patient treated with PBO, and all resolved without sequelae after discontinuation. The percentage of patients reporting severe pain was comparable between the galcanezumab pooled group (9.6%) and placebo (13.0%). Injection site events tended to occur more frequently with the autoinjector penn compared to the pre-filled syringe.

Gastrointestinal motility is considered to be modulated by CGRP. Persistent constipation (resolved in >30 days) occurred more frequently in GMB treated patients than in PBO. In three patients in the GMB 120 mg dose group constipation persisted for >90 days.

Vertigo has been identified as ADRs, also considering the biological plausibility of an association between the inhibition of CGRP and interference with cochlear and vestibular function. Although hearing disorders were reported in patients treated with galcanezumab (4 GMB treated patients reported events coded as hearing loss during treatment compared with no such events in PBO), the number of cases reported was low. For two patients there were well-described confounders, such as ear infections or cerumen impaction. None of the events coded as hearing loss were SAE and no patient discontinued treatment due to a hearing loss event. It is thus unclear whether the reported term truly reflects medically significant

hearing loss (deafness) versus a transitory phenomenon. The Applicant will keep this safety topic under close surveillance and will provide updates in future periodic safety update reports (PSURs)/periodic benefit-risk evaluation reports (PBRERs).

Hypersensitivity reactions, both immediate and non-immediate, were significantly more common in GMB patients (0.98%, 3.83%) than in placebo (0.34%, 2.31%). Injection site reactions were the most common hypersensitivity AEs. In analysis set A, two cases of urticaria in the GMB 120 mg group (0.3%) gave a statistically significant difference compared to placebo (no case). In total, urticaria was reported in 0.4% of patients treated with any galcanezumab dose in analysis set E. There were two SAEs, both due to non-immediate urticaria. These occurred during open label (study CGAI) or in the post treatment phase. Urticaria was the cause of discontinuation in 5 patients in analysis set E.

The incidence proportion of broad scope anaphylactic reactions was almost double in patients with TE ADA, a difference that is significant (p=0.019) when the post treatment phase is included. Hypersensitivity reactions don't reach statistical significance, but there is a trend (p=0.059) when post treatment phases is added. Injection site hypersensitivity and inflammation were also more frequent in ADA+ patients. The Applicant was thus requested to further assess a possible association between immunogenicity and TEAEs. A patient level examination of TEAEs of interest in patients with treatment-emergent ADA was conducted. Overall, this review did not demonstrate a clear temporal association between these AEs and the presence of treatment-emergent ADA.

For the following events that occurred with higher frequency in GMB treated patients compared with PBO, further discussion has been requested: weight increased (6.4% GMB, vs 5.2% PBO); gastric ulcers (3/1435 events, 0.2% vs no such event in PBO); pneumonia (GMB Pooled: 9/ 1435, 0.6%, PBO 2/1451, 0.14%). From the limited available long term data, it seems that there is a trend towards an increase in the frequency of weight increase with longer treatment duration, when comparing Analysis Set A (up to 6 months treatment duration) with Analysis Set E (up to 12 months treatment duration), even though the limited long term data do not allow to draw definitive conclusions. Overall, there does not appear to be a clear causal relationship between treatment with galcanezumab and weight gain. The updated safety data for Analysis Set E showed a lower proportion of patients with weight increase (6.6%) measured at Month 12 as compared with at the initial submission (9.3%) and there was no clear trend over time. There is conflicting literature data on the relationship between body weight and migraine but it can be agreed that migraine itself could form a confounding factor.

Combining the terms Gastric ulcer and Peptic ulcer, the following frequencies were observed: GMB 120 mg 1 patient 0.14%; GMB 240 mg 2 patients 0.27%; GMB Pooled 3 patients, 0.21%; PBO 2 patients 0.14%. The Applicant acknowledged the biological plausibility that implicates calcitonin gene-related peptide (CGRP) in ulcer healing. However, in the Applicant's view there is not sufficient evidence in the galcanezumab safety database, to indicate a possible causal relationship between gastric ulcer and galcanezumab treatment. It is acknowledged that the number of events is small and that available data do not allow to draw conclusions on a possible causal relationship between gastric and peptic ulcers and galcanezumab treatment. Available safety data on the occurrence of TEAEs potentially correlated to compromized ulcer/ wound healing (i.e. not limited to gastric and peptic ulcers) was requested. No clear imbalance in the frequencies of adverse events correlated to ulcer healing (GMB Pooled 0.4% vs PBO: 0.3%) and of wound-related events (GMB Pooled: 0.3% vs PBO: 0.2%) was observed in Analysis Set A between galcanezumab and placebo. None of the events were reported as serious. The only event reported as impaired healing occurred in a 52 year old patient, 19 days after the fifth monthly dose; the event was considered drug related by the investigator, even though the event was confounded by concomitant use of corticosteroids. The issue of impaired healing should be monitored in upcoming PSUR's.

In analysis by SOC, pneumonia occurred significantly more in GMB treated patients (9/1435) than in placebo treated patients (2/1451) p=0.033 (GMB Pooled: 9/ 1435, 0.6%: 5 patients GMB 240, 4 patients GMB 120; PBO 2/1451 0.14%). In the investigator's opinion all of these events except one were not related to study drug. None of the cases of pneumonia resulted in discontinuation of treatment or were reported as SAEs. There was no apparent pattern in time to onset of the events, with the cases resolving, and all of the patients completed the treatment phases of the respective studies. The available data, together with the lack of clear biological plausibility with galcanezumab treatment, do not currently support consideration of pneumonia as an ADR associated with galcanezumab treatment. The issue will be monitored in upcoming PSURs.

Regarding hepatic safety, no patient met criteria for Hy' s law. There were 13 GMB treated patients and 7 placebo treated patients who had ≥ 3 x ULN of ALT. Several of these had baseline elevation. Data on liver associated averse events from the different dose groups in analysis set E don't imply any dose dependent AEs related to hepatic safety, but increased ALP, ALT and AST occurred in slightly increased proportions of patients in the higher GMB doses. At this time there is insufficient evidence to classify increased hepatic enzymes an adverse reaction associated with galcanezumab treatment. The issue will be monitored in upcoming PSURs.

Data from patients in the Phase 3 migraine clinical program do not suggest a risk of suicidal behaviour or ideation among those treated with galcanezumab.

