27 February 2020
EMA/CHMP/137303/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emgality

International non-proprietary name: galcanezumab

Procedure No. EMEA/H/C/004648/X/0004

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

Eli Lilly Nederland B.V. submitted on 7 February 2019 an extension of the marketing authorisation.

Extension application to add a new strength of 100 mg/ml solution for injection in pre-filled syringe for Emgality, associated with a new indication (episodic cluster headache).

The MAH applied for the following indication for Emgality 100mg new pharmaceutical form:

prophylaxis of attacks throughout a cluster period in adults with episodic cluster headache.

The legal basis for this application refers to:

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

Information on Paediatric requirements

At the time of submission of the application, the PIP EMEA-001860-PIP04-16 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 MAH 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.

Additional Data exclusivity/Marketing protection

The MAH requested consideration of one-year marketing protection in regards of its application for a new indication in accordance with 14(11) of Regulation (EC) 726/2004.

Scientific advice

The MAH received Scientific advice from the CHMP on 18 December 2014 (EMEA/H/SAH/033/1/2014/II). The Scientific advice pertained to clinical aspects.

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	7 February 2019
The procedure started on	28 February 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 May 2019

The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 May 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	19 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 May 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	17 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 January 2020
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	29 January 2020
SAG was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	20 January 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting an extension to marketing authorisation to Emgality on	27 February 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication of Emgality solution for subcutaneous injection is for the *prevention of attacks throughout a cluster period in adults with episodic cluster headache*. The chronic form is not included.

Cluster headache (CH) is the most prominent among the so called trigeminal autonomic cephalalgias (TACs), a group of idiopathic headache entities that involve unilateral, moderate to severe recurrent headache attacks and typical autonomic symptoms ipsilateral to the pain and/or restlessness and agitation. These characteristics are the mainstay of current diagnostic Guidelines, including those provided by the International Headache Society (ICHD-3 2018). In this condition, two periods are usually recognized: an active period ("bout") in which several attacks tend to repeat near-daily to multiple times daily, and remission periods, in which patients are attack free.

According to ICHD-3 2018 Guidelines, each attack typically lasts 15 to 180 minutes when untreated and occurs between 1 every other day and 8 per day for more than half of the time when the disorder is active (e.g. during the cluster period). The episodic form is the most frequent type of CH (up to 90% of patients), differs from the chronic by the length of remission periods. Patients with episodic cluster headache have discrete cluster periods (typically lasting 2 to 12 weeks in duration) that are followed by attack-free remission periods that last for 1 month or longer according to the diagnostic

criteria in effect at the time of initiation and execution of this development programme (ICHD-3 2013). In comparison, patients with chronic cluster headache experience cluster periods that can last for a year or longer without any or only brief periods of remission.

2.1.2. Epidemiology and risk factors

Cluster Headache is a primary headache with a low prevalence (<1%). It mostly affects men, with an overall male to female ratio of 4.3:1. The ratio of episodic vs. chronic cluster headache is 6.0 and the higher prevalence in men is even more evident when considering the chronic (15.0 and 3.8) vs the episodic form. According to a meta-analysis from Fischera et al. (2008) the lifetime prevalence of cluster headache for adults of all ages is 124 per 100,000 (95% CI 101-154), or approximately 0.1 percent, without region-specific differences. The one-year prevalence of cluster headache is 53 per 100,000 (95% CI 26-95).

In contradistinction to migraine, which peaks by the early second decade, CH has onset in the late third or early fourth decade of life. The family history for CH is generally unremarkable and sufferers do not experience auras. There is a relationship between attacks occurrence and sleep, with a distinct chronobiologic pattern that follow seasonal changes implying daylight length, and increased frequency of CH in the spring and fall.

Headache disorders, especially migraine, are amongst all health disorders that drive massive economic losses to European society. The mean per-person annual costs is €1222 for migraine (95% CI 1055–1389; indirect costs 93%), €303 for tension-type headache (TTH, 95% CI 230–376; indirect costs 92%), €3561 for medication-overuse headache (MOH, 95% CI 2487–4635; indirect costs 92%), and €253 for other headaches (95% CI 99–407; indirect costs 82%). Cluster headache is supposed to bear costs similar to migraine and although it is a rare amongst headaches, it may be even more disabling than migraine during attacks (Linde et al., 2012; Berg and Stovner, 2005).

The disease burden remains high, as CH is regarded as one of the most painful conditions encountered in clinical practice. The impact of this condition on daily functioning can be very high, and includes job loss, disability leave, lost working days, increased suicide risk. There is no universally efficacious preventive treatment for CH, therefore individualized therapy should manage either cluster episodes recurrence as well as intensity and frequency of attacks within each cluster.

2.1.3. Aetiology and pathogenesis

The pathogenesis of cluster headache, as well as of other trigeminal autonomic cephalagias (cluster headache, paroxysmal hemicrania, and SUNCT), has not been completely elucidated yet. However, the most widely accepted theory is that primary cluster headache is characterized by a hypothalamic activation in its posterior region (that serves as biologic clock) with secondary activation of the trigeminal-autonomic reflex, probably due to anatomical connections between the hypothalamus and the trigemino-vascular system (May et al., 2018). The similarities between CH and migraine regard particularly their trigger factors, that include alcohol, stress, disrupted sleep, and weather changes, again pointing towards a role played by the trigeminovascular system as the neuroanatomic place in which the attacks are generated and from which they spread (Vollesen et al. 2018a). Another theory holds an involvement of the cavernous sinus whose obliterated walls due to neurogenic inflammation hamper the venous outflow, thus injuring the traversing sympathetic fibers of the intracranial internal carotid artery and its branches. A direct peripheral connection between the sphenopalatine ganglion (SPG) and trigeminal ganglion could support the nociceptive pathways projecting to higher centers and viceversa, via the caudal brainstem and upper cervical spinal cord.

With regard to CGRP, as already outlined in the initial assessment of galcanezumab use in the prevention of migraine, it is known that this neuropeptide 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, also facilitating the effects of other pain transmitters including glutamate and substance P (Ma et al. 2010).CGRP is abundant in perivascular trigeminal nerve fibres by which is activated, especially during migraine attacks. It also has the capability of dilating intracranial and extracranial blood vessels while modulating vascular nociception at central level. This is the mainstay for hypothesizing that CGRP may play an important role in the pathophysiology of migraine and, conversely, its receptors blockade 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).

Similar to the above observations on migraine, there exist clinical studies showing that CGRP levels as measured from the external jugular vein ipsilateral to the pain during CH attacks can be approximately 2.5-fold compared with controls and, on the other hand CGRP levels normalised after using subcutaneous sumatriptan or oxygen inhalation (Goadsby and Edvinsson, 1994). Comparable results were derived from nitroglycerin-induced cluster attacks in which increased CGRP levels returned to baseline levels after sumatriptan treatment or spontaneous recovery (Fanciullacci et al., 1995, 1997). Of note, Vollesen and coll. (2018) found that the infusion of CGRP provoked cluster headache attacks in 8 of 9 episodic cluster headache patients during an active cluster period but did not provoke a cluster headache attack in 9 patients with the episodic type, while in remission.

2.1.4. Clinical presentation and diagnosis

Cluster headache is characterized by relatively short-lived (15 to 180 minutes) attacks of severe orbital, supraorbital, or temporal pain, accompanied by autonomic phenomena and/or restless or agitation (in contrast to migraine, which generally causes patients to seek solitary and calm shelter from light, sounds and noise). The attacks are usually short-lived, stereotyped and may recur up to 8 times a day. CH symptoms are unilateral, and do not change side throughout each attack, whereas in approximately 15 percent of cases they can shift side during a different attack.

The unilateral autonomic symptoms (lacking in only 3% of patients) associated with an attack are ptosis/miosis (due to parasympathetic hyperactivity and sympathetic paralysis), profuse lacrimation, conjunctival injection, rhinorrhea, and nasal congestion. The ocular changes may even become permanent with repeated attacks. Additionally, peau d'orange skin over the malar region, deeply furrowed glabellar folds, and telangiectasia may be observed on the painful side, particularly in areas of sympathetic deficit.

The circadian periodicity is considered a further clinical landmark of the syndrome, the length of remission periods between consecutive clusters helping to differentiate the episodic from the chronic form. Patients are usually asymptomatic while in remission. In the episodic type - the most common, affecting 80 to 90 percent of patients with CH - attacks occur daily for some weeks followed by at least 3-month period of remission (1 month according to ICHD 2013 criteria, that were recently revised), whereas in the chronic type attacks occur without significant periods of remission, defined as less than 3 months for at least 1 year (less than 1 month according to ICHD 2013 criteria). Indeed, a cluster period (or bout) generally lasts 6 to 12 weeks, while remissions can last up to 12 months or longer.

Chronic CH may arise de novo (in which case it is called primary chronic cluster headache) or being the evolution from the episodic type (secondary chronic cluster headache).

2.1.5. Management

Treatment of cluster headache in the EU is generally based on the guidelines provided by the European Federation of Neurological Societies (EFNS, 2006) and the National Institute for Health and Care Excellence (NICE) [May et al. 2006; NICE 2012, updated 2015]. Current clinical practice and treatment guidelines have mostly followed an empirical approach, starting from clinical experience and with little use of data from studies on direct comparators, which yet remain poorly represented. Several widely used preventive treatments, although accepted as standard of care like verapamil, are used off-label in some EU countries, whereas methysergide and ergotamine tartrate are no longer available in EU countries for the treatment of CH since publication of the above-mentioned treatment guidelines. The management recommendations consist of the following:

- EFNS guidelines: Prophylactic treatments – Level A: verapamil (noted as drug of first choice), steroids (used as "transitional" prophylactics); Level B: methysergide (noted limitations of use due to risk of pulmonary and retroperitoneal fibrosis with long-term use), lithium, ergotamine tartrate (short-term prophylaxis); topiramate; melatonin; pizotifen (noted that it has a modest effect and should be used only in rare cases because of side effects).

- NICE clinical guideline 150: Prophylactic treatments – Consider verapamil for prophylactic treatment during a bout of cluster headache; seek specialist advice for cluster headache that does not respond to verapamil.

The availability of authorised prophylactic treatments for cluster headache in some EU countries includes lithium, pizotifen, and clonidine. It is then widely acknowledged that there still exists a substantial unmet need for well-studied, effective, safe, and tolerable treatments.

About the product

Galcanezumab is a humanised IgG4 monoclonal antibody that binds CGRP and inhibits its biological activity without blocking the CGRP receptor. Galcanezumab targets CGRP and binds with high affinity (KD = 31 pM) and high specificity (>10,000-fold versus related peptides adrenomedullin, amylin, calcitonin, and intermedin). Calcitonin gene-related peptide is implicated in the pathophysiology of migraine and episodic cluster headache.

Type of Application and aspects on development

The legal basis for this application refers to:

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

2.2. Quality aspects

2.2.1. Introduction

Emgality (galcanezumab) is a humanised IgG4 monoclonal antibody that binds calcitonin gene-related peptide (CGRP) and inhibits its biological activity without blocking the CGRP receptor. Emgality is currently authorised for the prophylaxis of migraine in adults (120 mg in 1 mL solution for injection in prefilled syringe (PFS) or prefilled pen). The scope of this extension application is the addition of a new

strength of 100 mg for use in a new indication for the treatment of episodic cluster headache. It is presented in a prefilled syringe (PFS) containing 1 mL of solution.

Galcanezumab 100 mg and 120 mg utilise the same formulation components and container closure system. The process only differs in the amount of active substance used in the manufacture of the finished product. Therefore, pharmaceutical development for galcanezumab 100 mg relies on the existing 120 mg strength, with additional strength-specific information.

2.2.2. Active Substance

The active substance used to support the 100 mg and 120 mg strengths is the same; however, the following updates to Module 3.2.S have been implemented and are acceptable:

Control of Raw Materials

Amended to correct a typographical error

Container Closure System

Amended with updated active substance leachable data through 36 months.

Additional data from the ongoing stability leachables study has been provided. Two batches are included in the study, and results are now available for up to 36 months. The study will continue up to 60 months. So far, no leachables have been reported.

The additional leachables data is found acceptable. There are no other changes proposed for this section.

Stability

Amended with updated stability data through 36 months.

The already approved active substance shelf life is 36 months when stored at -65°C based on real-time data for the supporting batches.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

The finished product is filled in a semi-finished syringe (SFS), which is further assembled into a delivery device. The 100 mg formulation SFS is assembled with device components to form the prefilled syringe (PFS); and the 120 mg formulation SFS is assembled with device components to form either the PFS or the prefilled pen (PFP) presentation. Each PFS contains either 100 mg or 120 mg of galcanezumab in 1 mL and each PFP contains 120 mg of galcanezumab in 1 mL.

The composition comprises only compendial components, typically used for formulating monoclonal antibodies and is acceptable.

Pharmaceutical development

Galcanezumab injection 100 mg and 120 mg have identical composition and container closure system. Most of the pharmaceutical development information previously provided for the authorisation of the 120 mg finished product formulation is also valid for the new 100 mg formulation. A new Pharmaceutical Development section, specific to 100 mg formulation, is included in the dossier. The new information provided describes new studies on formulation development, manufacturing process

development, which include finished product manufacturing process characterisation and stability; commercial scale batches; container closure system; and compatibility.

The studies presented in the former dossier (120 mg strength) that are also valid for the 100 mg strength include the pre-formulation studies.

The information provided is found adequate and the results of the studies performed with the new formulation are in line with the data previously obtained with the 120 mg strength.

The applicant considers that the data on safety of materials of construction provided and approved for the 120 mg strength are applicable also for the 100 mg strength. This is acceptable.

Specific studies on the 100 mg strength have been performed. The data provided are acceptable.

Compatibility has been confirmed from different aspects, and this is considered appropriate.

Manufacture of the product and process controls

Manufacture

The names and addresses of the manufacturing, packaging, labelling, and control facilities were provided.

The same manufacturing sites as registered for Emgality 120 mg are proposed for Emgality 100 mg. The process involves 5 unit operations: buffer excipient solution compounding, finished product formulation compounding, sterile filtration, aseptic syringe filling and plunger insertion, and inspection.

The manufacturing process is described in sufficient detail.

Process controls

The same controls are in place for the 100 mg strength as already approved for the 120 mg strength. Where appropriate, a specific proven acceptable range/acceptance criteria~~/~~ has been proposed for the 100 mg strength. These new criteria/ranges have been appropriately justified in development studies and/or process validation and are found acceptable.

No changes to processing time limits (hold times) are proposed as compared to hold times registered for the 120 mg strength.

Process validation

The validation program includes finished product process validation, sterilisation process validation and shipping validation.

The process validation study was executed on three consecutive finished product batches at commercial scale. 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, analytical procedures, batch analysis

Specifications

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

The specifications are found adequate and in line with the batch release data.

Analytical procedures and reference standards

Analytical procedure description and validation were already approved for the 120 mg finished product formulation and are valid for the 100 mg finished product formulation.

Batch analysis

Batch analysis data for representative finished product batches manufactured using the commercial process at full-production scale at the commercial manufacturing site are provided in the dossier.

All data complies with the proposed finished product specifications.

The batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for Emgality 100 mg finished product.

Container closure system

New information about container closure system has not been provided in this section in the context of the 100 mg finished product formulation.

The information provided for the container closure system is found sufficient.

Stability of the product

All stability studies were conducted in accordance with ICH guidelines

Based upon the stability profile during stability studies the claimed shelf-life for the finished product of 24 months when stored at 2°C to 8°C is acceptable. The finished product should be stored protected from excessive heat and light. A patient in-use period of 7 days up to 30°C is found justified taking in consideration the data provided.

The post-approval stability protocol and the stability commitment proposed by the applicant are considered adequate.

Adventitious agents

No changes have been applied for. As there is no change to the active substance manufacturing process the data provided for the registered 120 mg strength is valid also for the 100 mg strength. The adventitious agents safety evaluation remains satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The dossier presented in support of this line extension application is of good quality. No Major Objection was identified. After assessment of the clarifications provided by the Applicant in response to the few issues raised during the review, it is concluded that, from a quality point of view, Emgality is approvable. A Recommendation to the Applicant has been proposed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the data provided, this extension application is considered approvable from a quality point of view

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The Applicant is recommended, for consistency, that the data of all batches supporting this new application of galcanezumab for cluster headache indication should be provided in the batch release section of the 100 mg strength. The information related to the site of manufacture and manufacturing process carried out for the manufacture of these batches should be included.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

2.3.2. Pharmacokinetics

The PK of galcanezumab were previously characterised based on data from clinical studies submitted with the initial application for prophylaxis of migraine. Data from two phase 3 studies were pooled to characterize the population PK and evaluate the exposure – response relationship in the CH population.

Based on the population PK analysis, in patients with CH Cmax is expected to be achieved within 5-6 days after galcanezumab dosing. With the monthly dosing regimen, steady-state is reached after four doses based on a half-life of 26 days. The accumulation ratio was predicted to be approximately 2. Special populations were adequately addressed in the migraine submission, which used the same population PK model. Body weight on CL/F was the only covariate in the population PK model and CL/F increases in a less than proportional manner with body weight. When CH PK data was fit to the existing migraine model the allometric relationship remained unchanged.

Studies CGAL and CGAM ~~and CGAR~~ were evaluated using the population PK model developed for the migraine submission. The final model that described galcanezumab PK after s.c. administration to healthy subjects, patients with migraine and patients with episodic and chronic CH was a 1-compartment model using first order conditional estimation (FOCE) parameterized in terms of rate of absorption (ka), apparent clearance (CL/F) and apparent volume of distribution (V/F). The model accounts for the influence of body weight (BW) on CL/F that was characterized by a power model equation demonstrating that CL/F increases in a ~~statistically significant~~ less than proportional manner with BW. No galcanezumab data was BLQ.

The VPC shows that the observed data is well described by the model (see Figure 1 below).

Figure 1

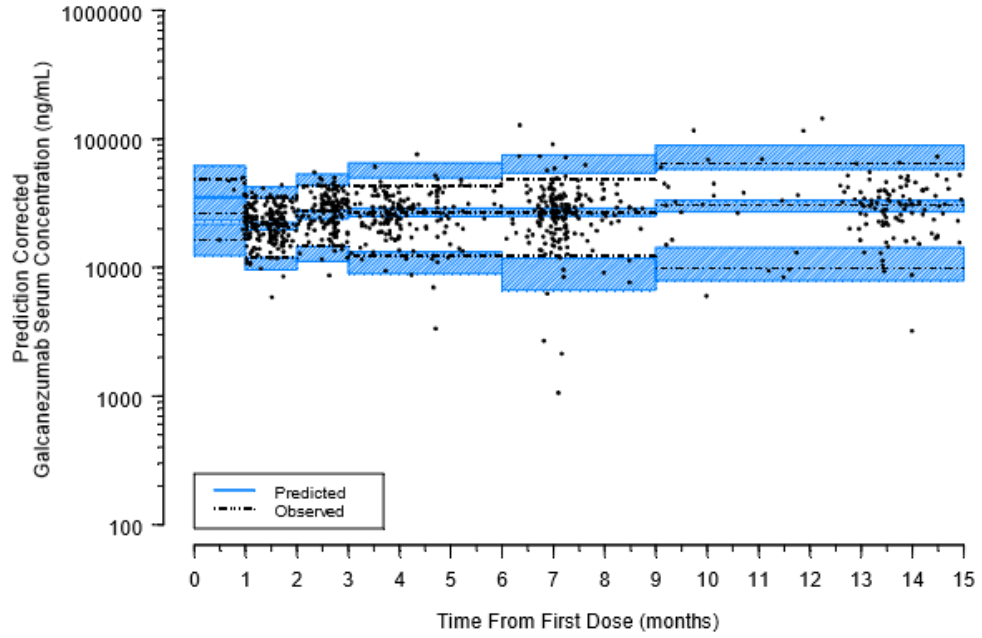
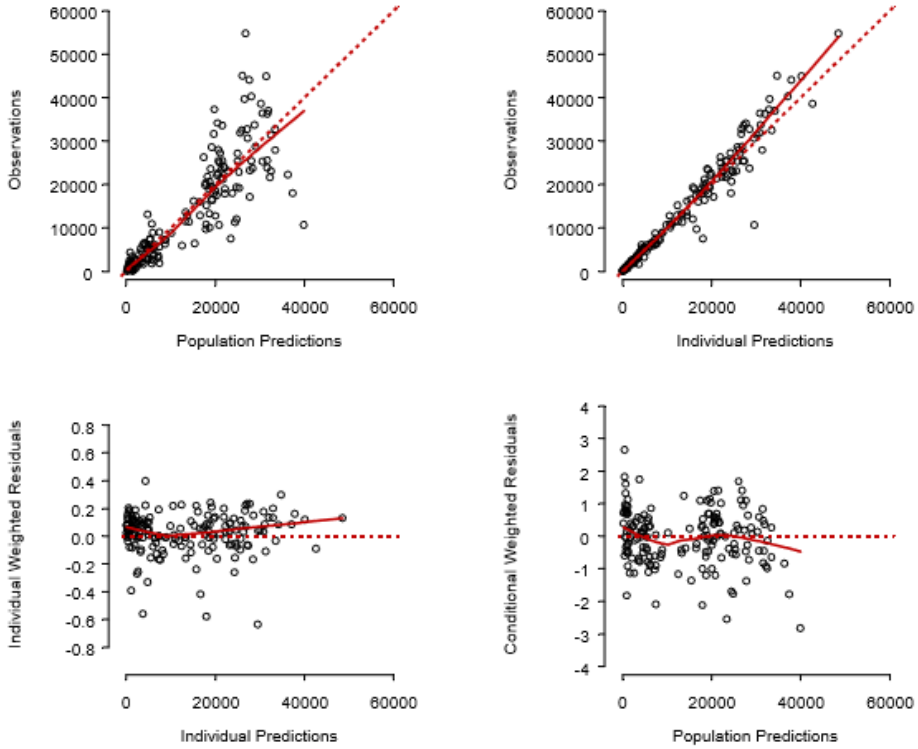


Figure 4.1. Visual Predictive Check of the Final PK Model in Episodic and Chronic Cluster Headache Patients

The following GOF and VPC plots, on the episodic cluster headache patients data demonstrate their good representation in the model:

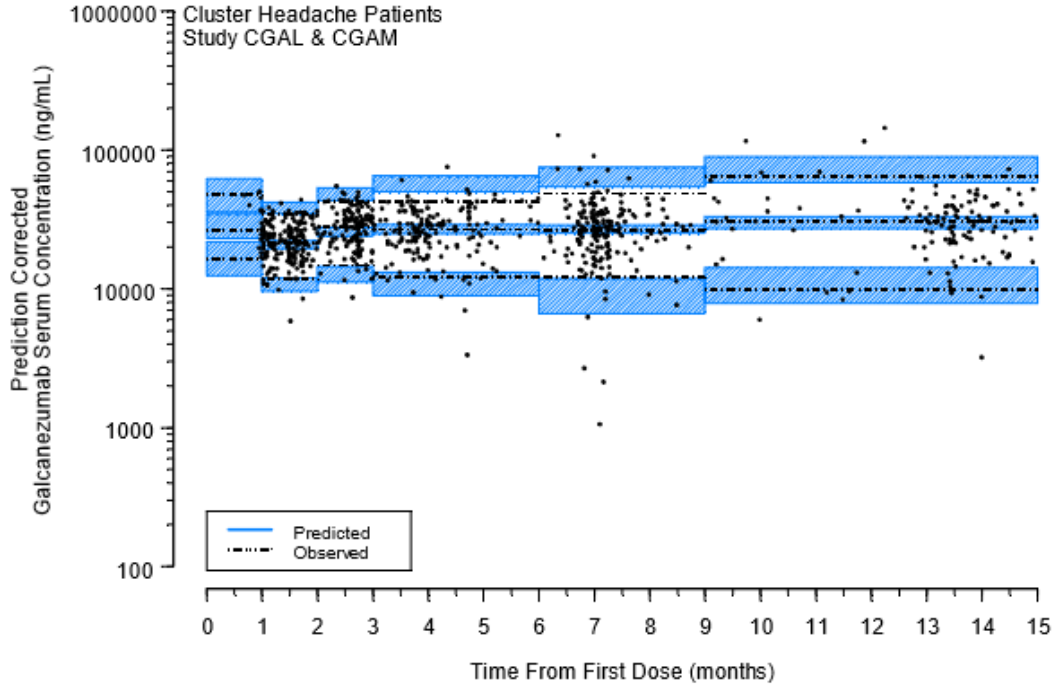
Figure 2



Circles represent patient data, dashed line represents line of unity, and red line represents LOWESS fit, a smoothed value given by a weighted linear least squares regression over the span of observations

Figure 4.2. Goodness of Fit Plots in Episodic Cluster Headache Patients

Figure 3



Dashed lines correspond to observed 5th, 50th, and 95th percentiles, while the width of the blue polygons corresponds to the simulated 95% confidence intervals of the predicted 5th, 50th, and 95th percentiles. Individual observations (•) are presented.

Figure 4.3. Visual Predictive Check in Episodic Cluster Headache Patients

The PK in the target population was similar to the migraine and healthy volunteers' groups. Inter-individual variability cannot be attributed to ADAs, regardless if baseline or treatment emergent. Presence of ADA, either baseline or treatment-emergent, did not affect the exposure to galcanezumab.

Exposure relevant for safety evaluation

Following an initial dose of 300 mg, the Cmax of galcanezumab was approximately 36 µg/mL (23% CV). A 300 mg monthly dosing regimen is predicted to achieve steady-state concentrations after 4 monthly dose administrations based on a half-life of 26 days (steady state Cmax of approximately 62µg/mL (24% CV)).

At steady state, AUC_{tau} in cluster headache patients amounted to 34700 h*µg/mL (1446 day*µg/mL).

2.3.3. Pharmacodynamics

Mechanism of action

The Applicant did not submit any new PD study performed in the CH population. After galcanezumab administration to CH patients, total CGRP concentrations increased, demonstrating evidence of target engagement. There was overlap of galcanezumab and CGRP concentrations from CH and migraine patients. This indicates that a similar galcanezumab–CGRP binding interaction exists across disease states where the CGRP mechanism is implicated. Galcanezumab-treated patients showed increases in total CGRP concentrations that was associated with a reduction from baseline in the CH attack

frequency. The effect was similar when contrasted by CGRP concentrations below and above the median concentration value. Similarly, galcanezumab concentrations were associated with a reduction from baseline in the CH attack frequency, but the effect was similar when contrasted by galcanezumab concentrations below and above the median concentration value.

2.3.4. Discussion on clinical pharmacology

The PK of galcanezumab had been characterized in the initial submission. In the present submission, the Applicant has used the population PK model previously developed in healthy subjects and patients with migraine to characterize the PK in patients with cluster headache. Diagnostic plots showed that the model adequately fits the data.

The lack of new PD studies is justified because the ability of the drug to block the vascular effect of CGRP had been previously demonstrated. The exposure-response analysis was very limited. This is partly due to the low number of available data points and the limited range of the observed galcanezumab and total CGRP concentrations obtained from the single dose adopted in the pivotal study. Nevertheless, a more detailed analysis may help supporting the claimed lack of necessity of dose adjustment based on BW and justifying the posology chosen in the CH target population.

2.3.5. Conclusions on clinical pharmacology

The PK of the drug have been adequately characterised. Disease was not expected to influence significantly the drug PK. Accordingly; the estimated PK parameters did not change after merging the CH population with the migraine population. Overall, the immunogenicity data in the current CH population are consistent with those previously reported in the migraine population. ADA presence did not affect the exposure to galcanezumab and there is no indication that presence or development of ADA may affect efficacy or safety, consistently with the migraine patient population.

2.4. Clinical efficacy

The clinical program to demonstrate efficacy and safety of galcanezumab 300 mg for the prophylaxis of cluster headache took into consideration the two different forms of the condition and included 3 phase 3 studies: one pivotal, placebo-controlled study for episodic cluster headache (CGAL), one placebo-controlled study for chronic cluster headache (CGAM) and one ongoing rollover open-label long-term safety study for subjects enrolled in CGAL and CGAM studies (CGAR).

The following table summarizes the main characteristics of each of the three studies:

Table 1 Tabular Listing of Clinical Studies for Cluster Headache Prevention

Study Identifier; Report Type; Status; Participating	Objective	Design; Control Type	Treatment and Regimen: Dose/Route/ Frequency		Number of Patients	Diagnosis or Inclusion Criteria	Treatment Duration
	PLACEBO-CONTROLLED CLINICAL STUDIES PERTINENT TO CLUSTER HEADACHE PREVENTION						

I5Q-MC-CGAL (Pivotal Study); Full; Ongoing; Belgium, Canada, Denmark, Finland, France, Germany, Greece, Italy, Netherlands	Efficacy of GMB compared with PBO in reducing the frequency of weekly cluster headache attacks in patients with episodic	Phase 3, multicenter, randomized, double-blind, PBO-controlled study	GMB 300 mg or PBO administered monthly (Q4W) via sc injection 4-month post-treatment (washout) phase		N = 106 GMB 300mg 49 PBO 57	18 to ≤65y ICHD-3beta criteria for episodic cluster headache, specified baseline weekly cluster headache attack frequency	8 weeks
I5Q-MC-CGAM Full; Ongoing; Belgium, Canada, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Spain, UK, USA	Efficacy and safety of GMB compared with PBO in reducing the frequency of weekly cluster headache attacks in patients with chronic cluster headache	Phase 3, multicenter, randomized, double-blind, PBO-controlled study with a long-term open-label extension	GMB 300 mg or PBO administered monthly (Q4W) via sc injection Open-label dosing monthly (Q4W): GMB 300 mg for up to 1 year 4-month post-treatment		N = 237 Double-Blind TreatmentPhase GMB 300 mg 117 PBO 120 N = 229 Open-Label Treatment Phase GMB 300 mg 229	18 to ≤65 y ICHD-3beta criteria for chronic cluster headache, specified baseline weekly cluster headache attack frequency as confirmed by a prospective baseline	DB phase: 3 months OL phase: 12 months
	UNCONTROLLED CLINICAL STUDY PERTINENT TO CLUSTER HEADACHE PREVENTION						
I5Q-MC-CGAR Ongoing; Belgium, Canada, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Spain, UK, USA	Safety of GMB in the context of expected medical practice in eligible pts with episodic or chronic cluster headache who complete Study CGAL or Study CGAM	Phase 3b, multicenter single-arm, open label safety study	GMB 300 mg administered up to once a month as determined by the investigator based upon symptoms and clinical judgment		N = 76 GMB 300mg 76	Patients who completed Study CGAL or Study CGAM	Region specific until Sponsor decision to end study or non-approval from regulatory agency where the patient is enrolled

(a) Patients who meet ICHD-3 beta diagnostic criteria for episodic cluster headache and have a specified baseline weekly cluster headache attack frequency confirmed during a 10- to 14-day prospective baseline period (maximum 8 attacks/day and a minimum of 1 cluster headache attack every other day and at least 4 total attacks).

