NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Galcanezumab for preventing migraine [ID1372]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Galcanezumab for preventing migraine [ID1372]

Technical Engagement papers

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Eli Lilly

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. The Migraine Trust
   b. Association of British Neurologists
   c. British Association for the Study of Headache

   The Royal College of Physicians endorse the statement submitted by the Association of British Neurologists

4. **Evidence Review Group report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

5. **Evidence Review Group report – response to factual accuracy check**

6. **Draft Technical Report**

7. **Technical engagement response** from Eli Lilly

8. **Technical engagement response** from consultees and commentators:
   a. The Migraine trust
   b. Association of British Neurologists
   c. British Association for the Study of Headache
   d. AbbVie
   e. Novartis Pharmaceuticals UK Limited
   f. Teva UK Limited

9. **Evidence Review Group critique of company response to technical engagement** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

EMGALITY® (galcanezumab) for preventing migraine [ID 1372]

Document B
Company evidence submission

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Abbreviations

Abbreviation	Definition
AAN	American Academy of Neurology
AE	Adverse event
AHS	American Headache Society
BASH	British Association for the Study of Headache
BSC	Best supportive care
CGRP	Calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EPAR	European public assessment report
FDA	Food and Drug Administration
EQ-5D-5L	EuroQol 5 Dimension 5 Level questionnaire
HCRU	Healthcare resource utilisation
HFEM	High frequency episodic migraine
HIT-6	Six-item Headache Impact Test
HRQoL	Health-related quality of life
IBMS	International Burden of Migraine Study
ICHD-3	International Classification of Headache Disorders version 3
IHS	International Headache Society
LFEM	Low frequency episodic migraine
MHD	Migraine headache day
MIDAS	Migraine disability assessment
MOH	Medication overuse headache
MSQ	Migraine-specific quality of life questionnaire
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
PSS	Personal Social Services
QALY	Quality adjusted life years
RCT	Randomized controlled trial
SLR	Systematic literature review
SmPC	Summary of product characteristics
WPAI	Work productivity and activity impairment

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 The decision problem addresses the clinical and cost-effectiveness of galcanezumab as migraine prophylaxis in adults who have a history of at least 3 prior preventive treatment failures

Galcanezumab received a marketing authorisation from the European Medicines Agency (EMA) on 14th November 2018 for the prophylaxis of migraine in adults who have at least four migraine headache days (MHDs) per month [1]. The decision problem focuses on a part of the marketing authorisation; the target population in this submission consists of people with migraine that have at least four MHDs per month, and who have a history of at least three (≥3) prior pharmacological preventive treatment failures.

The key evidence in this submission is based on results of CONQUER (NCT03559257), a randomised clinical trial (RCT) that evaluated the efficacy and safety of galcanezumab in patients who experienced 2 to 4 migraine preventive medication category failures due to insufficient efficacy or safety/tolerability reasons [2]. This population is of particular interest due to evidence of decreased quality of life and increased economic burden among people with migraine that is inadequately managed [3, 4] These data are therefore directly applicable to the target population within the NHS.

The decision problem addresses the evidence separately for people with chronic migraine or episodic migraine as these groups of patients are distinct clinical populations within the marketing authorisation

Migraine represents a spectrum of disorders along a continuum, however it can be divided into distinct clinical populations based on headache frequency: episodic migraine (<15 headache days per month) or chronic migraine ≥15 headache days with ≥8 migraine headache days) (Figure 1; described in Section B.1.3.2) [5]. While patients with episodic migraine and patients with chronic migraine were evaluated in separate studies, the marketing authorisation did not specify these subtypes as distinct clinical populations.

Figure 1: Subtypes of migraine

HD, headache day; MHD, migraine headache day

Targeting patients that have a history of at least 3 prior preventive treatment failures is appropriate for NHS clinical practice since it represents a population who would be prescribed specialised treatments

In NHS clinical practice, patients with chronic migraine and patients with episodic migraine are provided similar preventive options for the first three lines of treatment (described in Section B.1.3.4). After failing three treatments, patients have the option to try a fourth preventive treatment or manage their attacks with best supportive care (BSC). However, patients with

chronic migraine may also be prescribed botulinum toxin A as a fourth line preventive treatment if their condition is appropriately managed for medication overuse [6]. It should be noted that no specialist treatment is currently available in England and Wales for patients with episodic migraine (EM) who have a history of 3 preventive treatment failures.

Due to the low cost of currently available oral preventive treatments, galcanezumab is not expected to be used in treatment-naïve patients.

High Frequency Episodic Migraine represents a subgroup of patients with a substantial disease burden in need of specialist treatment options

Within episodic migraine, patients with 8-14 monthly MHDs who suffer <15 headache days per month are classified high frequency episodic migraine (HFEM) [7-9]. A growing body of evidence suggests that patients with HFEM have a burden of disease similar to CM and as a result, experts in the field have proposed revising the definition of chronic migraine to include patients with 8-14 MHDs per month or to recognise it as a separate clinical group [7, 10, 11]. Until such time that HFEM is recognized by the International Classification of Headache Disorders (ICHD) as a distinct clinical subgroup or is included within chronic migraine, patients with HFEM who fail three or more oral preventive treatments do not have access to specialist treatment options. In order to address the unmet need for specialist treatment in patients with HFEM, the submission also presents data to highlight the clinical and cost effectiveness of galcanezumab treatment in patients with HFEM who have a history of at least 3 prior preventive treatment failures as a distinct subgroup.

The final scope was issued in December 2019 as detailed in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with migraine	Adults with migraine who have ≥4 migraine headache days (MHDs) per month, who have a history of ≥3 prior preventive treatment failures. This submission will address the decision problem separately for the following populations 1. Patients with chronic migraine (≥15 headache days per 30-day period, of which ≥8 are MHDs) 2. Patients with episodic migraine (4-14 MHDs and <15 headache days per 30-day period)	The population is aligned to the marketing authorisation granted to galcanezumab in the UK, which restricts its use as prophylaxis of migraine in adults who have at least 4 MHDs per month. In addition, current clinical practice within the NHS, and feedback from clinicians suggests that galcanezumab is most suitable for use in patients who have a history of ≥3 prior preventive treatment failures.
Intervention	Galcanezumab	Galcanezumab (Initial loading dose of 240mg then 120mg once monthly)	In line with final scope
Comparator(s)	• Oral preventive treatments (such as topiramate, propranolol, amitriptyline) • Botulinum toxin type A (in chronic migraine that has not responded to at least 3 prior pharmacological prophylaxis therapies)	Episodic migraine: - Placebo (representing BSC) Chronic migraine: - Placebo (representing BSC) - Botulinum toxin A	The comparators have been selected in line with comments from the final appraisal document of erenumab for preventing migraine [12]. Most people with migraine who have a history of ≥3 prior preventive treatment failures would either use botulinum toxin A or BSC, and a fourth oral preventive treatment is

	• Erenumab (subject to ongoing NICE appraisal) • Fremanezumab (subject to ongoing NICE appraisal) • Best supportive care (BSC)		unlikely to have a clinically meaningful benefit. BSC and botulinum toxin A have been selected as comparators for episodic and chronic migraine, respectively. BSC is also presented as a comparator for chronic migraine, to allow comparison of galcanezumab and BSC in the whole patient population. Clinical trials evaluating galcanezumab in migraine were designed using placebo as a comparator. Patients in the placebo arms of these trials used acute treatments that would normally be prescribed in clinical practice for the management of migraine symptoms. Data from the placebo arms of the clinical trials is therefore presented as evidence supporting BSC. At the time of submission, erenumab and fremanezumab had undergone technology appraisals and were not recommended as preventive treatment by NICE. As a result, they are not relevant comparators within the scope of this appraisal.
Outcomes	The outcome measures to be considered include: • frequency of headache days per month	The outcome measures to be considered include: • frequency of headache days per month	In line with final scope

	• frequency of migraine days per month • severity of headaches and migraines • number of cumulative hours of headache or migraine on headache or migraine days • reduction in acute pharmacological medication • adverse effects of treatment • health-related quality of life	- overall mean change from baseline in mean monthly headache days • frequency of MHDs per month - overall mean change from baseline in mean monthly MHDs - percentage of patients with episodic migraine with ≥50% reduction from baseline in mean monthly MHDs - percentage of patients with chronic migraine with ≥30% reduction from baseline in mean monthly MHDs • number of cumulative hours of headache or migraine on headache or migraine headache days - Overall mean change from baseline in number of monthly migraine headache hours • reduction in acute pharmacological medication - Overall mean change from baseline in the number of monthly migraine headache days with acute headache medication use • Analysis of treatment-emergent adverse events • health-related quality of life Changes from baseline to month 3 in:	

		• MSQ v2.1 total score, Role Function-Restrictive, Role Function-Preventive and Emotional Function domain scores • EQ-5D-5L	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per the NICE reference case, the cost-effectiveness of galcanezumab is expressed in terms of incremental costs per QALY, and costs have been considered from the perspective of the NHS and PSS. A lifetime time horizon is employed in the base case analysis, as this was considered an appropriate duration over which to fully capture the lifetime costs and benefits of galcanezumab based on the final appraisal document for erenumab in the prevention of migraine [12]	In line with final scope

Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • people with chronic or episodic migraine • subgroups defined by the number of previous preventive treatments • subgroups defined by the frequency of episodic migraine. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	The following subgroups will be considered: • people with HFEM who suffer 8 -14 MHDs per month (with <15 headache days in a 30-day period) • Pooled analysis of people with HFEM and chronic migraine, to allow review of patients in whom chronic migraine is defined as ≥8 MHDs per month	• The base case analysis has been presented separately for patients with chronic and episodic migraine in patients who have a history of ≥3 prior preventive treatment failures • Clinical experts have proposed that the ICHD criteria for chronic migraine be revised to include patients who experience ≥8 MHDs per month [12]. These patients are unable to access botulinum toxin A since the European label and NICE recommendations restrict its use on patients with chronic migraine [6], and may benefit from galcanezumab treatment.

Abbreviations: BSC, best supportive care; EQ-5D-5L : 5 level EuroQol 5 dimensions 5 level; HCRU, healthcare resource utilisation; HFEM: high-frequency episodic migraine; ICER, incremental cost-effectiveness ratio; ICHD, International Classification of Headache Disorders; MHD, migraine headache days; MIDAS, migraine disability assessment; MSQ-v2.1, Migraine-Specific Quality of Life Questionnaire Version 2.1; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS: Personal Social Services; QALY: quality-adjusted life year; WPAI: Work Productivity and Activity Impairment.

B.1.2 Description of the technology being appraised

A summary of product characteristics (SmPC) or information for use and the European public assessment report (EPAR) regarding galcanezumab are listed in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Emgality® (galcanezumab)
Mechanism of action	Galcanezumab is a humanised IgG4 monoclonal antibody that binds CGRP thus preventing its biological activity. Elevated blood concentrations of CGRP have been associated with migraine attacks. Galcanezumab binds to CGRP with high affinity (KD = 31 pM) and high specificity (>10,000-fold vs related peptides adrenomedullin, amylin, calcitonin and intermedin).
Marketing authorisation/CE mark status	EMA Marketing authorisation was issued on 14 November 2018.
Indications and any restriction(s) as described in the SmPC	Emgality is indicated for the prophylaxis of migraine in adults who have at least four MHDs per month. Emgality is contraindicated to patients who have hypersensitivity to the active substance or any of the following excipients: L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80, Sodium chloride, Water for injections. Serious hypersensitivity reactions including cases of anaphylaxis, angioedema and urticaria have been reported. If a serious hypersensitivity reaction occurs, administration of galcanezumab should be discontinued immediately and appropriate therapy initiated. Patients with certain major cardiovascular diseases were excluded from clinical studies and no safety data are available in these patients.
Method of administration and dosage	• The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly via autoinjector, with a 240 mg loading dose as the initial dose. • Treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine. Patients should be instructed to inject a missed dose as soon as possible and then resume monthly dosing. • Treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue

	treatment is recommended regularly thereafter.
Additional tests or investigations	No additional tests or investigations are expected to be required for galcanezumab as compared to other currently available treatments
List price and average cost of a course of treatment	**List Price**: £386.50 per 120 mg dose The average costs of a course of treatment for a responder patient with EM migraine over a 25-year time period is [redacted] (versus BSC) The average cost of a course of treatment for a responder patient with CM over a 25-year time period is between [redacted] (versus BSC) and [redacted] (versus botulinum toxin A)
Patient access scheme (if applicable)	A simple PAS (confidential discount), making galcanezumab available at a fixed net price of [redacted] per 120 mg dose has been submitted for review by the NHS England Commercial Medicines and Devices Investment Group.

Abbreviations: CE, Conformité Européene; CGRP, calcitonin gene-related peptide; EMA, European Medicines Agency; IgG4, immunoglobulin G4; SmPC, Summary of Product Characteristics

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Clinical presentation

Migraine is a chronic and highly debilitating neurological disease characterised by episodic attacks of moderate to severe headache [13, 14]. The International Classification for Headache Disorders defines patients with migraine on the basis of headache frequency as suffering from episodic migraine, (<15 headache days per month) or chronic migraine, (≥15 headache days per month, with ≥8 days having the feature of migraine for >3 months) [14].

The headache pain is throbbing in nature and often unilateral, but can also be bilateral, at the front or back of the head, and in rare cases, may be felt in the face and body [15]. The intensity of pain varies, as does the pattern of associated symptoms, with photophobia, phonophobia, nausea, vomiting, osmophobia and movement sensitivity occurring in various combinations [16].

A migraine attack consists of distinct phases: a premonitory or prodrome stage that precedes the attack from several hours to a few days, an aura phase which may commence immediately before and accompany the headache lasting at least one hour, the headache phase that may last 4–72 hours, and a postdrome phase that may last for hours to days following resolution of the attack [17].

Premonitory phase symptoms include yawning, polyuria, mood changes, irritability, light sensitivity, neck pain, and concentration difficulties [18]. Prodromal and postdromal symptoms include symptoms such as fatigue, weakness, mood changes, gastrointestinal symptoms, difficulty concentrating, general malaise, and some enduring head pain [19, 20]. Auras include a combination of visual phenomena, sensory disturbances or aphasic speech disturbances [14, 15].

An additional burden of disease is caused by interictal symptoms in the period between attacks [21, 22]. These may manifest as excessive worry or anxiety about the next attack or lifestyle adaptations (e.g. cancelling or reducing social activities) to avoid migraine triggers, thus severely affecting quality of life [22, 23].

People with migraine may experience impairment of cognitive function during attacks including in executive functions that regulate, control, and manage other cognitive processes [24]. Cognitive impairment contributes to migraine-related disability and burden by negatively influencing an individual's ability to perform at work, school, or in other activities [24].

B.1.3.1.2 Pathophysiology

Migraine is a complex neurophysiological disorder involving multiple components of the central and peripheral nervous systems [25, 26]. Altered connectivity of the cortex, thalamus, hypothalamus, brainstem, amygdala and cerebellum have been reported during migraine attacks, consistent with the observed symptoms from multiple sensory and pain-processing circuits [18].