Cardiovascular safety was identified as AESI because calcitonin gene-related peptide, being a potent microvascular vasodilator, is hypothesized to play a protective role in cardiovascular health. Nonclinical studies suggest that CGRP plays an important role in facilitating vasodilatation to various stimuli including acute ischaemia (Russell et al. 2014), and CGRP receptors are known to be expressed on cardiomyocytes, particularly within the conduction system. The binding of GMB to soluble CGRP could thus counteract the effect of CGRP on cardiovascular system. Even though in the placebo-controlled studies (analysis set A) there is no apparent clear imbalance in cardiovascular TEAEs, there were several TEAEs likely cardiovascular in nature that occurred in galcanezumab clinical trials.. Furthermore, there were single occurrences of SAEs thrombotic or embolic in nature (such as myocardial infarction, transient ischemic attack), and a SAE of atrial fibrillation, in patients without cardiovascular risk factors or other possible alternative explanations, for whom, a causal relationship between galcanezumab and these events may not be excluded. In Analysis set A, no patient presented QTcF >500 ms and a similar proportion of galcanezumab-treated patients and placebo had treatment-emergent changes (low and high) in heart rate, PR interval, and QTcF. However, in Analysis set E, a trend towards higher frequency of QTcF prolongation with higher GMB dose was observed (>30 msec increase in QTcF: <120:1/130, 0.77%; 120 mg: 10/853, 1.17%, 240 mg: 26/1148, 2.26%; 300 mg: 9/165, 5.45%). Similarly a higher frequency of cases with QTcF >450 ms occurred with increasing doses (<120:0; 120 mg: 25/853, 2.93%, 240 mg: 37/1148, 3.22%; 300 mg: 18/165, 10.91%). Again differences in dose group sizes prevents sound conclusions. Concentration effect modelling has been provided. to investigate the effect of GMB serum concentrations on QT interval prolongation. Galcanezumab concentration-ΔQTcF modelling seams to support the conclusion that galcanezumab does not prolong QTcF interval at the doses evaluated in the Phase 3 migraine program.

In conclusion due to the trial exclusion criteria, the generalizability of the clinical trial results as regards to cardiovascular safety to the entire patient population in the sought indication is limited given that the following patients were excluded: Patients with recent acute cardiovascular events (including MI, unstable angina, CABG, stroke, DVT) and/or those deemed to be at serious cardiovascular risk. Furthermore, the consequences of chronic CGRP inhibition in patients are unknown. The limited number of patients exposed to galcanezumab up to 12 months -together with the decreasing number of patients

with higher number of doses- do not allow to assess if there is an increased cardiovascular risk associated with long term galcanezumab exposure. Further, no patient has received galcanezumab for more than 12 months, thus cardiovascular risks and safety, especially ischemic events, cannot be fully assessed yet.

Available data did not identify meaningful differences in SAEs, discontinuations due to AEs, TEAEs likely CV in nature, and hemodynamic parameters in patients with a history of either hypertension, hypercholesterolemia, hyperlipidaemia, and type 2 diabetes (the so-called "CV disease risk group") and in patients aged ⩾60 to 65 years. However patients at higher cardiovascular risk [i.e. patients with recent acute CV events and/or serious CV risk and elderlies (>65 years of age)] were excluded from galcanezumab clinical development program. Furthermore, long term safety data are missing. A warning in section 4.4 of the SmPC has been added on the absence of safety data in patients with major cardiovascular diseases.

The applicant is proposing to conduct a Category 3 post-authorisation observational study as an additional pharmacovigilance activity. This study will examine the utilisation of galcanezumab in patients with current or recent acute CV risk factors and also the incidence of serious CV outcomes in all galcanezumab-treated patients. The proposed PASS has been split into 2 similar studies based on region (US and Europe). In both studies, the primary objective is to evaluate the utilisation and long-term safety of galcanezumab, including cardiovascular safety, malignancy, and serious hypersensitivity events in routine clinical practice. In Europe, the primary objective will relate to a European cohort of galcanezumab users, with exposures to galcanezumab identified from pharmacy records and safety outcomes identified through medical claims or records. Medical record review will complement the database analysis where feasible to obtain additional information on confounders. 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). In the US study, a secondary objective is to conduct, based on the number of events observed, comparative safety analyses of cardiovascular events, serious hypersensitivity reactions, and malignancies using patients initiated on other prophylactic migraine medication as a control, as feasible based on the number of outcome events observed. For these comparative analyses, adult patients who initiated treatment with another prophylactic migraine medication will be included and matched to galcanezumab initiators using propensity score or similar methods. The proposal to conduct such a study is considered acceptable. The Applicant states that limitations in the anticipated size and access of data sources available in Europe are unlikely to make comparative assessment feasible in the European study. However, the size of the data sources under consideration is potentially sizeable, exceeding 100 million patients (as shown by the Applicant in table format in the RMP v 0.3) and as the number of pre-specified safety events observed is unknown, the Applicant should retain the possibility to conduct comparative analyses with new users of comparator medications in Europe as well. This has been accepted by the applicant and included as a secondary objective in the PASS synopsis for the European study, similar to the US study (RMP v 0.4).

Available data show a higher risk of TEAEs likely CV in nature among galcanezumab treated males compared to placebo (4.85/ 2.45= 1.98) compared to the same risk in females (4.68/ 5.60= 0.83), with a statistically significant treatment by sex subgroup interaction overall. Thus, available data suggest that galcanezumab treatment increases cardiovascular risk (evaluated as occurrence of TEAEs likely cardiovascular in nature) in males significantly more than in females. However given the limited number of events observed among males –as more than 80% of the migraine patient population included in the galcanezumab clinical development program was female- no definitive conclusion may be drawn. Cardiovascular safety data by sex will be further evaluated in the long term PASS.

A SAE of severe arterial thrombosis complicated by popliteal artery occlusion occurred in a 41 year old diabetic female, with multiple risk factors for cardiac, as well as thromboembolic, disease 43 days after the sixth and final dose of galcanezumab (300 mg every 2 weeks); despite thrombectomy and tissue plasminogen activator (TPA) administration, adequate arterial blood flow could not be restored to the lower limb and the patient underwent an above the knee amputation. The investigator considered the event of peripheral vascular disease as not related to galcanezumab. No patients reported a TEAE of peripheral vascular disease in Analysis Set A; 2 patients from the Phase 2 studies (Analysis Sets B and E) and 1 patient from the long-term safety study CGAJ (Analysis Set E) who reported Raynaud's phenomenon (1), peripheral coldness (1), and intermittent claudication (1). The intermittent claudication was due to a muscular problem, the Raynaud's phenomenon was a worsening event in pre-existing Raynaud and did not re-occur with continued treatment, and for the peripheral coldness ("coldness in hands and feet") no additional details were provided. Peripheral vascular disease will be monitored in upcoming PSURs.