(b) Patients who meet ICHD-3 beta diagnostic criteria for chronic cluster headache and have a specified baseline cluster headache attack frequency confirmed during a 2-week prospective baseline period (maximum 8 attacks/day and a minimum of 1 cluster headache attack every other day and at least 8 total attacks).

2.4.1. Dose response study(ies)

No dose-response studies were conducted for this application. In all three studies of the clinical program for galcanezumab in the prevention of cluster headache only the 300 mg dose was used. The Applicant derived the information regarding dosing recommendation according to the results of the phase 2a study on migraine prophylaxis I5Q-AR-ART01 (ART-01). This was a proof-of-concept, multicenter, randomized, placebo-controlled study in which galcanezumab was administered as 150

mg every two weeks (Q2W) to assess its efficacy and safety in the prevention of episodic migraine in patients suffering from migraine headache with or without aura over a 3-month period.

2.4.2. Main studies

Study I5Q-MC-CGAL (CGAL) for episodic cluster headache

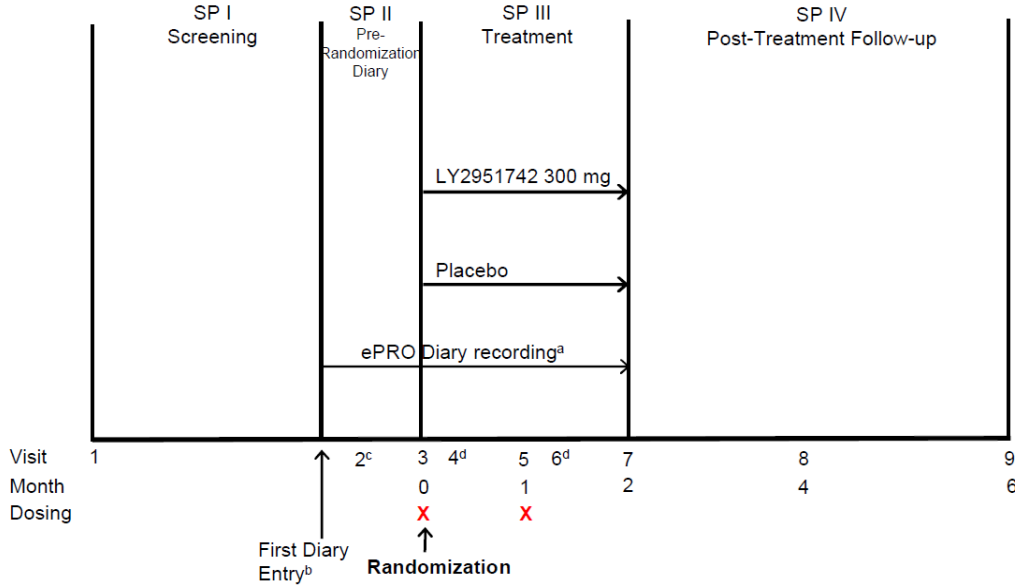
Methods

Study CGAL was is the only pivotal, phase 3 randomized, double-blind, placebo-controlled study of galcanezumab 300 mg.

Study CGAL had four periods: (i) up to one-year screening/washout period, to allow evaluation of patients to meet entry criteria while catching the start of the cluster for those in remission and to allow the discontinuation of excluded preventive medications like verapamil, ergot derivatives, valproate, opioids; (ii) a 10-14 days of pre-randomization period (run-in), the last 7 days of which provided the baseline mean weekly CHA count; (iii) an 8-week double-blind treatment period in which subjects were dosed with GMB 300 mg sc every 30 days (2 total doses); (iv) and 16-week post-treatment phase, ongoing as of the cutoff date 7 May 2018.

The MAH provided analyses from the completed DB phase as well as on the ongoing post-treatment phase (during washout of IMP), leaving to a subsequent report (CSR addendum) the inclusion of final data from the completed post-treatment phase.

Figure 4 CGAL.1. Illustration of study design for clinical protocol I5Q-MC-CGAL.



Abbreviations: ePRO = electronic patient reported outcomes; SP = study phase.

X = injection of investigational product

[a] ePRO diary will be completed daily during SP II and SP III. "Day" will be defined on a 24-hour clock day.

[b] SP II begins on the day that the patient first records a cluster headache attack in their ePRO diary.

[c] For patients who entered SP I while in remission, Visit 2 will occur during SP II, and the minimum time between Visit 2 and Visit 3 is five days.

[d] Telephone visit 7 days after office visit is only for assessment of spontaneously reported adverse events.

After 3-7 days of stabilization (off-remission), the baseline cluster attack frequency was assessed on 7-day prospective baseline period. The DB treatment phase lasted 8 weeks, and the primary endpoints were assessed at weeks 1 to 3 after first dosing.

Study Participants

Two-thirds of patients (66%) were enrolled in European sites located in 10 countries and the rest in USA and Canada, with a majority of white/Caucasian subjects (85%) and a male predominance (83%).

Main inclusion criteria

- male or female 18 to 65 years of age
- a history of episodic cluster headache as defined by IHS International Classification of Headache Disorders (3rd edition, 2013)
- a history of cluster period of at least 6 weeks' duration.
- A patient in an active cluster at visit 1 was expected to continue in the current period for another 6 weeks as deemed by the investigator based on previous history
- During baseline phase a patient was to have a weekly attack frequency between one attack every other day and at least 4/week and a maximum of 8 attacks per day.

Main exclusion criteria

- Medication overuse headache, a history of migraine variant that could be confused with ischemic symptoms, or suspicion of another trigeminal autonomic cephalalgia
- Are taking indomethacin, have taken botulinum toxin in head or neck area, or have a history of deep brain stimulation
- Significant active or unstable psychiatric disease
- ~~P~~patients considered by the investigator to be at significant risk for suicide.
- Cardiovascular-related conditions: ECG abnormalities compatible with acute events, significant risk, or QT prolongation
- Lifetime history of vasospastic angina or stroke, and any history of intracranial aneurysm, haemorrhage, tumor or significant head trauma, or seizures (excluding childhood febrile s's)
- Clinical evidence of peripheral vascular disease or a diagnosis of Raynaud's phenomenon
- Uncontrollable high blood pressure (BP >160/100 mmHg on two or more occasions before visit 3)
- Body mass index (BMI) ≥40 kg/m2

Treatments

Galcanezumab 300 mg (100-mg/mL) or placebo received once monthly by three 1-mL subcutaneous injections (sites included the abdomen, thigh, upper arm, and if appropriate, buttocks) at dosing visits administered by qualified study site personnel. Each treatment group received a total of 2 administrations during the 8-week treatment phase, ie, every 30 days for a total of 2 administrations during SP III. Injections were to be administered after all other study procedures were completed for the given visit.

Objectives

Primary objective was to assess the efficacy of GMB 300 mg administered once monthly compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with episodic cluster headache.

Once evidence of superiority of galcanezumab to placebo was provided on the primary objective, a single gated secondary objective had to assess the proportion of patients meeting response at Week 3, being response defined as a reduction from baseline of at least 50% in the weekly cluster headache attack frequency.

Baseline was defined as 7 days in the eligibility report (prospective baseline phase).

Other Secondary Objectives

- to assess whether galcanezumab was superior to placebo with respect to the following:

  - response rates (≥50% and ≥30%) for each weekly interval through Week 8
  - mean change in the weekly cluster headache attack frequency at each weekly interval from baseline through Week 8
  - proportion of patients reporting a score of 1 ("very much better") or 2 ("much better") on the Patient Global Impression of Improvement (PGI-I) at Week 4 and Week 8

Outcomes/endpoints

The primary endpoint was the overall mean change from baseline in weekly cluster headache attack frequency across Weeks 1 to 3 with galcanezumab compared with placebo, as recorded in the patient's daily ePRO diary.

The gated secondary outcome, 50% response, was the proportion of patients meeting the response criteria at Week 3.

The secondary efficacy measure was the PGI-I scale, a subjective scale by which the patient rates the global improvement since the first IMP intake on a 7-point scale (from 1 indicating "very much better" to 7 "very much worse") at Week 4 and Week 8.

At predefined dosing visits, venous blood samples were collected to determine the serum concentrations of galcanezumab, plasma concentrations of CGRP, and immunogenicity status, ie, ADA and neutralizing ADA (nAb) status, with validated assays and at an external laboratory approved by the sponsor.

Sample size

The study was planned to have a minimum of approximately 162 patients randomised 1:1 to placebo or galcanezumab. Justified by uncertainties in what treatment effect to expect, one sample size re-assessment was planned to be performed on unblinded data using an independent, external Statistical Analysis Centre (SAC).

Randomisation and blinding

Patients meeting all enrolment criteria were randomized to double-blind treatment at Visit 3 and assigned to treatment groups by a computer-generated random sequence using an IWRS, which also

assigned double-blind IP to each patient. The unblinded site personnel was to confirm the assigned packages prior to preparation and administration.

According to the dynamic allocation (minimization) method of Pocock and Simon (1975), factors of sex and average daily attack frequency (≤4 attacks per day, >4 attacks per day) were kept balanced within each treatment group and between investigative sites.

Statistical methods

The statistical analysis plan (SAP) was first approved on 18 December 2014 and was amended on 11 February 2015 (Version 2), 13 September 2016 (Version 3), 31 January 2018 (Version 4), and 05 April 2018 (Version 5).

Efficacy Analyses for the double-blind treatment phase were conducted using the intent-to-treat (ITT) population, which included data from all randomized patients who received at least 1 dose of IP.

Two interim analyses were initially planned.

Multiplicity

Adjustments for multiple comparisons were implemented for the analyses corresponding to the primary and gated secondary objectives. There were no adjustments for multiplicity for analyses of other data. Currently, the applicant proposes to include additional secondary outcomes in the SmPC having clarified that the p-values are nominal.

ePRO diary

Patients were asked to record the number of cluster headache attacks in their daily ePRO diary during the prospective baseline phase and double-blind treatment phase, which was used to derive the primary efficacy endpoint. The daily ePRO data were converted into 9 roughly 7-calendar day intervals (ie, baseline and Weeks 1 through 8). Each day, the patient may have had zero, one, or multiple cluster headache attacks.

The primary analysis was conducted by a repeated measures analysis that refers to a restricted maximum likelihood (REML)-based, mixed-effects repeated measures (MMRM) analysis using all the longitudinal observations from Week 1 to Week 3. The repeated measures models included the fixed, categorical effects of treatment, sex, pooled investigative site, visit/week, and treatment-by-visit/week interaction, as well as the continuous, fixed covariate of baseline value. An unstructured covariance structure was used to model the within-patient errors and alternative covariance matrices were pre-specified in case of not convergence. Rules for pooling of investigative sites were pre-specified in order to avoid sites with fewer than 2 patients per treatment group.

Sensitivity analyses. Several sensitivity analyses were conducted to assess the robustness of the primary analysis for each study, including the following: an analysis to assess the robustness of deviations from missing at random assumption, that is, a delta adjustment method as suggested by Permutt (2016); analyses to assess the robustness of deviations from the normality assumption, including an analysis of raw number of cluster headache attacks with a repeated measures negative binomial regression analysis and an MMRM analysis of change in cluster headache attack frequency after removing patients with outlier residuals; and a permutation test to confirm the results of the asymptotic inference (ICH E9 1998; Phipson and Smyth 2010).

Gated Secondary Analyses. The only gated secondary outcome, 50% response, is the proportion of patients meeting the response criteria at Week 3 and was assessed using Koch's Nonparametric Randomization-Based Analysis of Covariance method (Koch et al. 1998). This method adjusted for pooled investigative site by including it as a stratification variable and also adjusted for the continuous

baseline value and sex. All patients who discontinued study treatment at any time prior to Week 3, for any reason, were considered non-responders.

Other Secondary Analyses. Unlike the primary and gated secondary analyses which only used data up to Week 3, all the other secondary analyses used data from the full 8 weeks of the double-blind treatment phase.

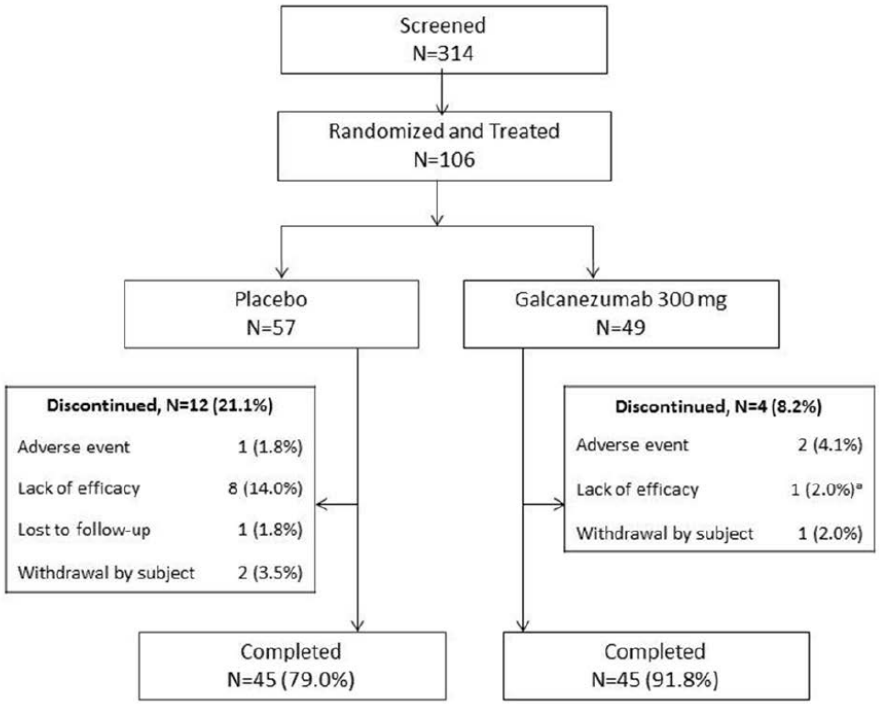
The study utilized a fixed sequential gatekeeper method for primary and gated secondary efficacy endpoints. There was no multiplicity adjustment for all other efficacy endpoints.

The interim analysis was not performed because enrolment was closed by the MAH due to enrolment infeasibility prior to reaching the sample size that would have triggered the interim analysis.

Results

Participant flow

Figure 5



[a] Statistically significant versus placebo; p=.036.
Source: Table CGAL.14.2 and
lillyce/prd/ly2951742/i5q_mc_cgal/intrm1/output/restricted/post_hoc/fqscreen11.rtf.

Recruitment

Date of first patient enrolled: 22 May 2015

Date of last patient completed double-blind phase: 12 February 2018

A total of 205 subjects were screen failures, most commonly due to *no cluster headache period within 12 months* after entering the study and *not meeting the baseline cluster headache attack frequency* requirements. Twenty subjects were re-screened, and of them 8 were randomized.

A total of 109 subjects were initially randomized to double-blind treatment (52 galcanezumab and 57 placebo), although 3 of them (randomized to galcanezumab) did not receive a dose of IMP, therefore the ITT population was finally made of 106 patients (49 galcanezumab and 57 placebo). Overall, 90 patients (84.9%) completed the double-blind treatment phase. A total of 16 patients (15.1%) discontinued and of them, 7 entered the post-treatment phase.

Conduct of the study

Among the four protocol amendments of study CGAL, the most relevant in terms of potential influence over the primary analysis and general implications, is the latest Amendment approved on 29 Mar 2018, namely a few weeks after the completion of the double-blind phase from the last patient (12 February 2018), prior to unblinding, and fiv~~e~~ weeks before the data lock date of 07 May 2018. By this amendment, the primary endpoint changed to be the overall treatment effect across Weeks 1 to 3 in weekly cluster headache attack frequency rather than the treatment effect at a single time point (Week 3) in that treatment period to enable evaluation of treatment effect over a 3-week period.

The MAH has explained that the endpoint change was a result of learnings from the phase 3 migraine programme and operational/execution results from the cluster headache programme (i.e. initial concern for a potential high dropout rate particularly in placebo patients that was not observed as study progressed). Although the change per se can be considered minor and outcomes using both definitions have been presented (see primary endpoint below, estimates per week), the explanation is not considered very transparent. Given that amendment (d) was implemented after the last patient had completed the last visit in the double-blind treatment period albeit, importantly, before the dates as reported for DBL and unblinding, the MAH was requested to further elaborate on the rationale for and background of the change in how the primary endpoint has been estimated, stating that ~~w~~ith a decreased sample size, it became important to try to optimize the power of Study CGAL. A key learning from the phase 3 migraine program was the increased power observed using an analysis of mean change over the evaluation period rather than an evaluation at a single time point. Thus, this change in the primary endpoint in Study CGAL from a single timepoint at Week 3 to across Weeks 1-3, which occurred prior to database lock and unblinding, was implemented to try to increase the power as the study did not reach the targeted minimum sample size.

Baseline data

Table 2 Summary of patient characteristics (ITT population)

Table CGAL.11.1. Summary of Patient Demographics ITT Population

Characteristic	Placebo N=57	Galcanezumab 300 mg N=49	Total N=106
Age (years)			
Mean (±SD)	45.40 (± 11.32)	47.49 (± 10.74)	46.37 (± 11.05)
Sex, n (%)			
Male	47 (82.46)	41 (83.67)	88 (83.02)
Female	10 (17.54)	8 (16.33)	18 (16.98)
Race, n (%)			
Asian	1 (1.75)	1 (2.04)	2 (1.89)
Black or African American	4 (7.02)	2 (4.08)	6 (5.66)
White	47 (82.46)	43 (87.76)	90 (84.91)
Multiple	5 (8.77)	3 (6.12)	8 (7.55)
Region, n (%)			
Europe	38 (66.67)	32 (65.31)	70 (66.04)
North America	19 (33.33)	17 (34.69)	36 (33.96)
Body Mass Index (kg/m^2)			
Mean (±SD)	27.12 (± 5.09)	26.20 (± 4.11)	26.69 (± 4.66)

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

Source: Table CGAL.14.8, Table CGAL.14.9.

Table 3

Table CGAL.11.2. Summary of Disease Characteristics ITT Population

Characteristic	Placebo		Galcanezumab 300 mg		Total	
	N		N		N	
Weekly attacks in baseline period, mean (±SD)	57	17.30 (±10.05)	49	17.82 (±10.12)	106	17.54 (±10.04)
Duration of cluster headache illness, years, mean (±SD)	56	17.61 (±11.46)	47	15.78 (±11.13)	103	16.78 (±11.29)
Severity of pain[a], mean (±SD)	57	2.57 (±0.65)	49	2.48 (±0.72)	106	2.53 (±0.68)
Daily cluster attack category, ≤4 per day, n (%)	57	50 (87.72)	49	41 (83.67)	106	91 (85.85)
Had attacks in last 7 days prior to Visit 1, n (%)	57	41 (71.93)	49	39 (79.59)	106	80 (75.47)
Lifetime suicidal ideation prior to screening, n (%)	57	5 (8.77)	49	9 (18.37)	106	14 (13.21)
Lifetime suicidal behavior prior to screening, n (%)	57	0	49	1 (2.04)	106	1 (0.94)

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

[a] Pain severity rated using a 5-point pain scale: 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, and 4=very severe pain (Sumatriptan Cluster Headache Study Group 1991)

Source: Table CGAL.14.8, Table CGAL.14.9, and Table CGAL.14.10.

The demographic characteristics of sex, age, race, and BMI were generally similar across treatment groups. Overall, 83.0% of subjects were male and 84.9% were white, with a mean age of 46.4 years, and a slight prevalence of the ≥ 40 years age group in the galcanezumab compared with placebo group (73.5 vs 66.7%, respectively). According to region, there were more patients from Europe than from North America (66.0 vs 34%, respectively).

Pre-existing most common (≥10%) conditions were GERD and insomnia, without statistically significant differences across group.

At baseline, the weekly number of times using acute medication was generally balanced between treatment groups. However, an unbalanced mean weekly number of times between galcanezumab and placebo was observed in the use of oxygen (9.5±9.5 vs 20.0±65.6 [p=.33], respectively), as well as in its use per CHA (mean 1.2 vs 0.6 [p=.32] in placebo vs galcanezumab, respectively). On the other hand, significant differences in the mean total weekly dose for oral triptan use was observed across placebo and galcanezumab groups at baseline (39.4±51.4 vs 320.0±408.9, respectively [p=.04], respectively). In line with this observation, a significantly different higher dose for Zolmitriptan nasal spray was observed in placebo compared with galcanezumab (29.4±25.0 vs 3.3±2.9 [p=.04], respectively).

Overall, 67% of patients reported in the eCRF at least one allowed concomitant medication.

During the post-treatment phase, patients were allowed to resume verapamil (maximum daily dosage 480mg), lithium, melatonin, valproate, gabapentin, and topiramate. Moreover, a single course of oral corticosteroids of ≤10 days was allowed. The interim data reported by the sponsor as of the data lock for the current application indicated that the most frequently used concomitant medications (≥5% total) in the post-treatment period were sumatriptan, paracetamol, verapamil, acetylsalicylic acid, levothyroxine sodium, oxygen, ibuprofen, and zolmitriptan

Numbers analysed

A total of 109 patients were randomised to double-blind treatment; 52 to galcanezumab and 57 to placebo. The primary analysis population used for all efficacy analyses required that a subject to be included, besides having been randomised, should have received treatment. This implied that three patients randomised to galcanezumab have been excluded not only from all analyses but all summaries as well. The MAH was requested to clarify the reason(s) for why these three patients did not receive any treatment (galcanezumab)explaining that they should have been screening failures, as "were discontinued the day they were randomised and did not receive investigational product". Since randomisation and treatment with IP were to occur at the same visit (visit 3) this is not considered to fully clarify why they were never treated or, why they were randomised, considering that the expected procedure at visit 3 should have been eligibility check, randomisation and treatment in that order. What is important is whether the decision to discontinue these patients was made with or without knowledge of assigned treatment. In this respect it should be remembered that this was a double-blind study and hence, the fact that these three patients were randomised but did not receive treatment could have been mistakes made at the sites as confirmed by the MAH. Regrettably, the MAH chose to present new analyses including not all three but only two of the patients excluded, however, the MAH explained that for the third patient, data required to determine baseline headache attack frequency was missing. The re-analysis of the primary endpoint requested at the second round, in which two alternative analyses were presented to represent the least and the most conservative baseline attack frequency value which had to be imputed for the "third" patient, earlier not included in any analysis, showed that such differences between these two and also, the analysis including 2/3

excluded patients presented with the responses at the first RSI (D121), was small and the primary endpoint remained significant. Regarding the re-analysis of the gated secondary endpoint, the difference between GMB and placebo was further decreased compared with the new analyses as presented within the D121 responses, as expected by the conservative approach used.

Efficacy analyses were performed on the ITT population, and all 106 ITT patients (randomised and received at least 1 dose of IP) were analysed for the primary efficacy measure. Three galcanezumab patients and 3 placebo patients had weeks excluded from the primary analysis due to ePRO compliance ≤50% or ≤3 days with non-missing answers to cluster headache attacks during the first 3 weeks as prespecified in the statistical plan. No patients were excluded from the primary efficacy analysis due to missing baseline or missing all post-baseline number of cluster headache attacks.

The mean compliance with diary across Weeks 1 to 3 that corresponded to the interval for the primary endpoint was not significantly different between galcanezumab and placebo (98.1 and 97.4%, respectively). The mean compliance with ePRO diary across the Weeks 1 to 8 in galcanezumab and placebo groups was, respectively, 97.3 and 93.8%.

It should be noted that although the methodological strengths claimed by the MAH encompassing randomisation, the prospective baseline design and the inclusion criteria #3 and #4 (respectively, prior history of cluster period lasting at least 6 weeks and for those in active cluster at consent, the anticipation by the clinical investigator to continue in the current period for at least another 6 weeks) to further ground the validity of the efficacy results, at the second round of questions different distributions of subjects by clinical status (being in active cluster as compared to remission at consent) and the corresponding post-hoc analyses results, give rise to uncertainties that the observed effects might have occurred by chance, due to unintentional introduction of bias within the placebo subgroups that could have driven the efficacy results in favor of galcanezumab, as well as the observed earlier first occurrence of ≥50% reduction in CHA frequency in galcanezumab.

Outcomes and estimation

Primary efficacy analyses

Table 4 Overall Mean Change from Baseline in Weekly Cluster Headache Attach Frequency across weeks 1 to 3 (Repeated Measures Analysis, ITT population, Study Phase III)

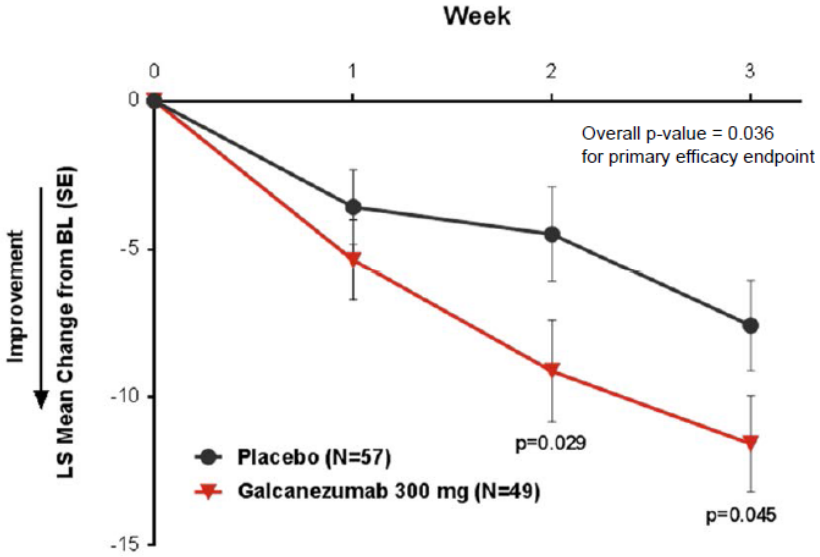
					Within-group	vs 1)		
Period	Treatment	N	LS Mean Change from Baseline (SE)	95% CI	P-value	LS Mean Change Difference (SE)	95% CI	P-value
Week 1	1)Placebo	57	-3.57 (1.27)	(-6.10, -1.04)	.006			
	2)GMB300mg	49	-5.37 (1.36)	(-8.06, -2.67)	<.001	-1.79 (1.53)	(-4.83, 1.24)	.243
Week 2	1)Placebo	54	-4.49 (1.61)	(-7.68, -1.30)	.006			
	2)GMB300mg	48	-9.13 (1.71)	(-12.52, -5.74)	<.001	-4.64 (2.09)	(-8.80, -0.49)	.029
Week 3	1)Placebo	53	-7.59 (1.52)	(-10.61, -4.57)	<.001			
	2)GMB300mg	46	-11.58 (1.62)	(-14.80, -8.36)	<.001	-3.99 (1.96)	(-7.88, -0.10)	.045
Overall	1)Placebo	57	-5.22 (1.33)	(-7.87, -2.57)	<.001			
	2)GMB300mg	49	-8.69 (1.42)	(-11.51, -5.87)	<.001	-3.47 (1.63)	(-6.72, -0.23)	.036*a

Abbreviations: GMB = galcanezumab; N = number of intent-to-treat patients with non-missing baseline value and non-missing value for that week; For 'Overall', N = number of intent-to-treat patients with non-missing baseline value and at least one non-missing postbaseline value; CI = confidence interval; LS = least square; SE = standard error. Repeated measures analysis model: Weekly attacks change from baseline = treatment, sex, pooled investigative site, week, treatment-by-week interaction, and baseline value. Estimates were obtained using an unstructured covariance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. *a, P-value for the primary efficacy endpoint. Source Table CGAL.11.3 of Study CSR

Galcanezumab dose of 300 mg was statistically significantly superior to placebo in the prevention of episodic cluster headache as demonstrated by an overall greater mean reduction in weekly cluster headache attack frequency across Weeks 1 to 3. The overall LSMean change from baseline during this

period was -8.7 attacks for galcanezumab compared with -5.2 attacks for placebo (LSMean change difference from placebo: -3.5 (standard error [SE] 1.6), 95% CI: -6.7, -0.2; p=.036).

Figure 6 Primary efficacy analysis: Mean change from baseline at weekly intervals from week 1 to 3



Abbreviations: BL = baseline; LSMean = Least Squares Mean; SE = standard error
Note: Repeated measures model included data from the first 3 weeks of double-blind treatment phase.

Sensitivity analyses for the primary endpoint results

All sensitivity analyses used diary data across weeks 1 to 3 and were consistent with the primary efficacy analysis.

Gated secondary endpoint

Table 5 Percentage of patients achieving ≥50% reduction from baseline in weekly cluster headache attack frequency at Week 3 (Nonparametric Randomization-Based Analysis of Covariance, ITT Population)

Placebo		Galcanezumab		Unadjusted	95% CI for	
N	n (%)	N	n (%)	Odds Ratio	Odds Ratio	p-value
53	30 (52.63)	46	35 (71.43)	2.250	(1.00, 5.05)	**.046**

Abbreviations: CI = confidence interval; n = number of patients within each specific category; N = number of intent-to-treat patients who have nonmissing values at baseline and postbaseline value at Week 3.

Source: Table CGAL.14.21.

The gated secondary endpoint, the percentage of patients achieving a ≥50% reduction from baseline in weekly cluster headache attack frequency at Week 3, was evaluated according to the fixed sequential gatekeeper method principle. This proportion was significantly greater in the galcanezumab treatment group compared with placebo (71.14% galcanezumab, 52.6% placebo; p=.046).