Migraine headaches are believed to originate upon activation of trigeminal sensory pathways which convey pain signals from the meninges to the brain [27, 28]. Transmission of nociceptive signals from peripheral trigeminal sensory afferents to second-order neurons involves release of calcitonin gene-related peptide (CGRP), nitric oxide and pituitary adenylate cyclase-activating polypeptide-38 [13]. CGRP is a potent vasodilatory neuropeptide that has been identified as a key mediator of migraine based on several studies [29]. Plasma levels of CGRP are elevated during migraine attacks and intravenous infusion of CGRP can trigger migraine-like attacks in people with migraine but not in healthy individuals [30-32]. Interictal levels of CGRP are higher in patients with CM versus those with EM or unaffected patients [33]. The therapeutic potential of blocking CGRP signalling in acute and preventive treatment of migraine has been demonstrated

using CGRP receptor antagonists, anti-CGRP antibodies and anti-CGRP receptor antibodies [29].

B.1.3.2 Migraine Types and Classification

B.1.3.2.1 ICHD-3 Classification

Migraine represents a spectrum of disorders consisting of episodic (<15 headache days per month) and chronic forms (≥15 headache days per month with ≥8 MHDs for >3 months) [34]. The use of a frequency score to define the subtypes is arbitrary and not based on clinical differences [35]. Based on the ICHD-3 criteria, migraine may be divided into two major types (with/ without aura) (Table 3) [14]. The latest version of the classification provides specific diagnostic criteria for chronic migraine including attacks of all subtypes and subforms, and additional coding was deemed unnecessary for episodic subtypes [14].

Table 3. Diagnostic criteria for migraine with aura and migraine without aura

1.1. Migraine without aura A. ≥5 attacks fulfilling criteria B–D B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated) C. Headache has ≥2 of the following: (1) unilateral location; (2) pulsating quality; (3) moderate or severe pain intensity; (4) aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) D. During headache, ≥1 of the following: (1) nausea and/or vomiting; (2) photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
1.2. Migraine with aura A. ≥2 attacks fulfilling criteria B and C B. ≥1 of the following fully reversible aura symptoms: (1) visual; (2) sensory; (3) speech and/or language; (4) motor; (5) brainstem; (6) retinal C. ≥3 of the following: (1) ≥1 aura symptom spreads gradually over ≥5 min; (2) ≥2 symptoms occur in succession; (3) each individual aura symptom lasts 5–60 min; (4) ≥1 aura symptom is unilateral; (5) ≥1 aura symptom is positive; (6) aura is accompanied, or followed within 60 min, by headache D. Not better accounted for by another ICHD-3 diagnosis
1.3. Chronic migraine A. Headache (tension-type-like and/or migraine-like) on ≥15 days/month for >3 months and fulfilling criteria B and C B. Occurring in a patient who has had ≥5 attacks fulfilling criteria B–D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On ≥8 days/month for >3 months, fulfilling any of the following: (1) criteria C and D for 1.1 Migraine without aura; (2) criteria B and C for 1.2 Migraine with aura; (3) believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis

B.1.3.2.3 Subtypes of episodic migraine

Two distinct subtypes of episodic migraine have been defined based on frequency of migraine headache days namely low frequency episodic migraine (LFEM) and high frequency episodic migraine (HFEM) that includes patients experiencing 0-8 and 8-14 days of migraine attacks per month, respectively [36-38]. Based on market research conducted on headache specialists and general practitioners , the majority of patients surveyed across the UK suffer from LFEM [39]. In this survey, the proportion of patients with HFEM and chronic migraine was similar to that reported in retrospective analyses of Danish and Russian cohorts [10, 39]. There is evidence to suggest that patients with HFEM (but not LFEM) are similar to those with chronic migraine with regards to annual migraine attack frequency, response to acute treatments, medication overuse, disability and Health Related Quality of Life (HRQoL) scores, and overall prevalence of comorbidities [7, 10]. Based on these findings, experts have proposed a revised set of diagnostic criteria for chronic migraine to include all patients who experience ≥8 MHDs per month [10]. Until such time when chronic migraine is redefined based on monthly MHDs, patients with HFEM are excluded from receiving the level of care and treatment options that are available to patients with chronic migraine [6]. A more recent publication suggests that HFEM be classified as an independent clinical subtype to allow identification of populations for specific clinical and public health interventions in a cost-effective manner [11]. At the time of this submission, there are no specialist treatments available to patients with episodic migraine, including HFEM, who have a history of ≥3 prior preventive treatment failures.

B.1.3.2.4 Migraine chronification

In some patients with episodic migraine, the headache frequency may increase over time until it crosses the threshold of 15 headache days per month with ≥8 MHDs for >3 months, at which point it evolves into chronic migraine. This process, termed migraine chronification is reported to occur annually in 2.5–3.0% patients with episodic migraine [40, 41], although rates as high as 14% have been reported in specialty headache clinics [42]. There are a number of risk factors associated with the development of chronic migraine including gender, lower socioeconomic status, migraine progression (i.e. an increase in the frequency and severity of migraine attacks), depression, obesity, and medication overuse [43].

B.1.3.3 Disease Burden

B.1.3.3.1 Epidemiology

Based on the 2017 Global Burden of Disease study, the age-standardised prevalence and incidence of migraine in the UK are 21.6% (95%CI 20.0–23.3) and 0.31% (95% CI 0.28–0.35), respectively[1] [44]. The prevalence is highest among individuals aged 25–55 years but declines after mid-life [13]. Age-standardised prevalence rates of migraine in the UK are higher in women compared with men regardless of age range (28% vs 15% respectively) although prevalence decreases with increasing age in both genders [44]. Prevalence data for migraine subtypes in the population are not available, however based on UK patients in the International Burden of Migraine (IBMS) study (N=1,070) and Eli Lilly commissioned market research ([redacted]), the

[1] Institute for Health Metrics and Evaluation (IHME), 2018.Available from http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2017-permalink/febc470d9078b0152029c41a79a4bea9 Retrieved October 1, 2019

proportion of people with chronic migraine is approximately 6%-16% and with episodic migraine is 84%-94% [39, 45].

B.1.3.3.2 Impact on Patient Quality of Life

Migraine was the leading cause of disability in people <50 years of age worldwide in 2017, with an estimated 0.5 million years of life lived with disability in the entire UK population [44, 46]. It has been proposed that the true burden may be even higher since these analyses do not consider disability associated with the interictal state of headache disorders [46]. Migraine attacks have a substantial impact on physical function, everyday activities, social, relationship and leisure activities and emotional responses [47].

A survey conducted in a random sample of adults in England revealed that 25% of respondents with migraine (N=574) reported high levels of pain (rated 9–10 on a 10-point scale) [48]. A mean pain rating of 7.5 on a 10-point scale (where 10=most intense pain) was observed in both males (n=113) and females (n=461) [48]. Pain and discomfort during attacks often results in poor quality of sleep, which in turn is associated with poor health, significant functional and cognitive impairment, and psychiatric comorbidity [49, 50].

Factors associated with patient history of migraine preventive medication use were evaluated in an analysis of data drawn from a cross-sectional survey of 444 physicians and their patients [51]. Of 4319 patients, 1865 were using preventive medications and 42.7% of these had a history of treatment failure and switching. Migraine-related disability was worse in those patients with a history of failure/switching compared with those on their initial preventive agent regardless of monthly headache days [51]. These data demonstrate that despite switching between different drugs, disability remains high, and highlight the need for more effective and better-tolerated preventive medications.

The impact of episodic and chronic migraine on HRQoL has also been examined in studies using disease-specific instruments such as the Migraine Specific Quality of Life Questionnaire (MSQ) and the six-item Headache Impact Test (HIT-6) [38, 45, 52]. In the International Burden of Migraine Study (IBMS), episodic migraine was associated with a detrimental impact on HRQoL that worsened as migraine frequency evolved to the chronic form [45]. Patients with chronic migraine exhibited lower scores compared to those with episodic migraine in all domains of the MSQ instrument, in unadjusted and adjusted univariate and multivariate analyses [45].

The negative impact of migraine on health utilities has been reported in a number of studies using the Health Utilities Index Mark 3, and a time trade-off approach [53-55]. As headache frequency increased, utility scores decreased indicating worsening of HRQoL with migraine chronification. It has been suggested that the impact of migraine on health utilities may be similar or worse compared with other debilitating diseases such as musculoskeletal disease and lower back pain [54, 55].

The disability associated with migraine can be evaluated using the Migraine Disability Assessment Score (MIDAS), a five-item, self-administered questionnaire that measures days of missed or substantially decreased activity because of headache in the previous 3 months [56] High proportions of patients with migraine report moderate-to-severe disability based on MIDAS scores, with disability increasing with greater headache frequency [38, 45, 53]

Despite an array of therapies for migraine prophylaxis, the findings summarised above suggest that detriments in HRQoL continue to be reported. In particular, it is apparent that as headache frequency increases HRQoL worsens indicating an unmet need for effective preventive medications that can limit migraine disease progression.

B.1.3.3.3 Economic burden

Migraine is responsible for an economic burden of £6.2 - £9.7 billion annually in the UK [57]. This includes direct healthcare costs (outpatient care, investigations, acute and prophylactic

medications and hospitalisations) of £0.6 - £1.0 billion [57]. A recent survey by the Migraine Trust in the UK found that 55% of respondents had been absent for more than 7 days in the last 12 months, with 15% absent for more than 31 days (Migraine Trust, 2012). Indirect costs due to migraine-related sick days off work (absenteeism) and reduced effectiveness at work (presenteeism) contribute to 55-86 million workdays lost every year in the UK, at a cost of £5.6-£8.8 billion [57]. In the Work Foundation analysis, it was estimated that presenteeism accounted for at least as much burden as absenteeism, meaning that the overall burden (absenteeism plus presenteeism) could be equivalent to 86 million workdays lost per annum in the UK; this is a conservative figure given that presenteeism is expected to have a larger impact than absenteeism [57]. Mean total annual costs associated with chronic migraine are substantially higher than those with episodic migraine, as evidenced by the results of the IBMS (€3,718, n=57 vs €867, n=1,013 in the UK respectively) [57, 58] An analysis of large US claims databases (Truven Health Analytics MarketScan Databases) has demonstrated that cycling through multiple migraine preventive medication classes is burdensome to the healthcare system [3]

B.1.3.4 Diagnosis and Treatment Pathway

B.1.3.4.1 Guidelines for the acute treatment of migraine in clinical practice

Within NHS England, the best supportive care for acute treatment of migraine depends on the severity of attacks and associated symptoms [59]. Unless contraindicated, these may include simple analgesics (i.e. ibuprofen, aspirin or paracetamol) or a triptan with or without paracetamol or an NSAID. Oral triptans (e.g. sumatriptan) are recommended unless vomiting restricts treatment. Anti-emetics (e.g. metoclopramide or prochlorperazine) should be considered even in the absence of vomiting.

B.1.3.4.2 Guidelines for prophylactic treatment of migraine in clinical practice

A frequency of 4 or more MHDs per month is associated with significant disability and patients who report this frequency of migraine attacks are eligible for preventive therapy [60]. The goal of preventive therapy in migraine is to decrease the overall clinical characteristics of migraine including frequency, intensity, and duration of attacks; to improve responsiveness to acute therapy; and to reduce migraine-related disability while avoiding occurrence of MOH [15, 33, 61-63]

A simplified flowchart of the clinical care pathway for the prophylaxis of migraine is depicted in

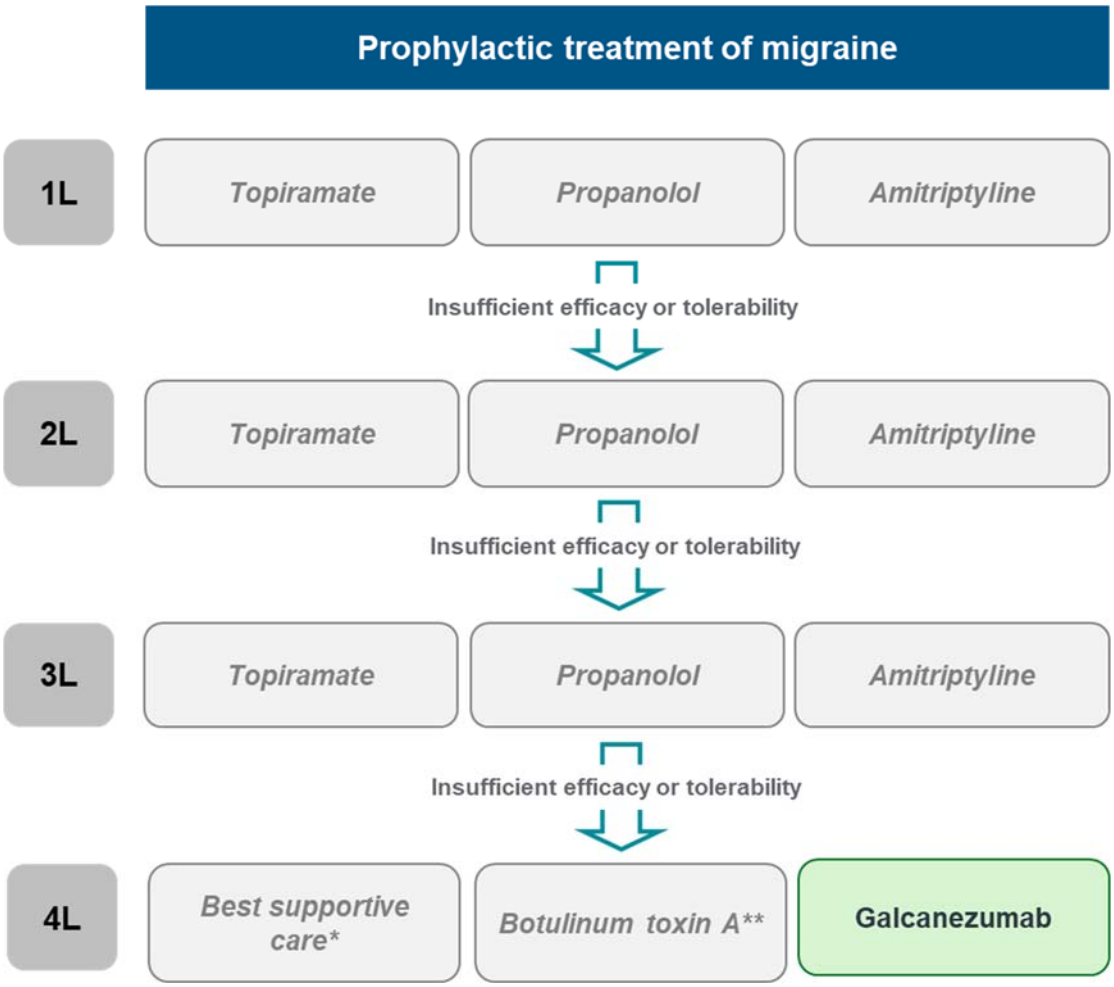
Figure 2**Error! Reference source not found.**. This is based on the guidelines listed below relevant to clinical practice in the UK for the treatment of patients with migraine:

1. NICE clinical pathway for the diagnosis and management of headaches in over 12s (CG150; last updated in November 2015) [64].