The Applicant provided safety data stratified by patients with and without aura. As regards to discontinuation due to an AE likely cardiovascular in nature a higher number of patients with aura discontinued due to a TEAE likely CV in nature compared to patients without aura, but this occurred both in galcanezumab treated patients and in PBO. EAIRs of TEAEs likely CV in nature using SMQs found no significant treatment-by-aura subgroup interaction in Analysis Set A, and no evidence that patients with aura treated with galcanezumab reported increased CV TEAEs. The EAIRs in Analysis Set E were comparable to Analysis Set A. As regards to Exposure Adjusted Incidence Rates (EAIRs) of Categorical Changes in Blood Pressure by Aura Status in Analysis Set A, a higher incidence of SBP high was observed both in galcanezumab and in placebo treated patients with aura status, compared to patients without aura; conversely a higher incidence of DBP high in patients with aura status, compared to those without aura was observed only among galcanezumab-treated patients but not in patients treated with placebo. There was no statistically significant treatment-by-aura subgroup interaction in Analysis Set A. To further investigate the possibility of an effect of galcanezumab mostly on DBP rather than on SBP, the Applicant conducted a time-to-event analysis for events of 2 consecutive measures of increased blood pressure $\geq$ 10 mmHg in DBP or increased blood pressure $\geq$ 20 mmHg in SBP. Because isolated increases of blood pressure might be due to inherent biological variability, the occurrence of 2 consecutive measurements of high blood pressure was considered a more reliable assessment of a true increase. These analyses showed that the incidence of sustained high diastolic blood pressure in patients treated for up to 6 months with galcanezumab was not greater than placebo across all timepoints.

The Applicant provided the requested safety data stratified by concomitant triptan use. Available data show a higher risk of EAIRs of TEAEs likely cardiovascular in nature among galcanezumab treated patients receiving concomitant triptans compared to placebo (5.54/ 4.43= 1.25) compared to the same risk in triptan non users (3.95/ 5.83= 0.68), even though the treatment-by-triptan subgroup interaction was not statistically significant. Available data also show a higher risk of potentially clinically significant DBP increase among galcanezumab treated patients receiving concomitant triptans compared to placebo (2.76/ 1.11= 2.49) compared to the same risk in triptan non users (0.72/ 1.96= 0.37), with a statistically significant treatment-by-triptan subgroup interaction. Considering the number of endpoints analysed to evaluate increases at any time in SBP and DBP (e.g., categorical and treatment-emergent high SBP or DBP, potentially clinically significant increases in SBP or DBP, sustained SBP or DBP increases), it is not possible to exclude that **t**he observed statistically significant treatment by triptan subgroup interaction observed for potentially clinically significant DBP increase -being an isolated treatment by subgroup interaction finding- could be a spurious finding due to multiplicity. Moreover, contributing to the observed interaction was a lower incidence rate of potentially clinically significant high DBP in galcanezumab patients compared to placebo among non triptan users.

The applicant provided a review of SAEs, discontinuation due to AEs, EAIRs of TEAEs, EAIRs of TEAEs likely CV in nature, and EAIRs of categorical changes in blood pressure. Overall, there were no signs of interaction by disease state (episodic or chronic migraine).

In placebo controlled trials, analysis of blood pressure does not show any increase for GMB-treated patients, rather a minimal decrease in the higher dose. However, looking at analysis set E which contains data from all clinical phase 2/3 trials, including lower and higher doses than in analysis set A, there might be an increase in blood pressure with increased dose. These data are difficult to interpret due to different study durations and imbalances in patient number among dose groups.

Incidence proportions and incidence rates for SBP $\geq$ 20 mm Hg increase from baseline and DBP increase $\geq$ 10mm Hg from baseline regardless of thresholds were provided. In the placebo-controlled Analysis Set A, no relevant differences were observed between galcanezumab and placebo. Some inconsistencies were noted in Set E which might be explained by small sample sizes for some of the groups. Spaghetti plots for SBP or DBP by dose level showed no notable differences in the patterns of fluctuation over time between the groups. The Applicant also provided a time-to-event analysis with event defined as 2 consecutive measures of increased blood pressure $\geq$ 10 mmHg in DBP and/or $\geq$ 20 mmHg in SBP OR new anti-hypertensive treatment. This analysis showed no increased risk in galcanezumab-treated patients compared to placebo based on the stratified hazard ratio.

There seems to more patients in the higher dose groups who received or increased anti-hypertensive drugs throughout the studies, but the same issue with data as described for high blood pressure applies. However, long term study CGAJ, where doses were fixed and exposure time similar for both GMB doses, shows a greater proportion of patients with an increase in anti-hypertensive treatment in the higher GMB dose group.

The incidences of several important adverse events, notably treatment emergent high blood pressure, use of cardiovascular medications, QTc interval, rash, and liver enzymes, suggest imbalances between the GMB groups in the overall integrated analysis set (analysis set E), but no corresponding imbalances are apparent in primary placebo-controlled comparisons (analysis set A). When looking at analysis set E, study CGAI, and study CGAJ, there is even some suggestion of a dose dependent increase of these events. In order to clarify if the previously mentioned imbalances indicate true adverse reactions or have other methodological explanations, the Applicant provided exposure-adjusted analyses using time-at-risk-adjusted incidence rate (per 100 patient-years) for treatment-emergent hypertension, QTc interval, use of CV medications, rash, and hepatic enzymes. Overall, these analyses do not show dose dependent effects compared between galcanezumab 120 mg and 240 mg. The EAIRs for the 300 mg dose are numerically more unfavourable compared to the other dose groups for a range of events, including treatment-emergent systolic blood pressure, use of concomitant antihypertensives (increase in dose or start of new medication), rash of potential or likely hypersensitivity in nature, and treatment-emergent abnormally high hepatic enzyme values (ALP, ALAT, ASAT). The apparent consistency in this unfavourable trend is something to be considered although the Applicant's explanation that the GMB 300 mg data originate from small patient numbers from Phase 2 studies and hence are associated with wide confidence intervals is acknowledged. Also, the duration of follow-up in these Phase 2 studies was limited, up to 12 weeks. Study CGAJ appears to be sufficiently consistent with Analysis Sets E and A except for a relatively low incidence rate of high DBP in the 120 mg treatment group compared to the other data sets. The EAIRs for the CV concomitant medications were higher for the galcanezumab 240 mg dose group compared to galcanezumab 120 mg for all 4 medication classes for the 'All Patients' group and CV Disease Risk Group-Yes. These differences appear to be driven by the patients in the CV Disease Risk Group-Yes; however, the numbers are small with only 50 patients in the Yes group for this study, with wide confidence intervals.