Additional analyses

Mean change in weekly cluster headache attack frequency across Weeks 1-8 by weekly interval

Table 6 Change From Baseline in Weekly Cluster Headache Attack Frequency Repeated Measures Analysis (ITT Population, Study Phase III)

Period	Treatment	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
Week 1	1) Placebo	57	-3.54 (1.29)	(-6.09, -0.99)	.007			
	2) GMB300mg	49	-5.07 (1.38)	(-7.81, -2.34)	<.001	-1.54 (1.75)	(-5.03, 1.95)	.384
Week 2	1) Placebo	54	-4.47 (1.54)	(-7.52, -1.42)	.004			
	2) GMB300mg	48	-8.84 (1.64)	(-12.09, -5.59)	<.001	-4.37 (2.14)	(-8.62, -0.12)	.044
Week 3	1) Placebo	53	-7.53 (1.39)	(-10.29, -4.78)	<.001			
	2) GMB300mg	46	-11.32 (1.48)	(-14.26, -8.38)	<.001	-3.79 (1.91)	(-7.58, 0.01)	.051
Week 4	1) Placebo	51	-11.03 (1.12)	(-13.25, -8.81)	<.001			
	2) GMB300mg	44	-11.51 (1.19)	(-13.87, -9.15)	<.001	-0.48 (1.48)	(-3.43, 2.47)	.748
Week 5	1) Placebo	44	-12.97 (1.13)	(-15.20, -10.74)	<.001			
	2) GMB300mg	46	-11.29 (1.16)	(-13.59, -8.99)	<.001	1.68 (1.46)	(-1.23, 4.59)	.254
Week 6	1) Placebo	45	-12.07 (1.37)	(-14.78, -9.36)	<.001			
	2) GMB300mg	46	-12.31 (1.39)	(-15.07, -9.54)	<.001	-0.24 (1.83)	(-3.87, 3.40)	.898
Week 7	1) Placebo	45	-13.73 (1.14)	(-15.99, -11.46)	<.001			
	2) GMB300mg	45	-12.93 (1.16)	(-15.24, -10.62)	<.001	0.80 (1.48)	(-2.15, 3.74)	.592
Week 8	1) Placebo	46	-14.41 (1.00)	(-16.39, -12.43)	<.001			
	2) GMB300mg	42	-13.12 (1.04)	(-15.19, -11.06)	<.001	1.29 (1.28)	(-1.25, 3.82)	.316
Overall	1) Placebo	57	-9.97 (0.95)	(-11.86, -8.08)	<.001			
	2) GMB300mg	49	-10.80 (1.00)	(-12.79, -8.80)	<.001	-0.83 (1.20)	(-3.23, 1.57)	.493

Abbreviations: GMB = galcanezumab; N = number of intent-to-treat patients with nonmissing baseline value and nonmissing value for that week; For 'Overall', N = number of intent-to-treat patients with nonmissing baseline value and at least one nonmissing postbaseline value; CI = confidence interval; LS = least square; SE = standard error. Repeated measures analysis model: Weekly attacks change from baseline = treatment, sex, pooled investigative site, week, treatment-by-week interaction, and baseline value. Estimates were obtained using an unstructured covariance structure.The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Source Table CGAL.14.24. of study CSR

- **Response Rates (≥50 and 30%) at each weekly interval through Week 8**:

Table 7

Table CGAL.14.23. Estimated Proportion of 50% Responders for Weekly Cluster Headache Attack Frequency Repeated Measures Analysis
Intent-to-Treat Population
Study Phase III

Period	Treatment	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
Week 1	1) Placebo	57	16 (0.281)	0.247 (0.061)	(0.146, 0.386)			
	2) GMB300mg	49	21 (0.429)	0.389 (0.076)	(0.252, 0.546)	1.939	(0.844, 4.454)	.117
Week 2	1) Placebo	54	22 (0.407)	0.357 (0.071)	(0.232, 0.505)			
	2) GMB300mg	48	30 (0.625)	0.583 (0.079)	(0.424, 0.727)	2.515	(1.119, 5.655)	.026
Week 3	1) Placebo	53	30 (0.566)	0.517 (0.075)	(0.372, 0.659)			
	2) GMB300mg	46	35 (0.761)	0.721 (0.072)	(0.560, 0.840)	2.411	(1.020, 5.700)	.045
Week 4	1) Placebo	51	39 (0.765)	0.732 (0.067)	(0.581, 0.843)			
	2) GMB300mg	44	35 (0.795)	0.768 (0.069)	(0.607, 0.876)	1.212	(0.461, 3.186)	.693
Week 5	1) Placebo	44	41 (0.932)	0.896 (0.046)	(0.765, 0.958)			
	2) GMB300mg	46	34 (0.739)	0.708 (0.070)	(0.554, 0.825)	0.281	(0.089, 0.881)	.030
Week 6	1) Placebo	45	38 (0.844)	0.811 (0.061)	(0.660, 0.904)			
	2) GMB300mg	46	37 (0.804)	0.781 (0.066)	(0.624, 0.884)	0.832	(0.289, 2.392)	.730
Week 7	1) Placebo	45	41 (0.911)	0.875 (0.050)	(0.737, 0.946)			
	2) GMB300mg	45	37 (0.822)	0.803 (0.061)	(0.654, 0.898)	0.583	(0.183, 1.856)	.357
Week 8	1) Placebo	46	41 (0.891)	0.881 (0.051)	(0.737, 0.951)			
	2) GMB300mg	42	32 (0.762)	0.740 (0.073)	(0.574, 0.858)	0.386	(0.117, 1.272)	.116
Overall	1) Placebo	57	(0.700)	0.704 (0.054)	(0.586, 0.800)			
	2) GMB300mg	49	(0.717)	0.696 (0.052)	(0.584, 0.789)	0.965	(0.512, 1.819)	.910

Table 8

Table CGAL.14.22. Estimated Proportion of 30% Responders for Weekly Cluster Headache Attack Frequency Repeated Measures Analysis Intent-to-Treat Population Study Phase III

						vs 1)		
Period	Treatment	N	n (Raw Rate)	Model Estimated Rate (SE)	95% CI of Estimated Rate	Odds Ratio	95% CI for Odds Ratio	P-value
Week 1	1) Placebo	57	27 (0.474)	0.406 (0.073)	(0.273, 0.555)			
	2) GMB300mg	49	32 (0.653)	0.593 (0.080)	(0.431, 0.738)	2.131	(0.945, 4.805)	.068
Week 2	1) Placebo	54	30 (0.556)	0.475 (0.076)	(0.332, 0.623)			
	2) GMB300mg	48	33 (0.688)	0.637 (0.078)	(0.473, 0.774)	1.938	(0.842, 4.461)	.119
Week 3	1) Placebo	53	39 (0.736)	0.670 (0.072)	(0.516, 0.795)			
	2) GMB300mg	46	36 (0.783)	0.729 (0.073)	(0.564, 0.849)	1.329	(0.527, 3.350)	.544
Week 4	1) Placebo	51	42 (0.824)	0.770 (0.065)	(0.618, 0.874)			
	2) GMB300mg	44	35 (0.795)	0.750 (0.072)	(0.583, 0.865)	0.896	(0.327, 2.454)	.829
Week 5	1) Placebo	44	41 (0.932)	0.861 (0.052)	(0.722, 0.937)			
	2) GMB300mg	46	38 (0.826)	0.788 (0.063)	(0.636, 0.887)	0.598	(0.196, 1.823)	.362
Week 6	1) Placebo	45	41 (0.911)	0.876 (0.052)	(0.731, 0.948)			
	2) GMB300mg	46	41 (0.891)	0.868 (0.054)	(0.720, 0.944)	0.930	(0.249, 3.468)	.912
Week 7	1) Placebo	45	43 (0.956)	0.923 (0.041)	(0.792, 0.974)			
	2) GMB300mg	45	41 (0.911)	0.894 (0.048)	(0.756, 0.958)	0.698	(0.155, 3.149)	.637
Week 8	1) Placebo	46	44 (0.957)	0.946 (0.036)	(0.810, 0.986)			
	2) GMB300mg	42	36 (0.857)	0.836 (0.062)	(0.674, 0.926)	0.291	(0.055, 1.526)	.142
Overall	1) Placebo	57	(0.793)	0.789 (0.048)	(0.678, 0.869)			
	2) GMB300mg	49	(0.801)	0.777 (0.047)	(0.671, 0.856)	0.929	(0.449, 1.923)	.841

Abbreviations: GMB = galcanezumab; N = number of intent-to-treat patients with nonmissing baseline value and nonmissing value for that week; For 'Overall', N = number of intent-to-treat patients with nonmissing baseline value and at least one nonmissing postbaseline value; n = number of responders among N; CI = confidence interval; SE = standard error.
Categorical, pseudolikelihood-based repeated measures model for binary outcomes: Responder indicator = treatment, sex, week, treatment-by-week interaction, 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.

- Patient Global Impression of Improvement (PGI-I) in Cluster Headache at Weeks 4 and 8

Table 9

						vs 1)		
Period	Treatment	N	n (Raw Rate)	Model Estimated Rate (SE)	95% CI of Estimated Rate	Odds Ratio	95% CI for Odds Ratio	P-value
Month 1	1) Placebo	49	23 (0.469)	0.464 (0.096)	(0.286, 0.652)			
	2) GMB300mg	44	32 (0.727)	0.725 (0.084)	(0.534, 0.859)	3.046	(1.242, 7.469)	.016
Month 2	1) Placebo	40	28 (0.700)	0.661 (0.091)	(0.465, 0.814)			
	2) GMB300mg	38	28 (0.737)	0.719 (0.086)	(0.524, 0.856)	1.312	(0.502, 3.426)	.575
Overall	1) Placebo	49	(0.585)	0.565 (0.089)	(0.388, 0.727)			
	2) GMB300mg	45	(0.732)	0.722 (0.076)	(0.550, 0.847)	1.999	(0.912, 4.380)	.083

Categorical, pseudolikelihood-based repeated measures model for binary outcomes: Outcome indicator = treatment, sex, baseline CH attack category, month, and treatment-by-month interaction. 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. Source: Table CGAL.14.25. of study CSR

Ancillary analyses

Exploratory endpoints

- *Attack frequency*: There were no statistically significant treatment group differences at any week in the percentage of patients who had ≥75% reduction or 100% reduction in weekly cluster headache attack frequency.
- *Attack pain severity*: There were no statistically significant treatment group differences overall or at any week in reduction in average weekly attack pain severity.
- *Attack duration*: there were no statistically significant treatment group differences overall or at any week in reduction of weekly total cluster headache attack duration.
- *Use of acute medications*: there were no statistically significant treatment group differences in the use of acute medication

Subgroup analyses

Table 10 CGAL.11.4 Summary of Subgroup Analyses

Subgroup Variable	Categories	Overall LS Mean Change from Baseline (SE) [a]		Treatment*subgroup Interaction p-value
		Placebo	GMB 300mg	
Sex	Male (n=88)	-6.78 (1.32)	-9.99 (1.42)	.823
	Female (n=18)	-1.61 (2.53)	-5.76 (2.65)	
Racial origin	White (n=90)	-3.08 (1.51)	-7.97 (1.57)	.106
	Multiple or Other (n=16)	-9.57 (2.90)	-8.02 (3.40)	
Ethnicity	Hispanic/Latino (n=7)	--[b]	--[b]	.298
	Not Hispanic/Latino (n=86)	-5.11 (1.68)	-9.03 (1.77)	
Age	<40 (n=32)	-4.47 (2.30)	-7.03 (3.02)	.998
	≥40 (n=74)	-5.57 (1.71)	-8.99 (1.71)	
Baseline average daily number of cluster headache attack category	≤4 attack per day (n=91)	-2.46 (1.36)	-6.76 (1.52)	.059
	>4 attack per day (n=15)	-26.98 (6.08)	-15.02 (5.53)	
	≤3 attacks per day (n=78)	-1.66 (1.38)	-6.63 (1.59)	.042
	>3 attacks per day (n=28)	-17.38 (5.08)	-11.52 (4.69)	
	≤2 attacks per day (n=52)	-2.24 (1.04)	-5.04 (1.10)	.998
	>2 attacks per day (n=54)	-6.94 (2.89)	-10.05 (3.18)	
Region	Europe (n=70)	-2.86 (1.54)	-7.39 (1.67)	.378
	North America (US and Canada) (n=36)	-7.64 (2.26)	-9.13 (2.36)	

Abbreviations: GMB = galcanezumab; n = number of patients in specific subgroup; SE = standard error

[a] Used the data within the specific subgroup only

[b] Cannot be calculated due to small number of patients

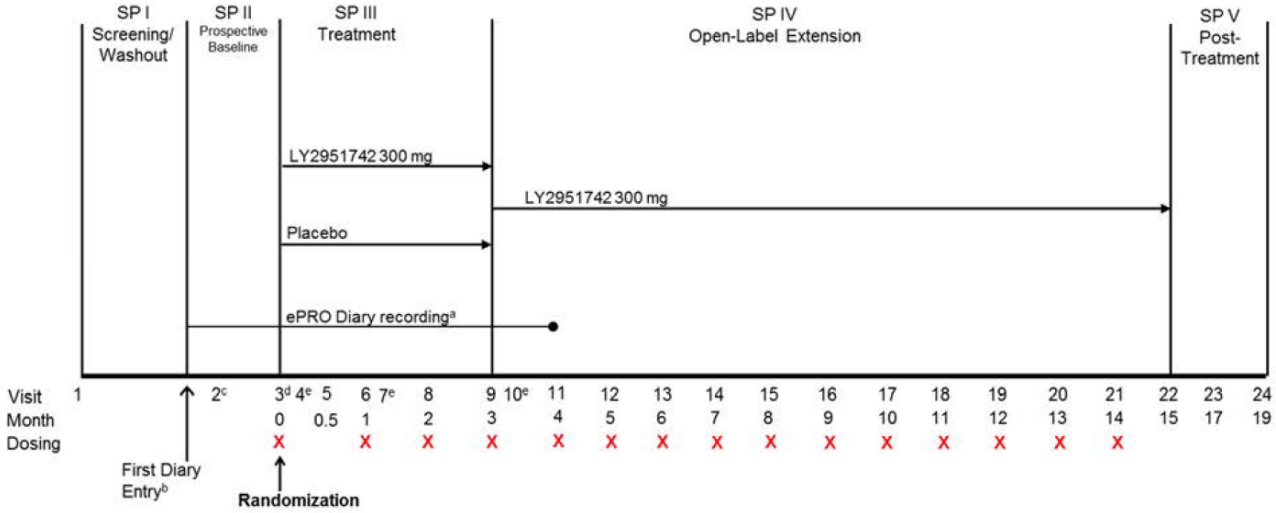
Sources: Table CGAL.14.45, Table CGAL.14.46, Table CGAL.14.47, Table CGAL.14.48, Table CGAL.14.49, Table CGAL.14.50, Table CGAL.14.51, Table CGAL.14.52.

Supportive study

Study I5Q-MC-CGAM (CGAM) for chronic cluster headache

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 with a Long-Term Open-Label Extension in Patients with Chronic Cluster Headache.

Figure 7 Study design:



Abbreviations: ePRO = electronic patient-reported outcome; LY2951742 = galcanezumab; SP = study phase; X = injection of investigational product.

[a] ePRO diary was completed daily during Study Phase II and Study Phase III. "Day" was defined on a 24-hour clock day.
[b] Patients began recording in their diary on a daily basis and called the site to schedule Visit 2 and Visit 3.
[c] Visit 2 was to occur during Study Phase II. The minimum time between Visit 2 and Visit 3 was to be 5 days.
[d] Scheduling of this office visit, Visit 3, was to take into consideration that patients must have had at least 14 days to record a baseline assessment of cluster headache attack frequency prior to Visit 3.
[e] Telephone visit 7 days after office visit only for assessment of spontaneously-reported adverse events.

Primary endpoint

Overall mean change from baseline in weekly cluster headache attack frequency during the 12-week double-blind treatment phase with galcanezumab compared with placebo. The baseline cluster headache attack frequency was based on the last 14 days in the eligibility report of the prospective baseline phase.

Gated secondary endpoints

The estimated mean proportion of patients with at least 50% reduction from baseline in the weekly frequency of cluster headache attacks during the 12-week double-blind treatment phase

The proportion of patients meeting sustained response through Week 12. For this analysis, sustained response is defined as a 50% or greater reduction in the weekly cluster attack frequency from baseline to Weeks 3/4 and maintained at Weeks 5/6, Weeks 7/8, Weeks 9/10, and Weeks 11/12.

Other endpoints

Secondary efficacy measures included 30% and 50% responder rates and PGI-I

Exploratory efficacy meansures included 75% and 100% responder rates

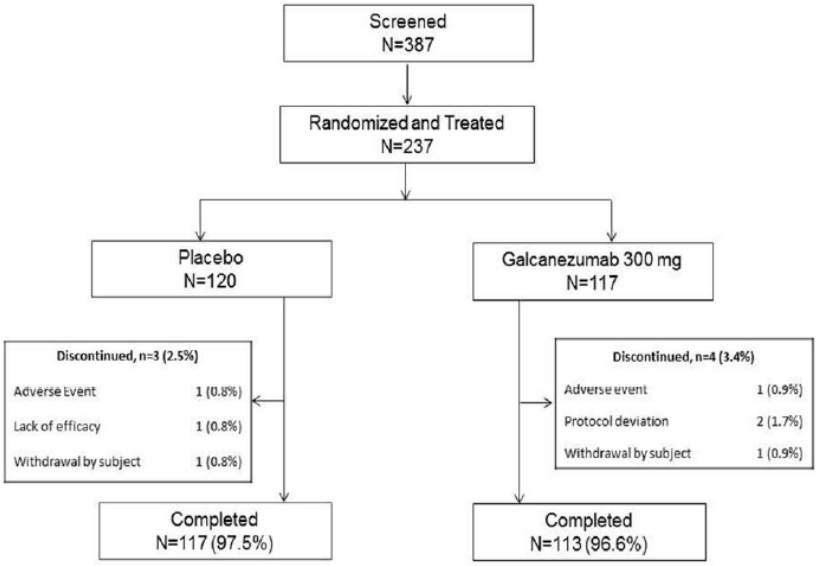
Main eligibility criteria **(other than the ones for the episodic cluster headache study (CGAL))**

Inclusion criteria:

- ICHD-3 beta diagnostic criteria for chronic cluster headache:
    A. Attacks fulfill criteria for cluster headache, and criterion B below
    B. Occurs without a remission period, or with remissions lasting <1 month, for at least 1 year
- Patients on preventive treatment for cluster headache had to be on a stable regimen of one of the allowed preventives (verapamil ≤480 mg/day, lithium, melatonin, valproate, gabapentin, and topiramate) for at least 2 months prior to the start of the prospective baseline and the dose had to remain stable throughout the double-blind treatment phase.
- In the opinion of the investigator, spontaneous remission during the double-blind treatment phase is not anticipated based on the patient's history of cluster periodicity.

Results

Figure 8 Patient disposition



Demographics

Table 11

Table CGAM.11.1. Summary of Patient Demographics ITT Population

Characteristic	Placebo N=120	Galcanezumab N=117	Total N=237
Age (years)			
Mean (±SD)	44.38 (±10.81)	45.62 (±11.03)	45.00 (±10.92)
Sex, n (%)			
Male	86 (71.67)	86 (73.50)	172 (72.57)
Female	34 (28.33)	31 (26.50)	65 (27.43)
Race, n (%)			
Black or African American	1 (0.83)	1 (0.85)	2 (0.84)
White	101 (84.17)	99 (84.62)	200 (84.39)
Multiple	18 (15.00)	17 (14.53)	35 (14.77)
Region, n (%)			
Europe	101 (84.17)	95 (81.20)	196 (82.70)
North America	19 (15.83)	22 (18.80)	41 (17.30)
Verapamil use, n (%)			
Yes	63 (52.50)	55 (47.01)	118 (49.79)
No	57 (47.50)	62 (52.99)	119 (50.21)
Body mass index (kg/m^2)			
Mean (±SD)	26.29 (±4.78)	26.42 (±4.83)	26.35 (±4.80)

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

Sources: Table CGAM.14.9 and Table CGAM.14.10.

Table 12

Table CGAM.11.2. Summary of Disease Characteristics ITT Population

Characteristic	Placebo		Galcanezumab		Total	
	N		N		N	
Weekly attacks in prospective baseline phase, mean (±SD)	120	18.47 (±10.66)	117	19.18 (±9.82)	237	18.82 (±10.24)
Duration of cluster headache illness, years, mean (±SD)	119	8.40 (±7.53)	116	7.66 (±6.60)	235	8.03 (±7.08)
Severity of pain[a], mean (±SD)	120	2.64 (±0.69)	117	2.76 (±0.70)	237	2.70 (±0.69)
Daily cluster attack category, ≤4 per day, n (%)	120	100 (83.33)	117	97 (82.91)	237	197 (83.12)
Had attacks in last 7 days prior to Visit 1, n (%)	120	120 (100.00)	117	117 (100.00)	237	237 (100.00)
Lifetime suicidal ideation prior to screening, n (%)	120	30 (25.00)	117	25 (21.37)	237	55 (23.21)
Lifetime suicidal behavior prior to screening, n (%)	119	5 (4.20)	117	4 (3.42)	236	9 (3.81)

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

[a] Pain severity rated using a 5-point pain scale: 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain, and 4=very severe pain (Sumatriptan Cluster Headache Study Group 1991)

Sources: Table CGAM.14.9, Table CGAM.14.10, and Table CGAM.14.11.

Concomitant medications

All but 1 patient on placebo used an acute medication for their cluster headache attacks during the double-blind treatment phase. Sumatriptan and oxygen were used by the majority of galcanezumab-treated patients and placebo-treated patients (84.0% and 70.5%, respectively). A greater percentage

of galcanezumab-treated patients used oxygen compared with placebo-treated patients (76.1% vs. 65.0%, respectively); however this difference was not statistically significant and was not believed to be clinically meaningful or have an impact on study outcomes.

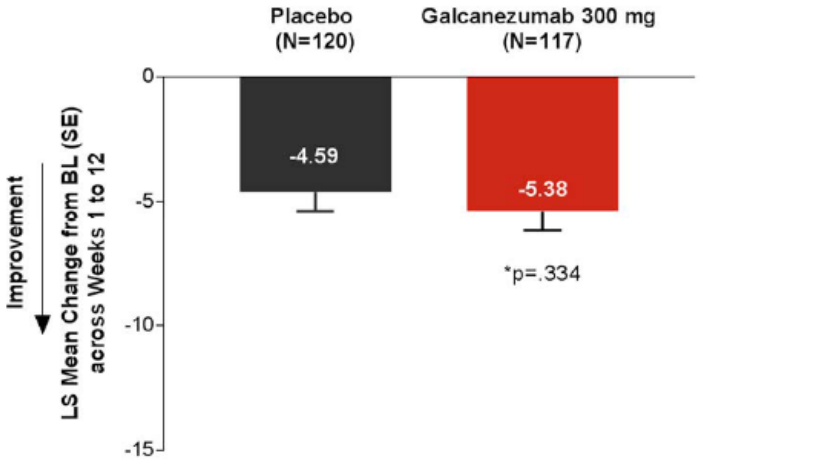
More patients took verapamil (50.2%) than any other preventive medications: lithium (13.1%), topiramate (9.3%), valproate (6.3%), gabapentin (2.5%), and melatonin (3.4%).

Efficacy results

Primary endpoint

Galcanezumab was not statistically significantly superior to placebo in the prevention of cluster headache in patients with chronic cluster headache based on the primary endpoint of overall mean reduction in weekly cluster headache attack frequency. The overall LSMean change from baseline in weekly cluster headache attack frequency during the double-blind treatment phase was -5.4 attacks in the galcanezumab group compared with -4.6 attacks in the placebo group (LSMean change difference from placebo: -0.8; p=.334). The change from baseline at each biweekly interval (repeated measures analysis of the ITT population) revealed a statistically significant difference for the week 1-2 interval (p=0.006). A number of sensitivity analyses of the primary endpoint yielded the same result as the primary analysis.

Figure 9



Abbreviations: BL = baseline; LSMean = least-squares mean; N = number of patients; SE = standard error.
*p-value reflects the Cui, Hung, and Wang adjusted p-value.
Source: lillyce/prd/ly2951742/i5q_mc_cgam/intrm1/output/restricted/rmeprp11.rtf.

Figure CGAM.11.1. Mean change from baseline in weekly cluster headache attack frequency across Weeks 1 to 12.

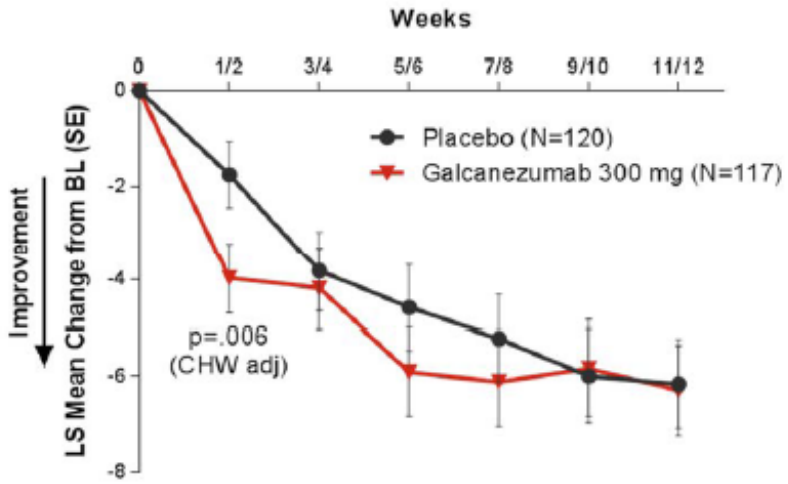
Gated secondary endpoint

A fixed sequential gatekeeper method was used to control type I error across the primary and gated secondary objectives. Because the primary efficacy analysis was not statistically significant, neither of the secondary endpoint analyses in the gatekeeper strategy could be considered significant. Regardless of the testing hierarchy, neither individual analysis included in the gatekeeper strategy met statistical significance.

☐ The mean percentage of patients with a ≥50% reduction in weekly cluster headache attack frequency from baseline across Weeks 1 to 12 was 32.6% in the galcanezumab group and 27.1% in the placebo group.

☐ Sustained response was defined as ≥50% reduction in the weekly cluster headache attack frequency from baseline to Weeks 3/4 and maintained at Weeks 5/6, Weeks 7/8, Weeks 9/10, and Weeks 11/12. A similar percentage of patients in each treatment group met the definition of sustained response (16.2% galcanezumab, 17.5% placebo).

Figure 10



Abbreviations: adj = adjusted; BL = baseline; CHW = Cui, Hung, and Wang; LSMean = least-squares mean; N = number of patients; SE = standard error.
Source: lillyce/prd/ly2951742/i5q_mc_cgam/intrm1/output/restricted/rmeprp11.rtf.

Figure CGAM.11.2. Mean change from baseline in weekly cluster headache attack frequency at each biweekly interval across Weeks 1 to 12.

Secondary/exploratory endpoints

30% responder rate

A statistically significantly greater percentage of galcanezumab-treated patients achieved ≥30% response at Weeks 1/2 compared with placebo-treated patients (35.2% vs. 23.0%, respectively; p=.037). A numerically greater percentage was observed with galcanezumab compared with placebo at all remaining measured time intervals and overall, and the overall effect was trending towards a positive effect for galcanezumab (p=0.057).

50% responder rate

The percentage of patients who achieved ≥50% response was numerically greater with galcanezumab compared to placebo at the majority of the measured time intervals and overall, although these differences were not statistically significant at any of the measured biweekly intervals and there was no overall trend for a positive effect for galcanezumab (p=0.170).

Pain severity

No statistically significant effects were seen for pain severity, although there was a trend for a decrease in pain severity during week 1-2 (p=0.053) and week 5-6 (p=0.064).

Cluster headache weekly total attack duration

No overall effect for week 1-12, but significantly decreased during the week 5-6 (p=0.038) and 7-8 (p= 0.047) measurements.

Use of acute treatment

Oxygen (NS), subcutaneous sumatriptan (borderline overall treatment effect p=0.052), oral triptan or nasal spray (NS)

Patient global impression (PGI-I)
No effects vs placebo.

Summary of main study(ies)

The following table summarises the efficacy results from the main study 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 13 Summary of efficacy for trial CGAL

Title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Episodic Cluster Headache			
Study identifier	Protocol Number: I5Q-MC-CGAL EudraCT Number: 2015-000149-22		
Design	Phase 3, randomized, double-blind, placebo-controlled, multicentre, international (EU and US), outpatient study to assess the efficacy of galcanezumab 300 mg (GBM 300mg) once monthly compared with placebo in reducing the frequency of weekly cluster headache attacks in patients with episodic cluster headache		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 weeks of double-blind treatment 10-14 days 16 weeks
Hypothesis	Superiority		
Treatments groups	Galcanezumab (GMB) 300 mg (three 1-mL sc monthly injections of 100 mg/mL each)		N=49
	Placebo (three 1-mL sc monthly injections of 0.9% Sodium Chloride, USP)		N=57
Endpoints and definitions	Primary endpoint	Cluster headache attacks (CHA)	Overall mean change from baseline in weekly cluster headache attack frequency across Weeks 1 to 3
	Gated secondary endpoint	50% responders	Proportion of patients meeting response at Week 3. Response was defined as a reduction from baseline of ≥50% the weekly CHA frequency.
	Other secondary endpoint	≥30%, ≥50% response rates	Response rates (50% and 30%) at each weekly interval through Week 8
		PGI-I score	Proportion of patients reporting a score of 1 ("very much better") or 2 ("much better") on the Patient Global Impression of Improvement (PGI-I) at Week 4 and Week 8.
		CHA frequency	Change in weekly CHA frequency at each weekly interval through Week 8

	Exploratory endpoints	≥75, ≥100% response rates	Proportion of patients in the reduction of weekly number of CHA from baseline for each weekly interval through Week 8
		Abortive medication use	Mean change in the weekly number of times an abortive medication was taken from baseline for each weekly interval through Week 8
		Oxygen use	Mean change in the weekly number of times using oxygen from baseline for each weekly interval through Week 8
		Triptan use	Mean change in the weekly number of times using triptans from baseline for each weekly interval through Week 8
		Acetaminophen/ paracetamol or NSAIDs	Mean change in the weekly number of times using Acetaminophen/paracetamol or NSAIDs from baseline for each weekly interval through Week 8
		Pain severity	Mean change in the CHA average weekly pain severity (based on 5-point scale) from baseline through Week 8
Database lock	07 May 2018		

Results and Analysis

Analysis description	**Primary Analysis:** Overall mean change from baseline in weekly cluster headache attack frequency across Weeks 1 to 3 with GMB compared with PBO		
Analysis population and time point	Intent to treat across months 1 to 3 (*ITT population was defined as those patients randomized and who received at least 1 dose of IP*)		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group (number of subjects)	PBO N=57	GMB 300 mg N=49
	LS Mean (SE) Difference vs Placebo (SE) 95% CI on Difference P-value vs placebo	-5.22 (1.33)	-8.69 (1.42) -3.47 (1.63) -6.72, -0.23 .036
Notes	MMRM model: weekly CHA change from baseline = treatment, sex, pooled investigative site, week, treatment-by-week interaction, and baseline value. Estimates were obtained using an unstructured covariance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.		
Analysis description	**Gated secondary analysis**: percentage of patients achieving a ≥50% reduction from baseline in weekly cluster headache attack frequency at Week 3		
Analysis population and time point description	Intent to treat, Week 3		
Descriptive statistics, estimate variability, and estimate of effect	Treatment group (number of subjects)	PBO N=30	GMB 300 mg N=35
	n (%) = number of pts within each category Unadjusted OR 95% CI for OR P-value vs placebo	30 (52.63)	35 (71.43) 2.250 1.00, 5.05 .046
Notes	Koch's nonparametric randomization-based ANCOVA model: Responder indicator = treatment, sex, and baseline value, stratified by pooled investigative site. Mantel-Haenszel weights is used for each pooled investigative site.		