2. British Association for the Study of Headache: National headache management system for adults (2019) [60]

This pathway has been validated by Eli Lilly commissioned market research conducted on [redacted] based in the UK and has been adapted to reflect current clinical practice [39].

Figure 2 Pharmacological treatments for the prophylaxis of migraine *in UK clinical practice*



*includes acute treatments such as triptans, analgesics and antiemetics **licensed for the treatment of chronic migraine only

The best supportive care for management of migraine includes acute treatments that can alleviate symptoms within ~2 hours of the attack e.g. analgesics, triptans and antiemetics [65]. BASH guidelines recommend use of a stratified approach based on severity of attack versus a stepped approach based on evidence supporting better health related outcomes and lower indirect costs [66, 67].

The current NICE guidelines recommend topiramate, propranolol and amitriptyline as first-, second- and third-line preventive treatment options [64]. These may be sequenced in any order based on the patient's preference, comorbidities and the risk of AEs. The decision to move to a next line of preventive treatment is based on lack of efficacy or poor tolerability. Patients should be reviewed every 6 months to assess a need for continuation of prophylaxis. For patients with chronic migraine who have a history of 3 or more failed oral treatments, botulinum toxin A is recommended as a 4th line treatment [6].

In addition, the BASH 2019 guidelines for the management of headache in adults also list candesartan and CGRP inhibitors (i.e. erenumab, fremanezumab and galcanezumab) as

recommended treatments for episodic and chronic migraine without specifying the line of treatment where they would be applicable [60].

Galcanezumab is not expected to be used in treatment-naïve patients due to the low cost and long-term experience with oral preventive treatments. However, while propranolol, amitriptyline, and topiramate are effective, rates of adherence and persistence to these treatments decrease over time necessitating the need for additional therapies as 4th-line and later-line treatments [68]. This submission therefore positions galcanezumab as a treatment option for migraine patients who have a history of ≥3 prior preventive treatment failures to address a significant unmet need in a population who currently lack alternative treatment options. It should be noted that while NICE guidelines also recommend botulinum toxin A as a treatment option for this population, it is restricted to patients with chronic migraine only, requires specialist training for its administration and most importantly, is not available across all hospitals in the UK [12].

B.1.3.4.4 Limitations of current treatments

There is expert consensus that currently available preventive drugs for the management of migraine are not ideal [69]. These treatments are supported by poor quality evidence, limited efficacy and lack of proven efficacy in chronic migraine [69]. For example, patients receiving topiramate report paraesthesia, fatigue, and cognitive difficulties including problems with memory, language, and concentration/attention [70]. The cognitive AEs are most likely to cause discontinuation and are a major contributor to non-adherence [71]. Propranolol is associated with AEs such as fatigue, sleep disorders, depression and decreased exercise tolerance [72]. There is also a risk that β-blockers may exacerbate angina or myocardial infarction if discontinued abruptly [73]. Given the higher rates of comorbid depression and CVD in people with migraine, these AEs may be of concern and prevent its use in a large proportion of the migraine population. In addition, these medications often require dose titration and special laboratory monitoring; and carry special precautions, warnings, or contraindications [74]. While titration may limit the occurrence of AEs, it can also delay the onset of effect of the medication. Preventive medications may take 6–8 weeks to demonstrate efficacy and up to 6 months for full efficacy to be realised [73]. As such, extended periods of titration could have a negative impact on adherence. A number of drug-drug interactions are associated with topiramate, propranolol, and amitriptyline that may compromise the effectiveness of migraine prevention treatment or worsen AEs [75] Lastly, poor adherence and persistence in clinical practice have been noted as a substantial constraint to optimal care [76, 77]. As such, there is a need for more targeted preventive migraine medications with fewer AEs. A UK study estimated health state utilities associated with routes of administration and AEs for different migraine treatments in the general population (n=200) and in patients with migraine (n=200) [78]. No significant differences in health utility were found between oral daily route of administration and one injection a month. When AEs were added to the treatments, the scores associated with oral medicines showed greater levels of disutility. Of the 15 adverse events studied, the disutility scores for oral treatments were highest for fatigue (-0.069), insomnia (-0.063) and brain fog (-0.132). The results were similar in both patient groups. Prevalence of migraine in the general population group was similar to that seen in migraine epidemiology studies (14.6%) [78].

Discontinuation rates have been reported for propranolol (23%), amitriptyline (45%), and topiramate (43%) after 16 to 26 weeks of treatment. AEs were the most common reason cited for discontinuing therapy, including 17% for amitriptyline and 24% for topiramate [68]. [75]

Due to poor tolerability of current standard of care, the only alternative for many patients is to manage this disease with acute medications. While the use of acute medications is appropriate in the proper therapeutic context, the overuse of these medications puts patients at significant risk of disease progression and chronification [33, 40, 79].

As migraine frequency increases, so does the impact on functioning, leading to the restriction or prevention of activities across multiple areas of life, such as work, daily obligations, family-related, friendships and social events, and leisure time [45, 80-82]. Notably, HFEM has been

acknowledged to be as debilitating as chronic migraine, and patients with medication overuse headache have been found to have higher levels of disability than those with chronic migraine [38, 45, 83]. Migraine-related disability is worse in patients with a history of failure/switching compared with those on their initial preventive agent regardless of monthly headache days [51] demonstrating that despite switching between different drugs, disability remains high; and support the need for more effective and better-tolerated preventive medications.

Healthcare resource utilisation is higher among patients with chronic migraine [84, 85]. The number of outpatient visits is nearly 2 times greater among patients with migraine versus patients without the disease, and this multiple is even greater when the condition is chronic [86-88]. In addition, migraine is the fourth-leading cause for emergency room visits where treatment continues to be suboptimal, with >35% of patients receiving opioids in this setting [89, 90].

Preventive medication has the potential to reduce headache-related disability, healthcare resource utilisation, and medication overuse, yet the current level of impaired functioning and disability in the migraine population remains high, indicating a continuing unmet medical need [76, 91-93]. In conclusion, currently available migraine preventives, make it difficult for clinicians and patients to achieve the treatment goals of (1) decrease attack frequency by 50% and decrease intensity and duration; (2) improve responsiveness to acute therapy; (3) improve function and decrease disability; and (4) prevent the occurrence of a medication overuse headache (MOH) and chronic daily headache'; due to the safety and tolerability profile of currently available options [33, 63, 94]. Therefore, the need for novel preventive agents specifically targeted to treat migraine has been recognised as an urgent unmet medical need by experts in the field [51, 95, 96]. Data indicates that optimal benefit may be gained by continuing preventive therapy for longer periods of time after patients become pain free [97]. However, this is not plausible for a substantial number of patients with current oral preventive treatments due to their limiting AEs [98]. Thus, for patients who are in need of migraine preventives, there is a substantial unmet need for a well-tolerated agent that can reduce the incidence of migraine attacks and improve daily functioning and quality of life [76].

B.1.4 Equality considerations

It is not anticipated that the provision (or non-provision) of galcanezumab would exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation tan on the wider population, or lead to recommendations that have an adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

The key clinical evidence for patients who have a history of ≥3 prior preventive treatment failures for this submission is primarily based on the CONQUER trial. The results are shown in , in which section B.2.7.3 CONQUER CM and EM subpopulations who failed ≥3 prior treatments presents the clinical evidence for chronic and episodic migraine patients who failed ≥3 treatments, respectively.

In total, the efficacy and safety of galcanezumab in migraine prophylaxis have been demonstrated in four randomized controlled trials (RCTs) and one open-label long-term study.

- **EVOLVE-1 (CGAG)**: phase III RCT (N=858) evaluating galcanezumab vs placebo in patients with episodic migraine [99, 100]

- **EVOLVE-2 (CGAH)**: phase III RCT (N=915) evaluating galcanezumab vs placebo in patients with episodic migraine [101, 102]

- **REGAIN (CGAI)**: phase III RCT (N=1,113) evaluating galcanezumab vs placebo in patients with chronic migraine [103, 104]

- **Study CGAJ:** phase III open-label long-term safety study (N=270) evaluating galcanezumab in patients with chronic or episodic migraine [105, 106]

- **CONQUER (CGAW)**: phase III RCT (N=462) evaluating galcanezumab vs placebo in patients with chronic or episodic migraine who have a history of 2-4 prior preventive treatment failures [2, 107]

All four randomized, double-blind, placebo-controlled trials met their primary objective, with statistically significant improvements from baseline on the primary endpoint of overall mean reduction of the number of monthly migraine headache days (MHDs) compared with placebo. Key results are shown in the paragraphs below.

In both episodic migraine studies (EVOLVE-1 and EVOLVE-2), galcanezumab 120mg treatment arm was superior to placebo in the reduction of the number of monthly MHDs (EVOLVE-1: mean change = -1.92, 95% confidence interval (CI): -2.48, -1.37, p<0.001; EVOLVE-2: mean change= -2.02, 95% CI: -2.55, -1.48, p<0.001) during the 6 months study period. All key secondary outcomes were also met, including:

- mean percentage of patients meeting ≥50% reductions in the number of monthly MHDs across the 6 months double-blind treatment period (EVOLVE-1: odds ratio = 2.63, 95% CI: 1.63,4.21, p<0.001; EVOLVE-2: odds ratio=2.60, 95% CI: 2.03, 3.32, p<0.001);

- reduction from baseline in the number of monthly MHDs with acute medication use over 6 months (EVOLVE-1: mean change = -1.81, 95% CI: -2.28, -1.33, p<0.001; EVOLVE-2: mean change=-1.82, 95% CI: -2.29, -1.36, p<0.001);

- improvement from baseline in functioning assessed via the migraine specific questionnaire MSQ Roles Function-Restrictive domain over 6 months (EVOLVE-1: mean change = 6.94, 95% CI: 4.67,9.22, p<0.001; EVOLVE-2: mean change=9.58, 95% CI: 7.37, 11.78, p<0.001); and

- change from baseline in patients' impression of disease severity measured by PGI-S rating over 6 months (EVOLVE-1: mean change = -0.28, 95% CI: -0.45, -0.11, p=0.001; EVOLVE-2: mean change=-0.33, 95% CI: -0.49, -0.17, p<0.001).

In the chronic migraine study REGAIN, galcanezumab 120mg arm was superior to placebo in the reduction of the number of monthly MHDs over the 3 months study period (mean change = -2.09, 95% CI: -2.92, -1.26, p<0.0001). In addition, all the key secondary outcomes except the patients' impression of disease severity scores were met in REGAIN. Key secondary endpoints results are shown below:

- mean percentage of patients meeting ≥50% reductions in the number of monthly MHDs across the 3 months double-blind treatment period (odds ratio = 2.09, 95% CI:1.56, 2.80, p<0.001);

- reduction in the number of monthly MHDs with acute medication use over 3 months (mean change = -2.51, 95% CI: -3.27, -1.76, p<0.001);

- improvement in functioning assessed via the migraine specific questionnaire MSQ Roles Function-Restrictive domain over 3 months (mean change = 5.18, 95% CI: 2.64, 7.72, p<0.001); and

- changes in patients' impression of disease severity measured by PGI-S rating over 3 months (mean change = -0.14, 95% CI: -0.52, -0.24, p=0.18);

The CONQUER trial was designed specifically to assess the efficacy and safety of galcanezumab in patients with 2-4 prior preventative medication category failures, among which a significant subset of patients had a treatment history of ≥3 prior preventive treatment failures (including all previous migraine preventive medications not just those considered in the standard-of-care categories). Patients previously failed an average of 3.5 individual migraine preventive medications based on lifetime history or 3.3 such medications if based on the past 10 years

The CONQUER study met its primary endpoint; galcanezumab 120mg was [redacted] to placebo in patients with treatment-resistant migraine in the overall mean reduction from baseline in the number of monthly MHDs [redacted]). In addition, all key secondary [redacted], including:

- mean percentage of patients meeting ≥50% reductions in the number of monthly MHDs across the double-blind treatment period (odds ratio = [redacted]);

- reduction in the number of monthly days (i.e. total number of days of medication use regardless whether it was a migraine headache day) with acute medication use over 3 months (mean change = [redacted]);

- improvement in functioning assessed via the migraine specific questionnaire MSQ Roles Function-Restrictive domain at month 3 compared to baseline (mean change = [redacted]); and

- changes in patients' impression of disease severity until the last-observation-carried-forward endpoint (mean change for galcanezumab (SE)= [redacted]); mean change for placebo (SE)=[redacted]);

The list of relevant clinical trials where the ITT or subgroup population or both are used for this submission is described in section B.2.2 . For patients who have a history of ≥3 prior preventive treatment failures, the clinical evidence is based on the CONQUER trial presented in B.2.7 Subgroup analysis. In addition, post-hoc analysis was conducted in subgroup of patients in REGAIN (galcanezumab 120mg treatment arm, N=36) [108](section B.2.7.5 REGAIN subpopulation who failed ≥3 prior treatments). One post hoc analysis was conducted for pooled subgroup patients from EVOLVE-1 and EVOLVE-2 (pooled galcanezumab 120mg treatment arm, N=30) for the 50% response rate during the 6-month study period, other endpoints were not evaluated due to small sample size (section B.2.7.5 REGAIN subpopulation who failed ≥3 prior treatments). No post hoc analyses were performed on patients who have a history of ≥3 prior

preventive treatment failures in study CGAJ, considering the limited sample size to perform any meaningful analyses.

Details of the pivotal trials and open-label long-term safety study and the key clinical endpoints results for the ITT population are provided in the appendices to reference the overall efficacy and safety data for galcanezumab in migraine prophylaxis.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant studies describing efficacy and safety of galcanezumab and botulinum toxin A for migraine prophylaxis in patients who have a history of prior preventive treatment failure. In total, the SLR identified 45 publications describing 16 unique RCTs, of which CONQUER and REGAIN trials were identified for galcanezumab. Out of the 16 trials, four RCTs were identified evaluating botulinum toxin A in the target population who had previously been unsuccessfully treated with preventive migraine treatments. Details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are described in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Table 4 provides a list of trials evaluating galcanezumab for the prophylaxis of migraine in chronic and episodic migraine patients, respectively. The trials include those identified by the clinical SLR (reported in Section B.2.1 and described in Appendix D) as well as those available to Eli Lilly as data on file. This submission is primarily based on clinical efficacy evidence from the CONQUER trial and supported by exploratory post hoc analyses from the REGAIN trial [104, 107, 108] for the chronic migraine subpopulation and one post hoc analysis for the 50% response rate for pooled EVOLVE-1 and EOLVE-2 episodic subpopulation who had a history of ≥3 prior preventive treatment failures.