The applicant was requested to provide a descriptive analysis of frequency of dose-changes in relation to dose and duration of exposure and to discuss the reasons for dose change. The majority of the dose changes occurred at the third dose where 62.2% patients moved up to galcanezumab 240 mg from 120 mg. An additional 11.4% moved up to 240 mg at the next dose with smaller numbers thereafter. Fewer patients moved back down to galcanezumab 120 mg across subsequent visits, about 3 to 5% per visit. Overall, there was a fair amount of fluctuation throughout the open-label phase. In study CGAI (open-label) the majority of dose changes relate to increased dosage in aiming for additional therapeutic benefit; thus available data do not indicate safety issues as a reason for dose change.

Acute pancreatitis. One SAE of pancreatitis and gallstones and another SAE with cholelithiasis are noted in the GMB 120 mg group. Among less common AEs, upper abdominal pain was significantly more common in GMB treated patients (pooled 0.98%) than placebo (0.34%). CGRP has been stated to be a regulator of biliary flow (Rasmussen et al) and to be involved in sphincter Oddi (Sand et al). Overall, based on the study data and literature references, it cannot be excluded that inhibition of CGRP could play a role in the pathogenesis of pancreatitis and/or bile duct related disorders. However, the current data do not evoke a safety concern. There will be renewed review of this issue when additional safety data become available.

The applicant has provided a discussion of the potential effects of CGRP on the urinary tract and whether inhibition of CGRP could lead to urinary tract related adverse events. Overall, based on the current data, there appears to be limited evidence for this. In Analysis Set A were 3 patients in the galcanezumab pooled dose group (0.21%) and 1 patient in the placebo group (0.07%) who reported pyelonephritis or acute pyelonephritis. While indicates a small imbalance, none of the events in the galcanezumab-treated patients was considered related to treatment by study investigator, none led to discontinuation, and none re-occurred. In addition, 1 case of nephritis was reported in a placebo-treated patient and none in galcanezumab-treated patients. Estimates of EAIRs related to these disorders did not indicate an increase in incidence rates by dose or continued exposure. Nephrolithiasis occurred more frequently in placebo-treated patients (0.41%) than in galcanezumab-treated patients (0.21%). Of interest, as stated by the Applicant, patients with migraine have been reported to have increased risk for developing urinary calculi. One of several possible explanations might be an inhibitory effect of CGRP on the motility of the human ureter, which may promote ureteral obstruction due to urine stasis and urinary calculi (Tsai et al, 2015). A presentation of other TEAEs (bladder dysfunction, renal colic, and hypertonic bladder) showed similar frequencies between the groups. Overall, the Applicant's conclusion that there was no clinically meaningful difference observed between galcanezumab 240 mg and placebo that suggests a relationship of the reported renal AEs to galcanezumab exposure can be agreed.

Malignancies. Three serious cases (0.3%) of malignant neoplasms (adenocarcinoma of the cervix, colon cancer, tubular breast carcinoma) were reported in the galcanezumab 120-mg dose group, compared to no such event in the PBO group. Furthermore one serious case of benign tumour (rectal polyp) occurred in another GMB treated subject. None of these cases were considered related to GMB treatment by the Investigator. A further event (galcanezumab 120 mg group, Analysis Set A) included in the initial submission with a PT of wound ("wound nipple left breast") that started on Study Day 19, was diagnosed months later as breast nipple cancer. In view of the relatively short time interval between the start of galcanezumab treatment and the event onset, a causal association with galcanezumab is unlikely. Non clinical data showed a single occurrence of fibrosarcoma in the skin/subcutis in the rat for which a relationship with the compound has not been excluded. In Analysis Set A, when combining all neoplasms, benign, malignant and unspecified (including cysts and polyps), these were more frequently reported among GMB exposed patients regardless of dose (0.71% and 0.68% for 120 mg and 240 mg, respectively) compared to placebo (0.28%). Almost all events were

single cases. The EAIR for the Neoplasm SOC in Analysis Set E was similar to that of Set A. The EAIR in Study CGAJ was numerically higher for the galcanezumab 240 mg dose group (EAIR 4.25) compared to the other data sets. However, confidence intervals were overlapping. In Analysis Set E, a total of 32 patients (1.24%) presented benign or malignant events during GMB-treated time and the post-treatment phase. No particular trends were observed. A long term safety study has been proposed by the applicant as a pharmacovigilance measure (Observational Cohort Study of Galcanezumab Utilisation and Long-Term Safety Including Cardiovascular Safety, Malignancy, and Serious Hypersensitivity). In this study, the incidence of malignancy among patients exposed to galcanezumab will be followed over a period of up to 5 years.

Pregnancy. Most patients with migraine are females of child bearing age. CGRP likely contributes to vascular adaptations during pregnancy. Pregnant women were excluded from participation in clinical studies. Experience in pregnancy is still very limited. Of 16 pregnancies, reported in total since the original submission, one pregnant patient has experienced pre-eclampsia (6.25% of pregnancies). Given the biological mechanism of galcanezumab and the role of CGRP in pregnancy, there is a rationale for including hypertension and pre-eclampsia among women exposed to galcanezumab during pregnancy as important potential risks in the RMP. As part of the pharmacovigilance plan, the applicant plans to conduct a cohort study (Category 3) of exposure to galcanezumab during pregnancy to collect more data on the incidence of pregnancy outcomes (including hypertension during pregnancy and preeclampsia) in comparison to women receiving other prophylactic migraine medication.

2.7.2. Conclusions on the clinical safety

Galcanezumab was generally well tolerated in migraine patients, although an increase in the incidence of injection site reactions, constipation, vertigo, pruritus and urticaria were observed in the 3 to 6 months-controlled studies. There is a concern that treatment with a CGRP antagonism may aggravate ischemic events such as stroke, TIA and MI, because CGRP is hypothesized to play a protective role in cardiovascular health. Available data did not identify meaningful differences in SAEs, discontinuations due to AEs, TEAEs likely CV in nature, and hemodynamic parameters in patients with a history of either hypertension, hypercholesterolemia, hyperlipidaemia, and type 2 diabetes (the so-called "CV disease risk group") and in patients aged ≥ 0 to 65 years. However, these data provide only limited reassurance as patients at higher cardiovascular risk [i.e. patients with recent acute CV events and/or serious CV risk and elderlies (>65 years of age)] were excluded from galcanezumab clinical development program. To address these concerns, the Applicant has proposed to conduct a Category 3 post-authorisation observational study as an additional pharmacovigilance activity. The primary objective of the study is to understand the utilization of galcanezumab and to characterize the incidence of cardiovascular events, malignancy, and serious hypersensitivity in real-world clinical practice.

526 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, including the risk of malignancies, is at present unknown.