Analysis description	**Other secondary analysis** (pre-specified)			
Analysis population and time point description	Intent-to-treat across weeks 1 to 8			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group (number of subjects)		PBO N=57	GMB 300 mg N=49
	30% [(1)] responders for weekly CHA frequency	Estimated rate, % (SE) Odds ratio vs PBO 95% CI for Odds Ratio P-value vs placebo	78.9 (4.8)	77.7 (4.7) 0.929 (0.449, 1.923) .841
	50% responders for weekly CHA frequency	Estimated rate, % (SE) Odds ratio vs PBO 95% CI for Odds Ratio P-value vs placebo	70.4 (5.4)	69.6 (5.2) 0.965 0.512, 1.819 .91
	Change From Baseline in Weekly CHA Frequency [(2)]	LS Mean (SE) Difference vs PBO (SE) 95% CI on Difference P-value vs placebo	-9.97 (0.95)	-10.80 (1.00) -0.83 (1.20) -3.23, 1.57 .493
	PGI-I Proportion of Patients with Score 1 or 2 [(3)]		PBO N=49	GMB 300 mg N=45
	At Week 4	n (raw rate) Estimated rate, % (SE) Odds Ratio 95% CI for Odds Ratio P-value vs PBO	23 46.4 (9.6)	32 72.5 (8.4) 3.046 1.242, 7.469 .016
	At Week 8	n (raw rate) Estimated rate, % (SE) Odds Ratio 95% CI for Odds Ratio P-value vs PBO	28 66.1 (9.1)	28 71.9 (8.6) 1.312 0.502, 3.426 .575
Notes	[(1)] Categorical, pseudolikelihood-based repeated measures model for binary outcomes: Responder indicator = treatment, sex, week, treatment-by-week interaction, 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. [(2)] Repeated measures analysis model: Weekly attacks change from baseline = treatment, sex, pooled investigative site, week, treatment-by-week interaction, and baseline value. Estimates were obtained using an unstructured covariance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. [(3)] Categorical, pseudolikelihood-based repeated measures model for binary outcomes: Outcome indicator = treatment, sex, baseline CHA category, month, and treatment-by-month interaction. 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.			
Analysis description	**Exploratory endpoints**			
Notes	None of the above listed exploratory endpoints was statistically significant between treatment groups across the 8 Weeks of double blind treatment. Please see the details in the AR.			

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant carried out two studies to provide evidence of efficacy of galcanezumab 300 mg for subcutaneous use once monthly vs placebo in the treatment of cluster headache (CH). Study I5Q-MC-CGAL (CGAL, n=106) was designed for the episodic form and study I5Q-MC-CGAM (CGAM, n=237) for

the chronic form. I5Q-MC-CGAR (CGAR) is an ongoing, open-label, roll-over, long-term safety study for patients who complete either CGAL or CGAM study, including the 4-month post-treatment follow-up.

The assessment of efficacy is based solely on the one study CGAL (with 57 patients receiving placebo and 49 patients receiving galcanezumab) which met its primary objective, and the claimed indication for Emgality is *for the* ***prevention of attacks throughout a cluster period in adults with episodic cluster headache***.

Dose-finding

Dose selection for the cluster headache studies was based on PK/PD simulations based on data from a Phase 2a study (ART-01) where patients with migraine were administered galcanezumab at 150 mg Q2W. The simulations showed that a dose of 300 mg Q4W was predicted to decrease unbound plasma CGRP concentrations by about 90% over a 4-week period and was similar to 150 mg Q2W that was used in Study ART-01. No proper dose-finding study for the new indication episodic cluster headache has been performed. Since the hypothesis that the concentration of CGRP is higher during cluster headache attacks or bouts than in migraine remains unsubstantiated by clinical evidence (Tfelt-Hansen & Le. J Headache Pain 2009; 10:137–143, for review), even the choice of the higher dose for the cluster headache indication was questionable.

The pivotal study in episodic cluster headache (study I5Q-MC-CGAL)

The pivotal trial in episodic cluster headache (study I5Q-MC-CGAL) was a randomised, placebo-controlled study with a duration of 8 weeks of active treatment versus placebo. The baseline period with measurements of the baseline weekly headache attack frequency using an e-diary was 7 days. The placebo-controlled design of the pivotal trial in episodic cluster headache is acceptable considering the character of the disease (controlling for spontaneous remission) as well as the absence of the evidence base for an established, well-studied active comparator.

To be included in the pivotal trial, patients be 18-65 years old adults, should have a diagnosis of episodic cluster headache in accordance with the ICHD-3 beta criteria (2013) with an expected duration of their cluster period/bout of at least 6 more weeks at randomisation and the attack frequency should be between once every other day to 8 times a day.

The design of the episodic CH study CGAL is in line with the only published guideline for clinical trials in cluster headache, the International Headache Society's: Guidelines for controlled studies in cluster headache (Lipton et al., 1995). This guideline states (among other things) that: "For prophylactic trials, no other prophylactic drugs should be taken for the period of the controlled study. The expected duration of the cluster episode should be at least a month after randomization. The duration of the patient's typical cluster episode must be tabulated. Patients should be stratified by the present duration of the current cluster episode. For prophylactic treatment, a treatment period of at least 2 weeks is required. Though only prolonged benefits are clinically relevant, spontaneous remissions make prolonged observation periods problematic."

Of note, the present ICHD-3 criteria for an episodic CH have changed since the previous version. In the current definition of episodic CH, the necessary minimum pain-free remission period for the diagnosis is at least 3 months per year. The potential influence of this change with a re-calculation of the results in both studies for the primary endpoint using the cut-off of 3 months instead of 1 month are not possible to be performed by the applicant, since historical cluster period durations were not collected in the studies. In addition, the Applicant argues that the typical episodic cluster headache patient has a mean cluster period duration of 30.8 days and 2.6 periods per year which may be clearly differentiated from the typical chronic cluster headache patients with no or brief remissions. Thus, the Applicant anticipates that there would be very few patients from the studies who would be re-classified due to the changed diagnostic criteria.–

The duration of the baseline phase of the study (minimum duration 10 days, maximum preferred 14 days) enhances the risk of spontaneous remission of the cluster during the treatment phase but also allows for stabilization of the frequency of CH attacks. Controlling for the risk of spontaneous improvement was intended by the medical history feature of a 6-week cluster duration and the investigator's assessment of the expected duration after the onset (inclusion criteria).

The evaluation of efficacy is based on the effect on attack frequency, which is acquired using an electronic self-reporting diary.

The primary endpoint was the **overall mean change from baseline in weekly cluster headache attacks (CHA) frequency across Weeks 1 to 3**, after the amendment to the initially planned single timepoint at Week 3. The decision to limit the primary objective measurement over a shorter time frame than the whole 8-week double blind period was explained by the MAH as aimed at reducing the anticipated decrease of intergroup differences due to spontaneous remission of the cluster. However, the evaluation of efficacy across the whole double-blind phase treatment periods was not considered as a key secondary outcome either. This is not in line with the primary objective of the study that was to assess the efficacy of galcanezumab 300 mg every 30 days compared with placebo in reducing the frequency of weekly cluster headache attacks, nor with the EMA Guidelines CPMP/EWP/788/01 Rev. 1 requesting to perform the "*analysis of the efficacy for the entire treatment period, as well as for the specified period corresponding to the recommended primary endpoint […]*". ~~Clarification on this issue have been requested.~~ The gated **secondary outcome** was, the percentage of patients achieving ≥50% reduction from baseline in weekly cluster headache attack frequency at Week 3.

The secondary efficacy measure was the PGI-I scale, a subjective scale by which patients rate their global improvement since the first IMP intake. Since PGI was the only subjective scale on improvement of ECH study (whereas several HRQoL scales were included in the pivotal trials supporting the initial submission in the prevention of migraine), clarifications were requested concerning its assessment (at Week 4 and 8), that was misaligned as compared with the primary endpoint assessment across weeks 1 to 3, and as such provides limited support to the primary endpoint. The timing of collection of data does matter especially for patients with CH, who after being forced into unbearable suffer for quite few days or even weeks, do know well whether they actually improved for some time in the recent past. The PGI-I score outcome although showing statistical significance at Week 4, was not significant anymore at Week 8 and at Month 6, namely the post-treatment period, when patients were not prohibited from taking their usual preventive medications. In order to strengthen the results on the PGI-I endpoint that was met at week 4 but not at week 8, the MAH performed a post-hoc analysis on the subgroup of subjects who reported feeling "much better" at Week 4, revealing a 43% median weekly CHA reduction from baseline across Weeks 1 to 3. Using the percentage as a responder threshold to taste for differences in the treatment groups, a greater proportion of responders under GMB was observed vs placebo (59.4% vs 36.1%, p=.009). Although the robustness of these analysis is hampered by the data driven approach, the results are acknowledged.

Of note, from the final CSR provided by the MAH for study CGAL in the part regarding PGI-I, it is evident that at Month 6 (post-treatment period), the percentage of patients who described their cluster headache condition as 'much better' or 'very much better' since the start of medication was not dissimilar between the galcanezumab group compared with placebo (78.0 vs 65.0%; p=.203). These aspects were reiterated by the MAH at the second round of questions within the response to the MO, by adopting some various approaches, including the anchor-based and distribution-based approaches. It is considered that these results only give some support to the notion that a clinically meaningful effect was achieved during week 1 -3 of the cluster headache period, and the uncertainties with regards to the effect duration beyond week 3 are not solved.

The study was originally designed following an adaptive design approach with an interim analysis for sample size reassessment. After more than two years from the start of the enrolment only 109 patients were randomized against the minimum planned sample size of 162 patients in 12 months. The interim analysis originally planned at 114 patients was considered final, as the enrolment was stopped due to infeasibility. The sample size was not fixed on the basis of statistical parameters, moreover neither the type I error nor the power of this study are known and the low effect size (0.42) along with a limited sample size, increase the risk of chance finding. The sample size calculation was based on a range of assumed standardized effect sizes, while considering an effect size of 0.3 clinically relevant.

Patients who met all criteria for enrolment were randomised (1:1) to double-blind treatment using dynamic allocation (minimization) (Pocock and Simon 1975) to balance the treatment groups for the factors of gender, average daily attack frequency (≤4 attacks per day, >4 attacks per day), and investigative site. To assess the dynamic allocation (minimization) assumption a sensitivity analysis, using a permutation test, was performed; this analysis supported the primary analysis conclusion.

To be included in the primary endpoint analysis patients needed to have a baseline and at least one post-baseline (weekly) measurement. No patients were excluded from the primary efficacy analysis due to missing baseline or missing all post-baseline number of cluster headache attacks. Weekly data was considered as missing if ePRO (/diary) compliance was ≤50% or ≤3 days with non-missing answers to cluster headache attacks. The reported compliance was nonetheless very high and the proportion of patients that were 80% compliant weeks 1 to 8 was still approximately 90%.

Efficacy data and additional analyses

A total of 314 subjects entered the study, of whom 205 were screen failures, most commonly due to *no cluster headache period within 12 months* after entering the study and *not meeting the baseline cluster headache attack frequency* requirements (not disclosed to patients at screening). Twenty subjects were allowed per I/E criteria to be re-screened and of them, 8 were then randomized. A total of 109 subjects were initially randomized to double-blind treatment (52 galcanezumab and 57 placebo), although 3 of them (randomized to galcanezumab) did not receive a dose of IMP and were excluded, which violates the ITT principle. The MAH stated that no bias of the results could be expected after excluding the three subjects who were randomized on galcanezumab while never receiving it, as the missing observation could be regarded as missing at random or missing completely at random. However, after including two of the three subjects in the analyses (which per se is deemed arbitrary and highly doubtful from a methodological perspective), for whom a baseline value was available, a heavy impact on either the primary and gated secondary endpoint was shown. Overall, 90 patients (84.9%) completed the double-blind treatment phase, a total of 92 patients entered and had a visit during the post-treatment phase and of them, 84 patients (91.3%) completed the post-treatment phase. A total of 16 subjects in galcanezumab group (32.7%) and 21 subjects in placebo group (36.8%) had at least one important protocol deviation and the per-protocol analysis requested failed to demonstrate the desired consistency with the results obtained from the ITT population of study CGAL, already affected by relatively low degree of statistical evidence as regards the primary efficacy assessment (p=.036). In addition, the sensitivity analyses provided after excluding from the ITT population the 11 subjects with protocol deviations that occurred in the double-blind phase within the category/subcategory "*Study procedures/Excluded conmeds*" with and without the addition of the 3 subjects who were positive at the baseline urine drug screen for substances of abuse not allowed prior to randomization did not yield to statistically significant differences among groups.

At baseline, the demographic characteristics of sex, age, race, and BMI were generally similar across treatment groups (overall, 83.0% of subjects were male and 84.9% were white, with a mean age of

46.4 years, and a slight prevalence of the ≥ 40 years age group in the galcanezumab compared with placebo group). The groups were representative of episodic cluster headache patients, with an expected male predominance (83.0%), mean age 46.6 years, and the average time from diagnosis 16.8 years. They were well balanced, and the differences reaching statistical significance (previous hypertension and suicidal ideation) are not expected to influence the outcome. The majority of subjects (85.9%) had ≤4 cluster headache attacks per day. The mean number of CHA reported by patients in the 7-day period prior to Visit 1 (screening) was 9.7 for placebo and 12.5 for galcanezumab groups, whereas the mean number of weekly CHA at baseline was 17.3 for placebo and 17.8 for galcanezumab. Comparable values were observed in mean weekly CHA at baseline among the overall population and the subgroup who entered the study in active cluster. Hence, the approximately 70% of patients being in an active cluster period and 30% of patients being in remission would have exerted the real influence on such different proportions, as the number of subjects using prophylactic medication at Visit 1 was low and balanced between groups Ideally, the efficacy profile of galcanezumab would have been at least more accurately assessed with inverted proportions than those presented, namely with the majority of subjects enrolled while in remission than in active cluster, receiving the IP once the cluster had started and after a prospective baseline, likewise in study CGAL, but having available all the necessary information on the actual start of the cluster gathered through an accurate time-locking of the data to accurately establish the baseline values. At the second round of RSI, it was in fact evident that the different distributions of subjects by clinical status (being in active cluster as compared to remission at consent) and the corresponding post-hoc analyses results, further uncertainties are raised that the observed effects might have occurred by chance, due to unintentional introduction of bias within the placebo subgroups that could have driven the efficacy results in favor of galcanezumab, as well as the observed earlier first occurrence of ≥50% reduction in CHA frequency in galcanezumab.

The average severity of pain at baseline was moderate to severe and the weekly total CHA duration (hours) was balanced between groups (overall mean 15.5 hours). The use of oxygen was only numerically in favour of placebo either in terms of mean weekly number of times or per attack.

At baseline, the mean total weekly dose for oral triptan use was significantly higher in the galcanezumab group compared to the placebo group (p=.04), while the mean total weekly dose for Zolmitriptan nasal spray use was statistically significant higher in the placebo group compared to galcanezumab.

However, when sumatriptan nasal spray use was added to the combination of the mean total weekly dose for oral triptan, and zolmitriptan nasal spray, a trend towards a larger use of all triptans (oral and nasal) was observed in the group randomised to galcanezumab.

Pre-existing most common (≥10%) conditions were GERD and insomnia, without statistically significant differences across group, however pre-existing hypertension was statistically significantly more reported in the galcanezumab group compared with placebo (12.2 vs 1.8%, respectively).

During the double-blind treatment period, the most frequently used acute medications were sumatriptan (56.14% of placebo and 59.18% of galcanezumab) and oxygen (49.12% of placebo and 53.06% of galcanezumab), followed by (≥5% total) ibuprofen, paracetamol and thomapyrin.

The trial met its primary endpoint. The primary analyses showed that the LSMean change from baseline of weekly CHA was significantly greater for galcanezumab compared with placebo in the first three weeks of treatment (-8.69 and -5.22, respectively, LSMean change difference from placebo -3.47 [95% CI: -6.72, -0.23; p=.036]). Results from sensitivity analyses that used diary data across weeks 1 to 3 were consistent with those of the primary analysis.

The gated secondary endpoint, the percentage of patients achieving ≥50% reduction from baseline in weekly cluster headache attack frequency at Week 3, although misaligned from the primary endpoint

assessment that was evaluated across weeks 1 to 3, was also statistically significant (p=0.046), with a gain over placebo of about 20%. Of note, after including only 2 additional randomised patients with a conservative BOCF imputation, the significance of the gated secondary endpoint was lost.

Regarding the lack of sufficient support from other secondary endpoints, the Applicant has performed additional post hoc analyses of a few secondary endpoints has given some further support to the results from the primary endpoint and responder analysis. A post hoc analysis showed that galcanezumab-treated patients achieved a response level of >50%, 75% or 100% reduction about 10 days earlier than placebo-treated patients. Reduction in acute medication use was not shown for smaller subgroups of individual acute medication types (as included in the planned analyses) but was significant when different kinds of acute medications were pooled together in a post hoc analysis over weeks 1-3 (p=0.017). There was also an effect over weeks 1-3 on total weekly time spent in cluster attack (p=0.040) with difference reaching significance for week 2 and 3. However, since the starting time of the cluster for the 70% of the enrolled subjects was not recorded, and many secondary endpoints were negative, the Applicant presented further evidence that the results may be interpreted as robust.

However, the strength of the evidence in support of treatment benefit is considered poor. Results on the primary endpoint are not statistically compelling (p=0.036), as requested for an application supported by one single pivotal trial (see EMA guidelines on one pivotal study CPMP/EWP/2330/99). Treatment effect was statistically significant starting from Week 2 (p=.029); however, from Week 4 of the double-blind treatment period, no difference in change from baseline between the two groups was observed anymore, despite the administration of the second galcanezumab dose. According to the MAH, this is likely due to spontaneous remission in the frame of the natural course of the condition as the cluster period progresses and the frequency of attacks declines. This explanation is difficult to accept as the improvement associated with galcanezumab administration would be expected to be maintained, after a second dose at week 4, even in the presence of a natural remission of the symptomatology observed in cluster bouts, at least in terms of number and duration of attacks per cluster. Instead, additional analyses facing other relevant aspects, like pain severity, attack duration, use of acute medication, through week 1 to 8, failed to show any difference from placebo, and although the Patient Global Impression of Improvement statistically significant differed from placebo at week 4, no difference were observed at later time points. The MAH reiterated that several measures were put into place to best disentangle the effect due to the active treatment from natural remission. To this aim it is essential that the timing of treatment initiation allows that patients are still actively involved into their cluster within the 3 weeks observation timeframe. However, despite the unbalanced distribution of the status of patients at screening between subjects who entered Study Phase I while in active cluster vs those in remission (70 vs 30%, respectively), no information was collected regarding the days elapsed from cluster beginning to the time of screening for subjects in active cluster. Thus, the length of time anticipated to remain in the cluster is obviously not soundly foreseen (nor evaluable by the assessors) if no recorded information of the time already elapsed at study entry is available. This impact on the reliability of the determination of the primary outcome.

Moreover, no evidence of treatment effect on weekly CHA was observed at week 3, when all longitudinal observations from Week 1 to Week 8 were used in the MMRM model. Indeed, starting from week 5, a steady improvement in placebo group compared with galcanezumab was observed (LS mean change from baseline of weekly CHA at Week 8 was -14.4 for placebo and -13.1 for galcanezumab). This indicates that many patients had already begun to recover from the current cluster period by then. However, it is possible that a clinically relevant effect may have been experienced during that limited time window. As explained by the Applicant this pertains to that when all data from the 8-week period is used in the model, the variance of the outcome measures at each time point, and the covariances between each of the repeated measures, are estimated using all data.

Therefore, the data for later time points were not only used for the estimates of the corresponding time point, but also negatively affected the estimates of the treatment effect at early time points. The Applicant points out that this observation of a negative influence by the latter weeks of the treatment phase should not diminish the interpretation of the primary outcome (where the first 3 weeks of data were included in the model). With regards to the results for the subgroups of episodic CH patients with a history of short-lasting bouts (e.g. <4 weeks), bouts of medium duration (e.g. ≥4-<8 weeks) and longer duration (e.g. ≥8 weeks), the requested re-calculations are not possible to perform as historical cluster period durations were not collected in the studies.

The ePRO compliance was found to be high-rate and balanced, and thus the impact of missing data was deemed very small; the sensitivity analysis challenging the MAR assumption is considered consistent with the primary efficacy analysis. The request to perform an analysis of the primary endpoint based on all randomised subjects; i.e. 52 (galcanezumab) vs 57 (placebo) was instead provided after including only two of the three patients that initially had been excluded from all analyses and summaries, and showed that the difference between the treatment arms was slightly smaller, -3.3 compared to the primary analysis -3.5 also reflected in the p-value; 0.045 instead of 0.036.

Not less importantly, the role of the second dose remains unexplained, which per se is considered to hamper the definition of the **dosing schedule** for galcanezumab. Considering that some patients were in remission at Week 4 (25.5 and 36.4% in placebo and galcanezumab, respectively) the requested calculation of the difference in the mean change in weekly CHA frequency from the second IMP dosing across the subsequent 3-week period for patients not in remission before the assumption of the second dose ie, with positive CHA count before the assumption of the second dose included a total of 63 pts (30 on GMB and 33 on PBO). No statistical significance among the two groups was found in terms of mean change from baseline in weekly CHA frequency, while confirming comparable magnitude of reduction in weekly CHA between the two treatment groups. . In addition, a decision point is needed to decide if the treatment has been successful or not. For migraine, it is stated that the treatment effects should be evaluated after three months of treatment and discontinued if not clinically meaningful effects have been achieved. In the case of episodic cluster headache this decision may take place during the first cluster period treated with galcanezumab or, in case that first treated cluster period has already spontaneously recovered when the patient sees the doctor again, the decision should be whether to treat the next cluster period or not. The absence of effect in the second part of double-blind period is not informative for clinicians to continue treatment with monthly administrations until the end of the cluster period, as it is not grounded on solid assumptions or clinical evidence. While it can be assumed reasonable to continue treatment if insufficient clinical response has been observed after the first administration, it is unjustified to further continue treatment beyond the second dose, due to lack of data in support of this, and given the proven efficacy of galcanezumab in reducing the freely circulating CGRP by 90% ever since the first 4 weeks after administration. From a regulatory point of view, this hindered the SmPC dosing instruction in 4.2 to be "monthly administration".

It is noted from the study protocol of the open-label extension study (CGAR) that the main efficacy endpoints being used in the CGAL study (e.g. weekly cluster headache attacks, responder rates, headache intensity, use of acute medication) are not collected in the open-label extension study (CGAR), not designed to collect efficacy data in detail and in which patients were only asked at their monthly visits "Are you currently in a cluster period?". Nevertheless, regarding longevity of clinical effects on number of headache attacks and an additional potential prophylactic effect of the occurrence of new bouts of galcanezumab on cluster headache, the Applicant reported that of the 31 patients who completed Study CGAL and received at least 1 dose of galcanezumab in Study CGAR, 14 reported not being in an active period followed by being in an active period, i.e. indicating that a new bout had

started and of them, 7 reported this while on active treatment with Emgality. It is however agreed that this information is too scarce to form any conclusions.

Of note, results from the subgroup analysis by number of baseline daily CHA, showed that in the small and probably not powered treatment groups with >3 daily CHA (n=14 each), subjects treated with galcanezumab performed worse than placebo, at all weeks (range 4.52 to 8.06, p>.05 at every time point). Conversely, in the subgroup of subjects with ≤3 daily CHA (n=43 for placebo, n=35 for galcanezumab at Week 1, the LS Mean change differences were always statistically significant in favour of galcanezumab (-3.82, -6.19 and -4.89 at Week 1, 2 and 3, respectively) with p<0.02. Similarly, in the subgroup of patients with $\leq$ 4 daily CHA (n=50 for placebo, n=41 for galcanezumab), the LS Mean change differences were always statistically significant in favour of galcanezumab. Whereas no treatment effect, and even a worse performance compared to placebo, was observed in the subgroup >4 daily CHA. These results could be influenced by the difference in numbers between groups, however, they could suggest that galcanezumab is efficacious only in milder forms of CH. The MAH provided the requested information, plotting the individual patient distributions as average percent change from baseline of weekly CHA frequency across Weeks 1 to 3 by baseline daily attack frequency (≤3 vs >3 daily attacks subgroups). Although the size of the latter group could effectively be not sufficiently powered to detect specific signals in favour of a weaker efficacy of galcanezumab at higher baseline attack frequencies than observed in placebo, there remains the evidence that galcanezumab is more efficacious in milder forms of CH.

Additional expert consultation

The minutes of SAG Neurology convened for this evaluation can be found below:

1) Please discuss the strength of evidence supporting the proposed indication *"Emgality is* ***indicated for the prevention of attacks throughout a cluster period in adults with episodic cluster headache"*** **taking the following aspects into account;**

a. The proposed indication is supported by one study (CGAL). In the analysis of the primary endpoint, the statistical strength of the difference between galcanezumab and placebo was not compelling (p =0.036) and there was no strong support from secondary endpoints. After including only 2 additional randomised patients who had baseline values but never received treatment (hence, assuming no treatment benefit for them), the significance of the primary outcome measure further decreased to p=0.045, whereas that of the gated secondary endpoint was lost.
b. No support came from study CGAM performed in patients with chronic CH. In addition, there is currently no external evidence from studies of (other) drugs with a similar mechanism of action.
c. The relevance of the mechanism of action of galcanezumab in relation to the pathophysiology of cluster headache and whether this mechanism is sufficiently verified.
d. The potential pathophysiologic differences between episodic and chronic cluster headache and if such differences may explain the differential effects seen in the CGAL and CGAM studies.

The SAG members agreed by consensus that the data provided by the single pivotal study were not considered robust enough to support the claim for efficacy in the proposed indication. They pointed out several methodological shortcomings that may have affected the credibility of the observed results:

- The size of the trial is very small, as there were not enough patients recruited from a pool which in EU is sufficiently big. The claim that approx. 250 patients are needed to provide enough power for a more robust conclusion is considered a feasible estimate of the number to recruit in Europe, and this was not done. It was noted by some SAG experts that RCTs in this particular disease are difficult, and that patients may not accept placebo due to the severity of the disease, this leading to recruitment problems.

- Premature termination of the recruitment makes it more likely that the observed effect may be spurious.

- The primary endpoint was amended after completion of double-blind phase, which was not pre-specified.

- The present ITT violation may have affected the results in such a small trial.

- There was no objective evidence of efficacy after the second injection application. Moreover, it is remarkable and unusual that study medication was injected after the moment the primary outcome of the study was assessed.

- Dose selection was not properly performed, and the dose used was only inferred from the experience in migraine patients, which is a condition with a different presumed pathophysiology.

- The way the patients were included in the trial limits the interpretation regarding the natural course of the disease (i.e. high placebo response). For some of them there were no precise data on the length of the bout that they were experiencing at the start of treatment – and while it was acknowledged that this type of trials are difficult to perform, it affects the external validity of the observed results.

- Approximately 8% of patients in the active group had injection site reactions, which could have led to a potential bias due to unblinding.

- The alignment of the baseline characteristics of the patients did not take into account potentially important clinical criteria like e.g. the length of bouts (cluster periods), usual number of attacks per day, intensity and duration of the single attacks in the bouts. The lack of especially length of bouts, usual number of attacks per day and intensity was considered as highly prejudicial to the interpretation of the main outcome.

While some experts considered that provided data make it impossible to decide whether there was an effect at all, others considered that an effect was probable, but that methodological shortcomings of the study hindered any robust conclusion.

Based on the clinical experience and data from epidemiology and family studies that transition from episodic to chronic cluster headache and vice versa happen, thus speaking in favour that episodic and chronic cluster headache is a spectrum of a single disorder. In that respect the lack of supportive efficacy data from study CGAM, performed in patients with chronic CH, was considered worrying.

The failures of other drugs with similar MoA were considered important when doubts about the mechanism of action of galcanezumab in relation to the pathophysiology of cluster headache were expressed by the SAG experts.

The role of CGRP in CH was discussed, and it was stated that even though it probably plays a role (e.g. evidence of triptans' effect in ECH supports that), there is no evidence to suggest a quantifiable relationship with levels of CGRP and disease pattern/severity. There may be a difference between the activity of the peripheral vs central nociceptive mechanisms and thus relative importance of CGRP pathways in Episodic vs Chronic CH that could be used to explain the differences in clinical trials.

2) Please discuss if the efficacy results in the episodic cluster headache population may be considered as clinically relevant, in particular considering:

a. the seemingly transient effect
b. whether the subjects were enrolled already while in an active cluster or in remission(70 vs 30%, respectively)

The discussion started with the statement that CH is a condition that presents with a significant unmet medical need.

The patient perspective as expressed by the present patients was that any new drug in this condition will be much appreciated, but especially for patients not responding to current standard of care (or with emerging safety concerns because of that) an alternative drug is needed. This was supported by the clinicians (headache experts), stating that there is a high need for preventative medication (not only for acute management of the bouts), but there is also the need for alternatives for treating patients with all forms of Cluster Headache.

In clinical practice there is a distinct sub-group of ECH patients who will not be suitable for the currently available treatments, and in these patients the unmet need is even higher.

- Some experts shared the view that it would have been preferable to have some additional efficacy data e.g. on 75% reduction of attacks in ECH, for short lasting bouts – no longer than 6 weeks. The endpoint of 50% reduction is clinically important for Chronic CH, but not so much for Episodic CH, and based on clinical experience. For ECH a 75% reduction would be preferred to be measured, especially when no clear effect is demonstrated on severity of attacks and on reduction of use of symptomatic drugs. Another potential clinically meaningful outcome could have been the number of nights with affected sleep due to headache.
- The experts agreed that it's not possible to address the question about patients in cluster or in remission, due to the lack of statistical power.

In summary, according to the SAG experts and the patient representatives, the observed reduction in the number of attacks, as demonstrated by the study data, could be considered as a clinically relevant outcome, if the validity and robustness of the results are confirmed (still lacking as described in the answer to Question 1). This was supported by the results of the secondary endpoints, and especially the registered effect in the global impression of change from the patients.

2.4.4. Conclusions on the clinical efficacy

The data presented to discuss the major objection were not sufficiently compelling to mitigate the uncertainties regarding the possibility that the effect of galcanezumab vs placebo is mainly due to a chance finding. The major concerns, which have been part of the discussion for the SAG neurology, are the following:

- the time-dependent decrease in treatment effect during the cluster period, which cannot be totally attributed to spontaneous remission and could have been affected by the actual length of cluster that was incompletely determined for 70% of subjects, cannot be considered solved solely based on randomisation, prospective baseline period design, and inclusion criteria that took into account the anticipated duration of the cluster for those in active bout for at least 6 weeks.

- the different distributions of subjects by clinical status (being in active cluster as compared to remission at consent) and the corresponding post-hoc analyses results, still raise uncertainties that the observed effects might have occurred by chance, due to unintentional introduction of bias within the placebo subgroups that could have driven the efficacy results in favor of galcanezumab, as well as the observed earlier first occurrence of ≥50% reduction in CHA frequency in galcanezumab.