Table 4 Overview of relevant clinical evidence informing the submission

Study (NCT number)	Presentation in submission	Primary Study References
Chronic Migraine		
CONQUER (NCT03559257)	Key evidence, described in Section B.2	Study CSR [2, 107]
REGAIN (NCT02614261)	Supportive evidence, described in Appendix O.	Detke *et al.* 2018 [103] Ruff *et al.* 2019 [108] Study CSR [104]
CGAJ (NCT02614287)	Supportive evidence, described in Appendix P.	Camporeale et al, 2018 Study CSR [105]
Episodic Migraine		
CONQUER (NCT03559257)	Key evidence, described in Section B.2	Study CSR [107]
EVOLVE-1 (NCT02614183)	Supportive evidence, described in Appendix M	Stauffer *et al.* (2018) [99] Stauffer *et al.* 2019 [109] Study CSR [100]
EVOLVE-2 (NCT02614196)	Supportive evidence described in Appendix N	Skljarevski et al 2018 [101] Stauffer *et al.* 2019 [109]

		Study CSR [102]
CGAJ (NCT02614287)	Supportive evidence, described in Appendix P	Camporeale et al, 2018 Study CSR [105]

Abbreviations: CSR, clinical study report

The REGAIN study in patients suffering from chronic migraine excluded patients who have a history of failure to respond to medications from ≥3 classes of migraine preventives defined as level A or level B evidence based on the American Academy of Neurology/ American Headache Society treatment guidelines [100, 102, 104, 108, 110, 111]. However, as patients were allowed to have switched to other treatments within the same class, REGAIN included patients who have previously failed to three or more migraine preventive treatments. Post hoc exploratory analyses in all patients regardless of the prior treatment classes revealed that galcanezumab is consistently efficacious and well-tolerated in patients with chronic migraine with ≥2 prior treatment failures due to efficacy and safety reasons [108].

The CONQUER trial was designed to enable a comprehensive clinical assessment of galcanezumab specifically in patients with a history of 2 to 4 standard-of-care migraine preventive medication category failures in the past 10 years due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months) and/or safety/tolerability reasons [107]. Patients with episodic and chronic migraine were both included in the CONQUER study. However, in line with the decision problem detailed in Section B.1.1, the data for these two populations is presented separately across the submission.

An overview of the clinical trials that were used to evaluate the effectiveness and safety of galcanezumab for migraine prophylaxis are presented in Table 5. Data for patients with ≥3 prior treatment failures are represented for the CONQUER and REGAIN studies and provide the inputs for the economic model.

Table 5. Overview of clinical trials evaluating efficacy and safety of galcanezumab in migraine prophylaxis

Study	CONQUER (NCT03559257)	REGAIN (NCT02614261)	EVOLVE-1 (NCT03559257)	EVOLVE-2 (NCT02614196)	Study CGAJ (NCT02614287)
Number of patients	N=462	N=1,113	N=858	N=915	N=270
	ITT **Safety** **GMB 120** 232 232 **PBO** 230 230	**ITT** **Safety** **GMB 120** 278 273 **GMB 240** 277 282 **PBO** 558 558	**ITT** **Safety** **GMB 120** 213 206 **GMB 240** 212 220 **PBO** 433 432	**ITT** **Safety** **GMB 120** 231 226 **GMB 240** 223 228 **PBO** 461 461	**ITT** **Safety** **GMB 120** 135 129 **GMB 240** 135 141
Study design	Phase III, multicentre, randomised, double-blind, parallel, placebo-controlled study. 3-months double blinded treatment + 3-months open-label treatment.	Phase III, multicentre, randomised, double-blind, placebo-controlled 3-months double blinded treatment + 9-months open-label treatment + 4 months post-treatment follow-up period	Phase III, multicentre randomised, double-blind, placebo-controlled, parallel group study. 6-month double blind treatment + 4- months post-treatment follow-up period	Phase III, multicentre, randomised, double-blind, placebo-controlled 6-months double blinded treatment + 4 months post-treatment follow-up period	Phase III, multicentre, randomised open-label study with 12 months open-label treatments and 4 months post-treatment follow-up.
Population	Patients aged 18-75 years inclusive who meet ICHD-3 criteria for a diagnosis of migraine with or without aura or chronic migraine, and who have previously	Patients aged 18-65 years inclusive who meet ICHD-3 beta criteria for chronic migraine (1.3) as confirmed in prospective baseline	Patients with episodic migraine aged 18 to 65 years inclusive who meet ICHD-3 beta criteria 1.1 or 1.2 as confirmed during a prospective	Patients with episodic migraine aged 18 to 65 years inclusive who meet ICHD-3 beta criteria 1.1 or 1.2 as confirmed during a prospective	Patients aged 18 - 65 years inclusive who meet ICHD-3 beta criteria for episodic or chronic migraine (1.1, 1.2 or 1.3) and have an

	failed 2 to 4 standard-of-care treatments (categories) for migraine prevention	period; migraine frequency established during prospective baseline period must be 15 or more headache days per month, of which at least 8 headache days have features of migraine headache, and at least one headache-free day per month	baseline period; migraine frequency established during prospective baseline period must be 4 to 14 migraine headache days and at least 2 separate migraine attacks per month)	baseline period; migraine frequency established during prospective baseline period must be 4 to 14 migraine headache days and at least 2 separate migraine attacks per month)	average of 4 or more migraine headache days per month for previous 3 months
Intervention(s)	Galcanezumab (120 mg/month) with Galcanezumab 240 mg loading dose	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month
Comparator(s)	Placebo for 3 months.	Placebo for 3 months.	Placebo for 6 months.	Placebo for 6 months.	-
Indicate if trial supports application for marketing authorisation	No	Yes	Yes	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes	No	No	Yes

Rationale for use/non-use in the model	Trial evaluated galcanezumab in target population described in the decision problem	Trial evaluated galcanezumab in target population described in the decision problem Post hoc of REGAIN subgroup of the target population was evaluated for three endpoints (see B.2.7.5 REGAIN subpopulation who failed ≥3 prior treatments	Trial evaluated galcanezumab in target population described in the decision problem but the sample size is too small to be evaluated on its own Post hoc of pooled EVOLVE-1 and EVOLVE-2 population was evaluated for one endpoint (50% response rate) (see B.2.7.6 EVOLVE-1 and EVOLVE-2 pooled subpopulation who failed ≥3 prior treatments)	Trial did not evaluate galcanezumab in target population described in the decision problem but the sample size is too small to be evaluated on its own Post hoc of pooled EVOLVE-1 and EVOLVE-2 population was evaluated for one endpoint (50% response rate) (see B.2.7.6 EVOLVE-1 and EVOLVE-2 pooled subpopulation who failed ≥3 prior treatments)	Trial did not evaluate galcanezumab in target population described in the decision problem Safety data is used in the model to adjust the discontinuation rate in the patients after 3 months
Reported outcomes specified in the decision problem	• Frequency of headache days per month o Overall mean change from baseline in monthly headache days • Frequency of migraine days per month	• Frequency of headache days per month o Overall mean change from baseline in monthly headache days • Frequency of migraine days per month	• Frequency of headache days per month o Overall mean change from baseline in monthly headache days • Frequency of migraine days per month	• Frequency of headache days per month o Overall mean change from baseline in monthly headache days • Frequency of migraine days per month	• Frequency of headache days per month o Overall mean change from baseline in monthly headache days • Frequency of migraine days per month

	o **Overall mean change from baseline in monthly MHDs** o **Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline** o **Proportion of patients with chronic migraine with ≥30% reduction in mean monthly MHDs from baseline** • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days	o **Overall mean change from baseline in monthly MHDs** o Proportion of patients with chronic migraine with ≥30% reduction in mean monthly MHDs from baseline • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days o Overall mean change from baseline in the number of monthly migraine headache hours	o Overall mean change from baseline in monthly MHDs o **Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline** • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days o Overall mean change from baseline in the number of monthly migraine headache hours	o Overall mean change from baseline in monthly MHDs o **Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline** • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days o Overall mean change from baseline in the number of monthly migraine headache hours	o Overall mean change from baseline in monthly MHDs o Proportion of patients with episodic or chronic migraine with ≥50% reduction in mean monthly MHDs from baseline • Severity of headaches and migraines • Number of cumulative hours of headache or migraine on headache or migraine days o Overall mean change from baseline in the number of monthly migraine headache hours

	o Overall mean change from baseline in the number of monthly migraine headache hours • Reduction in acute pharmacological medication use o **Overall mean change from baseline in the number of monthly days with acute headache medication use** • Analysis of treatment-emergent adverse events • Health-related quality of life o Changes from baseline at month 3 in: ▪ **MSQ v2.1 total score, Role**	• Reduction in acute pharmacological medication o Overall mean change from baseline in the number of monthly days with acute headache medication use • Analysis of treatment-emergent adverse events • Health-related quality of life o Changes from baseline at month 3 in: ▪ MSQ v2.1 total score, Role Function-Restrictive, Role Function-Preventive and Emotional Function domain scores	• Reduction in acute pharmacological medication o Overall mean change from baseline in the number of monthly days with acute headache medication use • Analysis of treatment-emergent adverse events • Health-related quality of life o Changes from baseline at month 3 in: ▪ MSQ v2.1 total score, Role Function-Restrictive, Role Function-Preventive and Emotional Function domain scores	• Reduction in acute pharmacological medication o Overall mean change from baseline in the number of monthly days with acute headache medication use • Analysis of treatment-emergent adverse events • Health-related quality of life o Changes from baseline at month 3 in: ▪ MSQ v2.1 total score, Role Function-Restrictive, Role Function-Preventive and Emotional Function	• Reduction in acute pharmacological medication o Overall mean change from baseline in the number of monthly days with acute headache medication use • Analysis of treatment-emergent adverse events • health-related quality of life o Overall mean changes from baseline during the treatment period: ▪ MSQ v2.1 total score, Role Function-Restrictive, Role Function-Preventive and Emotional

	Function-Restrictive, Role Function-Preventive and Emotional Function domain scores ▪ EQ-5D-5L	•		domain scores	Function domain scores
All other reported outcomes	• Health-related quality of life o Changes from baseline at 3 months in: ▪ MIDAS total score and individual items • WPAI • HCRU	• Health-related quality of life o Changes from baseline to month 3 in: ▪ MIDAS total score and individual items • HCRU	• Health-related quality of life o Changes from baseline to month 3 in: ▪ MIDAS total score and individual items	• Health-related quality of life o Changes from baseline to month 3 in: ▪ MIDAS total score and individual items	• Health-related quality of life o Overall mean changes from baseline: ▪ MIDAS total score and individual items • HCRU

Abbreviations: EQ-5D-5L: 5 level EuroQol 5 dimensions 5 levels questionnaire; GMB: galcanezumab; ICHD: International Classification of Headache Disorders; ITT: intention-to-treat; MHD: migraine headache days; MIDAS, migraine disability assessment; MSQ-v2.1: Migraine-Specific Quality of Life Questionnaire Version 2.1; PBO, placebo; WPAI: Work Productivity and Activity Impairment.

Outcomes informing the cost-effectiveness model are highlighted in **bold**

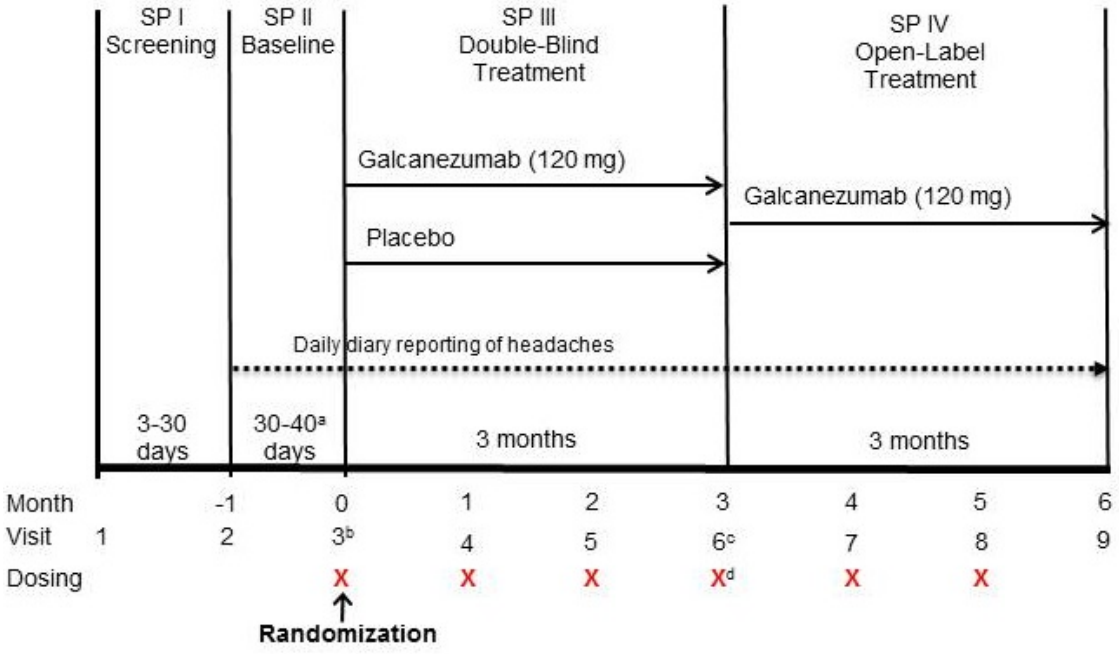
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Overview of Study Methodology of CONQUER trial

CONQUER was a Phase III, multicenter, randomised , double-blinded parallel, placebo controlled trial to assess the efficacy and safety of galcanezumab as migraine prophylaxis in patients who had failed 2 to 4 different migraine preventive medications categories in the past 10 years due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months) and/or safety/tolerability reasons. A total of 462 randomized patients received at least 1 dose of investigational product and were included in the ITT population, including 232 in the galcanezumab group, and 230 in the placebo group.

As shown in , the CONQUER trial was comprised of four study periods: a screening period of up to 30 days, a 1-month prospective baseline period, a 3-month double-blind treatment phase, and an optional 3 month open-label treatment phase.

Figure 3. Study design of CONQUER trial



Abbreviation: SP = study period.

a. Eligibility period determined between a minimum of 30 days and a maximum of 40 days, with up to 5 additional days to schedule randomization visit, if necessary.

b. Patients randomized to galcanezumab received a loading dose of 240 mg at the first injection only.

c. Patients randomized to placebo who entered the open-label treatment phase received a loading dose of galcanezumab 240 mg at the first injection only of Study Period IV.

d. First injection of the open-label treatment phase occurred at Visit 6 once all study procedures for the double-blind phase were completed

An overview of the study methodology of CONQUER is summarised in Table 6. Briefly, patients who met all eligibility requirements were randomized to one of two treatment groups in a 1:1 ratio to receive galcanezumab 120 mg/month or placebo. Patients randomized to the galcanezumab treatment group received a loading dose of 240 mg, administered as two injections of 120 mg

each. To preserve blinding, patients in both treatment groups received two injections of investigational product at the first dosing visit and single injections for the next two visits. Patients who completed the double-blind treatment phase could enter an open-label treatment phase for 3 months of treatment with galcanezumab. Patients continued to have efficacy and safety assessed, including daily completion of the ePRO diary and recording of acute headache medication use.