2.8. Risk Management Plan

Safety concerns

Table 23 - Summary of Safety Concerns

Important identified risks	None
Important potential risks	Serious hypersensitivity 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

Pharmacovigilance Plan

Table 24 - Summary Table of Additional Pharmacovigilance Activities

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**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 (Planned)	To actively monitor exposure to galcanezumab during pregnancy among women with migraine, 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	Within 6 months following EU Commission Decision To be provided annually with the PSUR/ PBRER Anticipated Q4 2024
Galcanezumab European Drug Utilization and Safety Outcomes Study (Planned)	To describe, in real-world clinical practice, the utilization 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	Within 6 months following EU Commission Decision To be provided annually with the PSUR/ PBRER Currently under discussion with vendor Anticipated Q4 2026
Galcanezumab US Drug Utilization and Safety Outcomes Study (Planned)	To describe, in real-world clinical practice, the utilization 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. 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.	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	Within 6 months following EU Commission Decision To be provided annually with the PSUR/ PBRER Currently under discussion with vendor Anticipated Q4 2026

Risk minimisation measures

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 id 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 • 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. • 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 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. • 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. • 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 risk of cardiovascular and cerebrovascular events	Routine risk minimisation measures: 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 advised patients to inform their HCP if they have serious cardiovascular disease	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: 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 • 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. • To understand the risk of specified safety events in adult patients receiving galcanezumab relative to other adult

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		patients who initiated treatment with other prophylactic migraine medication, as feasible, given the availability of data. 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. • 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. • 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 use in pregnancy in SmPC 4.6.	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: Cohort Study of Exposure to Galcanezumab during Pregnancy • To actively monitor exposure to galcanezumab during pregnancy among women with migraine • 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. PL Section 2 advised women to avoid becoming pregnant while using galcanezumab. 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: Cohort Study of Exposure to Galcanezumab during Pregnancy • To actively monitor exposure to galcanezumab during pregnancy among women with migraine, using administrative (secondary) data. • 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:	Routine phamacovigilance activities beyond adverse reactions reporting signal detections:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 5.3	Spontaneous case AE follow-up forms for suspected adverse reactions (cancer-neoplasm) 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 • 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**. • 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 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. • 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**. • To understand the risk of specified safety events in patients receiving galcanezumab relative to adult patients who initiated treatment with another prophylactic migraine medication.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.10. New Active Substance

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

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

2.11. Product information

2.11.1. User consultation

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

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Emgality (galcanezumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU. In addition, it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Migraine is a chronic neurological disease characterized by severe headache attacks with associated hypersensitivity to environmental stimuli, as well as gastrointestinal, cognitive, and vestibular symptoms that can be severe and disabling (Buse et al. 2009). Typically, the headaches affect one half of the head, are pulsating in nature, and last from 4 to 72 hours without treatment. The disease is associated with higher frequencies of depression, anxiety disorders, sleep disturbances, cardiovascular risk, chronic pain syndromes, and suicide attempts.

3.1.2. Available therapies and unmet medical need

In case of infrequent migraine attacks (less than 2 times per month), treatment is limited to acute medications that include: triptans, nonsteroidal anti-inflammatory drugs, combination of analgesics, opioids, and ergots.

In case of frequent migraine attacks (2-6 times or more per month) prophylactic drugs are introduced on a daily basis, including antihypertensive, anti-epileptic, or antidepressant drugs. Most of the commonly used prophylactic drugs have a registered indication, however others are used off-label with limited evidence of efficacy. The safety profile of these drugs is not optimal with neurological AEs including dizziness, vertigo, nausea, anorexia, fatigue, memory problems, paraesthesia, often requiring dose titration, and carrying contraindications and warnings.

3.1.3. Main clinical studies

Three randomized, double-blind, placebo-controlled studies in CM and EM provide efficacy and safety data of galcanezumab in the prophylaxis of migraine in adults.

Study **CGAG** and Study **CGAH** are pivotal for EM and Study **CGAI** is pivotal for CM. They all include the proposed registration dose of 120 mg, with a loading dose of 240 mg, as well as the 240 mg dose regimen.

Studies **CGAG** and **CGAH** have identical design. They are phase 3, randomized, double-blind, placebo-controlled to evaluate the effect of galcanezumab compared to placebo on the overall change from baseline in mean monthly migraine days in subjects with episodic migraine. The studies consisted of a screening phase; a prospective baseline; 6-month placebo-controlled double-blind treatment and a 4-month post treatment follow-up (ongoing).

The studies enrolled patients aged 18 to 65 with a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD) -3rd edition, beta guidelines (1.1 and 1.2) (ICHD-3 2013), with a history of migraine headaches of at least 1 year prior to Visit 1, and migraine onset prior to age 50. Recruited patients were to have had a history of 4 to 14 MHDs and at least 2 migraine attacks per month on average within the past 3 months.

Study **CGAI** is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of galcanezumab through the overall mean change from baseline in mean monthly migraine headache days as prevention of chronic migraine. The study consisted of a screening phase, a prospective baseline phase, a 3-month double blind, placebo-controlled treatment phase, an optional 9-month open-label extension phase (ongoing) and a 4-month post-treatment follow-up phase (ongoing).

The study enrolled patients 18 to 65 years of age with a diagnosis of chronic migraine as defined by IHS ICHD-3 beta guidelines (1.3) (ICHD-3 2013), i.e. a headache occurring on 15 or more days per month for more than 3 months, with at least 8 days having features of migraine, and at least 1 headache-free day per month for more than 3 months.

3.2. Favourable effects

For patients with episodic migraine (CGAG and CGAH studies), the superiority over placebo was shown both for the primary endpoint as well as for the key secondary endpoints for both galcanezumab doses.

For patients with chronic migraine (CGAI study), the superiority of both galcanezumab doses vs placebo was shown for the primary endpoint and for the key secondary endpoint of Percentage of ≥50% Responders for MHDs for both galcanezumab doses. Other key secondary endpoints were met only by the 240 mg dose.

Several sensitivity analyses supported the results of the primary analyses in the 3 trials. Overall, there was a consistency of treatment effect among several endpoints including impact of disease on functioning and patients' perception of illness severity.

Primary endpoint. After multiplicity adjustment, the overall LSMean *reduction from baseline in the number of monthly MHDs* during the double-blind treatment phase was:

In study CGAG: 4.73 days for galcanezumab 120 mg [effect size -0.59] and 4.57 days for galcanezumab 240 mg compared with 2.81 days for placebo [effect size -0.54] (LSMean change difference from placebo -1.92 and -1.76; p<.001 for each dose group versus placebo).

In study CGAH, 4.29 days for galcanezumab 120 mg [effect size -0.61] and 4.18 days for galcanezumab 240 mg compared with 2.28 days for placebo [effect size -0.57] (LSMean change difference from placebo -1.9 and -1.8; p<.001 for each dose group versus placebo).