2.5. Clinical safety

The safety of galcanezumab in patients with episodic or chronic cluster headache was evaluated in 3 Phase III studies, including 2 placebo-controlled studies plus a long-term, open-label, rollover study (ongoing), summarised below:

Table 14 Overview of the Episodic and Chronic cluster Headache studies

Study Identifier	Study Description	Population	Treatment by Study Phase	Randomized Patients[a]	Patient Completion	Status
I5Q-MC-CGAL Phase 3	Multicenter, randomized, double-blind, placebo-controlled study	Patients aged 18-65 years old inclusive who meet ICHD-3 beta criteria for episodic cluster headache[b]	Double-Blind (2 mo) Monthly: GMB 300 mg or PBO administered via SC injection	Placebo 57 GMB 300 mg 49	Completed DB Treatment Phase: 90 Completed post-treatment phase: 84 (as of data cutoff date (LPV); 12 Feb 2018)	Double-blind treatment phase complete; post-treatment (washout) phase complete[d]
I5Q-MC-CGAM Phase 3	Multicenter, randomized, double-blind, placebo-controlled study with a long-term open-label extension	Patients aged 18-65 years old inclusive who meet ICHD-3 beta criteria for chronic cluster headache[c]	Double-Blind (3 mo) Monthly: GMB 300 mg or PBO administered via SC injection Open-Label (12 mo) Monthly: GMB 300 mg administered via SC injection	Placebo 120 GMB 300 mg 117	Completed DB Treatment Phase: 230 Completed post-treatment phase: 90 (as of data cutoff date (LPV); 27 Mar 2018)	Double-blind treatment phase complete; open-label and post-treatment (washout) phases ongoing
I5Q-MC-CGAR Phase 3b	Multicenter, single-arm, open-label safety study	Patients who completed Study CGAL or Study CGAM	GMB 300 mg administered up to once a month as determined by the investigator based upon symptoms and clinical judgment	N/A 76 roll-over patients	N/A	Ongoing

Study I5Q-MC-CGAR (CGAR) is a long-term, uncontrolled, open-label treatment phase of indefinite duration, that enrols only patients who completed Study CGAL (double blind and post treatment phase) or Study CGAM (double-blind and open-label treatment phases, and post-treatment phase). In study CGAR the study investigator used clinical judgment to determine whether or not to dose galcanezumab 300 mg at each monthly interval, based on clinical symptoms and response. A total of 76 patients entered and have received at least one dose of galcanezumab in the study, including 31 patients from Study CGAL and 45 patients from Study CGAM. Available data indicate that among patients treated for up 10 months or more, most patients (N=39/52, 75%) were treated with consecutive monthly doses or skipped only 1 monthly dose per the clinician's judgement.

Patient exposure

Safety Pools

Cluster Headache Only Placebo-Controlled Analysis Set F: includes data from the double blind treatment phase from the two Phase 3 placebo-controlled cluster headache studies (CGAL and CGAM), including galcanezumab (300 mg) and placebo. This is the primary analysis set used for evaluation of safety in cluster headache as it provides a placebo comparison.

Cluster Headache Only All-Exposure Analysis Set G: The Cluster Headache Only All-Exposure Analysis Set G includes data from all galcanezumab treated patients from the Phase 3 cluster headache studies (CGAL, CGAM, and CGAR) through the data cutoff dates.

Safety data from Study CGAL are included through 12 February 2018 (LPV for the double-blind treatment phase). For Studies CGAM and CGAR, the data cutoff date in the initial submission was 27 March 2018 (LPV of double-blind treatment phase for Study CGAM). Following the request to provide updated safety data, the new safety cut off date was 4 September 2018.

For this line extension application for Cluster Headache, the pooled Analysis Set F (primary safety data set) and G are critically assessed.

In addition to these 2 integrated analysis sets, 2 additional integrated analysis sets were presented:

Galcanezumab Placebo-Controlled Analysis Set H: includes data for migraine and cluster headache from the double-blind treatment phase of all Phase 3 galcanezumab clinical trials that included a placebo-control (CGAG, CGAH, CGAI, CGAL, and CGAM). Different doses of galcanezumab (120 mg, 240 mg, and 300 mg) are included across the studies. Patients from all galcanezumab doses are combined ("GMB_All") and compared with placebo.

In Analysis Set H, the combined number of patients exposed to galcanezumab at any of these 3 doses is 1601.

Table 15

Dose	N
GMB 120 mg	705
GMB 240 mg	730
GMB 300 mg	166
GMB_All	1601

Galcanezumab All-Exposure Analysis Set I: includes data for migraine and cluster headache from all galcanezumab-treated patients from all Phase 2 and Phase 3 galcanezumab studies (ART-01, CGAB, CGAG, CGAH, CGAI, CGAJ, CGAL, CGAM, and CGAR). Data from all galcanezumab-treated patients (doses range from 5 mg to 300 mg) were combined and presented as a single group ("GMB_All").

For Cluster Headache Only All-Exposure Analysis Set G and Galcanezumab All-Exposure Analysis Set I, analyses were conducted for Galcanezumab -treated time (Study periods in which galcanezumab treatment was Administered) and Galcanezumab -treated time plus post/off-treatment (Contains data from the GMB-Treated Time period as well as any post- or off-treatment time for GMB-treated patients).

Ongoing Migraine Prophylaxis Studies: Study CGAI for chronic migraine prevention is now completed; however data were not available for inclusion in the pooled safety database (Analysis Set I). For three ongoing migraine prevention trials, I5Q-MC-CGAN and I5Q-MC-CGAP (Japan only studies), and I5Q-MC-CGAW (multi-country study) information on SAEs have been provided .

Patient exposure

Table 16

Table 2.7.4.3.2. Overall Exposure to Galcanezumab

	Cluster Headache Only Placebo-Controlled Analysis		All Cluster Headache Exposure Analysis	All GMB Placebo-Controlled Analysis		All GMB Exposure Analysis (cluster headache + migraine)
	CGAL, CGAM		CGAL, CGAM, CGAR	CGAL, CGAM, CGAG, CGAH, CGAI		CGAL, CGAM, CGAR, CGAG, CGAH, CGAI, CGAJ, ART-01, CGAB
Treatment Group	PBO	300 mg GMB	300 mg GMB	PBO	GMB All	Total GMB
Any dose	177	166	296	1628	1601	2882
≥3 Doses	117	114	225	1448	1473	2671
≥6 Doses	N/A	N/A	168	749	756	2088
≥12 Doses	N/A	N/A	106	N/A	N/A	632
TPY	38.8	37.1	216.3	571.5	573.4	1703.6

Table 17

Table APP.3.1. Overall Exposure to Galcanezumab

	Cluster Headache Only All-Exposure Analysis Set G		Galcanezumab All-Exposure Analysis Set I	
	Original Submission	Safety Update	Original Submission	Safety Update
Treatment Group	300 mg GMB		GMB_All	
Any dose	296	303	2882	2889
≥3 Doses	225	252	2671	2698
≥6 Doses	168	209	2088	2129
≥12 Doses	106	132	632	750
Total Patient-Years	216.3	274.5	1703.5	1799.4

Abbreviation: GMB_All = all galcanezumab doses combined.

With updated safety data, Analysis Set G includes 58.26 additional patient-years of exposure in the cluster headache program, accrued in the ongoing, open-label treatment phases of Studies CGAM and CGAR (from the previous cluster headache safety database lock of 27 March 2018 to the new safety cut-off date of 4 September 2018). No new patients were included in the updated safety data; however 7 patients who received placebo in Study CGAL rolled over to study CGAR and began treatment with galcanezumab. Furthermore, with this safety update 41 more CH patients compared to the original submission received ≥6 GMB doses (N= 209 in total) and 26 more CH patients compared to the original submission received ≥12 GMB doses (N= 132 in total). Both in Analysis Set F and in Analysis Set G, additional Post treatment time was included.

Demographic and other characteristics of study population

Baseline characteristics in the Cluster Headache Only Placebo-Controlled Analysis Set F were generally balanced between treatment groups. Summary of the baseline demographics in the analysis set F and G are presented in the table below:

Table 18 Summary of Baseline Patient Demographics Analysis Set F (Studies CGAL and CGAM)

	PBO N=177 n (%)	GMB 300 mg N=166 n (%)
Age[a]		
<30 years old	18 (10.17)	16 (9.64)
≥30 to <40 years old	35 (19.77)	32 (19.28)
≥40 to <50 years old	62 (35.03)	44 (26.51)
≥50 years old	62 (35.03)	74 (44.58)
Sex		
Male	133 (75.14)	127 (76.51)
Female	44 (24.86)	39 (23.49)
Race		
White	148 (83.62)	142 (85.54)
Black or African American	5 (2.82)	3 (1.81)
Other/Multiple Races	23 (12.99)	20 (12.05)
Ethnicity		
Hispanic or Latino	19 (10.73)	21 (12.65)
Not Hispanic or Latino	158 (89.27)	145 (87.35)
Region		
North America	38 (21.47)	39 (23.49)
Europe	139 (78.53)	127 (76.51)
Cardiovascular Disease Risk Group		
Yes	36 (20.34)	40 (24.10)
No	141 (79.66)	126 (75.90)
Smoking Status		
Never	39 (22.03)	34 (20.61)
Current	103 (58.19)	101 (61.21)
Former	35 (19.77)	30 (18.18)
Lifetime Suicide Ideation[b]		
Yes	35 (19.77)	34 (20.48)
No	142 (80.23)	132 (79.52)
Lifetime Suicide Behavior[b]		
Yes	5 (2.82)	5 (3.01)
No	172 (97.18)	161 (96.99)

Summary of Baseline Patient Demographics
Analysis Set F (Studies CGAL and CGAM)
Abbreviations: GMB = galcanezumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population with nonmissing demographic measures; n = number of patients within each specific category; PBO = placebo; SMQ = Standardized MedDRA Query.
[a] The age range for enrollment in Studies CGAL and CGAM was 18 to 65 inclusive.
[b] Prior to screening.
Note: (1) Age = (informed consent date − imputed birthdate + 1). Patient's birthdate is imputed as July 1 in reported birth year. (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), and Hyperglycaemia/new onset diabetes mellitus (SMQ, narrow terms only).
Source: Table APP.1.4.

The majority of the study population is male (75-76%). Study CGAM allowed the concomitant use of preventive medications for patients with chronic cluster headache during the double-blind treatment

phase provided they were on a stable dose at least 2 months prior to the baseline period. The percentage of patients who used at least 1 allowed preventive medication during the baseline phase was 63.3% (150/237) and was balanced across treatment groups (galcanezumab-treated = 75/117 [64.1%]; placebo = 75/120 [62.5%]). Verapamil was the drug most commonly used.

Disposition

The summary of Patient disposition in Cluster Headache Only Placebo-Controlled Analysis Set F is presented in the table below:

Table 19

Table 2.7.4.4.3. Summary of Patient Disposition
Safety Population
Analysis Set F (Studies CGAL and CGAM)
Double-Blind Treatment Phase

	Placebo			GMB300mg				
Overall Patient Disposition	N	n	(%)	N	n	(%)	OR (95% CI)*a	P-value*b
Patients Who Completed Double-Blind Treatment Phase	177	162	(91.53)	166	158	(95.18)	1.78 (0.72,4.37)	.207
Discontinued from Double-Blind Treatment Phase due to Any Reason	177	15	(8.47)	166	8	(4.82)	0.56 (0.23,1.38)	.207
Discontinued from Double-Blind Treatment Phase due to:								
Adverse Event	177	2	(1.13)	166	3	(1.81)	1.67	.572
Death	177	0	(0.00)	166	0	(0.00)		
Lack of Efficacy	177	9	(5.08)	166	1	(0.60)	0.11	.016
Lost to Follow up	177	1	(0.56)	166	0	(0.00)	0.00	.354
Physician Decision	177	0	(0.00)	166	0	(0.00)		
Protocol Violation	177	0	(0.00)	166	2	(1.20)		.151
Withdrawal by Patient	177	3	(1.69)	166	2	(1.20)	0.73	.736
Concern about study procedures/perceived risk	177	0	(0.00)	166	0	(0.00)		
Health insurance changes	177	0	(0.00)	166	0	(0.00)		
Scheduling conflicts	177	2	(1.13)	166	0	(0.00)	0.00	.176
Patient incarcerated	177	0	(0.00)	166	0	(0.00)		
Patient is moving or has moved	177	0	(0.00)	166	0	(0.00)		
Other	177	1	(0.56)	166	2	(1.20)	2.28	.500
Study Terminated by IRB/ERB	177	0	(0.00)	166	0	(0.00)		
Study Terminated by Sponsor	177	0	(0.00)	166	0	(0.00)		
Other	177	0	(0.00)	166	0	(0.00)		

In the galcanezumab treatment groups, most of the patients (95.2%) completed the double-blind treatment phase of Studies CGAL (2 months) and CGAM (3 months) which are similar to that for placebo (91.5%). Less than 5% of patients discontinued for any reason including 3 patients discontinuing due to an AE. Significantly more patients discontinued due to lack of efficacy on placebo (5.1%; n=9) than the galcanezumab group (0.6%; n=1). Patients discontinued due to other reasons are numerical low and were balanced in both groups.

Study CGAM Open-Label Phase

Of the 230 patients who completed the double-blind treatment phase, 229 patients entered the optional open-label treatment phase. Of these, 79 patients (34.5%) completed this phase as of the data cutoff, 60 patients (26.2%) discontinued, and 90 (39.3%) are ongoing. Discontinuation from the open-label treatment phase was higher among patients who received placebo during the double-blind period compared to patients who had previously received galcanezumab (31.0% vs 21.2%, respectively). The reasons for discontinuation from the open-label treatment phase were lack of efficacy (16.2%), AE (6.1%), and withdrawal by subject (3.1%).

Study CGAR Open-Label Safety Study

A total of 76 patients entered and received at least 1 dose of galcanezumab in Study CGAR, including 31 patients (40.8%) from Study CGAL and 45 patients (59.2%) from Study CGAM. At the time of the interim database lock, 7 patients had discontinued. The most frequent reason for discontinuing was lack of efficacy.

Adverse events

Table 20 Overview of Adverse Events with Exposure-Adjusted Incidence Rates Cluster Headache Only Placebo-Controlled Analysis Set F and Cluster Headache Only All-Exposure Analysis Set G

	CH Only Placebo-Controlled Analysis Set				CH Only All-Exposure Analysis Set	
	Placebo (N = 177)		GMB 300 mg (N = 166)		GMB 300 mg (N = 296)	
	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)
Deaths	0		0		0	
SAEs	3/38.5	7.8 (1.6, 22.8)	2/37.0	5.4 (0.7, 19.5)	18/210.9	8.5 (5.1, 13.5)
DCAEs	2/38.8	5.2 (0.6, 18.6)	3/36.9	8.1 (1.7, 23.7)	17/214.9	7.9 (4.6, 12.7)
TEAEs	94/22.7	414.7 (335.1, 507.5)	105/19.4	540.5 (442.1, 654.36)	206/71.0	290.1 (251.9, 332.6)

Abbreviations: CH = cluster headache; CI = confidence interval; DCAE = discontinuation due to adverse event; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; N = number of patients in the analysis population; n = number of patients within each specific category; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TPY = total patient-years at risk.

Source: /lillyce/prd/ly2951742/cluster_submission/output/shared/fqdcsae_eair1_db.rtf; /lillyce/prd/ly2951742/cluster_submission/output/shared/fqdcsae_eair1_gmb.rtf; /lillyce/prd/ly2951742/cluster_submission/output/shared/fqoaep1_db.rtf; /lillyce/prd/ly2951742/cluster_submission/output/shared/fqoaep1_gmb.rtf; /lillyce/prd/ly2951742/cluster_submission/output/shared/fqteae_eair1_db.rtf; /lillyce/prd/ly2951742/cluster_submission/output/shared/fqteae_eair1_gmb.rtf.

Table 21 Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class Safety Population – All Analysis Sets

System Organ Class	Analysis Set F		Analysis Set G	Analysis Set H		Analysis Set I
	PBO N=177 n (%)	GMB 300 mg N=166 n (%)	GMB 300 mg N=296 n (%)	PBO N=1628 n (%)	GMB 300 mg N=1601 n (%)	GMB_All N=2882 n (%)
Blood and lymphatic system disorders	--	--	2 (0.68)	11 (0.68)	9 (0.56)	20 (0.69)
Cardiac disorders	8 (4.52)	2 (1.20)	14 (4.73)	19 (1.17)	14 (0.87)	48 (1.67)
Congential, familial and genetic disorders	--	--	--	3 (0.18)	1 (0.06)	2 (0.07)
Ear and labyrinth disorders	6 (3.39)	5 (3.01)	8 (2.70)	17 (1.04)	32 (2.0)[a]	67 (2.32)
Endocrine disorders	--	--	--	4 (0.25)	2 (0.12)	13 (0.45)
Eye disorders	5 (2.82)	1 (0.60)	11 (3.72)	25 (1.54)	24 (1.50)	75 (2.60)
Gastrointestinal disorders	23 (12.99)	19 (11.45)	46 (15.54)	180 (11.06)	183 (11.43)	449 (15.58)
General disorders and administration site	31 (17.51)	52 (31.33)[a]	103 (34.80)	275 (16.89)	421 (26.30)[a]	794 (27.55)
Hepatobiliary disorders	--	--	--	8 (0.49)	3 (0.19)	13 (0.45)
Immune system disorders	--	--	4 (1.35)	10 (0.61)	7 (0.44)	35 (1.21)
Infections and infestations	35 (19.77)	39 (23.49)	109 (36.82)	380 (23.34)	409 (25.55)	1045 (36.26)
Injury, poisoning and procedural complications	7 (3.95)	3 (1.81)	17 (5.74)	100 (6.14)	86 (5.37)	238 (8.26)
Investigations	3 (1.69)	3 (1.81)	21 (7.09)	48 (2.95)	55 (3.44)	179 (6.21)
Metabolism and nutrition disorders	2 (1.13)	3 (1.81)	5 (1.69)	28 (1.72)	31 (1.94)	78 (2.71)
Musculoskeletal and connective tissue disorders	22 (12.43)	14 (8.43)	55 (18.58)	175 (10.75)	165 (10.31)	496 (16.27)

Percentage of Patients with Treatment-Emergent Adverse Events by System Organ Class
Safety Population – All Analysis Sets

System Organ Class	Analysis Set F		Analysis Set G	Analysis Set H		Analysis Set I
	PBO N=177 n (%)	GMB 300 mg N=166 n (%)	GMB 300 mg N=296 n (%)	PBO N=1628 n (%)	GMB 300 mg N=1601 n (%)	GMB_All N=2882 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.56)	0 (0.0)	5 (1.69)	5 (0.31)	11 (0.69)	31 (1.08)
Nervous system disorders	17 (9.60)	18 (10.84)	48 (16.22)	144 (8.85)	143 (8.93)	328 (11.38)
Pregnancy, peurperium and perinatal conditions	--	--	--	1 (0.06)	0 (0)	1 (0.03)
Product issues	--	--	--	1 (0.06)	0 (0)	--
Psychiatric disorders	8 (4.52)	9 (5.42)	34 (11.49)	66 (4.05)	54 (3.37)	186 (6.45)
Renal and urinary disorders	2 (1.13)	1 (0.60)	3 (1.01)	22 (1.35)	21 (1.31)	55 (1.91)
Reproductive system and breast disorders	0 (0.0)	5 (3.01)[a]	7 (2.36)	36 (2.21)	51 (3.19)	113 (3.92)
Respiratory, thoracic and medistinal disorders	9 (5.08)	8 (4.82)	19 (6.42)	82 (5.04)	111 (6.93)[a]	248 (8.61)
Skin and subcutaneous tissue disorders	6 (3.39)	9 (5.42)	17 (5.74)	66 (4.05)	90 (5.62)[a]	217 (7.53)
Social circumstances	--	--	2 (0.68)	1 (0.6)	2 (0.12)	8 (0.28)
Surgical and medical procedures	3 (1.69)	3 (1.81)	13 (4.39)	30 (1.84)	28 (1.75)	110 (3.82)
Vascular disorders	6 (3.39)	8 (4.82)	20 (6.76)	34 (2.09)	39 (2.44)	99 (3.44)

Abbreviations: Analysis Set F = Cluster Headache Only Placebo-Controlled Analysis Set; Analysis Set G = Cluster Headache Only All-Exposure Analysis Set G; Analysis Set H = Galcanezumab Placebo-Controlled Analysis Set H; Analysis Set I = Galcanezumab All-Exposure Analysis Set I; GMB = galcanezumab; N = number of patients in the analysis population, n = number of patients within each specific category; PBO = placebo.

[a] Statistically significant versus placebo.

Source: Table APP.1.30; Table APP.1.31; Table APP.1.32; and Table APP.1.33.

Table 22 Overview of Common Treatment-Emergent Adverse Events Reported in ≥2% among Galcanezumab-Treated Patients Safety Population Cluster Headache Only Placebo-Controlled Analysis Set Double-Blind Treatment Phase

Preferred Term	Placebo N = 177 n (%)	GMB 300 mg N = 166 n (%)
Injection site pain	11 (6.2)	17 (10.2)
Injection site erythema	1 (0.6)	9 (5.4)**
Nausea	6 (3.4)	6 (3.6)
Back pain	4 (2.3)	5 (3.0)
Dizziness	5 (2.8)	5 (3.0)
Influenza like illness	2 (1.1)	5 (3.0)
Injection site pruritus	2 (1.1)	5 (3.0)
Pyrexia	2 (1.1)	5 (3.0)
Dysmenorrhoea[a]	0 (0.0)	1 (2.6)
Menstrual disorder[a]	0 (0.0)	1 (2.6)
Myalgia	3 (1.7)	4 (2.4)
Pain in extremity	1 (0.6)	4 (2.4)
Constipation	2 (1.1)	3 (1.8)
Gastroenteritis	1 (0.6)	3 (1.8)
Hot flush	0 (0.0)	3 (1.8)
Influenza	3 (1.7)	3 (1.8)
Injection site swelling	1 (0.6)	3 (1.8)
Non-cardiac chest pain	1 (0.6)	3 (1.8)
Pruritus	0 (0.0)	3 (1.8)
Tinnitus	2 (1.1)	3 (1.8)
Vomiting	3 (1.7)	3 (1.8)
Prostatitis[b]	0 (0.0)	2 (1.6)

Abbreviations: GMB = galcanezumab; n = number of patients in specific category; N = number of patients in the analysis population.

[a] Denominator adjusted for female-specific event.

[b] Denominator adjusted for male-specific event.

** p-value <.01 (versus placebo).

Source: /lillyce/prd/ly2951742/cluster_submission/output/shared/ fqteae1_db.rtf.

Additionally for TEAEs that occurred among GMB treated subjects with a frequency higher than PBO (chills, memory impairment, migraine, irritability, asthma, injection site erythema), the number of patients who reported the events were small (N=2 for each event) compared to no events or 1 event (for migraine and injection site erythema) among PBO treated subjects. Some events, such as irritability and migraine, may be related to the underlying disease. A case level review of these AEs commonly identified alternative explanations.

Few TEAEs such as hot flush, dysmenorrhea, menstrual disorder and prostatitis were only reported in the GMB treated patients and were specified below. The frequency of flushing events reports was significant different in the galcanezumab group (n=15, 0.9%) compared with the placebo (n=4, 0.3%; p=.01). In the Galcanezumab Placebo-Controlled Analysis Set H, the majority were reported as hot flush (galcanezumab: n=12, 0.8%; p=.04). Review some of the details of the events indicated that time to onset was variable and lacking a close temporal relation. Majority of the patients also had other medical conditions potentially associated with flushing and/or concomitant use of medications could

contribute to the events. None of the flushing-related events was considered serious or led to discontinuation.

There is numerically imbalance for the reported events of menstrual disorder or menstruation irregular between treatment groups (galcanezumab: n=10, 0.6% versus placebo: n=3, 0.2%; p=.05, OR: 3.5 in the analysis H). Of the 10 events, 7 were rated as mild, 2 moderate, and 1 severe. All of the events resolved and did not reoccur. For all of these events reported, the causal relation to galcanezumab-treatment is unlikely due to lacking a temporal relation to the time onset and other possible cause of the events.

Treatment-Emergent Adverse Events by Maximum Severity: In Cluster Headache Only Placebo-Controlled Analysis Set F, among patients who reported TEAEs, most reported events of mild or moderate severity (galcanezumab: n=97, 92.4%; placebo: n=88, 93.6%). The percentage of patients reporting severe TEAEs was similar between treatment groups (galcanezumab: n=8, 4.8%; placebo: n=6, 3.4%). Injection site pain was the only severe TEAE reported by both treatment groups (galcanezumab: n=2; placebo: n=1) and 1 additional galcanezumab-treated patient reported injection site erythema as severe. For galcanezumab, the remaining TEAEs reported as severe were nasopharyngitis, constipation, cluster headache, nasal operation, and amaurosis (for all events n=1), and events were spread across 5 SOCs with no pattern of events or commonalities of organ involvement. None of these severe events reported by galcanezumab treated patients led to treatment discontinuation in the Cluster Headache Only Placebo- Controlled Analysis Set F.

AEs of special interest

Injection Site Reactions

In the **Cluster Headache Only Placebo-Controlled Analysis Set F**, adverse events related to injection occurred in 21.7% of galcanezumab-treated patients, compared with 7.9% in placebo. Injection site pain was the most commonly reported AE related to injection sites, followed by injection site erythema, injection site pruritus, and injection site swelling. The majority of the events were of mild or moderate severity, occurred on the day of injection, and resolved on average in 5 days. Among patients who reported TEAEs related to injection sites, severe injection site TEAEs were reported by 8.3% (3/36) of galcanezumab-treated patients. No discontinuations due to AEs related to injection sites nor SAEs related to injection sites were reported in the Cluster Headache Only Placebo-Controlled Analysis Set.

The percentage of patients with ≥1 TEAE related to injection sites in the **Cluster Headache Only All-Exposure Analysis Set G** for the galcanezumab treatment group was 24.0%. There were 2 additional event terms of injection site haemorrhage (n=2, 68%) and injection site paraesthesia (n=2, 68%) reported in Cluster Headache Only All-Exposure Analysis Set G, which were not reported in the Cluster Headache Only Placebo-Controlled Analysis Set F. In addition, there was 1 patient that reported an SAE of injection site urticaria and discontinued treatment due to this AE. The highest percentage of events (14.5%) is reported at Month 1 and then begins to decrease at Month 4 (8.0%) and continues to remain under 8.0% for the 15-month duration. In comparison to Cluster Headache Only Placebo-Controlled Analysis Set F, four additional patients reported ≥1 TEAEs related to injection sites as severe. Two additional patients reported severe injection site pain. Both patients reported injection site pain that occurred on the day of injection and lasted 1 day. Two patients reported severe injection site pruritus lasting 3 and 7 days, respectively. No treatment was received for these events. In Analysis Set G, the duration of TEAEs related to injection sites in the galcanezumab all dose group was an average of 5.9 days. One patient reported two events of injection site discoloration that lasted 3 days ("discoloration at IP injection site" on bilateral abdomen) and 296 days ("hyperpigmentation at IP injection site on left arm"), respectively. The investigator considered the adverse events of injection site discoloration possibly related to study drug.

Adverse Events Related to Injection Sites by Treatment-Emergent Anti-Drug Antibody Status:

Adverse events related to injection sites were reviewed because of the biological plausibility of a potential relationship existing between immunogenicity and these types of AEs. The results discussed include the immunogenicity evaluable population from Studies CGAL, CGAM, and CGAR.

Of 6 patients who became TE ADA+ during treatment, 2 patients (33.3%) reported TEAEs related to injection sites (injection site pain and injection site pruritus), while 66 patients (26.1%) of 253 who were TE ADA- during treatment reported TEAEs related to injection sites. Injection site pain was reported, with a similar frequency between patients who became TE ADA+ during galcanezumab treatment (16.7%; n=1) and patients without TE ADA during treatment (13.4%; n=34). Injection site pruritus, reported by 16.7% (n=1) of patients who became TE ADA+ during galcanezumab treatment and 3.6% (n=9) of patients without TE ADA during treatment, was the only PT that met flagging criteria for further review (OR: 6.93): Case-level review of one patient revealed that the patient reported 3 events of mild injection site pruritus on Study Days 118 to 121, 149 to 151, and 176 to 178, respectively. TEAEs were not reported at all the time points where TE ADA was present, particularly when maximum TE ADA titer (1:40) was detected. These events were non-serious and did not lead to treatment discontinuation.

- **Hypersensitivity Events**

Potential Immediate Hypersensitivity Events

Hypersensitivity SMQ: The Hypersensitivity SMQ narrow search identified 2 patients in the galcanezumab-treated group (1.2%) and no patients in the placebo group. The reported TEAEs were injection site rash (1) and injection site urticaria.

The Hypersensitivity SMQ broad search identified 4 additional patients in the galcanezumab treated group (3.6%) and no patients in the placebo group (p ≤0.05). The reported TEAEs, pruritus (2), asthma (1).

Anaphylactic Reaction SMQ: No galcanezumab or placebo-treated patients reported TEAEs of potential anaphylaxis that met the criteria for an anaphylaxis event as defined by the Anaphylactic reaction SMQ narrow search or by algorithmic criteria.

The Anaphylactic reaction SMQ broad search identified 5 patients in the galcanezumab-treated group (3.0%) and no patients in the placebo group (p≤.05). The reported TEAEs were pruritus (2, was clarified as injection site-related events adjudged by the investigator), erythema (1, was clarified as injection site-related events adjudged by the investigator), asthma (1) and injection site urticaria (1).

A male patient, with history asthma, food allergy, and angioedema, reported asthma (“asthma worsening”) on the same day of first dose. Event resolved in 39 days, prior to discontinuing treatment early, and the event did not reoccur.

Potential Non-Immediate Hypersensitivity Events

Hypersensitivity SMQ:

The Hypersensitivity SMQ narrow search did not show meaningful differences between galcanezumab (n=3; 1.8%) and placebo (n=4; 2.3%). Galcanezumab-treated patients reported rash (1), contact dermatitis (1), and injection site hypersensitivity (1). Placebo-treated patients reported rash (2), eczema (1), and urticaria (1).

Anaphylactic Reaction SMQ:

No patients reported TEAEs of potential anaphylaxis that met the criteria for an anaphylaxis event as defined by the Anaphylactic reaction SMQ narrow search.

Angioedema SMQ:

In the broad search strategy analysis across the 3 SMQs, the potential non-immediate hypersensitivity events reported by at least 2 patients were pruritus (2) and cough (2) in galcanezumab-treated patients and rash (2) in placebo-treated patients.

There was 1 patient treated with galcanezumab who discontinued due to a likely hypersensitivity event of asthma aggravation. No patients treated with placebo discontinued due to a likely hypersensitivity event.

A male patient, with history of asthma, reported an episode of mild asthmatic crisis ("asthma crisis") the day after first dose (GMB 300 mg). Event resolved in 14 days. The day after second dose, the patient reported another episode of asthma ("asthma aggravation") and was discontinued.