Table 6. Overview of Study Methodology of CONQUER

Trial number	NCT03559257
Trial design	Phase III, multicenter, randomized, double-blind, parallel, placebo-controlled
Method of randomisation	Patients who met all criteria for enrolment were randomised to treatment groups based on a computer-generated random sequence using an interactive web-response system.
Duration of study	3-month double-blind randomised period, followed by a 3-month open-label treatment period
Method of blinding	Patients, investigators and the sponsor were all blinded to treatment allocation.
Population	Patients with episodic or chronic migraine who had failed 2 to 4 standard-of-care migraine preventive medication categories in the past 10 years due to inadequate efficacy and/or safety/tolerability reasons.
Study site locations	64 study sites in 12 countries (Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, Netherlands, South Korea, Spain, United Kingdom, and United States).
Trial drugs	Galcanezumab 120 mg/month (with a loading dose of 240 mg) or placebo administered subcutaneously
Permitted and disallowed concomitant medications	• Concomitant use of acute medications to treat migraine was allowed, with restricted use of opioid- and barbiturate-containing medications (≤4 days per month) and steroids (a single dose of injectable steroids was allowed only once during the study, in an emergency setting) • Nutraceuticals and non-pharmacological interventions used for the prevention of migraine were not allowed during the study period. • Botulinum toxin A or B in the head or neck area for therapeutic use was not allowed within 3 months prior to Visit 2 • Nerve blocks or use of therapeutic devices, such as transcranial magnetic stimulation, in the head or neck area or for migraine prevention, was not allowed within 30 days before Visit 2.
Primary outcomes	Overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind treatment phase
Secondary outcomes	**Key secondary endpoints**: • All key secondary endpoints were tested both in the total population (episodic and chornic migraine) and in the episodic and chronic subpopulations, unless otherwise specified.

	• The overall mean change from baseline in the number of monthly headache days during the 3-month double-blind treatment phase • The percentage of patients with ≥50% reduction from baseline in monthly MHDs during the 3-month double-blind treatment phase • The mean change from baseline in the Role Function-Restrictive domain score of the MSQ v2.1 at Month 3 • The percentage of patients with ≥75% reduction from baseline in monthly MHDs during the 3 month double-blind treatment phase • The percentage of patients with 100% reduction from baseline in monthly MHDs during the 3 month double-blind treatment phase **Other secondary endpoints** • Changes from baseline at month 3 on the following measures: o MIDAS total score and individual items o MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores o HCRU and Employment Status o EQ-5D-5L o MIBS-4 o WPAI • Mean change from baseline in the PGI-S until the LOCF endpoint • The overall mean change from baseline in the number of monthly migraine attacks during the 3-month double-blind treatment phase in patients with episodic migraine • The percentage of chronic migraine patients with ≥30% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase • Analysis of: TEAEs, SAEs, discontinuation due to AEs, discontinuation rates, vital signs and weight, ECGs, laboratory measurements • In Study Period IV: o Mean changes in all continuous measures of efficacy, safety, and functional outcomes that were also assessed in the double-blind phase (SP III) o Among patients previously treated with galcanezumab who met 50% response criteria at Month 3 in the double-blind treatment phase, the proportion of patients who demonstrated 50% response for all 3 months in the open-label treatment phase
Pre-planned subgroups	Subgroup analyses for the efficacy and quality of life measures as pre-specified in the decision problem were conducted in subpopulations of patients with 3 or more prior preventive medication category failures. Subgroups from the ITT population, episodic subpopulation, chronic subpopulation, high frequency episodic (HFEM) subpopulation, and pooled HFEM and chronic subpopulation were included in the subgroup analysis.
Protocol amendments	There were no protocol amendments. There were 4 country-specific addenda to the protocol (Canada, Japan, Korea, and United Kingdom).

Abbreviations: AE, adverse event; ECG, electrocardiogram; EQ-5D-5L, European Quality of Life Questionnaire 5-Dimensions 5-Levels; HCRU, Health Care Resource Utilization; MHD, migraine headache days; MIBS-4, 4-item Migraine Interictal Burden Scale; MIDAS, Migraine Disability Assessment test; MSQ v2.1, Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-S, Patient Global Impression of Severity; SAE, serious adverse event; TEAE, treatment-emergent adverse event; WPAI, Work Productivity and Activity Impairment Questionnaire

B.2.3.1.1 Eligibility Criteria

B.2.3.1.1.1 Inclusion Criteria

Patients aged 18-75 years old at the time of screening were required to have a diagnosis of migraine as defined by ICHD-3 guidelines (1.1, 1.2, or 1.3), migraine onset prior to age 50 and a history of migraine headaches of ≥1 year with ≥4 MHDs and ≥1 headache-free day per month within the past 3 months [14].

Patients were required to have documentation of previous failure to 2 to 4 migraine preventive medication categories in the past 10 years from the following list due to inadequate efficacy (that is, maximum tolerated dose for at least 2 months) and/or safety/tolerability reasons

a) propranolol or metoprolol
b) topiramate
c) valproate or divalproex
d) amitriptyline
e) flunarizine
f) candesartan
g) botulinum toxin A or B (if documented that botulinum toxin was taken for chronic migraine)
h) medication locally approved for prevention of migraine

During the prospective baseline period, patients were required to have a frequency of ≥4 MHDs and ≥1 headache-free day per 30-day period and to demonstrate compliance with ePRO daily headache entries (as evidenced by completion of ≥80% of daily diary entries).

B.2.3.1.1.2 Exclusion Criteria

Patients were excluded from CONQUER if they were currently enrolled or had participated in another clinical trial involving an investigational product within the last 30 days or within 5 half-lives (whichever was longer) or had previously used galcanezumab or another CGRP antibody or CGRP receptor antibody. Patients were required to discontinue any other migraine preventive treatment prior to Visit 2 (≥3 months for botulinum toxin A and B, ≥30 days for nerve blocks or device use and ≥5 days for all other medications). Patients who had previously failed >4 migraine preventive medications from the prespecified list in the past 10 years were excluded from the trial.

Patients with a history of cluster headache or migraine subtypes and those who suffered other types of headache in the 3 months prior to randomization besides migraine, tension type headache, or medication overuse headache (as defined by IHS ICHD-3) were also excluded from the trial.

B.2.3.2 Study Outcomes

Assessments of migraine and headache-related endpoints were based on headache information captured via an electronic patient-reported outcomes (ePRO) diary. Starting from visit 2, patients logged in daily to the ePRO system to record the headache occurrence, duration, headache features, and severity and use of acute medication. Patients also maintained a headache

medication log which recorded acute medication name, dose, and date of use. The ePRO system also was used to collect information about migraine-associated symptoms (e.g. photophobia, phonophobia, nausea, and/or vomiting). The baseline period established data for comparison of endpoints during the double-blind treatment phase.

Table 7 provides a list of migraine and headache endpoint definitions, which is consistent among all trials including CONQUER, REGAIN, EVOLVE-1, EVOLVE-2 and CGAJ. Each month was defined as a 30-day period with migraine or headache measures normalised to a 30-day period from the actual visit intervals. Health outcome measures included several scales summarized in Table 8.

Table 7. Migraine and Headache Endpoint Definitions

Outcome	Definition
Migraine headache	A headache, with or without aura, of ≥30 minutes duration, with both of the following required features (A and B): A. ≥2 of the following headache characteristics: Unilateral location Pulsating quality Moderate or severe pain intensity Aggravation by or causing avoidance of routine physical activity AND B. During headache ≥1 of the following: Nausea and/or vomiting Photophobia and phonophobia
Probable migraine headache	A headache of ≥30 minutes duration, with or without aura, and meeting either ≥2 A criteria and zero B criteria, or 1 A criteria and ≥1 B criteria.
Migraine headache day (primary objective)	A calendar day on which a migraine headache or probable migraine headache occurred.
Migraine headache attack	Began on any day a migraine headache or probable migraine headache was recorded and ended when a migraine-free day occurred.
Non-migraine headache	All headaches of ≥30 minutes duration not fulfilling the definition of migraine or probable migraine.
Non-migraine headache day	A calendar day on which a non-migraine headache occurred.
Headache day	A calendar day on which any type of headache occurred (including migraine, probable migraine, and non-migraine headache).

Table 8. Health Outcome Measures and Definitions

Outcome	Definition

Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1)	• Self-administered, addresses physical and emotional impact of migraine on functioning, 4 -week recall period
	• 14 items that address 3 domains [112]
	  o Role Function-Restrictive: impact on performance of normal activities
	  o Role Function-Preventive: complete functional impairment
	  o Emotional Function: feelings related to disabling migraine
	• Responses: 6-point Likert-type scale, ranging from "none of the time" to "all of the time"
	• Raw scores: Sum of responses for each domain, Total raw score converted to a 0 to 100 scale
	
	Higher scores indicate a better health status, and a positive change in scores reflecting functional improvement [113, 114]

Migraine Disability Assessment (MIDAS):	• Patient-rated scale, quantifies headache-related disability over a 3-month period
	• 5 items that reflect the number of days reported as missed, or with reduced productivity at work or home and social events; days missed are not counted as days with reduced productivity
	• Responses: Number of days during the past 3 months of assessment, ranging from 0 to 90
	• Total score: Summation of the 5 numeric responses, range 0-270
	• Higher value is indicative of more disability, with 4 categories [115, 116]
	  o Grade I (0 to 5) is for little or no disability
	  o Grade II (6 to 10) is for mild disability
	  o Grade III (11 to 20) is for moderate disability
	  o Grade IV-A (21 to 40) is for severe disability
	  o Grade IV-B (41 to 270) is for very severe disability [45]

Health Care Resource Utilization and Employment Status (HCRU):	• Solicited by study site personnel while documenting patient responses about the number of healthcare events (all-cause and migraine-specific), recall since the patient's last study visit
	  o Baseline visit recall was over the last 6 months
	• Consists of 3 questions, asking about the number of:
	  o hospital emergency room visits (and whether due to migraine)
	  o overnight stays in a hospital (and whether due to migraine)
	  o any other visits with a healthcare professional (outside of visits associated with their participation in the clinical trial) (and whether due to migraine)
	• Also includes a question on employment status

Migraine Interictal Burden Scale (MIBS-4):	• Self-administered measure of burden related to headache in the time between attacks (I.e., days without a headache attack), 4 -week recall period

	• 4 items that address disruption at work and school, diminished family and social life, difficulty planning, and emotional difficulty • Responses: don't know/not applicable (0), never (0), rarely (1), some of the time (2), much of the time (3), or most or all of the time (3), (numerical scores associated with each response) • Total score: Summation across all 4 items, range from 0 to 12 • Higher score indicates greater interictal burden, with 4 categories [117, 118].
European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L):	• Patient-rated scale that assesses current health status, recall period is "today"; consists of 2 parts [119, 120] o Health utility: 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) ▪ Responses: no problems, slight problems, moderate problems, severe problems, extreme problems ▪ Health state index score (compute quality-adjusted life years for utilization in health economic analyses), including UK population-based index value and US population-based index value • Provides a single value on a scale from less than 0 to 1 Visual analog scale (VAS): Patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine).
Work Productivity and Activity Impairment Questionnaire (WPAI):	• Patient-reported instrument measures the impact on work productivity and regular activities attributable to a specific health problem which, in this study, was migraine; 7-day recall period [121] • 6 items that measure: o employment status o hours missed from work due to the specific health problem o hours missed from work for other reasons o hours actually worked o degree health affected productivity while working o degree health affected productivity in regular unpaid activities • 4 calculated scores: absenteeism, presenteeism, work productivity loss, activity impairment o Reported as impairment percentages, higher numbers indicate greater impairment, less productivity
Patient Health Questionnaire-9 (PHQ-9)	• Patient-completed instrument for detecting depression and measuring the severity of depressive symptoms over the past 2 weeks [Kroenke et al. 2001} o A threshold for identifying patients who may have depression (Major Depressive Syndrome) can be derived as described in the study SAP; however, a formal diagnosis of Major Depressive Disorder requires a more complete clinical evaluation

	• 9-items: anhedonia; depressed mood; trouble sleeping; feeling tired; change in appetite; guilt, self-blame, or worthlessness; trouble concentrating; feeling slowed down or restless; and thoughts of being better off dead or hurting oneself • Responses: 4-point scale (0=never, 1=several days, 2=more than half the time, 3=nearly every day) • Total Score: Ranges from 0 to 27, levels of depression severity defined as follows: o 0-4 minimal, 5-9 mild, 10-14 moderate, 15-19 moderately severe, and 20-27 severe
7-Item Generalized Anxiety Disorder Scale (GAD-7):	• Patient-completed questionnaire to screen for anxiety and measure the severity of anxiety symptoms over the past 2 weeks [122] o A threshold for identifying patients who may have an anxiety disorder can be derived as described in the study SAP; however, a formal diagnosis of Generalized Anxiety Disorder requires a more complete clinical evaluation • 7 items address the following: feelings of nervousness, uncontrollable worrying, excessive worrying, trouble relaxing, restlessness, irritability, and fearfulness • Responses: Rated on a 4-point scale (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day) • Total score ranges from 0 to 21, levels of anxiety severity defined as follows: 0-4 minimal, 5-9 mild, 10-14 moderate, and 15--21 severe

Abbreviations: SAP, statistical analysis plan

Safety outcomes were based on measurements of adverse events, laboratory data, vital signs and electrocardiograms (ECGs).

B.2.4 CONQUER statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Patient populations

The analysis populations in the CONQUER trial are defined in Table 9. Unless otherwise stated, all analyses were conducted according to the intent-to-treat (ITT) principle on the ITT population. That is, patients were analysed according to the treatment to which they were randomized.

The target population of interest for this submission is the ITT population who have a history of ≥3 prior preventive treatment failures. Detailed results are presented in section B.2.7.

Table 9. Analysis Populations in CONQUER trial

Population	Definition
Intent-to-treat	All patients who were randomized and received at least 1 dose of investigational product
ITT episodic subpopulation	All patients with episodic migraine who were randomized and received at least 1 dose of investigational product
ITT chronic subpopulation	All patients with chronic migraine who were randomized and received at least 1 dose of investigational product
Safety population	All patients who were randomised and received ≥1 dose of investigational product

Abbreviations: ITT, Intention-to-treat

B.2.4.2 Analysis Specifications and Adjustments for Covariates

Table 10 provides an overview of the predetermined statistical analyses in CONQUER.

Treatment effects for the double-blind treatment phase were evaluated based on an overall 2-sided significance level of 0.05 for all efficacy and safety analyses. The 95% confidence intervals (CIs) or standard errors for the difference in Least Squares Means (LSM) between treatment groups are presented. When change from baseline was assessed, a patient was included in the analysis only if the patient had a baseline and at least one post-baseline measurement.