In Study CGAI: 4.83 days for galcanezumab 120 mg and 4.62 days for galcanezumab 240 mg compared with 2.74 days for placebo (LSMean change difference from placebo: -2.09 and -1.88; p<.001 for each dose group versus placebo).

Key secondary endpoints.

Percentage of ≥50% responders in terms of reduction of MHDs:

In study CGAG, 38.6% for placebo, 62.3% for 120 mg and 60.8% for 240mg group with odds ratio vs placebo 2.63 and 2.48 for 120 mg and 240 mg groups, respectively (<0.001 for both comparisons)

In study CGAH, 36% for placebo, 59.3% for 120 mg and 56.5% for 240mg group with odds ratio vs placebo 2.6 and 2.31 for 120 mg and 240 mg groups, respectively (<0.001 for both comparisons).

In Study CGAI: 15.4% for placebo, 27.6% for 120 mg and 27.2% for 240 mg group with odds ratio vs placebo 2.09 and 2.08 for 120 mg and 240 mg groups, respectively (<0.001 for both comparisons).

Percentage of ≥75% responders *in terms of reduction of MHDs*:

In study CGAG, 19.3% for placebo, 38.8% for 120 mg and 38.5% for 240mg group with odds ratio vs placebo 2.65 and 2.62 for 120 mg and 240 mg groups, respectively (<0.001 for both comparisons)

In study CGAH 17.8% for placebo, 33.5% for 120 mg and 34.3% for 240mg group with odds ratio vs placebo 2.34 and 2.42 for 120 mg and 240 mg groups, respectively (<0.001 for both comparisons).

In Study CGAI 4.5% for placebo mg and 8.8% for 240mg group odds ratio vs placebo 2.04 for 240 mg group (<0.001).

3.3. Uncertainties and limitations about favourable effects

In all 3 studies, the magnitude of treatment effect seems limited; however, it is acknowledged that there is no agreed minimal clinically relevant effect in terms of decrease in MHD in the literature or in the clinical practice. The applicant has provided tabulated indirect comparison data with available treatments in order to contextualise treatment benefit. Overall, galcanezumab treatment effect seems comparable with that of historical data from topiramate and Botox published studies. However, although the applicant's efforts are appreciated, the indirect comparison is not supported by a sound methodology, and its usefulness for the evaluation of treatment benefit is limited.

After considering the assumptions for the determination of the sample size in the EM as well as CM trials of a mean difference of 1.2 migraine headache days with a SD of 3.6 (corresponding to an effect size of 0.33), it was evident that the statistical significance would have been reached even with a mean change difference compared to placebo smaller than 1 MHD. The provided sensitivity analysis further showed that, with the selected sample size, highly statistically significant differences versus placebo could be observed even for very small, clinically non-relevant improvements (as reflected by negligible LS mean differences). Favourable effects of galcanezumab were shown in patients (age 18-65 years) with episodic migraine restricted by frequency of migraine attacks with 4 to 14 monthly migraine headache days in two pivotal studies. Upon resolution of a Major Objection raised by the CHMP, the initial indication for "the prophylaxis of migraine in adults" has been changed to now include only adult subjects with at least 4 migraine days per month. Results of a subgroup analysis of primary outcome measure seem to indicate that the effect of galcanezumab occurs irrespectively of the baseline number of MHDs (<8 vs ≥8 in EM and <19 vs ≥19 in CM) also in patients aged ≥ 50 years. Therefore, the treatment effect of galcanezumab can be extrapolated to older patients (≥65 years). The magnitude of treatment benefit appears limited, especially in CM. In the current SmPC, only the 120 mg dose is proposed for all patients. However, it is noted that the proportion of patients dosed with 240 mg was increasing with time during open-label phase of the CGAI study. The investigators preferred the 240 mg dose when allowed to choose freely for patients with chronic migraine. In addition, there were 9.6% of patients in the 120 mg dose group and 3.7% of patients in the 240 mg dose group who discontinued the treatment because of lack of efficacy (CGAJ study). Based on these observations, the discussion on whether up titrating the effective dose could be justified for some patients, e.g. those with chronic migraine, in the case of absence of response to the 120 mg dose, brought to the conclusion that it remains at the clinician discretion to choose the best dose on an individual basis.

It is not possible to infer from the data provided that treatment effect induces a statistically significant reduction in acute medication use, because the change in MHDs with acute medication is considered irrespective of the corresponding monthly total number of migraine days. Indeed, looking at the percent change in the mean use of paracetamol and triptans from baseline (considered over the past 5 years prior to enrolment), to the DB period in the 3 pivotal studies, there seems to be a small decrease in the 3 studies for galcanezumab when looking at acute treatment overall that reaches statistical significance in 2 studies (CGAH and CGAI for both doses). For the specific acute medication of triptans, paracetamol and

NSAIDS, there were overall small reduction seen for galcanezumab treatment with only small increases for paracetamol in study CGAG at 240 mg galcanezumab dose and study CGAH at 120 mg galcanezumab dose. When the severity of remaining migraine days in patients treated with galcanezumab is taken into consideration, no difference with placebo is observed across the EM and CM trials. When the severity of remaining migraine days is taken into consideration, no difference with placebo is observed in the episodic migraine trial CGAG whereas a very small difference of questionable clinical relevance is apparent in the chronic migraine trial and episodic migraine trial CGAH. The additional treatment benefit of galcanezumab in patients with CM on treatment with either topiramate or propranolol seems relatively small, i.e. 1-day gain. As such, the benefit of galcanezumab treatment in add on to topiramate and propanol in CM patients is at present questionable.

At the time of the dossier submission there were methodological concerns in the conduct of the pivotal studies, with a large number of protocol deviations and the lack of a per-protocol analysis. The responses provided by the applicant after two rounds of supplementary information in order to bridge this gap (i.e., considering the per-protocol population, as well as after excluding subjects with any protocol deviation), showed that although the number of subjects in each group for each study was significantly reduced, the differences in the reduction of MHDs with respect to the baseline between the groups actively treated with galcanezumab vs placebo remained statistically significant in either EM and CM.

3.4. Unfavourable effects

Based on the findings from three placebo-controlled trials, two with six months duration and one with 3 months duration, the following adverse events were considered as adverse drug reactions based on a more frequent occurrence than in placebo, dose response finding and biological plausibility:

- *Injection site pain* was reported in 9.51%, 10.07% and 11.64% in subjects in the placebo, 120 mg and 240 mg groups, respectively. Injection site pain was considered as severe in 9.6% of patients. One patient discontinued due to injection site pain.