Exposure-Adjusted Treatment-Emergent Hypersensitivity Events (Hypersensitivity SMQ)

Table 23

Table 2.7.4.12.11. **Exposure-Adjusted Treatment-Emergent Hypersensitivity Events from Hypersensitivity SMQ Cluster Headache Only Placebo-Controlled Analysis Set F and Cluster Headache Only All-Exposure Analysis Set G**

	Analysis Set F				Analysis Set G	
	Placebo N=177		GMB 300 mg N=166		GMB 300 mg (N=296) (GMB-Treated Time)	
	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)
Potential Hypersensitivity						
Narrow Search	4/38.12	10.49 (2.86, 26.86)	5/36.33	13.76 (4.47, 32.12)	18/204.56	8.80 (5.21, 13.91)
Narrow or Broad Search	5/37.91	13.19 (4.28, 30.78)	13/35.02	37.12 (19.77, 63.48)	30/198.47	15.12 (10.20, 21.58)
Likely Hypersensitivity						
Narrow Search	4/38.12	10.49 (2.86, 26.86)	4/36.48	10.96 (2.99, 28.07)	15/206.44	7.27 (4.07, 11.98)
Narrow or Broad Search	4/38.12	10.49 (2.86, 26.86)	9/35.43	25.41 (11.62, 48.23)	23/201.79	11.40 (7.23, 17.10)

Abbreviations: Analysis Set F = Cluster Headache Only Placebo-Controlled Analysis Set F; Analysis Set G = Cluster Headache Only All-Exposure Analysis Set G; CI= confidence interval; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; N = number of patients in the analysis population; n = number of patients within each specific category; TPY = total patient-years at risk.

Hypersensitivity Events by Treatment-Emergent ADA Status

No patients who became TE ADA+ during galcanezumab treatment had a TEAE related to the narrow scope or broad scope PTs in the Anaphylactic reaction, Angioedema, and Hypersensitivity SMQs during the treatment phases in Studies CGAL, CGAM, and CGAR. These findings are consistent with those seen in the migraine development program.

Upper Respiratory Tract Infections (URTIs)

Preferred terms within the HLT of URTIs were determined to be AEs of interest based on findings from the Phase 2 migraine studies (ART-01 and CGAB).

Overall, in the Cluster Headache Only Placebo-Controlled Analysis Set F, the incidence of treatment-emergent URTIs was similar for the galcanezumab (13.3%) and the placebo treatment groups (13.6%). No patients in either of the treatment groups reported an SAE or discontinued due to an AE. Among the patients who reported treatment-emergent URTIs, only 1 TEAE was reported as severe.

Overall, in the Cluster Headache Only All-Exposure Analysis Set G, the comparison of the EAIRs between the Cluster Headache Only Placebo-Controlled Analysis Set F of treatment emergent URTIs did not suggest an increase in incidence with longer duration of treatment. No patients reported an SAE or discontinued due to an URTI AE. Among the patients who reported treatment-emergent URTIs during treatment, most reported events were of mild to moderate severity.

Cardiovascular safety

Similar to the analyses provided in the migraine submission, potential treatment-emergent cardiovascular events for the cluster headache population were identified using the MedDRA SMQs listed below (specifically broad and narrow terms), and a listing of patients having a TEAE potentially cardiovascular in nature was generated. Only those events that were judged medically to represent likely cardiovascular events are discussed by the applicant.

Broad and narrow terms in the following 9 SMQs were analyzed: Cardiac arrhythmias; Cardiac failure; Cardiomyopathy; Central nervous system vascular disorders; Embolic and thrombotic events; Hypertension; Ischaemic heart disease; Pulmonary hypertension; Torsade de pointes/QT prolongation. In addition, cardiovascular disease risk evaluation of the potential effect of galcanezumab on cardiovascular safety was also discussed.

Safety finding

Across treatment groups, 22% of patients were identified to be in the cardiovascular disease risk subgroup for the Cluster Headache Only Placebo- Controlled Analysis Set F and Cluster Headache Only All-Exposure Analysis Set G with the placebo (20.34%) and GMB 300mg groups (22-24%).

The Cluster Headache Only Placebo-Controlled Analysis Set F

The most common baseline conditions (≥5% in galcanezumab group) in the cardiovascular disease risk "yes" subgroup (galcanezumab-treated patients) were hypertension (57.5%), hypercholesterolemia (30.0%), hyperlipidemia (12.5%), dyslipidemia (7.5%), myocardial infarction (5.3%), and diabetes (5.0%).

Framingham Risk Score:

Compared to migraine population, females in cluster headache have a similar estimated 10-year coronary heart disease risk (<1 to 1%, respectively). Males in the cluster headache population have a higher estimated coronary heart disease 10-year risk (Total males 6-8%; Cardiovascular disease risk group "yes":12.0% to 16.0%) than males in the migraine placebo controlled studies population (Total males 4%; Cardiovascular disease risk group "yes":6% to 8%).

TEAEs likely cardiovascular in nature after medical review

In short term (up to 3 months) placebo controlled analysis set F, no relevant differences were observed between galcanezumab and placebo treated group in TEAEs cardiovascular in nature across 9 SMQs (GMB 4.2% vs placebo 6.2%). One GMB treated patient reported a serious event of atrial fibrillation that led to study drug discontinuation that occurred 29 days after the second galcanezumab dose and was considered by the investigator as not related to study drug. 1 placebo patient discontinued due to a TEAE of palpitations. No other cardiovascular SAEs or events leading to discontinuation were reported in Analysis Set F.

Non cardiac chest pain occurred in 4/166 (2.4%) galcanezumab treated patients, all considered drug related by the investigator, compared to 3/177 (1.7%) in placebo group, though any cardiac etiology was ruled out.

Categorical changes of interest in blood pressure and pulse

Of the 15 placebo-treated patients experiencing categorical or treatment-emergent changes in blood pressure and pulse, 3 TEAEs likely cardiovascular in nature were reported by 2 patients (tachycardia and hypertension reported by 1 patient and another patient reported bradycardia). Two of the 19 galcanezumab-treated patients experiencing categorical or treatment-emergent changes in blood pressure and pulse reported hypertension. See also data in Vital Sign section.

Cardiovascular medications

The use of cardiovascular medications including antihypertensives, antiarrhythmics, antithrombotics, and antianginals was evaluated. The frequency of galcanezumab-treated patients receiving antithrombotics at baseline (6.6%) was more than 2 times that of placebo-treated patients (2.8%). The frequencies of antihypertensives was comparable between treatment groups (galcanezumab: 11.5%; placebo: 9.6%), and only placebo-treated patients were taking an antiarrhythmic (1.7%). In the cardiovascular disease risk group "yes", the frequency of those taking antihypertensives was similar between treatment groups (galcanezumab: 37.5%; placebo: 33.3%).

Overall, low numbers of patients had increases or new starts of concomitant cardiovascular medications during the double-blind treatment phase: 1.2% (n=2) of all patients in the galcanezumab treatment group versus 1.1% (n=2) in placebo had an increase or a new start of antihypertensives.

One (5.56%) of the 18 galcanezumab-treated patients with treatment-emergent qualitative ECG changes reported an SAE of atrial fibrillation leading to discontinuation discussed in SAE section.

Cluster Headache Only All-Exposure Analysis Set G

Treatment-Emergent Adverse Events Likely Cardiovascular in Nature

In Analysis Set G (including patients exposed to galcanezumab up to 12 months), the percentage of galcanezumab-treated patients reporting ≥1 TEAE likely cardiovascular in nature across all 9 SMQs in the Cluster Headache Only All-Exposure Analysis Set G was 11.2%. SMQs with at least 1 narrow scope PT reported in the Cluster Headache Only All-Exposure Analysis Set G include Cardiac arrhythmia (n=5, 1.7%), Central nervous system vascular disorders (n=2; 0.7%), Embolic and thrombotic events (n=2, 0.7%), and Hypertension (n=10, 3.4%).

In addition to the cardiovascular-related SAE noted for the Cluster Headache Only Placebo-Controlled Analysis Set F (galcanezumab: atrial fibrillation), 2 cardiovascular SAEs were reported by 2 patients during galcanezumab treatment in the Cluster Headache Only All-Exposure Analysis Set G: cerebral ischaemia (considered possibly related to the study drug by the investigator; led to study drug discontinuation, was severe and occurred 3 days since the eleventh galcanezumab dose (in the open-label treatment period) and palpitations [considered not related to study drug by the investigator; the SAE occurred 18 days following the fourth dose of galcanezumab in the open-label treatment phase, (Study CGAM). Risk factors included obesity, smoking (40 cigarettes/day and uses a nicotine patch weekly), pre-existing hypercholesterolaemia, and a family history of cardiovascular disease. It lasted 2 days until it resolved and led to discontinuation)].

Other non serious cardiovascular AEs leading to discontinuation included: ECG PR prolongation, that occurred in a male, 2 days after starting open-label treatment with galcanezumab; Transient ischemic attack, that occurred in ~~39 year old~~ male, obese, and 33 days since eleventh dose in the open-label treatment period. The investigator considered the event of transient ischaemic attack as possibly related to study drug.

Dyspnoea exertional ("dyspnea during the effort" of moderate severity, which occurred in a female, 89 days after starting open-label treatment with galcanezumab (300-mg/month) and 5 days since fourth dose in the open-label treatment period. On the same day of onset of the event dypnoea exertional the patient experienced also the non-serious adverse event of visual impairment ("episode of bilateral

vision problems") of mild severity, which occurred 89 days after starting open-label treatment with galcanezumab (300-mg/month) and 5 days since fourth dose in the open-label treatment period. The patient experienced also a non-serious adverse event of abdominal pain of mild severity, which occurred on the same day of starting open-label treatment with galcanezumab (300-mg/month). The follow-up information reported by the investigator for the event of abdominal pain included that the patient did not have a history of abdominal pain and this was probably associated to stenosis of iliac artery due to smoking which was discovered later. The patient experienced the non-serious adverse events of peripheral artery stenosis ("left common iliac artery stenosis") and peripheral artery stenosis ("right external iliac artery stenosis"), both of moderate severity and occurred, 141 days after starting open-label treatment with galcanezumab (300-mg/month) and 57 days since fourth dose in the open-label treatment period (the events occurred during the post-treatment follow-up period). The investigator considered the adverse events of abdominal pain and both the events of peripheral artery stenosis as not related to study drug. However, the patient's narrative states that for both the dyspnoea exertional and the event of visual impairment "it was reported that the reason for the event was probably due to treatment with study drug".

Overall, based on the Hypertension SMQ, 10 patients reported hypertension events during galcanezumab-treated time including 2 during the double-blind phase and 8 during open-label treatment in Study CGAM or Study CGAR. Four patients who had clinically significant DBP increase during open label phase of the cluster headache studies. Three of the patients had initiated anti-hypertensive medication. One of these 4 patients who were not included in the table experienced SAE and discontinued study. Eight of the 10 patients had elevated blood pressure values (systolic or diastolic or both) prior to dosing with galcanezumab, 6 were current smokers and 2 were former smokers.

Table 24 Exposure-Adjusted SMQ Narrow Search for TEAEs Likely Cardiovascular in Nature Cluster Headache Only Placebo-Controlled Analysis Set F and Cluster Headache Only All-Exposure Analysis Set G

	Analysis Set F				Analysis Set G	
	Placebo (N=177)		GMB 300 mg (N=166)		GMB 300 mg (N=296) (GMB-Treated Time)	
	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)
SMQ Preferred Term						
Cardiac arrhythmias	0/38.82	0.00 (NA, 9.50)	1/37.07	2.70 (0.07, 15.03)	5/214.48	2.33 (0.76, 5.44)
Central nervous system vascular disorders	0/38.82	0.00 (NA, 9.50)	0/37.07	0.00 (NA, 9.95)	2/216.18	0.93 (0.11, 3.34)
Embolic and thrombotic events	0/38.82	0.00 (NA, 9.50)	0/37.07	0.00 (NA, 9.95)	2/216.18	0.93 (0.11, 3.34)
Hypertension	3/38.40	7.81 (1.61, 22.83)	3/36.67	8.18 (1.69, 23.91)	10/211.77	4.72 (2.26, 8.68)

Abbreviations: Analysis Set F = Cluster Headache Only Placebo-Controlled Analysis Set F; Analysis Set G = Cluster Headache Only All-Exposure Analysis Set G; CI = confidence interval; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis population; n = number of patients within each specific category; NA = not applicable (not calculated); SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event; TPY = total patient-years at risk.

Source: Table APP.1.215 and Table APP.1.216.

Table 25 Exposure-Adjusted Incidence Rates by SMQ Narrow Search for Likely Cardiovascular Treatment-Emergent Adverse Events in Analysis Set G – Submission and Safety Update

	Original Cluster Headache Submission N = 296				Updated Safety Database N = 303			
	Galcanezumab-Treated Time		Galcanezumab-Treated Time Plus Post/Off-Treatment		Galcanezumab-Treated Time		Galcanezumab-Treated Time Plus Post/Off-Treatment	
Cardiovascular SMQ	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)
Cardiac arrhythmias	5/214.48	2.33 (0.76, 5.44)	5/268.34	1.86 (0.61,4.35)	6/271.79	2.21 (0.81, 4.81)	6/341.66	1.76 (0.64, 3.82)
Cardiac failure	0/216.25	0.00 (NA, 1.71)	0/271.29	0.00 (NA, 1.36)	0/274.51	0.00 (NA, 1.34)	0/345.57	0.00 (NA, 1.07)
Cardiomyopathy	0/216.25	0.00 (NA, 1.71)	0/271.29	0.00 (NA, 1.36)	0/274.51	0.00 (NA, 1.34)	0/345.57	0.00 (NA, 1.07)
Central nervous system vascular disorders	2/216.18	0.93 (0.11, 3.34)	2/270.21	0.74 (0.09, 2.67)	3/274.38	1.09 (0.23, 3.20)	3/344.28	0.87 (0.18, 2.55)
Embolic and thrombotic events	2/216.18	0.93 (0.11, 3.34)	2/270.21	0.74 (0.09, 2.67)	2/274.44	0.73 (0.09, 2.63)	2/344.49	0.58 (0.07, 2.10)
Hypertension	10/211.77	4.72 (2.26, 8.68)	12/264.11	4.54 (2.35, 7.94)	13/267.54	4.86 (2.59, 8.31)	15/334.79	4.48 (2.51, 7.39)
Ischaemic heart disease	0/216.25	0.00 (NA, 1.71)	0/271.29	0.00 (NA, 1.36)	0/274.51	0.00 (NA, 1.34)	0/345.57	0.00 (NA, 1.07)
Pulmonary hypertension	0/216.25	0.00 (NA, 1.71)	0/271.29	0.00 (NA, 1.36)	0/274.51	0.00 (NA, 1.34)	0/345.57	0.00 (NA, 1.07)
Torsade de pointes/QT prolongation	0/216.25	0.00 (NA, 1.71)	0/271.29	0.00 (NA, 1.36)	0/274.51	0.00 (NA, 1.34)	0/345.57	0.00 (NA, 1.07)

Table 26 Summary of Exposure-Adjusted Incidence Rates in Patients with At Least 1 Narrow or Broad Scope Likely Cardiovascular Treatment-Emergent Adverse Events in Cluster Headache Studies CGAL, CGAM, and CGAR

Analysis Set	Dose	n(%)	TPY	EAIR (95% CI)	n(%)	TPY	EAIR (95% CI)
Analysis Set F	PBO N = 177	11 (6.21)	37.64	29.23 (14.59, 52.29)	–	–	–
	GMB 300 mg N = 166	7 (4.22)	36.25	19.31 (7.76, 39.78)	–	–	–
Analysis Set G – safety update	GMB 300 mg N = 303	**Galcanezumab-Treated Time**			**Galcanezumab-Treated Time Plus Post/Off-Treatment**		
		39 (12.87)	252.21	15.46 (11.00, 21.14)	43 (14.19)	311.48	13.81 (9.99, 18.60)

Abbreviations: CI = confidence interval; EAIR = exposure-adjusted incidence rate; GMB = galcanezumab; PBO = placebo; TPY = total patient years.

Evaluation of Hepatic Safety

One patient in Study CGAM in the open-label treatment phase reported the TEAE of ALT increased from >1xULN at baseline to >2xULN returning to >1xULN at last visit assessed, with no interruption or discontinuation of the galcanezumab treatment. There was no other patient in the cluster headache studies, with treatment-emergent abnormal hepatic function tests or hepatic-related TEAEs.

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

Suicidal ideation and behavior was assessed in all galcanezumab clinical trials using the C-SSRS. Migraine clinical trials revealed no association between galcanezumab treatment and suicidality risk in

that population. Cluster headache is a disease associated with increased risk of comorbid depression and suicidality. At baseline in Studies CGAL and CGAM 20.1% (69/343) of patients reported history of suicidal ideation (i.e. a "yes" answer to any of the 5 suicidal ideation questions on the C-SSRS) and 3.0% (10/343) of patients reported prior suicidal behaviours (i.e. a "yes" answer to any of the 5 suicidal behavior questions on the C-SSRS. In the Cluster Headache Only Placebo-Controlled Analysis Set F (double-blind treatment period of Studies CGAL and CGAM) there were no TEAEs related to suicidal ideation, behavior, or self-injurious behaviour. When using C-SSRS, the percentage of GMB treated patients reporting suicidal ideation (items 1-5 suicidal ideation of the C-SSRS) in Analysis Set F was 3.0% [n=5/165]), similarly to PBO group (3.5%, n= 6/173).

Occurrence of suicidal ideation (including serious suicidal ideation) during the studies (assessed through C-SSRS) was compared to recent history and all prior history at baseline. In Safety Analysis Set F, treatment-emergent non-serious suicidal ideation compared to all prior history was reported by 0.6% of placebo-treated patients (1 patient) compared with 1.9% of galcanezumab-treated patients (3 patients, OR: 3.1, p=0.3). None of the events involved actual suicide intent (Categories 3 to 5). Reports of nonspecific active suicidal thoughts (rating 2) were made by 0.6% of placebo-treated patients (1 patient) compared to 1.2% of galcanezumab-treated patients (2 patients, OR: 2.1, p=0.5).

In Safety Analysis Set G, one patient treated with galcanezumab with a prior history of suicidal behavior and current diagnosis of depression, attempted suicide during the open-label phase of Study CGAM. This patient also had an aborted suicide attempt during the post-treatment follow-up period. The percentage of patients reporting suicidal ideation in the Cluster Headache Only All-Exposure Analysis Set G galcanezumab-treated patients was greater compared to the Cluster Headache Only Placebo-Controlled Analysis Set F (5.0% [n=14]; 3.0% [n=5], respectively); this is not unexpected given the background rate of suicidal ideation in patients with CH and the increased duration of treatment. When adjusted for time of exposure, available data do not indicate and increase in suicidal ideation with increasing exposure to GMB.

Compared to the original cluster headache submission, 1 additional patient reported suicidal ideation on the C-SSRS in the safety update. Additionally, 1 patient died by suicide 46 days after the last galcanezumab dose in Study CGAR and after the safety update data cut-off. This patient reported a lifetime history of suicidal ideation, prior to participation in study CGAM. The investigator reported the completed suicide was due to severe family trouble and was not related to treatment.

Serious adverse event/deaths/other significant events

Deaths

No deaths were reported while patients were enrolled in the cluster headache studies.

Serious adverse events

In short term placebo controlled safety analysis set F, 2/166 (1.2%) GMB treated patients experienced SAEs (one event each of atrial fibrillation and constipation), compared to 3/177 (1.69%) SAEs in placebo group (one event each of melena, non cardiac chest pain and depression).

The SAE of atrial fibrillation occurred in a patient with risk factors such as being a heavy smoker and consuming 10 cups of coffee and 2 espressos daily. The event resolved the same day. Three weeks following the event of atrial fibrillation, the patient was diagnosed with thyroid nodules.

One patient reported SAE of constipation who had concomitant medication of verapamil and losartan. The event resolved 3 days later.

Table 27 Overview of Adverse Events with Exposure-Adjusted Incidence Rates Cluster Headache Only Placebo-Controlled Analysis Set F and Analysis Set F plus Post-Treatment (washout)

	Analysis Set F Original Submission				Analysis Set F plus Post-Treatment Safety Update			
	Placebo (N = 177)		GMB 300 mg (N = 166)		Placebo (N = 177)		GMB 300 mg (N = 166)	
	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)	n/TPY	EAIR (95% CI)
Deaths	0		0		0		0	
SAE	3/38.46	7.80 (1.61, 22.80)	2/36.98	5.41 (0.66, 19.54)	5/54.61	9.16 (2.97, 21.36)	2/53.20	3.76 (0.45, 13.58)
DCAE	2/38.77	5.16 (0.62, 18.63)	3/36.93	8.12 (1.68, 23.74)	2/55.20	3.62 (0.44, 13.09)	3/52.84	5.68 (1.17, 16.59)
TEAE	94/22.67	414.71 (335.12, 507.49)	105/19.43	540.54 (442.11, 654.36)	98/32.76	299.19 (242.89, 364.61)	110/27.30	402.94 (331.17, 485.66)

Table 28 Overview of Adverse Events - Cluster Headache Only All-Exposure Analysis Set G

		Original Submission GMB 300 mg N = 296			Safety Update GMB 300 mg N = 303		
		%	n/TPY	EAIR (95% CI)	%	n/TPY	EAIR (95% CI)
Galcanezumab-Treated Time	Deaths		0			0	
	SAE	6.08	18/210.87	8.54 (5.06, 13.49)	7.26	22/266.95	8.24 (5.16, 12.48)
	DCAE	5.74	17/214.93	7.91 (4.61, 12.66)	6.27	19/273.07	6.96 (4.19, 10.87)
	TEAE	69.59	206/71	290.14 (251.87, 332.58)	73.27	222/85.34	260.15 (227.05, 296.71)
Galcanezumab-Treated Time plus Post/Off-Treatment	Deaths		0			0	
	SAE	6.08	18/261.88	6.87 (4.07, 10.86)	7.92	24/332.95	7.21 (4.62, 10.73)
	DCAE	5.74	17/265.23	6.41 (3.73, 10.26)	6.27	19/339.04	5.60 (3.37, 8.75)
	TEAE	72.64	215/84.28	255.09 (222.13 291.56)	76.90	233/101.61	229.31 (200.81, 260.72)

The frequency of SAEs reported in the galcanezumab-treated patients in **Cluster Headache Only All-Exposure Analysis Set G** was 6.1% (n=18). When adjusted for exposure, the incidence rate for SAEs in the galcanezumab-treated population (8.54 [5.06, 13.49]) was within the range of incidence rates for placebo in the Cluster Headache Only Placebo-Controlled Analysis Set F (7.80 [1.61, 22.80]). The SOCs with more than 2 SAEs reported were in decreasing order: Infections and infestations (n=5; 1.7%); Neoplasms benign, malignant and unspecified (n=4; 1.4%); and Nervous system disorders (n=3; 0.1%). Cluster headache (n=2) was the only SAE term reported by more than 1 patient. The 5 Infections and infestations SOC SAEs [one patient each: diverticulitis, gastroenteritis (acute), helicobacter pylori, rectal abscess, and urinary tract infection] are unlikely to be due to a common mechanism, given that the suspected etiology for the rectal abscess was local trauma, and some patients had risk factors for the SAE they reported: the patient with a urinary tract infection had a recent history of sepsis, prior bladder repair and ureteric cancer, and the patients with diverticulitis and helicobacter gastritis had risk factors such as age, obesity, and current or prior smoking habits. For the 4 Neoplasm SOC SAEs (a male patient experienced metastasis with a history of prostate and laryngeal cancer; a female patient was diagnosed with breast cancer stage III approximately 2 weeks after the first dose of open-label galcanezumab; a male patient was diagnosed with colon neoplasm (stage III) following 7 doses of galcanezumab; a male patient was diagnosed with bladder neoplasm after 4 doses of galcanezumab in Study CGAR), no type of malignant neoplasm was reported by more than 1 patient, and, based on the relatively short exposure times to galcanezumab prior to diagnosis, it seems unlikely that these are related to galcanezumab treatment.

Among SAEs one event of amaurosis occurred in Safety Analysis Set G. The patient reported separate episodes of non-serious right and left eye amaurosis (one event was severe in intensity) following the second dose of galcanezumab. The SAE of right eye amaurosis leading to discontinuation began approximately 1 week following the third dose and lasted 4 days. Events of vision blurred, in some cases followed by events of amaurosis, occurred on the day of galcanezumab administration following each galcanezumab administration (first, second, third and fourth galcanezumab monthly dose). The patient reported 31 additional episodes of right eye amaurosis, lasting from 1 to 3 days, throughout the 4-month post-treatment follow-up phase. These amaurosis events were all judged possibly related to investigational product by the investigator. The MAH consulted an external ophthalmologist on this case and his opinion was that these episodes likely represented ocular migraine.

In the updated safety data in Analysis Set G, 7 SAEs were reported: 5 occurring during GMB treatment (one case each of epidural hematoma from post-lumbar puncture syndrome, motor vehicle accident, rhabdomyolysis, reversible cerebral vasoconstriction syndrome and gastroenteritis) and 2 occuring post treatment (lymphadenopathy and small intestinal obstruction). All these events were considered not related to study drug by the investigators, apart from one SAE of reversible cerebral vasoconstriction syndrome.

Study CGAI (in chronic migraine): Serious Adverse Events Reported Between 17 August 2017 and 27 March 2018 in Phase 3 Study CGAI for chronic Migraine prevention included one event each of pre-eclampsia, pulmonary embolism, myocardial infarction. The serious event of pre-eclampsia occurred in a woman, previously treated with galcanezumab (240 mg during the 3 months double blind period, and subsequently 120 mg for 9 months), with no risk factors of pre-eclampsia. The serious event of pre-eclampsia leading to emergency cesarian section and delivery of a premature baby (gestational age 31 weeks) occurred 10 months after last galcanezumab dose. The SAE of pulmonary embolism was reported in a female patient and occurred in the post-treatment phase, 150 days since the last and final dose of galcanezumab in the open-label treatment phase. The event of pulmonary embolism lasted 13 days until it resolved. The investigator considered the event as not related to study drug, and the patient subsequently completed the study. The SAE of myocardial infarction was reported in a male patient and occurred 94 days after study completion and 241 days since the last dose of

galcanezumab in the open-label treatment phase. The event lasted 3 days until it resolved. The investigator considered the AE as not related to study drug.

Final safety data from study CGAI have been provided. For some SAEs that occurred in the open label phase of Study CGAI in chronic migraine, it is difficult to draw definitive conclusions on GMB role (2 cardiovascular SAEs, a SAE of seizure, esophageal adenocarcinoma, cancer of the tongue, suicidal behaviour).

Updated safety data on SAEs from ongoing migraine studies have been provided.

Study CGAN (randomized, double blind, 6 months treatment phase) enrolled 459 Japanese patients and was completed on 18 January 2019. The MAH presented an overview of final safety data. Of note, one SAE of sudden neurosensory hearing loss considered by the investigator as related to GMB and leading to study drug discontinuation occurred in a female, 71 days after starting treatment with GMB and 8 days since third dose and with a "not resolved" outcome.

For **Study CGAP** (a 12 month open label safety study in Japanese patients), the last patient visit is scheduled for 10 August 2019. As of 31 May 2019, 255 patients have completed the Study. Of note, among SAEs that occurred in study CGAP, a female experienced a SAE of stress cardiomyopathy approximately 4 months and 11 days since beginning open label GMB, 10 days since last dose, considered potentially related to study treatment by the investigator and leading to study drug discontinuation. The event resolved and was possibly confounded by concomitant sumatriptan.

For **Study CGAW** (ongoing randomized double blind study, to assess GMB 120 mg/ month vs PBO in patients with treatment resistant episodic and chronic migraine), the last patient visit for the open label treatment phase is 23 September 2019. As of 31 May 2019, 461 patients entered treatment in Study CGAW; of these 438 have completed the double blind treatment phase. Eleven patients reported a total of 13 SAEs. None were judged drug related by the investigator. Of note, a female reported a SAE of acute onset hemiplegia the day after the second GMB open label injection. The description of this case is difficult to interpret; the case narrative was requested, as well as updated information on the outcome of this case. The reported event of hemiplegia resolved 2 days after onset. Computed tomography (CT) and MRI were conducted on the day of the event onset and ruled out a brain hemorrhage or cerebral infarction. The investigator considered the serious adverse event of hemiplegia as not related to study drug. The patient had a second headache attack with hemiplegia, approximately 4.5 months after completion of Study CGAW and 5.5 months after the last dose of galcanezumab. An MRI scan including DWI sequence was normal again. After the second episode, a diagnosis of sporadic hemiplegic migraine was made by the site investigator.

Laboratory findings

Cluster headache placebo controlled analysis set F:

During the double-blind treatment phases of the cluster headache studies, there were 5 parameters including Basophil count, Hemoglobin A1C, Albumin, Uric acid, and Urine pH, the mean change from baseline was statistically significantly different between placebo and galcanezumab.

No significant differences were observed in the percentages of treatment-emergent high or treatment-emergent low values when compared to placebo in the Cluster Headache Only Placebo-Controlled Analysis Set F.

The applicant's review of individual data for galcanezumab-treated patients with treatment-emergent laboratory analyte abnormalities showed that these changes were generally transient, not associated with other clinically significant findings, and could be explained by other medical conditions.

No galcanezumab-treated patients had any lab abnormalities meeting the criteria of potentially clinically significant limits based on the CTCAE Grade 3 limits when they existed for a certain laboratory measure.

Cluster Headache All-Exposure Analysis Set G

There were numerical more treatment emergent Lab abnormalities including Leukocytes High where the percentage in All-Exposure Analysis Set G was >3 times the frequency in Placebo-Controlled Analysis Set F. It is noticed that no clear trend was observed. Some of the events were also observed during the post/off treatment period.

Five galcanezumab-treated patients had lab abnormalities meeting the potentially clinically significant criteria including high potassium (1 patient), high uric acid (2 patients), low segmented neutrophil count (2 patients). The applicant's review of individual data for galcanezumab-treated patients showed that these changes were generally transient and could be explained by other medical conditions.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs were taken at scheduled and unscheduled office visits and included body temperature, blood pressure, and pulse. Analyses of blood pressures and pulse included assessments of mean changes from baseline as well as categorical and treatment-emergent changes.

The table below presents the predefined criteria for categorical and treatment emergent changes of interest defined by the applicant.