Table 10. Predetermined statistical analyses in the CONQUER trial

Hypothesis objective	The primary efficacy objective of this study was to test the hypothesis that galcanezumab 120 mg per month with a 240-mg loading dose was superior to placebo in the prevention of migraine headache days in patients with treatment-resistant migraine (i.e. patients with a history of failure to 2-4 medication categories).
Sample size and Power calculation	The study planned to enroll approximately 420 patients. With the assumption of a 10% discontinuation rate and an effect size of 0.39, it is estimated that this sample size will provide approximately 96% power that galcanezumab will separate from placebo at a 2-sided significance level of 0.05 for the ITT population in this study.
Statistical analysis for efficacy endpoints	• For continuous efficacy variables with repeated measures, a restricted maximum likelihood based using mixed model repeated measures (MMRM) was used all the longitudinal observations at each post-baseline visit. Unless otherwise specified, the MMRM included the fixed, categorical effects of treatment, baseline migraine frequency category, pooled country, month, and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value and baseline value-by-month interaction. • For continuous efficacy variables without repeated measures, an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation was used, which contains the main effects of treatment, baseline migraine headache day frequency category, and pooled country, as well as the continuous fixed covariate of baseline.

	Type III sum-of-squares for the Least Squares Means (LSMeans) was used for the statistical comparisons. • For binary variable with repeated measures, the generalized linear mixed model (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis was used. The GLIMMIX models for the repeated binary outcomes included the fixed, categorical effects of treatment, month, baseline migraine frequency category, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value. When the fixed covariate of the continuous baseline value was the number of monthly MHDs, the baseline migraine frequency category was excluded. Pooled country and the baseline value-by-month interaction were excluded from the model in order to increase the likelihood of convergence. • For categorical variables without repeated measures, comparisons between treatment groups was performed using logistic regressions with the same model terms as the ANCOVA model.
Adjustment for multiplicity	For the primary and key secondary endpoints, type I errors due to multiple testing was adjusted by using a gatekeeping hierarchical approach at a 2-sided alpha level of 0.05. If the null hypothesis was rejected for the primary endpoint, key secondary endpoints were to be sequentially tested as follows: • MHD reduction in EM + CM • MHD reduction in EM • 50% response in EM + CM • 50% response in EM • MSQ RR in EM + CM • MSQ RR in EM • 75% response in EM • 100% response in EM • 75% response in EM + CM • 100% response in EM + CM No adjustments were made for multiplicity for analyses of the other secondary or tertiary endpoints.
Health outcomes/ HRQoL analyses	• MSQ v2.1, MIDAS, MIBS-4, WPAI, EQ-5D-5L, PHQ-9, and GAD-7 were evaluated using MMRM (for repeated measures) or an ANCOVA model (for single post baseline measures) • Binary indicators were used for major depressive disorder (PHQ-9) and anxiety (GAD-7) and analysed using GLIMMIX method. For PHQ-9 overall level of depression severity and GAD-7 overall level of anxiety severity, as the severity categories do not follow normal distribution, the treatment comparison was evaluated using Kruskal–Wallis test. • As HCRU data are count data with excess zeros for migraine patients, HCRU data were summarized for the number of events per 100 patient years. Wilcoxon signed-rank test was performed for

	comparisons within treatment group and Kruskal-Wallis test for comparisons between treatment groups [123, 124].
Safety analysis	• For continuous safety variables with repeated measures, MMRM methods will be used, as well as an ANCOVA model with LOCF imputation if deemed appropriate. • For safety categorical variables, comparisons between treatment groups were performed using Fisher's exact test as baseline migraine frequency was not expected to have an impact on the safety profile and does not have an impact on baseline measures.
Handling of dropouts or missing data	Two statistical approaches to handling missing data were used as appropriate: • Repeated measures analyses: model parameters were simultaneously estimated using restricted likelihood estimation incorporating all the observed data. Estimates have been shown to be unbiased when data are missing at random • ANCOVA/ANOVA model using change from baseline to last-observed-carried-forward (LOCF) endpoint
Handling of missing diary data	In calculating the number of MHDs for each monthly interval, the number of MHDs was normalised to a 30-day period by multiplying the number of MHDs by (30/x) where 'x' was the total number of non-missing diary days in the monthly interval. • This approach to missing ePRO diary data assumed that the rate of migraine headache per day was the same for days with missing and non-missing ePRO diary days. • The same approach was also applied to secondary and exploratory efficacy measures that were derived from ePRO data as well as for the ePRO diary data collected during the open-label treatment period. For the derivation of the number of monthly migraine attacks, the LOCF method was used to impute the missing ePRO diary days. The imputation was carried out for all the missing diary days between the first non-missing to the last day • If the patient was migraine headache-free on the day before the missing ePRO diary day, this was carried forward as no MHD until the actual next non-missing diary day. • If the day before the missing ePRO diary day was an MHD, then it was carried forward as MHD until the next non-missing diary day. If the diary compliance rate for a monthly interval was ≤50%, then all endpoints to be derived from the ePRO diary data for that 1-month period were considered missing.

Abbreviations: ANOVA, analysis of variance; ANCOVA, analysis of covariance; CM, chronic migraine; EM, episodic migraine; ePRO, electronic patient reported outcome; EQ-5D-5L, 5-level EuroQoL 5 dimensions test; GAD-7, 7-item generalised anxiety disorder score; GLIMMIX, generalized linear mixed model; HCRU, healthcare resource utilisation; LOCF, last observation carried forward; MHD, migraine headache day; MIBS-4, 4-item migraine interictal burden score; MIDAS, migraine disability assessment; MMRM, mixed model repeated measures; MSQ, migraine-specific quality of life questionnaire; PHQ-9, 9-item patient health questionnaire; REML, restricted maximum likelihood

B.2.4.3 Subgroup Analyses in the Clinical Trials

Subgroups in the CONQUER trial were analysed for the primary efficacy measure for the ITT patients in the double-blind treatment phase. Subgroup variables for the primary efficacy measure included:

- Sex
- Race
- Age
- Region
- Baseline migraine frequency category
- Number of failed preventive migraine medication categories in the past 10 years.

The subgroup-by-treatment interaction was tested at a 2-sided 0.10 significance level. Treatment group differences were evaluated within each category of the subgroup variable.

Key endpoints for the subgroups from CONQUER ITT are shown in Section B.2.7 Subgroup analysis, and the subgroups from CONQUER ITT population are summarised in Table 11.

Table 11. Pre-specified and post hoc analysis of key outcomes for the included CONQUER ITT subgroups

Analysis\Population	EM	CM	3+ prior preventive category failures	EM with 3+ prior preventive category failures	CM with 3+ prior preventive category failures	HFEM with 3+ prior preventive category failures
Primary efficacy endpoint						
Monthly migraine headache days (MHDs)	Pre-specified	Pre-specified	Pre-specified	Pre-specified	Pre-specified	Post-hoc
Key Secondary endpoints						
Monthly headache days	Pre-specified	Post-hoc	Post-hoc	Post-hoc	Post-hoc	Post-hoc
Monthly Migraine Headache Hours	Pre-specified	Post-hoc	Pre-specified	Post-hoc	Post-hoc	Post-hoc
Monthly migraine headache days with acute headache medication use	Pre-specified	Pre-specified	Pre-specified	Pre-specified	Pre-specified	NA
Patient Global Impression (PG-I) of Severity Rating	Pre-specified	Post-hoc	Post-hoc	Post-hoc	Post-hoc	Post-hoc

Analysis\Population	EM	CM	3+ prior preventive category failures	EM with 3+ prior preventive category failures	CM with 3+ prior preventive category failures	HFEM with 3+ prior preventive category failures
50% Response MHD	Pre-specified	Post-hoc	Pre-specified	Pre-specified	Pre-specified	Pre-specified
30% Response MHD	NR	Pre-specified	NR	NR	Pre-specified	NR
Health outcomes						
MSQ Total Score	Pre-specified	Post-hoc	Pre-specified	Pre-specified	Pre-specified	Pre-specified
EQ-5D-5L health state index (UK)	Pre-specified	Post-hoc	Pre-specified	Pre-specified	Pre-specified	Pre-specified

Abbreviations: ITT=intention-to-treat; EM=episodic migraine; CM=chronic migraine; HFEM= high frequency episodic migraine; NA=Not available; NR= not relevant to the decision problem

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The accuracy and reliability of the CONQUER clinical trial data were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the sponsor. In addition, an independent Data Monitoring Committee (DMC) was established with the responsibility of safeguarding the interests of study participants.

Randomisation in the trial was successfully carried out such that baseline characteristics of patients randomised were well balanced across treatment groups. Patient withdrawals during the study period were accounted for with pre-defined, standard censoring methods. Patients and investigators remained blinded throughout the trial, and all outcome assessments were conducted in accordance with trial validated methodology and were based on the ITT principle.

A summary of the quality assessment for the CONQUER trial is presented in **Table 12**. Details of assessment for REGAIN, EVOLVE-1, EVOLVE-2 and CGAJ are described in Appendix M-P.

Table 12 Quality assessment of relevant clinical evidence

Study Question	CONQUER trial (NCT03559257)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No

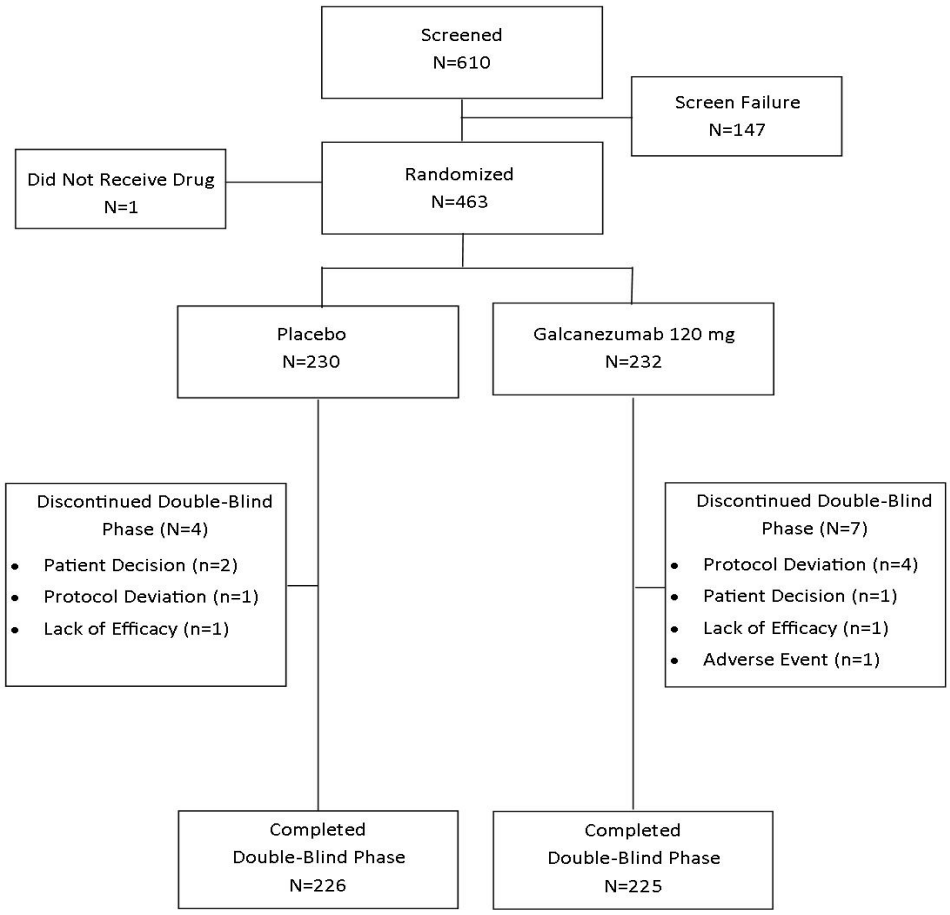
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Evidence for clinical effectiveness results in CONQUER

B.2.6.1 Intent-to-treat (ITT) population

A total of 610 patients entered the study and 147 patients failed screening due to not meeting enrolment criteria. A total of 463 patients were randomized. One patient that was a screen failure was inadvertently randomized and immediately discontinued. Thus, a total of 462 randomized patients received at least 1 dose of investigational product and were included in the ITT population Completion rate was high with [redacted] completing the double-blind treatment phase, including [redacted] in the galcanezumab group, and [redacted] in the placebo group. Patient disposition is summarised in Figure 4. Reasons for study drug discontinuation included protocol deviation (in patients with chronic migraine only), patient decision, lack of efficacy or adverse events. 449 patients entered the open-label treatment phase, of which 432 (96.2%) completed the open-label phase including 217 (96.9%) in the prior galcanezumab group, and 215 (95.6%) in the prior placebo group.

Figure 4 Patient disposition through the double-blind treatment phase, intent-to-treat population.



B.2.6.2 Baseline Characteristics

The baseline characteristics for the CONQUER ITT population is presetned in this section. The baseline characteristics for the subgroup of patients from CONQUER and REGAIN who have a history of ≥3 prior preventive treatment failures are included in Appendix L.

In the ITT population, the treatment groups were generally well balanced with regard to demographic characteristics of sex, race, age, region, and body mass index, with no [redacted]. Key baseline disease characteristics are summarized in Table 13. Patients were [redacted] and from [redacted] the mean age was [redacted] years old. Overall, treatment groups were balanced with respect to baseline disease characteristics, with [redacted] between treatment groups on any baseline disease characteristics. In order to meet study eligibility criteria, patients needed to have a history of documented treatment failure of 2 to 4 standard-of-care migraine preventive medication categories in the past 10 years. Most patients had [redacted] of these prior medication category failures. In addition, considering all previous migraine preventive medications taken not restrictied to the standard-of-care categories, patients previously failed an average of [redacted] individual migraine preventive medications based on lifetime history at baseline, had had ana average of [redacted] previous medications in the past 10 years.

Table 13 Summary of demographic characteristics in ITT population

Characteristic	Placebo (N=230)	GMB 120 mg (N=232)	Total (N=462)
Demographic characteristics			
Age (years)			
Mean (±SD)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Race, n (%)			
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Body Mass Index (kg/m^2)			
Mean (±SD)	[redacted]	[redacted]	[redacted]
Region, n (%)			
North America	[redacted]	[redacted]	[redacted]

Europe	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]
Disease characteristics			
Qualifying preventive medication failures in past 10 years[a], n (%)			
2 medication failures	[redacted]	[redacted]	[redacted]
3 medication failures	[redacted]	[redacted]	[redacted]
4 medication failures	[redacted]	[redacted]	[redacted]
Total number of failed individual preventive meds lifetime, mean (±SD)	[redacted]	[redacted]	[redacted]
Total number of failed individual preventive meds past 10 years, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of monthly headache days, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of monthly MHDs, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of monthly migraine attacks, mean (±SD)	[redacted]	[redacted]	[redacted]
MSQ Role Function-Restrictive domain, mean (±SD)	[redacted]	[redacted]	[redacted]
MIDAS total score, mean (±SD)	[redacted]	[redacted]	[redacted]
Duration of migraine illness, years, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of comorbidities, mean (±SD)	[redacted]	[redacted]	[redacted]
PGI-S, mean (±SD)	[redacted]	[redacted]	[redacted]

Abbreviations: ITT = intent-to-treat; N = number of ITT patients; n = number of patients within each specific category; SD = standard deviation. PGI-S, Patient Global Impression – Severity; meds,

medications; MHDs, migraine headache days; MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality of Life Questionnaire; SD, standard deviation; yrs, years.

a. Based on any medications taken for migraine prevention in the patient's lifetime; not limited to standard-of-care treatments from inclusion criterion. Failure defined as discontinuation due to no response/inadequate response, or medical history event (safety/tolerability). Contraindications did not count as treatment failures.