Likely immunological ADR:

- Injection site reaction was reported in 1.0%, 3.1% and 6.2% in subjects in the placebo, 120 mg, and 240 mg groups, respectively. The data indicate a dose relationship with twice as many patients in the galcanezumab 240-mg dose group reporting an injection site reaction than the galcanezumab 120-mg dose group. Four patients discontinued due to injection site reaction.
- Injection site erythema was reported in 1.4%, 2.8% and 4.0% in subjects in the placebo, 120 mg, and 240 mg groups, respectively. One patient discontinued due to injection site erythema.
- Injection site pruritus was reported in 0.1%, 2.1% and 3.3% in subjects in the placebo, 120 mg, and 240 mg groups, respectively. 20% of patients in the 120 mg group experienced injection site pruritus as severe and 25% in the 240 mg group. No patient in the placebo group experienced injection site pruritus as severe.
- Urticaria was reported in 0.4%, 0.4% and 0.1% in subjects in the placebo, 120 mg, and 240 mg groups, respectively. Five patients discontinued due to urticaria.
- Pruritus was reported in 0.28%, 0.71% and 1.23% in subjects in the placebo, 120 mg, and 240 mg groups, respectively.

Other ADRs with known biological plausibility:

- Constipation was reported in 0.55%%, 0.99% and 1.51% in subjects in the placebo, 120 mg, and 240 mg groups, respectively. No patients experienced constipation as severe. This ADR could be persistent > 30 days or even longer, > 90 days.
- Vertigo was reported in 0.21%, 0.7% and 1.23% in subjects in the placebo, 120 mg, and 240 mg groups, respectively.

3.5. Uncertainties and limitations about unfavourable effects

Due to the exclusion criteria of the clinical trials, the generalizability of the safety results to the entire patient population of the sought indication is limited. Patients with less than 4 MHDs at baseline, patients older than 65 years and patients at high risk of cardiovascular events were excluded from the 3 pivotal trials. Migraine patients are at higher risk of ischemic cardiovascular events and have increased cardiovascular morbidities compared to the non-migraine population. Nonclinical studies suggest that CGRP plays an important role in facilitating vasodilatation to various stimuli including acute ischaemia, and CGRP receptors are known to be expressed on cardiomyocytes, particularly within the conduction system. There is a concern that treatment with a CGRP antibody may aggravate ischemic events such as stroke, TIA and MI. Even though in the placebo-controlled studies there was no apparent clear imbalance in cardiovascular TEAEs, there were several TEAEs likely cardiovascular in nature that occurred in galcanezumab clinical trials. Furthermore, there were single occurrences of SAEs thrombotic or embolic in nature (such as myocardial infarction, transient ischemic attack, superficial thrombophlebitis), and a SAE of atrial fibrillation, in patients without cardiovascular risk factors or other possible alternative explanations, for whom, a causal relationship between galcanezumab and these events may not be excluded. The exposure-adjusted incidence rates (EAIRs) for the 300 mg dose are numerically more unfavourable compared to the other dose groups for a range of events, including treatment-emergent systolic blood pressure, use of concomitant antihypertensives (increase in dose or start of new medication), rash of potential or likely hypersensitivity in nature, and treatment-emergent abnormally high hepatic enzyme values (ALP, ALAT, ASAT). The apparent consistency in this unfavourable trend is something to be considered although the Applicant's explanation that the GMB 300 mg data originate from small patient numbers from Phase 2 studies and hence are associated with wide confidence intervals is acknowledged. Also, the duration of follow-up in these Phase 2 studies was limited, up to 12 weeks. Study CGAJ appears to be sufficiently consistent with Analysis Sets E and A except for a relatively low incidence rate of high DBP in the 120 mg treatment group compared to the other data sets. The EAIRs for the CV concomitant medications were higher for the galcanezumab 240 mg dose group compared to galcanezumab 120 mg for all 4 medication classes for the 'All Patients' group and CV Disease Risk Group-Yes. These differences appear to be driven by the patients in the CV Disease Risk Group-Yes; however, the numbers are small with only 50 patients in the Yes group for this study, with wide confidence intervals.

Serious cardiovascular outcomes in patients at high risk of cardiovascular and cerebrovascular events are considered as important potential risk, together with serious hypersensitivity, hypertension during pregnancy and pre-eclampsia. The Applicant is proposing to conduct a Category 3 post-authorisation observational study as an additional pharmacovigilance activity. The primary objective of the study is to understand the utilization of galcanezumab and to characterize the incidence of cardiovascular events, malignancy, and serious hypersensitivity in real-world clinical practice. The proposed PASS has been split into 2 similar studies based on region (US and Europe). The applicant has submitted the proposed synopses as requested. However, the PASS synopsis for the European study should include the objective to conduct comparative analyses with new users of comparator medications, similar to the US study. Long

term data are at present missing, so the implications of chronic CGRP inhibition in migraine patients is at present unknown.

There is currently insufficient evidence to classify increased hepatic enzymes, hearing loss, impaired ulcer and wound healing and peripheral vascular disease as ADRs associated with galcanezumab treatment but these events will be further monitored in future PSURs.

3.6. Effects Table

Table Effects Table for Emgality (galcanezumab) as migraine prophylaxis in adults

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
Favourable Effects in Episodic migraine (results in brackets refer to the twin study CGAH)						
Migraine headache (MHDs)	Change from baseline during the 6-month DB phase	Days	PBO 120 mg 240 mg	-2.81 (-2.28) -4.73 (-4.29) -4.57 (-4.18)	 p<.001 (p<.001) p<.001 (p<.001)	CGAG (CGAH)
Reponder rate	≥50%	%	PBO 120 mg 240 mg	38.6 (36) 62.3 (59.3) 60.9 (56.5)	 p<.001 (p<.001) p<.001 (p<.001)	CGAG (CGAH)
	≥75%	%	PBO 120 mg 240 mg	19.3 (17.8) 38.8 (33.5) 38.5 (34.3)	 p<.001 (p<.001) p<.001 (p<.001)	CGAG (CGAH)
	100%	%	PBO 120 mg 240 mg	6.2 (5.7) 15.6 (11.5) 14.6 (13.8)	 p<.001 (p<.001) p<.001 (p<.001)	CGAG (CGAH)
MHDs with acute medication use	Change from baseline across Month 1 to 6	Days	PBO 120 mg 240 mg	-2.15 (-1.85) -3.96 (-3.67) -3.76 (-3.63)	 p<.001 (p<.001) p<.001 (p<.001)	CGAG (CGAH)
MSQ v. 2.1 Role Function-Restrictive Score	Change from baseline (avg. of Months 4, 5, and 6)		PBO 120 mg 240 mg	24.69(19.65) 32.43(28.47) 32.09(27.04)	 p<.001 (p<.001) p<.001 (p<.001)	CGAG (CGAH)
PGI-Severity	Change from baseline (avg. of Months 4, 5, 6)		PBO 120 mg 240 mg	-1.27 (-0.94) -1.59 (-1.22) -1.55 (-1.17)	 .002 (0.002) .008 (.012)	CGAG (CGAH)
Favourable effects in Chronic migraine						
Migraine headache (MHDs)	Change from baseline during the 3-month DB phase	Days	PBO 120 mg 240 mg	-2.74 -4.83 -4.62	 p<.001 p<.001	CGAI
Reponder rate	≥50%	%	PBO 120 mg 240 mg	15.4 27.6 27.5	 p<.001 p<.001	CGAI
	≥75%	%	PBO 120 mg 240 mg	4.5 7.0 8.8	 .031 <.001	CGAI
	100%	%	PBO 120 mg 240 mg	0.5 0.7 1.3	 .597 .058	CGAI
MHDs with acute medication use	Change from baseline across Month 1 to 3	Days	PBO 120 mg 240 mg	-2.23 -4.74 -4.25	 <.001 <.001	CGAI