Table 29

Table 2.7.4.7.2. Criteria for Categorical Changes of Interest in Vital Signs

Parameter	Direction	Criteria	Patients Population Defined by Baseline Categories
Systolic BP (mm Hg) (sitting)	Low	≤90 and decrease ≥20	All patients; >90; ≤90
	High	≥140 and increase ≥20	All patients; <140; ≥140
	PCS high	≥180 and increase ≥20	All Patients; <180; ≥180
	Sustained elevation	≥140 and increase ≥20 at 2 consecutive visits	All patients; <140; ≥140
Diastolic BP (mm Hg) (sitting)	Low	≤50 and decrease ≥10	All patients; >50; ≤50
	High	≥90 and increase ≥10	All patients; <90; ≥90
	PCS high	≥105 and increase ≥15	All Patients;<105; ≥105
	Sustained elevation	≥90 and increase ≥10 at 2 consecutive visits	All patients; < 90; ≥90
Systolic BP or Diastolic BP (mm Hg) (sitting)	Sustained elevation	Meeting criteria for systolic BP for 2 consecutive visits or meeting criteria for diastolic BP for 2 consecutive visits or both	All patients
Pulse (bpm) (sitting)	Low	<50 and decrease ≥15	All patients; ≥50; <50
	High	>100 and increase ≥15	All patients; ≤100; >100
	Sustained elevation	>100 and increase ≥15 at 2 consecutive visits	All patients; ≤100; >100
Temperature (°F)	Low	<96°F and decrease ≥2°F	≥96°F
	High	≥101°F and increase ≥2°F	<101°F
Weight (kg)	Low	(Loss) decrease ≥7%	All patients
	High	(Gain) increase ≥7%	All patients

Blood pressure and Pulse

Cluster Headache Only Placebo-Controlled Analysis Set F

In cluster headache double blind trials mean changes from baseline in SBP, DBP and pulse were all in the direction of an increase observed in GMB group compared to PBO, both in the Pooled cluster headache studies (Safety Analysis set F) and in individual studies (CGAL and CGAM).

For both systolic and diastolic blood pressure, the difference in LSMean change from baseline to maximum postbaseline between galcanezumab and placebo was <2.0 mm mm Hg in the CH Only Placebo-Controlled Analysis Set F and in Study CGAM. The difference in LSMean changes were 2.8 mm Hg for systolic blood pressure and for diastolic blood pressure. In Study CGAL, the difference in LSMean changes were 3.6 mm Hg for systolic blood pressure and 2.4 mm Hg for diastolic blood pressure. There were two postbaseline distinct galcanezumab outliers in the Study CGAM and CGAL+CGAM plots (near 170 mm Hg systolic blood pressure and 110 mm Hg diastolic blood pressure) and were included in the discussion below.

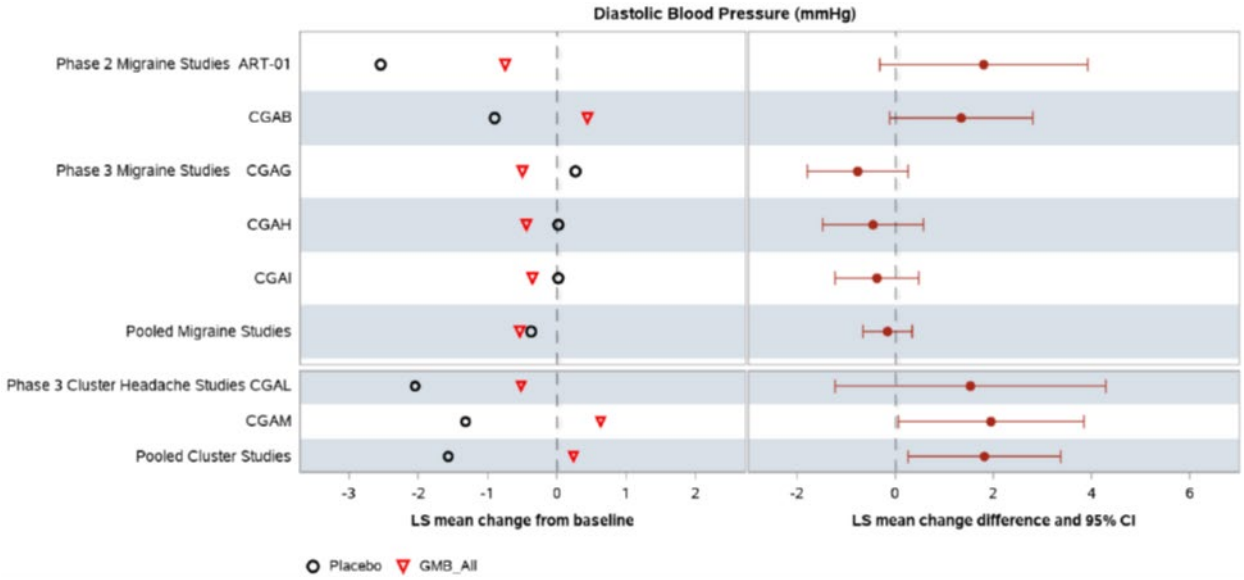
Post hoc analyses of blood pressure using forest plots were performed for the individual and integrated cluster headache studies. Forest plots of the individual and integrated migraine studies (Phase 2 and Phase 3) are provided for reference. The forest plots show the difference in LSMean changes from last baseline to last postbaseline (or to maximum or to minimum) in blood pressure with the 95% CI.

Forest plots of change from last baseline to last postbaseline in blood pressure by study and pooled–Studies is presented in the figure below:

For cluster headache, the LSMean change differences were all above zero and the CIs did not cross zero for the integrated cluster studies and Study CGAM, demonstrating these results were statistically

significant. However, some of these differences seem also driven by the under 0 score of LS mean change from baseline in placebo group.

Figure 11



Treatment-Emergent Changes in BP

The percentage of patients meeting treatment-emergent high systolic blood pressure was small and similar between placebo and galcanezumab-treatment groups in the Cluster Headache Only Placebo-Controlled Analysis Set F with no galcanezumab-treated patient reporting TEAEs related to hypertension or changes related to blood pressure medications

A higher percentage of galcanezumab-treated patients met treatment-emergent high diastolic blood pressure at any time compared to placebo (n=13, 9.5% versus n=7, 5.1%, respectively), and 4 galcanezumab-treated patients met sustained diastolic blood pressure elevation (defined as DBP ≥90 mm Hg and increase ≥10 at 2 consecutive visits) compared to none in placebo (3.0% versus 0%, respectively, p=.048). Of the 13 galcanezumab-treated patients who met treatment-emergent high diastolic blood pressure criteria, some key characteristics were described below:

- The majority were male (n=11) with 10 patients being current or former smokers
- Five patients had high systolic or diastolic blood pressure values prior to randomization and 2 patients had a pre-existing condition of hypertension
- No change was made to existing antihypertensive medication for the 2 patients with pre-existing hypertension, and no medication was initiated to treat blood pressure for any patient who met treatment-emergent high diastolic blood pressure criteria.
- 4 met sustained elevation criteria for diastolic blood pressure. Of these, one patient had elevated blood values prior to treatment. Two patients met treatment-emergent high diastolic blood pressure criteria and experienced a TEAE of hypertension and also reported chest pain.

Of patients with elevated diastolic blood pressure at baseline (≥90 mm Hg), 1 galcanezumab treated and one in placebo-treated patient had a 10 mm Hg increase during double-blind treatment.

Two cluster headache patients had clinically significant postbaseline blood pressure increased (defined as DBP ≥105 and increase ≥15; or SBP ≥180 and increase ≥15) during the study (near 170 mm Hg

systolic blood pressure and 110 mm Hg diastolic blood pressure). The patients were both smokers (6 or 15 cigarettes/day) with BMI values >30 kg/m2, and each had elevated systolic and diastolic blood pressure values at baseline. One Patient had multiple cardiovascular risk factors, including pre-existing hypertension and was discontinued from the double-blind treatment phase due to protocol violation. Another patient did not have a pre-existing diagnosis of hypertension but was initiated on antihypertensive medication during the screening period prior to randomization (the dose remained unchanged during the study). The patient completed all study phases. This patient also reported two TEAEs of hypertension, each resolved the same day and were judged not related to study treatment by the investigator.

Table 30 Exposure-Adjusted Incidence Rates in Patients with Treatment-Emergent Increase or Categorical Increase in Systolic Blood Pressure during Galcanezumab-Treated Time

Dose Group	Analysis Set F				Analysis Set G Original Submission				Analysis Set G Safety Update			
	N	n/TPY	%	EAIR (95% CI)	N	n/TPY	%	EAIR (95% CI)	N	n/TPY	%	EAIR (95% CI)
Treatment-Emergent high SBP (BL <140 mmHg)												
Placebo	150	5/32.99	3.33	15.16 (4.92, 35.37)		NA	NA	NA		NA	NA	NA
GMB 300 mg	143	3/32.05	2.10	9.36 (1.93, 27.35)	248	25/175.80	10.08	14.22 (9.20, 20.99)	265	31/218.54	11.70	14.18 (9.64, 20.13)
Categorical High SBP (BL ≥140 mmHg)												
Placebo	22	0/4.55	0	0.00 (NA, 81.12)		NA	NA	NA		NA	NA	NA
GMB 300 mg	23	0/5.02	0	0.00 (NA, 73.47)	42	3/25.99	7.14	11.54 (2.38, 33.73)	46	4/33.39	8.70	11.98 (3.26,30.67)

Note: For systolic blood pressure, SBP High: ≥140 mmHg and increase ≥20 mmHg.

Cluster Headache Only All-Exposure Analysis Set G

Data for the Cluster Headache Only All-Exposure Analysis Set G is provided up to the data cutoff for the studies that were ongoing at that time, including Study CGAL (post-treatment follow-up), Study CGAM (open-label and post-treatment follow-up), and Study CGAR (open-label and off-treatment).

Similarly, in the Cluster Headache Only All-Exposure Analysis Set G, 10.1% of patients met treatment-emergent criteria for high systolic blood pressure, however twice (20.7%) of patients met treatment-emergent criteria for high diastolic blood pressure.

To evaluate the higher percentage of patients meeting treatment-emergent high criteria for systolic and diastolic blood pressure in Analysis set G compared to Analysis set F an EAIR analysis was conducted. No increase in incidence rate was observed with longer follow-up for treatment-emergent high systolic or high diastolic blood pressure. For patients whose baseline diastolic pressure was ≥90 mm Hg, an increase in incidence rate was observed with longer follow-up in Analysis Set G compared to the Cluster Headache Only Placebo- Controlled Analysis Set F.

Temperature

Cluster Headache Only Placebo-Controlled Analysis Set F: The percentage of galcanezumab-treated patients with treatment-emergent changes in high/low temperatures was either similar to or lower than placebo, with no statistically significant or clinically meaningful differences between treatment groups.

Safety Analysis set G: A similar percentage of galcanezumab-treated patients in the Cluster Headache Only All-Exposure Analysis Set G and the Cluster Headache Only Placebo-Controlled Analysis Set F met the high threshold (>38ºC: 1.08% versus 0.6%, respectively). The percentage of galcanezumab-treated patients meeting the low threshold in the Cluster Headache Only All-Exposure Analysis Set G was higher than in the Cluster Headache Only Placebo-Controlled Analysis Set F;

(<36ºC: 38.4% versus 21.8%, respectively), and similar to the percentage observed for placebo-treated patients in the Cluster Headache Only Placebo-Controlled Analysis Set F (32.2%).

Pulse:

One galcanezumab-treated patient (0.6%) and 3 placebo-treated patients (1.8%) met criteria for treatment-emergent low pulse. In the only galcanezumab-treated patient who met low pulse criteria no cardiovascular AEs were reported and the patient continued study.

Three galcanezumab-treated patients (1.8%) and 1 placebo-treated patient (0.6%) met criteria for treatment-emergent high pulse during the double-blind treatment phase. No cardiovascular AEs were reported by the 3 galcanezumab-treated patients and all continued study.

Weight

Cluster Headache Only Placebo-Controlled Analysis Set F: A similar percentage of galcanezumab-treated patients and placebo either gained (3% to 4%) or lost (1% to 2%) ≥7.0% of their baseline weight, with no statistically significant changes observed between treatment groups

Safety Analysis set G: In Safety analysis set G, the percentages of galcanezumab-treated patients with either a gain or loss ≥7.0% of their baseline weight were similar (Loss: 7.3%; Gain: 8.1%).

Electrocardiogram Analysis

Treatment-Emergent Changes in Quantitative ECGs

The **Placebo-Controlled Analysis Set F**: A low percentage (<3%) of galcanezumab-treated patients and placebo had treatment-emergent changes (low and high) in heart rate, PR interval, QRS interval, and QTcF. No galcanezumab-treated patients experienced treatment-emergent abnormalities in heart rate, QRS interval, or PCS High QTcF. Two patients (1.3%) in the galcanezumab treatment group met treatment-emergent high PR criteria compared to 3 patients (1.9%) on placebo. One galcanezumab-treated patient (0.6%) had a QTcF increase >30 msec compared to 4 placebo patients (2.5%).

No patients experienced a QTcF value of >480 msec or >500 msec in QTcF. One patient in each treatment group experienced a QTcF >450 msec at any time

The **all exposure Analysis Set G**: Some additional findings to the Placebo-Controlled Analysis Set F were observed which included numerically more patients reporting nonspecific T-wave abnormalities, Axis deviation, First degree of AV blocks and sinus bradycardia. Based on the applicant's review, all these patients were not associated with clinical symptoms and were continued in the study except two with a treatment-emergent rhythm finding of sinus bradycardia.

The two patients had a cardiovascular-related TEAE: 1 patient (CGAL-110-~~01254~~ 1) with a history of supraventricular tachycardia and supraventricular ablation reported tachycardia during open-label CGAR. The patient is continuing in the study. The other patient experienced the TEAE of ECG PR prolongation, which eventually led to discontinuation.

Discontinuation due to adverse events

Cluster Headache Only Placebo-Controlled Analysis Set F

Table 31 Summary of AEs leading Treatment discontinuation (safety analysis F)

Preferred Term	Placebo N = 177 n (%)	Galcanezumab 300 mg N = 166 n (%)
Patients with DCAEs	2 (1.1)	3 (1.8)
Atrial fibrillation	0 (0.0)	1 (0.6)
Vertigo	0 (0.0)	1 (0.6)
Asthma	0 (0.0)	1 (0.6)
Palpitations	1 (0.6)	0 (0.0)
Cluster headache	1 (0.6)	0 (0.0)

Cluster Headache Only All-Exposure Analysis Set G

In the Cluster Headache Only All-Exposure Analysis Set G (with exposures up to 15 months), the percentage of patients reporting an AE leading to treatment discontinuation was 5.7%. When adjusted for exposure, the incidence rate of patients with AEs leading to treatment discontinuation in the Cluster Headache Only All-Exposure Analysis Set G (7.9/100 PY) is similar to the EAIRs for the Cluster Headache Only Placebo-Controlled Analysis Set F (8.1/100 PY).

While additional AE PTs and SOCs leading to treatment discontinuation were observed in the Cluster Headache Only All-Exposure Analysis Set G and not in the Cluster Headache Only Placebo-Controlled Analysis Set F, no AE PT leading to discontinuation was reported by more than 1 galcanezumab-treated patient (<1%). Of the 17 patients who discontinued due to an AE, 8 reported non-serious AEs (vertigo, ECG PR prolongation, transient ischemic attack, depression, insomnia, dermatitis, asthma, and dyspnea exertional) and 9 reported serious AEs (atrial fibrillation, palpitations, amaurosis, injection site urticaria, breast cancer stage III, colon neoplasm, metastasis, cerebral ischaemia, and anxiety). Details of SAEs are described in SAE section.

Post marketing experience

Galcanezumab was approved for the preventive treatment of migraine in adults in the US on 27 September 2018. Galcanezumab was also approved for the prophylaxis of migraine in adults who have at least 4 migraine days a month in the EU on 14 November 2018. In this extension application MAA the MAH did not include any postmarketing data, as the datalock for the cluster headache submission occurred prior to the approval for migraine in the EU or US.

2.5.1. Discussion on clinical safety

Safety Pools and baseline characteristics: Galcanezumab's safety in Cluster Headache at the proposed therapeutic dose of 300 mg/month (through three 100 mg subcutaneous injections) was evaluated in two safety Pools:

Safety Analysis Set F, is the primary analysis set and includes 166 galcanezumab treated patients and 177 PBO treated patients, from the short term 2 months and 3 months double blind treatment phase from the two placebo-controlled cluster headache Phase 3 studies respectively in episodic and chronic CH (CGAL and CGAM). Safety Analysis Set G, includes 296 episodic and chronic cluster headache patients, with varying lengths of galcanezumab exposure data. This safety pool includes all galcanezumab treated patients from the three Phase 3 cluster headache studies (CGAL, CGAM, and CGAR) through the data cutoff dates (12 February 2018 for Study CGAL and 27 March 2018 for studies CGAM and CGAR). 2 additional supportive Safety Pools have been presented by the MAH:

Safety Analysis Set H: includes data from the double-blind treatment phase of all Phase 3 migraine and CH galcanezumab clinical trials that included a placebo comparison (CGAG, CGAH, CGAI, CGAL, and

CGAM). Different doses of galcanezumab (120 mg, 240 mg, and 300 mg) are included across the studies, but patients from all dose groups are combined ("GMB_All") and compared with placebo.

Galcanezumab All-Exposure Analysis Set I: includes all galcanezumab-treated patients from all migraine and cluster headache Phase 2 and Phase 3 galcanezumab studies (ART-01, CGAB, CGAG, CGAH, CGAI, CGAJ, CGAL, CGAM, and CGAR). Data from all galcanezumab-treated patients regardless of dose (doses range from 5 mg to 300 mg) are combined in a single group ("GMB_All").

In these two supportive safety Pools (Safety Analysis Set H and Safety Analysis Set I) the overall group mostly reflects the safety observed in the initial submission (migraine population), with very small influence of the newly added cluster headache data. For instance, Analysis set H (GMB N=1601; PBO= 1628) mostly includes migraine patients (N=1435 GMB Pooled; 1451 PBO) compared to a much smaller Cluster Headache group (N= 166 GMB 300 mg; 177 PBO). Even though it may be partially acknowledged that available migraine safety data may be of relevance also for the CH patient population, there are relevant differences between the two clinical development programs, in terms of dose and baseline differences in patients characteristics, that must be considered. As regards to GMB dose, a higher GMB dose is being proposed in cluster headache compared to migraine (300 mg/ month in CH vs 120 mg and 240 mg evaluated in Phase 3 migraine studies). In Analysis set H, only a minority of patients (N= 166, 10%) received GMB 300 mg, while the majority of patients either received GMB 120 mg (N=705, 44%) or GMB 240 mg (N= 730, 46%). In terms of baseline differences in patients' characteristics due to the higher prevalence of migraine among females, more than 80% of patients included in GMB migraine trials were females, while a higher male prevalence is observed for cluster headache and thus 75% of patients enrolled in cluster headache trials were males. Furthermore, consistently with CH's epidemiology, CH patients enrolled in galcanezumab Phase 3 controlled trials were older (≥50 - ≤65 years years old 44.58%) compared to migraine patients (25.85%) and more frequently were current smokers (61.21% vs 13.53%). As in the migraine development program, patients at risk for acute cardiovascular events and/or had serious cardiovascular risk were excluded from cluster headache clinical studies; however, patients with comorbid cardiovascular conditions were included. CH patients reported higher percentages of the following baseline conditions compared to migraine patients: hypertension (57.5% vs 41.7%), hypercholesterolemia (30.0% vs 25.9%), myocardial infarction in the past (7.5% vs 0).

These differences between the CH and migraine clinical development programs must be carefully considered, also in light of the trend observed in the migraine Safety data in the initial galcanezumab submission (Safety analysis Set E) of EAIRs numerically more unfavourable for the 300 mg dose, compared to the lower 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), even though differences in dose group sizes prevented sound conclusions.

Exposure: Including updated safety data, a total of 303 patients with cluster headache were exposed to galcanezumab, representing 274.5 patient-years of exposure (Cluster Headache Only All-Exposure Analysis Set G). At the proposed therapeutic cluster headache dose 300 mg, including updated safety data, 209 patients were exposed to galcanezumab for ≥6 doses and 132 patients were exposed to galcanezumab for ≥12 doses; most of these patients came from chronic cluster headache study CGAM. No patients in other indications received the 300 mg dose for ≥6 months. The extent of exposure at the dose of 300 mg in the cluster headache studies is limited.

Overview of Adverse Events: In Short term placebo-controlled Analysis Set F, any TEAE occurred in 63% of GMB treated patients and in 53% of placebo; serious AEs (1.2% vs 1.7%) and discontinuations due to adverse events (1.8% vs 1.2%) occurred with similar frequency between GMB and PBO group. The three events leading to discontinuation for GMB were the SAE of atrial fibrillation, plus one event each of vertigo and asthma. In Analysis Set F, most reported TEAEs were mild or moderate in severity.

Severe TEAEs occurred in 4.8% of GMB treated patients vs 3.4% in placebo. Apart from 2 events of injection site pain, all other severe TEAEs were single occurrences (nasopharyngitis, constipation, cluster headache, nasal operation, and amaurosis).

Exposure adjusted incidence rates showed that with longer exposure in Analysis Set G, the rate of SAEs was higher compared to GMB short term treated subjects in Analysis set F (8.54 vs 5.41), even though confidence intervals largely overlapped (95% CI: 5.06, 13,49) vs (95% CI: 0.66, 19.54). The incidence rates of SAEs in Analysis Set G safety update were similar to the original cluster headache submission [8.24 (95% CI: 5.16, 12.48)].

In Analysis Set F, the biggest differences between GMB and PBO as regards to TEAEs by SOC was observed for the General disorders and administration site conditions (31.3% vs 17.5%, p=0.003), primarily driven by the higher frequency of TEAEs related to injection sites. The only other SOC with a statistically significant difference between GMB and PBO was Reproductive system SOC (5/166, 3.0%) compared to placebo (0/177; p=.021). In the updated Galcanezumab All-Exposure Analysis Set I (cluster headache plus migraine) a total of 7 patients reported events of prostatitis, orchitis, and urethral stenosis in the migraine and cluster headache development program; in two patients these events previously occurred in their medical history. All events, except the urethral stenosis, resolved or were resolving while continuing on treatment. The absence of significant difference for these events in the larger migraine Placebo-Controlled Analysis Set A (galcanezumab: 3.2% vs placebo: 2.4%) is of limited reassurance, given that the vast majority of migraine enrolled subjects were females. Given that there is literature suggesting that CGRP may play a role in the genitor-urinary system, the issue will be monitored in upcoming PSURs, through cumulative analysis, including safety data from clinical studies, post marketing and published literature.

Common Adverse Events: Given the limited number of patients enrolled in Safety Analysis Set F, TEAEs occurring in 2 subjects (2/166=1.2%) fulfilled the criteria for common (≥1%) adverse events. Among common TEAEs occurring in Analysis Set F, there were the following events already identified as ADRs in the migraine safety database: injection site pain (10.2%), injection site reactions, vertigo (1.7%), constipation (1.1%) and pruritus (1.8%).

Other common TEAEs which were not identified as ADRs in the migraine submission and were observed in Safety Analysis Set F in the galcanezumab-treated group with a frequency higher than in placebo, were not considered based on medical judgment as ADRs.

AESI

Adverse events related to injection sites: Adverse events related to injection occurred in 21.7% of galcanezumab-treated patients, compared with 7.9% in placebo. The PTs and the characteristics of AEs related to injection sites in patients with cluster headache were generally consistent with the observed safety findings in patients with migraine, with the addition of injection site induration among common PTs.

Hypersensitivity events: In general, the evaluation of hypersensitivity events in the Cluster Headache Only Placebo-Controlled Analysis Set F is consistent with the established profile of galcanezumab. Hypersensitivity TEAEs are reported more frequently with galcanezumab treatment compared to placebo, with most patients reporting as mild or moderate in severity and resolved, with the immediate events mainly characterized by local injection site reactions or skin events such as urticaria and pruritus. There was 1 serious likely hypersensitivity AE reported as an injection site urticaria event which resolved in 13 days. Two serious cases of urticaria were reported in galcanezumab-treated patients during open-label and post-treatment phases. The current SmPC includes safety information regarding serious hypersensitivity reactions which is considered adequate given the safety information concerning new SAEs observed in the cluster headache studies.

In addition, there was 1 patient treated with galcanezumab who discontinued due to a likely hypersensitivity event of asthma aggravation. Although the patient had a medical history of asthma, based on the close temporal relation and positive re-challenge, asthma aggravation trigged by galcanezumab treatment is likely. There were also patients reported AEs of "asthma worsening" at the first day exposure. Asthma is one of the important comorbidities in cluster headache population with a prevalence of 7-9% in adult cluster headache population. Following the identification of a safety signal in the post-marketing safety database of Emgality and based on a cumulative review of the clinical trial and postmarketing data in the recently concluded PSUR procedure (PSUSA/00010733/201903) anaphylaxis, angioedema, and rash were identified as adverse drug reactions of galcanezumab treatment.

Evaluation of cardiovascular safety: From available short term (up to 3 months) data there does not seem to be an increase in short term cardiovascular risk associated with galcanezumab treatment (Analysis Set F: TEAEs cardiovascular in nature across 9 SMQs: GMB 4.2% vs placebo 6.2%). In Analysis Set G (including patients exposed to galcanezumab up to 12 months), the percentage of galcanezumab-treated patients reporting ≥1 TEAE likely cardiovascular in nature across all 9 SMQs in the Cluster Headache Only All-Exposure Analysis Set G was 11.2%. In order to assess whether the higher frequency observed in Safety Analysis Set G is a consequence of the longer exposure, EAIRs for occurrence of ≥1 TEAE likely cardiovascular in nature across all 9 SMQs in Safety Analysis Sets F and G showed no increase in incidence rate. After adjustment for time of exposure from the limited available data- incidence of cardiovascular TEAEs does not increase with longer treatment duration.

Of note in Analysis Set G there were single occurrences of cardiovascular events leading to discontinuation, for whom a relationship with study drug may not be excluded.

In GMB placebo-controlled Analysis Set H (migraine plus cluster headache), TEAEs of Peripheral Artery Stenosis and related terms occurred in 16/1601 (1%) GMB treated patients, compared to 6/1628 (0.4%) in PBO. The most frequent TEAEs by PT were hot flush, flushing, Raynaud's phenomenon, with all other PTs occurring in one subject each (peripheral coldness, amaurosis, peripheral artery stenosis, peripheral vascular disorder, intermittent claudication). Calcitonin gene-related peptide is known to be a potent vasodilator, and there is a theoretical risk that its inhibition may cause peripheral vasoconstriction. However, based on the review of the individual cases reporting events of peripheral artery stenosis or related terms in the updated Galcanezumab All-Exposure Analysis Set I (cluster headache plus migraine), a clear causal relationship with galcanezumab treatment has not been found. The number and frequency of reported events is small and in most cases there were alternative etiologies and possible confounding factors, such as intermittent claudication due to a muscular problem, peripheral vascular disease due to diabetes, or the pre-existing condition in those reporting Raynaud's phenomenon. Peripheral vascular events reported in the postmarketing data were non-serious and consistent with previously reported types of events. As reported in the RMP, the MAH has a targeted follow-up form for peripheral vascular disease to assess reported postmarketing events.

Evaluation of Suicidal Ideation and Behavior and Non-Suicidal Self-Injurious Behavior: One patient treated with galcanezumab with a prior history of suicidal behavior and current diagnosis of depression, attempted suicide during the open-label phase of Study CGAM. This patient also had an aborted suicide attempt during the post-treatment follow-up period. Compared to the original cluster headache submission, 1 additional patient reported suicidal ideation on the C-SSRS in the safety update. Additionally, 1 patient died by suicide 46 days after the last galcanezumab dose in Study CGAR and after the safety update data cut-off. This patient reported a lifetime history of suicidal ideation, prior to participation in study CGAM and the event was reported as not related to treatment by the investigator. Data from patients in the Phase 3 cluster headache studies do not suggest an increased risk of suicidal ideation or behavior among patients treated with galcanezumab, compared to those treated with placebo, as assessed by the C-SSRS. The percentage of patients reporting suicidal

ideation in the Cluster Headache Only All-Exposure Analysis Set G galcanezumab-treated patients was greater compared to the Cluster Headache Only Placebo-Controlled Analysis Set F (5.0% [n=14]; 3.0% [n=5], respectively). This is not unexpected given the background rate of suicidal ideation in patients with CH and the increased duration of treatment. Available data comparing EAIRs for Analysis F with Analysis G do not indicate an increase in suicidal ideation with increasing exposure to galcanezumab. Available data do not support an association between galcanezumab treatment and suicidal behavior or ideation.

Serious adverse events: In short term placebo controlled safety analysis set F, 2/166 (1.2%) GMB treated patients experienced SAEs (one event each of atrial fibrillation and constipation), compared to 3/177 (1.69%) SAEs in placebo group (one event each of melena, non cardiac chest pain and depression). The frequency of SAEs reported in the galcanezumab-treated patients in Cluster Headache Only All-Exposure Analysis Set G was 6.1% (n=18). When adjusted for exposure, the incidence rate for SAEs in the galcanezumab-treated population (8.54 [5.06, 13.49]) was within the range of incidence rates for placebo in the Cluster Headache Only Placebo-Controlled Analysis Set F (7.80 [1.61, 22.80]).

Of note, one subject in study CGAM experienced recurring episodes of amaurosis, that were all judged possibly related to the study drug by the investigator. One event of amaurosis was serious and one event led to study drug discontinuation. It is acknowledged that concomitant sumatriptan use is a possible confounder for the occurrence of these events. Further discussion has been requested on the occurrence of other events of amaurosis following GMB administration throughout all available GMB safety data. In Analysis Set H the percentage of galcanezumab-treated patients reporting 1 or more TEAEs related to impaired vision (6/1601, 0.37%) was less than that of placebo patients (10/ 1628, 0.61%). In Analysis Set I 25/ 2889 (0.87%) TEAEs related to visual impairment occurred, with vision blurred (N= 17) and visual impairment (N= 7) being the most frequent events. Cumulatively, as of 31 May 2019 in the postmarketing data, there have been 34 events associated with impaired vision reported. Of the 34 events that were reported, 2 were serious events:1 blindness, and 1 blindness unilateral. The MAH states that the serious cases of blindness were from a consumer who reported they were legally blind, but there were no details with respect to temporal relation to galcanezumab use. Given the lower frequency of reports of impaired vision in patients receiving galcanezumab when compared to placebo, and the multitude of confounds that patients with cluster headache and migraine present it may be acknowledged that available data do not allow to draw definitive conclusions on a causal relationship between galcanezumab treatment and visual impairment events. The MAH committed to further monitor amaurosis and related terms in upcoming PSURs.

Among SAEs that occurred in the updated safety data in Analysis Set G, there was one SAE of reversible cerebral vasoconstriction syndrome, considered drug related by the investigator . Although there is biological plausibility for a possible causal relationship between the SAE of reversible cerebral vasoconstriction syndrome and galcanezumab treatment, available data do not allow a definitive conclusion on this single event, due to other confounding factors (including triptan use and history of sleep apnoea) . This is the only case of reversible cerebral vasoconstriction syndrome reported in the entire galcanezumab safety database.

Also in ongoing or recently concluded migraine studies, there were single occurrences of SAEs, leading to discontinuation, for whom it is difficult to draw definitive conclusions on GMB role.