B.2.6.3 Clinical Efficacy Results

B.2.6.3.1 Summary of key outcomes

The primary and relevant secondary outcomes are presented for the ITT population as well as for the episodic migraine and chronic migraine subpopulations, respectively. A summary of the outcomes included in this submission is shown in Table 14.

Table 14 Efficacy and health outcomes presented in this submission and the relevant sections

Analysis\Population	ITT	EM	CM
Primary efficacy endpoint			
Monthly migraine headache days	B.2.6.3.2 Primary	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
Key Secondary endpoints			
Monthly headache days	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
Monthly Migraine Headache Hours	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
Monthly migraine headache days with acute headache medication use	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
PG-I of Severity Rating	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
50% Response MHD	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
30% Response MHD	Not relevant	Not relevant	B.2.6.3.4 ITT chronic and episodic sub-populations
Health related quality of life outcomes			
MSQ Total Score	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and	B.2.6.3.4 ITT chronic and

Analysis\Population	ITT	EM	CM
		episodic sub-populations	episodic sub-populations
MSQ Role Function-Restrictive	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
MSQ Role Function-Preventive	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
MSQ Role Function-Emotional	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations
EQ-5D-5L health state index (UK)	B.2.6.3.3 Key secondary outcomes in ITT	B.2.6.3.4 ITT chronic and episodic sub-populations	B.2.6.3.4 ITT chronic and episodic sub-populations

Abbreviations: CM= Chronic Migraine; EM=Episodic Migraine; EQ-5D-5L= EuroQol 5 Dimension 5 Level questionnaire; ITT=Intent-to-treat; MHDs= Monthly Migraine Headache days; MSQ= Migraine-Specific Quality of Life Questionnaire; NA=not available; PG-I=Patient Global Impression; UK= United Kingdom

B.2.6.3.2 Primary Outcome in ITT

The primary objective of the study was met. The overall mean reduction from baseline in the number of monthly MHDs in the ITT population during the double-blind treatment phase was [redacted] for galcanezumab compared with [redacted] (Table 15). Results at each month are shown in

Figure **5** for ITT population.

Table 15 Change from baseline in the number of monthly migraine headache days during the 3-month double-blind phase

	Placebo (N= 228)	GMB 120mg (N=230)
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
LS Mean Difference vs. placebo (SE)	-	[redacted]
95% CI	-	[redacted]
***P*-value vs. placebo**	-	[redacted]

Abbreviations: CI=confidence interval; GMB=Galcanezumab; LS=least square; SD=standard deviation; SE=standard error

[a] Baseline values are for the entire ITT population ([redacted])

Figure 5 Change from baseline in the number of monthly migraine headache days in ITT population

*** denotes p<.001. At each month, comparisons were also p<.0001.

Abbreviations: GMB=galcanezumab; LS=least square; SE=standard error.

B.2.6.3.3 Key secondary outcomes in ITT

Efficacy outcomes

All the secondary headache related efficacy endpoints were [redacted] as shown in Table 16.

Compared with placebo, galcanezumab was associated with [redacted] from baseline in the overall number of monthly headache days, monthly headache and migraine headache hours, reduced number monthly migraine headache days with acute medication use and headache severity measured by PGI-S rating (Table 16).

The mean percentage of patients with ≥50% reduction from baseline in monthly MHDs during the 3-month double-blind phase was [redacted] greater in the galcanezumab group compared to placebo ([redacted]) (Table 16)

Table 16 Key secondary efficacy outcomes in ITT population

	Placebo (N=228)	**GMB 120 mg (N=230)**
Change from baseline in the number of monthly headache days during the 3-month double-blind treatment phase		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]

Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Change from baseline in number of monthly migraine headache hours during the 3-month double-blind treatment phase		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Change from baseline in number of monthly migraine days with acute headache medication use during the 3-month double-blind treatment phase		
Baseline (SD) [b]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Change from baseline in PG-I of severity rating to LOCF endpoint [c]		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Proportion of patients with ≥50% reduction from baseline in monthly MHDs in ITT population during the 3-month double-blind treatment phase		
Responders, %	[redacted]	[redacted]
Odds Ratio (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: GMB=galcanezumab; ITT = intent-to-treat; CI = confidence interval; LOCF = last observation carried forward; LS = Least Squares; MHDs= Monthly Migraine Headache days; N = number of intent-to-treat subjects with non-missing baseline value and at least one non-missing post-baseline value; PGI-S = Patient Global Impression of Severity; SD = standard deviation; SE = standard error; vs. = versus.

[a] Baseline values are for the entire ITT population ([redacted])

[b] This evaluated any day on which acute headache medication was taken, regardless of whether it was a migraine headache day. Note that a separate post hoc analysis was conducted to evaluate migraine headache days with acute headache medication use

[c] For the PGI-S, the number of patients with a baseline and post-baseline value was [redacted] in the ITT population

Health related quality of life outcomes

Selected quality of life measures from the CONQUER trial relevant to the decision problem include changes from baseline at month 3 of the MSQ total score and MSQ Role Function-Restrictive domain and the changes until the LOCF endpoint for the EQ-5D-5L index. Compared with placebo, galcanezumab was associated with [redacted] indicating improvement of functional impairment due to migraine.

The EQ-5D-5L questionnaire is a patient-rated scale that assesses current health status at the time of questionnaire completion. There was [redacted] difference between treatment groups on mean change from baseline to LOCF endpoint in EQ-5D-5L health state index scores in the UK based population [redacted]) (Table 17).

Table 17 Key quality of life endpoints in ITT population

Mean change from baseline in MSQ Total Score at month 3		
	Placebo (N=222)	**GMB 120 mg (N=223)**
Baseline (SD)[a]	[redacted]	[redacted]
LS Mean Change (SE)	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]
95% CI on Difference	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Mean change from baseline in MSQ Role Function-Restrictive at month 3		
	Placebo (N=222)	**GMB 120 mg (N=223)**
Baseline (SD)[a]	[redacted]	[redacted]
LS Mean Change (SE)	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]
95% CI on Difference	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Mean change from baseline in EQ-5D-5L health state index (UK) to LOCF endpoint		
	Placebo (N=230)	**GMB 120 mg (N=232)**
Baseline US population based (SD) [a]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: CI= Confidence Interval; diff= difference; EQ-5D-5L= EuroQol 5 Dimension 5 Level questionnaire; GMB=galcanezumab; ITT= Intent-to-treat; LOCF = last observation carried forward; LS=least square; MSQ= Migraine-specific quality of life questionnaire; SE=standard error; SD=standard deviation; UK=United Kingdom; vs= versus

[a] Baseline values are for the entire ITT population ([redacted])

B.2.6.3.4 ITT chronic and episodic sub-populations

Key efficacy outcomes

The overall reduction from baseline in the number of monthly MHDs in both the chronic subpopulation and episodic subpopulation were significant in the treatment group compared to control during the double-blind treatment phase (Table 18).

In the chronic subpopulation, the galcanezumab group had [redacted](Table 18). Results of the response rates were as follows:

- The mean percentage of patients with ≥30% reduction from baseline in monthly MHDs during months 1 to 3 was [redacted] in the galcanezumab group compared to placebo ([redacted]) (Table 18).
- The mean percentage of patients with ≥50% reduction from baseline in monthly MHDs during months 1 to 3 was [redacted] in the galcanezumab group compared with placebo ([redacted]) (Table 18).

The episodic subpopulation demonstrated consistent results with the ITT population. The galcanezumab group had [redacted] greater overall mean reductions from baseline compared to placebo in all headache endpoints, including [redacted](Table 18). The mean percentage of patients with ≥50% reduction from baseline in monthly MHDs was [redacted] greater in the galcanezumab group compared with placebo ([redacted] (Table 18).

Table 18 Key headache related efficacy outcomes in ITT chronic and episodic subpopulations

	CM subpopulation		**EM subpopulation**	
	Placebo (N=96)	**GMB 120 mg (N=93)**	**Placebo (N=132)**	**GMB 120 mg (N=137)**
Change from baseline in the number of monthly migraine headache days (MHDs) over 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in the number of monthly headache days over 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in Number of Monthly Migraine Headache Hours over 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]

Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in number of monthly migraine days with acute headache medication use over 3 months				
Baseline (SD) [b]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in Patient Global Impression (PG-I) of Severity Rating until LOCF[c]				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ≥50% reduction from baseline in monthly MHDs				
Responders, %	[redacted]	[redacted]	[redacted]	[redacted]
Odds Ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients the with ≥30% reduction from baseline in monthly MHDs in chronic migraine subpopulation				
Responders, %	[redacted]	[redacted]	NA	NA
Odds Ratio (95% CI)	[redacted]	[redacted]	NA	NA
***P*-value vs. placebo**	XXX	[redacted]	NA	NA

Abbreviations: CI = confidence interval; CM= Chronic Migraine; EM= Episodic Migraine; GMB=galcanezumab; diff = difference; ITT = intent-to-treat; MHDs= Monthly Migraine Headache days; LOCF = last observation carried forward; LS = Least Squares; N = number of intent-to-treat subjects with nonmissing baseline value and at least one nonmissing postbaseline value; NA= Not available; PGI-S = Patient Global Impression of Severity; SD = standard deviation; SE = standard error; vs. = versus

[a] Baseline values are for the entire chronic subpopulation ([redacted]) or the episodic subpopulations ([redacted]), respectively

[b] This evaluated any day on which acute headache medication was taken, regardless of whether it was a migraine headache day. Note that a separate post hoc analysis was conducted to evaluate migraine headache days with acute headache medication use

[c] For the PGI-S, the number of patients with a baseline and postbaseline value was [redacted] in the ITT population, and [redacted] in the episodic subpopulation.

Health related quality of life outcomes

In the chronic subpopulation, there was a statistically [redacted]) (Table 19).

Results in the episodic subpopulation for MSQ total score (p<0.001) and EQ-5D-5L index (p=0.26) were consistent with the results observed in the ITT population (Table 19).

Table 19 Key quality of life outcomes of the ITT chronic and episodic subpopulations

	CM		EM	
	Placebo (N=95)	**GMB 120 mg (N=88)**	**Placebo (N=127)**	**GMB 120 mg (N=135)**
Mean change from baseline in MSQ Total Score at 3 months				
Baseline [a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean Change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in MSQ Role Function-Restrictive at 3 months				
Baseline [a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean Change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI on difference	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in EQ-5D-5L health state index (UK) to LOCF endpoint				
Baseline US population based (SD) [a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI=confidence interval; CM= Chronic Migraine; diff= difference; EQ-5D-5L= EuroQol 5 Dimension 5 Level questionnaire; EM= Episodic Migraine; GMB=galcanezumab; LOCF= last-observation-carried-forward; LS=least square; MSQ= Migraine-specific quality of life questionnaire; N = number of intent-to-treat subjects with nonmissing baseline value and at least one nonmissing postbaseline value; SE=standard error; SD=standard deviation; UK=United Kingdom; vs= versus

[a] Baseline values are for the entire chronic subpopulation ([redacted]) or the episodic subpopulations ([redacted]), respectively.

B.2.6.3.5 Long-term effectiveness of galcanezumab in CONQUER CM and EM patients

In CONQUER, the open-label phase started from month 4 to month 6 where both the placebo and the galcanezumab groups during the 3 month double-blind phase were treated with galcanezumab. The comparison between the month 6 efficacy outcomes to the month 3 outcomes for the prior placebo group and the prior galcanezumab treatment group are presented in this section.

Primary efficacy outcomes

In the ITT population, change in the number of monthly MHDs through to Month 6 indicates durability of treatment effect, with the prior galcanezumab group demonstrating further improvement from the double-blind treatment phase and the prior placebo group demonstrating a [redacted] in the first month after initiation of galcanezumab (

Figure 6 and

Table 20). This rapid improvement of the prior placebo group once initiated on open-label galcanezumab parallels the rapid improvement seen in the prior galcanezumab group during the double-blind treatment phase.

In the chronic subpopulation, the prior galcanezumab group demonstrated [redacted] phase and the prior placebo group demonstrated a [redacted] in the first month after initiation of galcanezumab (

Figure 6 and

Table 20). While both treatment groups had [redacted] from baseline in the number of monthly MHDs during the open-label treatment phase, the magnitude of reduction was [redacted] in the prior galcanezumab group.

In the episodic subpopulation, the difference between the episodic migraine treatment groups was [redacted] (

Figure 6 and

Table 20). A possible [redacted] [125]

Table 20 Change from baseline in the number of monthly migraine headache days at Month 6

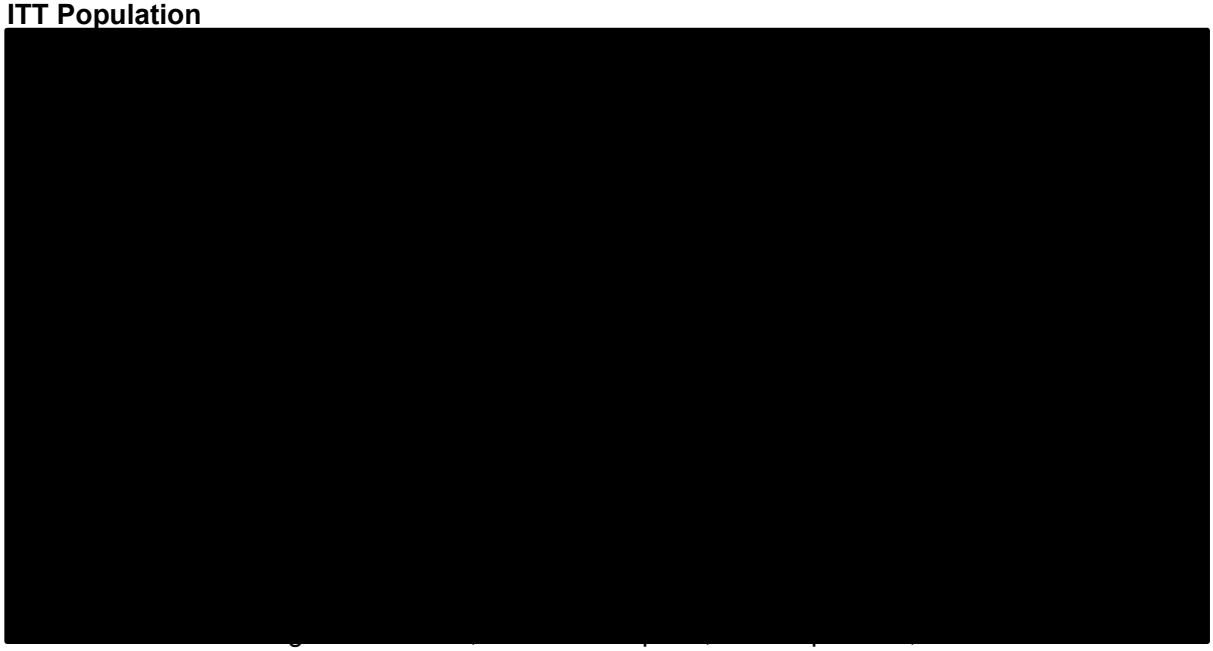
	ITT	CM	EM

	Prior Placebo (N=211)	Prior GMB (N=215)	Prior Placebo (N=88)	Pior GMB (N=84)	Prior Placebo (N=123)	Prior GMB (N=131)
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