Effect	Short Description	Unit	Treatment	Result	Uncertainties/ Strength of evidence	References
MSQ v. 2.1 Role Function-Restrictive Score	Mean change from baseline (at Month 3)		PBO 120 mg 240 mg	16.76 21.81 23.05	 <.001 <.001	CGAI
PGI-Severity	Mean change from baseline (at Month 3)		PBO 120 mg 240 mg	-0.62 -0.76 -0.91	 .181 .006	CGAI
Unfavourable Effects						
Injection site reactions		%	GMB 120 mg: 18.2% GMB 240 mg: 22.8%	PBO: 12.8%		Pool A
Constipation		%	GMB 120 mg: 1.0% GMB 240 mg: 1.5%	PBO: 0.6%	More GMB treated patients than PBO had persistent constipation (>30 days)	Pool A
Vertigo		%	GMB 120 mg: 0.7% GMB 240 mg: 1.2%	PBO: 0.2%		Pool A
Urticaria		%	GMB 120 mg: 0.3% GMB 240 mg: 0.1%	PBO: 0.3%	2 SAEs and 5 discontinuation in GMB treated patients	Pool A
Pruritus		%	GMB 120 mg: 0.7% GMB 240 mg: 1.2%	PBO: 0.3%		Pool A

Abbreviations: DB = double blind; GMB = galcanezumab; MHD=migraine headache day; OL = Open label; TE AE = treatment emergent adverse event; PGI = patient global impression; MSQ = Migraine Specific Quality of Life; PBO = placebo

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Superiority of Galcanezumab compared to placebo in decreasing the burden of migraine episodes and symptoms in both EM and CM patients is considered demonstrated. The reduction of migraine headache days (MHD) and the proportion of patients with 50% reduced number of MHD are important and clinically relevant endpoints for both episodic and chronic migraine. In addition, the 30% responder endpoint is considered as relevant and clinically important endpoint for patients with chronic endpoints. However, the magnitude of treatment effect appears limited, especially in CM, and the possibility to up-titrate the recommend dose of 120 mg/day to 240 mg/day in the case of absence of response to the 120 mg dose should be left to the clinicians' judgement. The discussion on possible criteria for the definition of "non-responder" to the 120 mg dose has been defined within three months from initiation of treatment and introduced into the SmPC 4.2. When looking at the decrease in monthly moderate to severe MHDs, the magnitude of treatment effect is reduced compared to the primary endpoint.-Furthermore, when the severity of remaining migraine days is taken into consideration, no difference with placebo is observed in

the episodic migraine trial CGAG whereas a very small difference of questionable clinical relevance is apparent in the chronic migraine trial and episodic migraine trial CGAH. Reduction of acute medications, could be considered a clinically relevant additional benefit, however this is at present not demonstrated. It is not possible to infer from the data provided that treatment effect induces a statistically significant reduction in acute medication use, because the change in MHDs with acute medication is considered irrespective of the corresponding monthly total number of migraine days. Indeed, looking at the percent change in the mean use of paracetamol and triptans from baseline, to the DB period in the 3 pivotal studies, there seems to be a small decrease in the 3 studies for galcanezumab when looking at acute treatment overall that reaches statistical significance in 2 studies (CGAH and CGAI for both doses). For the specific acute medication of triptans, paracetamol and NSAIDS, there were overall small reduction seen for galcanezumab treatment with only small increases for paracetamol in study CGAG at 240 mg galcanezumab dose and study CGAH at 120 mg galcanezumab dose. It is also not clear if in patients with CM, the addition of galcanezumab to either topiramate or propranolol, which are common drugs used in prophylaxis and which, as per the claimed indication, could well be combined with galcanezumab, adds any additional benefit or only exposes patients to a high risk of adverse events. Available data are limited to patients with at least 4 MHDs per month, hence the indication has been changed to reflect this, whereas patients older than 65 years old could be treated after extrapolating efficacy from younger patients. In addition, methodological concerns in the conduct of the pivotal studies with regard to protocol deviations were alleviated by three sets of sensitivity analyses which showed consistent efficacy results.

The safety profile of galcanezumab is manageable, with few discontinuations due to AEs registered in the clinical trials, although no information is at present available in patient older than 65 years old. However, due to the mechanism of action there is the potential risk of cardiovascular toxicity that may be exaggerated in migraine patients who are at higher risk of cardiovascular events. Unfortunately, patients at high cardiovascular risk were excluded from the clinical trials, and thus no conclusion can be drawn on this issue. The same holds true for the potential for drug-induced hypertension during pregnancy that may be derived by the attenuation of the vasodilatative action of CGRP.

Long-term safety is largely unknown and given that the claimed indication is for a chronic disease, this is also considered important missing information, limiting the favourable effects of galcanezumab in the claimed indication.

3.7.2. Balance of benefits and risks

The benefit of galcanezumab treatment in the claimed indication is currently considered to outweigh the risks. The claimed indication is in line with the patient population recruited in the pivotal studies, however the magnitude of treatment effect appears limited, especially in CM. Despite the potential cardiovascular risk and the missing information on long term safety, galcanezumab was generally well tolerated. An increase in the incidence of injection site reactions, constipation, vertigo and hypersensitivity TEAEs was observed in the 3 to 6 months-controlled studies compared to placebo.

3.8. Conclusions

The overall B/R of Emgality is positive.

4. Recommendations

Outcome

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

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

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

New Active Substance Status

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

Union.