In particular, due to the occurrence of a SAE of sudden neurosensory hearing loss in a 46 year old Japanese female in Study CGAN, considered related to GMB by the investigator and leading to study drug discontinuation, , the MAH was requested to discuss the need to consider hearing loss as an ADR to GMB, in light of overall available safety data. When considering only the double blind treatment phase 6/2062 (0.3%) GMB treated patients experienced events of hearing loss or related terms during the double blind treatment phase, compared to 1/2089 (0.05%) in the PBO group. Event terms included

sudden hearing loss (3), deafness unilateral (3) and hypoacusis (1). Two of the 6 events that occurred in GMB treated patients were considered drug related by the investigator. One SAE (described above) occurred in a Japanese patient with no other alternative explanations for the recurring events of hearing loss that occurred following the 3rd, 4th and 5th GMB dose and ultimately leading to study drug discontinuation. Eight subjects experienced the event of hearing loss or related terms during the open label treatment time and 2 subjects experienced the event during the post treatment phase (1 month after the last dose). In the post-marketing reports cumulatively through 27 September 2019, actual hearing loss was reported in 11 cases (reporting deafness or hypoacusis). Three of these 11 cases (27.3%) were judged by the MAH to be serious. These 11 cases were too poorly documented to make an accurate medical assessment. The applicant's conclusion that there is a lack of consistency in the clinical presentation of the clinical trial events of hearing loss and that the majority of the cases had other confounding factors may be acknowledged. The MAH should further monitor hearing loss (or related terms) in upcoming PSURs.

Blood pressure:

In the Cluster Headache Only Placebo-Controlled Analysis Set F, a small mean difference in blood pressure was observed between galcanezumab and placebo and more galcanezumab-treated patients (n = 13, 9.5%) met criteria for categorical high change in diastolic blood pressure compared with placebo (n = 7, 5.1%); whereas no difference was observed for categorical high change in systolic blood pressure. The applicant argued that the difference of mean changes of blood pressure from baseline compared to placebo (approximately 1.8-3.6 mm Hg depending the individual study results) is considered small and might not be clinically significant. However, a higher percentage of galcanezumab-treated patients met treatment-emergent high diastolic blood pressure (DBP ≥90mmHg and increase ≥10mmHg) compared to placebo. Of these, 4 patients met sustained elevation criteria for diastolic blood pressure (defined as ≥90mmHg and increase ≥10mmHg at 2 consecutive visits), none were observed in the placebo group.

In the Cluster Headache Only All-Exposure Analysis Set G, 10.1% of patients met treatment-emergent criteria for high systolic blood pressure, of these, 2.2% of patients had Treatment-emergent sustained elevation (defined as SBP≥140mmHg and increase ≥20mmHg at 2 consecutive visits). 20.7% of patients met treatment-emergent criteria for high diastolic blood pressure. Of these, 7.1% had Sustained elevation in diastolic BP and 1.4% (4 patients) were considered Clinically Significant (defined as ≥105 mmHg and increase ≥15mmHg). Three of the 4 patients had initiated anti-hypertensive medication during the study period. One of these 4 patients experienced SAE and discontinued study. In reviewing some details of the few patients reaching a post-baseline DBP>105mmHg and increase ≥ 15mmHg, few patients started new anti-hypertensive treatment during the study period. Majority were already Hypertensive or Pre-Hypertensive (defined as SBP ≥140mmHg or DBP≥90mmHg) at baseline and had medical history of hypertension or other confounding factors such as smoking. To evaluate the higher percentage of patients meeting treatment-emergent high criteria for systolic and diastolic blood pressure in Analysis set G compared to Analysis set F an EAIR analysis was conducted. For patients whose baseline diastolic pressure was ≥90 mm Hg, an increase in incidence rate was observed with longer follow-up in Analysis Set G compared to the Cluster Headache Only Placebo- Controlled Analysis Set F.

The MAH provided case description for each individual patient who reported high blood pressure during the double blind phase of clinical trials. The detailed data suggested that for the majority of GMB treated patients who had diastolic blood pressure increases during double blind period, the elevated blood pressure values did not persist with continued open-label exposure or the values were associated with considerable variability.

Of note, an analogous difference concerning blood pressure was not observed in the placebo-controlled migraine primary analysis set when 240/120mg dose were given. But unfavourable effect including potential effect on blood pressure associated with highest dose (e.g 300mg) were also discussed during the assessment of MAA.

Despite the limits in assessing dose-response from available data, due to differences in dose group sizes and due to differences in study designs, Analysis Set I (All GMB exposure, cluster headache plus migraine) seems to confirm that TE High Systolic blood pressure occurs with higher frequency with higher GMB doses (300 mg), compared to lower doses (120 and 240 mg): the EAIR for the 300 mg dose was higher compared to lower doses, with non overlapping 95% CI [300 mg: 15.32 (10.90, 20.95); 120 mg 5.22 (3.41, 7.65); 240 mg 8.62 (6.73, 10.87)].

Inhibition of the effects of CGRP could theoretically attenuate compensatory vasodilation in ischaemic related conditions. There is a lack of data on the safety of galcanezumab in patients at higher risk for cardiovascular or cerebrovascular events (e.g patients with uncontrolled hypertension, BMI>40 and any type of notable cardiovascular disease were excluded from the trials). Hypertension is one of the important comorbidities in cluster headache population. The prevalence of hypertension in cluster headache population is high. Based on the publication data (Joshi et al 2017), 35% of 60 cluster headache patients participated in a study had hypertension, defined as ≥ 140/90 on average of 3 blood pressure group readings. Cluster headache patients also had a higher prevalence of smoking (approximately 20-60% depending publication and current or former smoking status).

After thorough assessment, the totality of the data indicate a trend towards increase of blood pressure in cluster headache population exposed to galcanezumab 300mg monthly dose. Taken together with the possible plausible mechanism, and the likely dose dependent trend observed in the clinical trials this finding supports the notion that CGRP blockade may affect blood pressure at higher doses. Also considering the limited exposure available at the 300 mg dose, a firm conclusion concerning a causal relationship of a sustained effect of study drug on blood pressure is difficult to make.

2.5.2. Conclusions on the clinical safety

At the proposed therapeutic cluster headache dose 300 mg, including updated safety data, 209 patients were exposed to galcanezumab for ≥6 doses and 132patients were exposed to galcanezumab for ≥12 doses. No patients in other indication received the 300 mg dose for ≥6 months. The extent of exposure at the dose of 300 mg in the cluster headache studies is limited.

In comparison with migraine patient population enrolled in GMB clinical development programme, CH patients were older, more frequently males, smokers, and more frequently had a history of comorbid cardiovascular conditions (such as hypertension, hypercholesterolemia and history of myocardial infarction in the past), even though as in migraine clinical trials, patients at risk for acute cardiovascular events and/or had serious cardiovascular risk were excluded from cluster headache clinical studies.

The observed safety profile in CH was generally consistent with the safety profile observed in migraine.

However, differently from what observed in galcanezumab migraine clinical development program, in cluster headache double blind trials, data show a small but consistent galcanezumab effect of blood pressure increase compared to placebo (both in terms of mean change from baseline and in terms of higher frequencies of categorical increases). In patients whose baseline diastolic pressure was ≥90 mmHg EAIRs of treatment emergent elevations in blood pressure increased over time with longer follow up (Analysis Set G, including open label long term trials). The MAH provided case description for each individual patient who reported high blood pressure during the double blind phase of clinical trials. The detailed data suggested that for the majority of GMB treated patients who had diastolic

blood pressure increases during double blind period, the elevated blood pressure values did not persist with continued open-label exposure or the values were associated with considerable variability.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is the prevention of attacks throughout a cluster period in adults with episodic cluster headache.

Cluster headache is a chronic neurological condition belonging to trigeminal autonomic cephalalgias (TACs), a group of idiopathic headache entities that involve unilateral, moderate to severe recurrent headache attacks and typical autonomic symptoms ipsilateral to the pain and/or restlessness and agitation. The natural course of cluster headache consists of 2 periods: (1) cluster periods /"bouts" (during which time the attacks occur) and (2) remission periods (in which patients are attack free). According to ICHD-3 2018 Guidelines, each attack typically lasts 15 to 180 minutes when untreated and occurs between 1 every other day and 8 per day for more than half of the time when the disorder is active (e.g. during the cluster period). The intensity of pain during the attack is very high, leading to increased risk for depression and suicidality. In addition, higher frequencies of anxiety disorders, sleep disturbances, and cardiovascular risk are associated with the disease. There are 2 recognised subtypes of cluster headache, episodic cluster headache and chronic cluster headache. The episodic form is the most frequent type of CH (up to 90% of patients), differing from the chronic type by the length of remission periods. The currently used cut-off for the distinction between episodic and chronic cluster headache was set to a yearly remission period of 3 months in the new diagnostic criteria of 2018. However, the present studies use the previous cut-off of at least 1 month yearly remission for episodic cluster headache.

3.1.2. Available therapies and unmet medical need

The treatments for CH are distinguished among prophylactic (preventive) and acute. The EFNS guidelines include in the former group, with Level A evidence, verapamil (noted as drug of first choice), and steroids (used as "transitional" prophylactics to fill the gap in time until the primary prophylactic drugs start to show an effect); whereas lithium, methysergide (noted limitations of use due to risk of pulmonary and retroperitoneal fibrosis with long-term use), ergotamine tartrate (short-term prophylaxis), topiramate, melatonin, and pizotifen (rarely used due to modest effect and side effects) are classified as level B evidence. In addition, NICE clinical guideline 150 considers verapamil as the first choice for prophylactic treatment during a bout of CH, while inviting to seek specialist advice in case of no response.

Although several drugs are available for the prophylaxis of the disease, there is still an unmet clinical need for drugs with high efficacy in promptly reducing the number and intensity of cluster headache attacks and a manageable safety profile.

3.1.3. Main clinical studies

The phase 3 Study **CGAL** is the only pivotal study to provide evidence of efficacy of galcanezumab for the prophylactic treatment of episodic cluster headache. The study **CGAM** designed for the chronic type did not meet its primary objective.

CGAL is a phase 3, randomized, double-blind, placebo-controlled trial to evaluate the effect of galcanezumab compared to placebo on the overall mean change from baseline in weekly cluster headache attack frequency across Weeks 1 to 3 in subjects with episodic cluster headache (ECH). The study consisted of a screening phase (up to 1 year); a 10 to 14 days prospective baseline; 8 weeks placebo-controlled double-blind treatment period; a 16-week post treatment follow-up (ongoing as of the cut-off date 7 May 2018).
The study enrolled patients aged 18 to 65 with a diagnosis of cluster headache as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD) -3rd edition, beta guidelines (ICHD-3 beta, 2013). Subjects in remission at enrolment had to have a prior history of a cluster period lasting 6 weeks or greater; subjects currently in an active cluster period not taking any excluded medications that required washout were to be expected, in opinion of the investigator, to continue in the current period for at least another 6 weeks based on previous cluster period history.

Patients were required to have a baseline weekly cluster headache attack frequency (based on ePRO vendor eligibility report) of a minimum of 1 cluster headache attack every other day and at least 4 total attacks, up to a maximum of 8 cluster headache attacks per day.

3.2. Favourable effects

The CGAL trial met its primary endpoint, *overall mean change from baseline in weekly cluster headache attack frequency across weeks 1 to 3.*

The LSMean change from baseline was -8.69 attacks for galcanezumab and -5.22 attacks for placebo. The LSMean change difference from placebo across Weeks 1 to 3 was -3.47 (-6.72, -0.23; p=.036). The effect size was 0.42.

The difference at Week 3 was -3.99 (p=0.045).

All sensitivity analyses used diary data across weeks 1 to 3 and were consistent with the primary efficacy analysis.

The gated secondary endpoint was statistically significant (p=0.046), with a gain of galcanezumab over placebo of about 20% (71.4% galcanezumab vs 52.6% placebo).

Among other secondary endpoints, response analysis based on ≥50% reduction showed significantly greater reduction during Week 2 (58.3% versus 35.7%; p=.026) and Week 3 (72.1% versus 51.7%; p=.045). However, at Week 5 significantly greater portion of ≥50% reduction were observed in the placebo group compared with galcanezumab (89.6% vs. 70.8%; p=.030).

Responder analysis based on ≥30% reduction in weekly cluster headache attack frequency was not statistically significant across treatment groups.

PGI-I score (proportion of patients with score 1 [Much Better] or 2 [Very Much Better] at Week 4 and at Week 8)

At month 1 only, a larger proportion of patients treated with galcanezumab reported a global impression of their disease as *much better or very much better compared to placebo (*PGI-I score: 72.5% vs 46.4%; p=.016). A post-hoc analysis on the subgroup of subjects who reported feeling "much better" at Week 4, revealed a 43% median weekly CHA reduction from baseline across Weeks 1 to 3. Using the percentage as a responder threshold to taste for differences in the treatment groups, a greater proportion of responders under GMB was observed vs placebo (59.4% vs 36.1%, p=.009).

No statistically significant gain on pain intensity, attack duration and use of acute medication was shown for galcanezumab compared to placebo.

In the supportive study in patients with chronic cluster headache (N=237), i.e. with a history of long-lasting cluster headache with remission periods of less than 1 month yearly, the primary endpoint of reduction of the number of weekly cluster headache attacks during the full 12 weeks double-blind treatment period compared to baseline wasn't met. The overall LSMean change from baseline in weekly cluster headache attack frequency during the double-blind treatment phase was -5.4 attacks in the galcanezumab group compared with -4.6 attacks in the placebo group (LSMean change difference from placebo: -0.8; p=.334). However, the change from baseline at each biweekly interval (repeated measures analysis of the ITT population) revealed a statistically significant difference for the week1-2 interval (p=0.011).

The gated secondary endpoint of mean proportion of patients with at least 50% reduction from baseline in the weekly frequency of cluster headache attacks during the 12-week double-blind treatment phase was 32.6% in the galcanezumab group and 27.1% in the placebo group (NS).

Other secondary and exploratory efficacy endpoints:

No significant differences in neither the 30% nor 50% responder rates and no effects on PGI-I. For exploratory endpoints, no overall statistically significant effects were seen for pain severity, total weekly attack duration, or use of acute medications.

3.3. Uncertainties and limitations about favourable effects

With the current documentation, the PK/PD modelling is very basic with a stratification as above or below the median concentration making the assessment of the exposure-response very challenging.

Although the pivotal trial met its primary endpoint, the strength of the evidence in support of treatment benefit yet remains poor. The time-dependent decrease in treatment effect during the cluster period, which cannot be totally attributed to spontaneous remission and could have been affected by the actual length of cluster that was incompletely determined for 70% of subjects, cannot be considered solved solely based on randomisation, prospective baseline period design, and inclusion criteria that took into account the anticipated duration of the cluster for those in active bout for at least 6 weeks.

Results on the primary endpoint are not sufficiently statistically compelling (p=0.036), as instead it is requested for an application supported by one single pivotal trial (see EMA guidelines on one pivotal study CPMP/EWP/2330/99). No support of efficacy is available from the trial in chronic CH (CGAM).

It is noted that the dose in the pivotal study CGAL for episodic cluster headache was 2.5 times the therapeutic dose approved for the migraine indication. However, no dose-finding studies have been performed in the cluster headache population. The rationale proposed by the Applicant for the chosen dose and dosing interval in the CH population were gathered by the results from other studies, namely the original submission of galcanezumab and the responses to several other PD questions. The 150 mg dose twice monthly was effective in migraine and had the same AUC as the 300 mg monthly dose. The 300 mg monthly dose is stated to decrease unbound plasma CGRP by 90%. In conclusion, no definitive model exists to support the choice of dose for the cluster headache studies.

The study design was changed, the sample size was not fixed on the basis of statistical parameters, and both the type I error and the power of the study are not known. Neither the expected mean difference between groups nor the supposed variability were indicated, preventing a sound evaluation of the clinical relevance of the treatment effect. On such bases, adequate reassurance on the risk of chance finding due to the limited sample size of the study was not provided, and on the other hand, the low effect size (0.42) of the study , do increase the risk of chance finding. Therefore, the risk of a

false positive result is still considered a concern together with the lack of a clear definition of the expected clinically relevant effect.

No support is provided from secondary endpoints (pain severity, attack duration, use of acute medication) with the exception of the gated secondary endpoint, the percentage of patients achieving ≥50% reduction from baseline in weekly CH attack frequency, which is however positive only at week 3 (p=0.04). Of note, after including only 2 additional randomised patients with a conservative BOCF imputation, the significance of the gated secondary endpoint was lost. Further analyses are expected on all randomised patients, that include either the primary or the secondary endpoint. With regard to the Patient Global Impression of Improvement, a statistical difference from placebo was observed only at month 1 (p=0.016).

From Week 4 of the double-blind treatment period, no difference in change from baseline in weekly CH between the two groups was observed anymore, despite the administration of the second galcanezumab dose.

No evidence of treatment effect on weekly CHA was observed at week 3, when all longitudinal observations from Week 1 to Week 8 were used in the MMRM model. Indeed, starting from week 5, a steady improvement in placebo group compared with galcanezumab was observed (LS mean change from baseline of weekly CHA at Week 8 was -14.4 for placebo and -13.1 for galcanezumab).

In the supportive study in patients with chronic cluster headache, the overall LSMean change from baseline in weekly cluster headache attack frequency during the double-blind treatment phase, did not statistically differ from placebo: -5.4 attacks in the galcanezumab group compared with -4.6 attacks in the placebo group (p=0.334). The Applicant presented the outcomes of smaller clinical CGRP provocation studies supporting the notion that CGRP levels are elevated during an active cluster period and that treatment with oxygen or s.c. sumatriptan (i.e., the gold standard acute medications) could lower the CGRP levels. The reviewed studies considered the baseline CGRP levels, and pointed towards a differential (though not uniquely interpretable) CGRP relationship to episodic or chronic cluster headache, being the latter somewhat less engaged. However no final conclusive pathophysiologic mechanism can be ruled out for CGRP in CH, nor sound conclusions on a differential role of CGRP in episodic and chronic CH may be drawn at present due to the (very) small size of the reviewed trials CGAL and CGAM for galcanezumab. In line with that, it is acknowledged that the activation of trigeminovascular pathway during acute headache attacks in both migraine and CH, as well as the satisfactory response usually observed to triptans intake in either condition, represent pathophysiologic common factors.

The gated secondary endpoint of mean proportion of patients with at least 50% reduction from baseline in the weekly frequency of cluster headache attacks during the 12-week double-blind treatment phase was also not statistically significant: 32.6% in the galcanezumab group and 27.1% in the placebo group.

The present ICHD-3 criteria for an episodic CH have changed since the previous version. In the current definition of episodic CH, the necessary minimum pain-free remission period for the diagnosis is at least 3 months per year. The response to the question on how many of the patients from the episodic cluster headache study CGAL would have been included into the chronic cluster headache study CGAM instead if the current ICHD-3 diagnostic criteria would have been applied in the present studies, has been explained by the Applicant with the mean cluster period duration of the typical episodic cluster headache patient of 30.8 days and 2.6 periods per year, which would clearly differentiate from the typical chronic cluster headache patients with no or brief remissions. Thus, it was anticipated that there would be very few patients from the studies who would be re-classified due to the changed diagnostic criteria. The clarification on the potential influence of this change while providing a re-calculation of the results in both studies for the primary endpoint using the cut-off of 3 months instead

of 1 month cannot be solved as historical cluster period durations were not collected in the studies. With regard to the results for the subgroups of episodic CH patients with a history of short-lasting bouts (e.g. <4 weeks), bouts of medium duration (e.g. ≥4-<8 weeks) and longer duration (e.g. ≥8 weeks), the requested re-calculations are not possible to perform as historical cluster period durations were not collected in the studies.

3.4. Unfavourable effects

A higher dose is being proposed in cluster headache compared to migraine (300 mg/ month in CH vs 120 mg and 240 mg evaluated in Phase 3 migraine studies).

The observed safety profile in CH was generally consistent with the safety profile observed in migraine. TEAEs, including those identified as ADRs, were mostly transient in nature and resolved.

Based on the findings from two placebo-controlled trials, one in episodic CH, with 2 months duration and one in chronic CH with 3 months duration, the following adverse events were considered adverse drug reactions consistently with what observed in migraine clinical development program:

• **Injection site pain** (reported in 10% GMB 300 mg vs 6% in PBO group). Among GMB treated patients who experienced injection site pain, Injection site pain was considered as severe in 11.8% of patients. No patient discontinued due to injection site pain.

• **Injection site reactions** (reported in 21.7% GMB 300 mg vs 7.9% in PBO groups). The majority of the events were of mild or moderate severity, occurred on the day of injection, and resolved on average in 5 days. Among patients who reported TEAEs related to injection sites, severe injection site TEAEs were reported by 8.3% (3/36) of galcanezumab-treated patients. No discontinuations due to AEs related to injection sites nor SAEs related to injection sites were reported in the double blind treatment phase.

• **Urticaria**: One serious case of injection site urticaria that led to discontinuation of galcanezumab was reported in galcanezumab-treated patients during the open-label treatment phase of Study CGAM.

• **Pruritus** was reported in 1.8% GMB 300 mg vs 0% in PBO groups.

• **Constipation** was reported in 1.8% GMB 300 mg vs 1.1% in PBO groups. One SAE of constipation occurred in a GMB treated patient in the double blind phase.

• **Vertigo** was reported in 1.8% GMB 300 mg vs 0% in PBO groups.

In the Cluster Headache Only Placebo-Controlled Analysis Set F, a small mean difference in blood pressure was observed between galcanezumab and placebo. Although the changes (approximately 1.8-3.6 mm Hg) is considered small, almost twice of the galcanezumab-treated patients (n = 13, 9.5%) met treatment-emergent criteria of high change in diastolic blood pressure compared with placebo (n = 7, 5.1%). The observations support the notion that CGRP blockade may affect the blood pressure. In reviewing some details of the patients reaching a Clinically Significant post-baseline BP elevation, majority were already Hypertensive or Pre-Hypertensive at baseline and had medical history of hypertension or other confounding factors such as smoking. The MAH provided case description for each individual patient who reported high blood pressure during the double-blind phase of clinical trials. The detailed data suggested that for the majority of GMB treated patients who had diastolic blood pressure increases during double blind period, the elevated blood pressure values did not persist with continued open-label exposure or the values were associated with considerable variability.

Taken together with the possible plausible mechanism and a likely dose dependent trend observed in the clinical trials, a causal relationship between galcanezumab and blood pressure increase may not be excluded.

3.5. Uncertainties and limitations about unfavourable effects

The extent of exposure at the dose of 300 mg in the cluster headache studies is limited (209 patients were exposed to galcanezumab for ≥6 doses and 132 patients were exposed to galcanezumab for ≥12 doses) and does not meet the requirement stated in the ICH E1 in which 300-600 patients treated at the proposed dosage levels is recommended. However, the long-term safety data for exposure at the dose of 300 mg could be considered adequate given the supportive data coming from the exposures with galcanezumab 240 mg in the migraine studies (1119 patients with ≥6 monthly doses and 111 patients with ≥12 monthly doses). The limitations and uncertainties due to exclusion criteria in the studies were similar for both the cluster headache and migraine programmes. CH clinical studies excluded also patients with poorly controlled hypertension or BMI >40. Hence, there still exists a lack of data in patients at high risk of cardiovascular and cerebrovascular events, patients 65 years and older and female patients who use galcanezumab while pregnant or breastfeeding. Furthermore, there are still missing information regarding long-term safety including malignancies.

Exposure adjusted incidence rates showed that with longer exposure (Analysis Set G), the rate of SAEs was higher compared to GMB short term treated subjects in Analysis set F (8.54 vs 5.41), even though confidence intervals largely overlapped.

Short-term exposure (up to 3 months) to galcanezumab does not seem to be associated with increased cardiovascular risk. However, in patients exposed to galcanezumab up to 12 months (Analysis Set G), the percentage of galcanezumab-treated patients reporting ≥1 TEAE likely cardiovascular in nature was 11.2%, including patients with cardiovascular events leading to discontinuation for whom a relationship with study drug may not be excluded. From the limited available data comparing EAIRs for Analysis F with Analysis G do not indicate an increase in incidence of cardiovascular TEAEs (at least 1 narrow or broad scope preferred term) with increasing exposure to galcanezumab.

Calcitonin gene-related peptide is known to be a potent vasodilator, and there is a theoretical risk that its inhibition may cause peripheral vasoconstriction. The topic will be closely monitored in future PSURs/periodic benefit–risk evaluation reports.

Given the higher frequency of TEAEs in the Reproductive SOC among galcanezumab-treated patients (3%), compared with placebo patients (0%) observed in Safety Analysis Set F and given that there exists literature suggesting that CGRP may play a role in the genito-urinary system, the issue should be monitored in upcoming PSURs, through cumulative analysis, including safety data from clinical studies, post marketing and published literature.

Hypertension during pregnancy and pre-eclampsia in patients at high risk are considered as important potential risks in the Emgality RMP. Two events of pre-eclampsia occurred among migraine patients, out of 21 women exposed to galcanezumab who became pregnant during their migraine study participation. One event of pre-eclampsia had been already described in the initial migraine submission. The other event of pre-eclampsia occurred in a woman with no risk factors of pre-eclampsia (last galcanezumab dose approximately 4 months prior to pregnancy start) in Study CGAI in chronic Migraine prevention. A possible contribution of study drug to the pre-eclampsia event may not be excluded.

The MAH should further monitor in upcoming PSURs amaurosis and related terms and hearing loss (or related terms), through cumulative analysis, including safety data from clinical studies, post marketing and published literature.

3.6. Effects Table

Table 32 Effects Table for Emgality

Effect	Short Description	Unit	GMB 300	PBO	Uncertainties/ Strength of evidence	References
Favourable Effects						
Cluster headache attacks (CHA)	Overall mean change from baseline in weekly CHA frequency across Weeks 1 to 3	CHA	-8.69 (-11.51, -5.87)	-5.22 (-7.87, -2.57)	The p-value (0.036) is not considered sufficiently compelling for a one pivotal trial	CGAL
Responder rate	Proportion of patients with a reduction from baseline of ≥50% the weekly CHA frequency	%	71.43	52.63	The p-value (0.046) is not considered sufficiently compelling for a one pivotal trial	CGAL
Unfavourable Effects						
Injection site reactions		%	GMB 300 mg: 21.7%	PBO: 7.9%		Pool F
Constipation		%	GMB 300 mg: 1.8%	PBO: 1.1%		Pool F
Pruritus		%	GMB 300 mg: 1.8%	PBO: 0%		Pool F
Vertigo		%	GMB 300 mg: 1.2%	PBO: 1.7%		Pool F
TE high DBP	Approach 1	%	GMB 300 mg: 9.5%	PBO: 5.1%		Pool F
	Approach 1 sustained elevation		GMB 300 mg: 3.0%	PBO: 0%		Pool F
	Approach 2		GMB 300 mg: 34%	PBO: 26%		Pool F
Urticaria		%	GMB 300 mg:0.68%	-		Pool G

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Superiority of galcanezumab compared with placebo in reducing the burden of headache attacks within a cluster bout remains not sufficiently demonstrated. Although the primary endpoint was met, results were not sufficiently statistically compelling as requested for an application based on one single pivotal trial, and several methodological flaws in the trial design impact on their reliability. In addition, results

on the primary endpoint were supported only by some secondary endpoints all measured at early time points, and no evidence of maintenance of treatment effect after week 3-4 is at present available, which seriously limits the perceived efficacy of the treatment. The disparity in the distribution of subjects enrolled while in cluster with respect to those enrolled while in remission (70 vs 30%) along with the lack of knowledge of the cluster effective beginning for the former group only, prevents an adequate assessment of the primary outcome. Moreover, the randomisation in the trial design, as well as the adoption of a prospective baseline period, while and including per criteria subjects in active bout anticipated to stay in the cluster for at least 6 weeks, are not considered sufficient to exclude that the observed effect due to galcanezumab vs placebo actually overwhelmed the one expected from a spontaneous remission, as it could have been affected by the actual length of cluster that was incompletely determined for 70% of subjects. On the contrary, the magnitude of the effect shows a clear decline over time, partly due to the narrow time window of observation (3 weeks) before the remission of cluster, with an increased response of placebo, although a second dose of galcanezumab was administered at week 4, a monthly administration of the drug cannot be recommended. Moreover, the effect of galcanezumab on relevant aspects of disease control, including pain severity, attack duration, and the frequency and amount of acute medications use was not significantly different from placebo, adding uncertainties to the quantification of the treatment benefit.

The observed safety profile in CH was generally consistent with the safety profile observed in migraine. However, differently from what observed in the migraine clinical development program, in cluster headache double blind trials, data show a small but consistent galcanezumab effect of increase in diastolic blood pressure compared to placebo (both in terms of mean change from baseline and in terms of higher frequencies of categorical increases). In particular, in patients whose baseline diastolic pressure was ≥90 mmHg, elevations in blood pressure increased over time with longer follow up. This is a concern, given the epidemiological evidence that even small sustained increases in blood pressure in existing high blood pressure, increases rates of major cardiovascular events. The MAH provided case description for each individual patient who reported high blood pressure during the double-blind phase of clinical trials. The detailed data suggested that for the majority of GMB treated patients who had diastolic blood pressure increases during double blind period, the elevated blood pressure values did not persist with continued open-label exposure or the values were associated with considerable variability. A higher therapeutic dose has been chosen for the cluster headache indication (2.5 times that of the maintenance dose for migraine). In comparison with migraine patient population enrolled in GMB clinical development programme, CH patients were older, more frequently males, and more frequently had a history of comorbid cardiovascular conditions (such as hypertension, hypercholesterolemia and history of myocardial infarction in the past), even though as in migraine clinical trials, patients at risk for acute cardiovascular events and/or had serious cardiovascular risk and elderly (>65 years old) were excluded from cluster headache clinical studies. Although it may be acknowledged that the observed effect on blood pressure did not appear to result in clinically meaningful adverse effects in galcanezumab short term treated patients in Analysis Set F, this finding supports the notion that CGRP blockade may affect blood pressure at higher doses. Also considering the limited exposure available at the 300 mg dose, a firm conclusion concerning a causal relationship of a sustained effect of study drug on blood pressure is difficult to make.

3.7.2. Balance of benefits and risks

Given the uncertainties in the evaluation of treatment benefit, the benefit risk balance in the sought indication is at present negative.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of Emgality in the claimed indication is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Emgality 100mg, in the prophylaxis of cluster headache the CHMP considers by consensus that

the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the extension(s) of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

Efficacy has not been sufficiently shown:

- The results from the CGAL study, in episodic cluster headache, are not statistically compelling, as requested in case of an application based on a single pivotal trial.

  Moreover, support is not available from the galcanezumab study in chronic cluster headache, which yielded negative results. In this context, the evidence from epidemiology and family studies that transition from episodic to chronic cluster headache and vice versa occur, indicates that cluster headache is a spectrum of a single disorder, further questioning the efficacy of emgality in episodic cluster headache.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the MAH's request for an additional year of market protection/data exclusivity and in light of the negative recommendation, the CHMP does not consider that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.