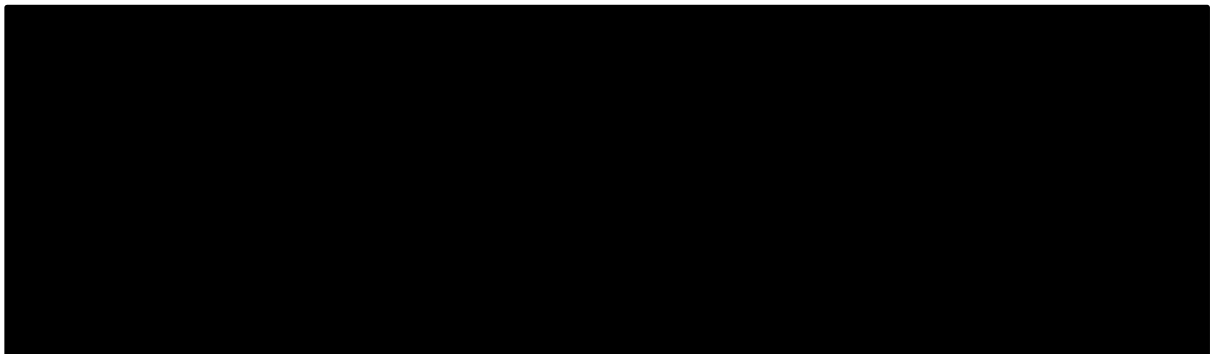
Abbreviations: CI=confidence interval; CM=chronic migraine; EM=episodic migraine; ITT= Intent-to-treat; GMB=Galcanezumab**;** LS=least square; SE=standard error; SD=standard deviation; vs= versus

Figure 6 Change from baseline in the number of monthly migraine headache days at Month 6

ITT Population



CM Subpopulation



*** denotes p<.001. At Months 1 and 3, comparisons were also p<.0001.
Abbreviations: GMB = galcanezumab; LS = least square; PBO = placebo; SE = standard error.

EM Subpopulation

*** p-values also <.0001.
Abbreviations: GMB = galcanezumab; LS = least square; PBO = placebo; SE = standard error.

Key secondary efficacy outcomes

In the ITT population and EM subpopulation, headache-related endpoints with galcanezumab treatment during the double-blind phase was further improved during the open-label phase. This

included the [redacted] (Table 21)

In the ITT population, [redacted]. Additionally, [redacted], which is considered a marker of clinically meaningful response. (Table 21)

In the chronic subpopulation, the mean reduction in the number of monthly days with use of acute headache medication observed with double-blind galcanezumab treatment was further [redacted] The percentage of patients in the prior galcanezumab group with at [redacted] Additionally, [redacted], which is considered a marker of clinically meaningful response in this subpopulation. (Table 21)

Table 21 Key headache related efficacy outcomes in ITT population, chronic subpopulation and episodic subpopulations at month 6

	ITT population		CM population		EM population	
	Prior placebo (n=211)	Prior GMB (n=215)	Prior Placebo (n=88)	Prior GMB (n=84)	Prior Placebo (n=123)	Prior GMB (n=131)
Change from baseline in the number of monthly headache days						
Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in Number of Monthly Migraine Headache Hours						
Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in Number of Monthly Days with Acute Headache Medication Use[b]						
Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in Patient Global Impression (PG-I) of Severity Rating until LOCF[c]						

Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ≥50% reduction from baseline in monthly MHDs						
Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ≥30% reduction from baseline in monthly MHDs						
Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM=chronic migraine; EM=episodic migraine; GMB=Galcanezumab; ITT= Intent-to-treat; LOCF = last observation carried forward; LS = Least Squares; MHDs= Monthly Migraine Headache days; N = number of intent-to-treat subjects with non-missing baseline value and at least one nonmissing postbaseline value; NA= Not available; PGI-S = Patient Global Impression of Severity

[a] This evaluated any day on which acute headache medication was taken, regardless of whether it was a migraine headache day. Note that a separate post hoc analysis was conducted to evaluate migraine headache days with acute headache medication use

[b] For the PGI-S, the number of patients with a baseline and postbaseline value was [redacted], and [redacted] in the episodic subpopulation.

Health related quality of life outcomes

In the ITT population and episodic subpopulation, the functional improvement on the [redacted].(Table 22)

In the ITT population and episodic subpopulation, at the end of the double-blind treatment phase, neither the [redacted]t. However, at the end of the open-label treatment phase, both the [redacted] from baseline on all UK population-based index values, ranging from [redacted]. (Table 22)

In the chronic subpopulation, the functional improvement on the MSQ total score and all domain scores with double-blind galcanezumab treatment was maintained or further improved during open-label treatment. (Table 22)

Table 22 Key quality of life outcomes of the ITT chronic and episodic subpopulations at Month 6

	ITT		CM		EM	
	Placebo (n=211)	**GMB (n=215)**	**Placebo (n=88)**	**GMB (n=84)**	**Placebo (n=123)**	**GMB (n=131)**
Mean change from baseline in MSQ Total Score						
Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline to LOCF endpoint in EQ-5D-5L health state index (UK)						
Month 3 (double-blind phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6 (open-label phase)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM=chronic migraine; EQ-5D-5L= EuroQol 5 Dimension 5 Level questionnaire; EM=episodic migraine; GMB=Galcanezumab; ITT= Intent-to-treat; LOCF = last observation carried forward; MSQ= Migraine-specific quality of life questionnaire; N = number of intent-to-treat subjects with nonmissing baseline value and at least one nonmissing postbaseline value; NA= Not available; UK= United Kingdom

B.2.7 Subgroup analysis

B.2.7.1 Patient populations for subgroup analysis

Patient subpopulations from the CONQUER trial relevant to the decision problem are defined in Table 23. Patients with 3 or more prior migraine preventive medication category failures may be considered in line with some definitions of refractory migraine, particularly for chronic migraine. Such patients have historically been more likely to be excluded from clinical trials of migraine preventive medications and as such are a subpopulation of clinical and scientific interest. Therefore, the target population of interest for this submission is the intention-to-treat (ITT) population who have a history of ≥3 prior preventive treatment failures.

Table 23. Analysis of subpopulations in CONQUER trial

Population	Definition
ITT patients with ≥3 prior preventive medication failures	A subpopulation of patients who have a history of ≥3 prior preventive treatment failures who were randomised and received ≥1 dose of investigational product
ITT patients with chronic migraine with ≥3 prior preventive medication failures	≥8 migraine headache days per 30-day period, with ≥15 headache days per 30-day period

ITT patients with episodic migraine with ≥3 prior preventive medication failures	<8 migraine headache days or less than 15 headache days per 30-day period
ITT patients with HFEM with ≥3 prior preventive medication failures	8 to <15 migraine headache days per 30-day period, with <15 headache days per 30-day period
Safety population	All patients who were randomised and received ≥1 dose of investigational product

Abbreviations: HFEM, high frequency episodic migraine; ITT, Intention-to-treat

The subpopulations included in this section include:

- CONQUER ITT patients with 3 or more prior preventive medication category failures
- CONQUER chronic and episodic migraine patients with 3 or more prior preventive medication category failures (B.2.7.3 CONQUER CM and EM subpopulations who failed ≥3 prior treatments)
- CONQUER high frequency episodic migraine (HFEM) patients with 3 or more prior preventive medication category failures, and post-hoc pooled analysis of the HFEM and chronic migraine patients with 3 or more prior preventive medication category failures (B.2.7.4 CONQUER HFEM and HFEM+CM subpopulations who failed ≥3 prior treatments)
- Post-hoc analysis of REGAIN (chronic patients) and one endpoint for EVOLVE (episodic patients) with 3 or more prior preventive medication category failures (B.2.7.5 REGAIN subpopulation who failed ≥3 prior treatments).

People with HFEM suffer 8-14 MHDs per month and are believed to suffer a burden of disease similar to people with chronic migraine [7-9]. While HFEM is not defined as a distinct clinical subgroup in the ICHD-3 guidelines, it has been proposed that the definition of chronic migraine be revised to include these patients [7, 10]. Thus, post-hoc analyses were conducted on pooled data from patients with HFEM and patients with chronic migraine, all of whom had a history of ≥3 prior preventive treatment failures.

Baseline characteristics for subgroup populations are reported in Appendix L.

B.2.7.2 CONQUER ITT population who failed ≥3 prior treatments

B.2.7.2.1 Primary outcome

In the ITT subpopulation of patients with 3 or more prior preventive medication failures, galcanezumab [redacted] reduced the overall mean number of monthly MHDs during the 3 month- double-blind treatment phase compared with placebo ([redacted]) (Table 24).

Table 24 Change from baseline in the number of monthly migraine headache days (MHD) in ITT patient with 3 or more prior preventive medication failures

	Placebo (n=86)	GMB 120mg (n=98)
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: CI=confidence interval; GMB=Galcanezumab; LS=least square; SE=standard error; SD=standard deviation; vs= versus

[a] Baseline values are for the entire the ITT subpopulation with 3+ prior preventive medication failures ([redacted])

B.2.7.2.2 Key secondary outcomes

Efficacy outcomes

In the ITT subpopulation of patients with 3 or more prior preventive medication failures, [redacted]) (Table 25).

In addition, the mean percentage of patients who [redacted] (Table 25).

Compared with placebo, galcanezumab was associated with a [redacted] (Table 25).

Table 25 Key secondary efficacy outcomes in ITT subpopulation with 3 or more prior preventive medication category failure

	Placebo (N=86)	GMB 120 mg (N=98)
Change from baseline in the number of monthly headache days over 3 months		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI		[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Change from baseline in number of monthly migraine headache hours over 3 months		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
Difference vs. placebo (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Change from baseline in number of monthly migraine days with acute headache medication use over 3 months		
Baseline (SD)[b]	[redacted]	[redacted]

Overall LS Mean (SE) from baseline	[redacted]	[redacted]
Difference vs. placebo (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Change from Baseline in PG-I of Severity Rating until LOCF[c]		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE) from baseline	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Proportion of patients with ≥50% reduction from baseline in monthly MHDs in ITT population over 3 months		
Responders, %	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Proportion of patients with ≥30% reduction from baseline in monthly MHDs in ITT population over 3 months		
Responders, %	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: GMB=galcanezumab; ITT = intent-to-treat; CI = confidence interval; LOCF = last observation carried forward; LS = Least Squares; MHDs= Monthly Migraine Headache days; N = number of intent-to-treat subjects with non-missing baseline value and at least one non-missing post-baseline value; PGI-S = Patient Global Impression of Severity; SD = standard deviation; SE = standard error; vs. = versus.

[a] Baseline values are for the entire the ITT subpopulation with 3+ prior preventive medication failures ([redacted])

[b] This evaluated any day on which acute headache medication was taken, regardless of whether it was a migraine headache day. Note that a separate post hoc analysis was conducted to evaluate migraine headache days with acute headache medication use

[c] For the PGI-S, the number of patients with a baseline and postbaseline value was [redacted] in the episodic subpopulation

Health related quality of life outcomes

In the ITT subpopulation of patients with 3 or more prior preventive medication category failures, the mean change from baseline in MSQ Total Score at Month 3 was [redacted] greater in the galcanezumab group compared with placebo [redacted] In addition, compared to placebo, the mean change from baseline in MSQ Role Function-Restrictive, -Preventive and -Emotional was also [redacted] However, there was no [redacted] between the two treatment groups for EQ-5D-5L index change [redacted] (Table 26).

Table 26 Key quality of life endpoints in ITT subpopulation with 3 or more prior preventive medication category failures

Mean change from baseline in MSQ Total Score at month 3		
	Placebo (N=84)	**Galcanezumab 120 mg (N=94)**
Baseline (SD)[a]	[redacted]	[redacted]

LS Mean Change (SE)	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value vs. placebo	[redacted]	[redacted]
Mean change from baseline in MSQ Role Function-Restrictive at month 3		
Baseline (SD)[a]	[redacted]	[redacted]
LS Mean Change (SE)	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value vs. placebo	[redacted]	[redacted]
Mean change from baseline in MSQ Role Function-Preventive at month 3		
Baseline (SD)[a]	[redacted]	[redacted]
LS Mean Change (SE)	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value vs. placebo	[redacted]	[redacted]
Mean change from baseline in MSQ Role Function-Emotional at month 3		
Baseline (SD)[a]	[redacted]	[redacted]
LS Mean Change (SE)	[redacted]	[redacted]
Diff. vs. Placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value vs. placebo	[redacted]	[redacted]
Mean change from baseline to LOCF endpoint in EQ-5D-5L health state index (UK)		
Baseline, US population based (SD)[a]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]
***P*-value versus placebo**	[redacted]	[redacted]

Abbreviations: LS=least square; SE=standard error; SD=standard deviation; CI=confidence interval; Q=quarter

[a] Baseline values are for the entire the ITT subpopulation with 3+ prior preventive medication failures ([redacted])

B.2.7.3 CONQUER CM and EM subpopulations who failed ≥3 prior treatments

B.2.7.3.1 Primary outcome

In both chronic migraine (CM) and episodic migraine (EM) patients with 3 or more prior preventive medication failures, galcanezumab [redacted] reduced the overall mean number of monthly

MHDs during the 3 month double-blind treatment phase compared with placebo for both sub-populations (for CM, mean change difference from placebo [redacted] (Table 27).

Table 27 Change from baseline in the number of monthly migraine headache days (MHD) in ITT patient with 3 or more prior preventive medication failures

	CM		EM	
	Placebo (n=42)	**GMB 120mg (n=42)**	**Placebo (N=44)**	**GMB 120 mg (N=56)**
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]		[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]

[a] Baseline mean values are for the entire the CM subpopulation with 3+ prior preventive medication failures ([redacted])

B.2.7.3.2 Key secondary outcomes

Efficacy outcomes

In the ITT subpopulation of CM patients with 3 or more prior preventive medication failures, the galcanezumab group had a [redacted] (Table 28).

In addition, the mean percentage of CM patients who [redacted] (Table 28).

In the ITT subpopulation of EM patients with 3 or more prior preventive medication failures, the galcanezumab group had a [redacted] (Table 28).

Compared to placebo, EM patients in the galcanezumab group achieved [redacted] (Table 28).

In the ITT subpopulation of CM and EM patients with 3 or more prior preventive medication failures, the galcanezumab group was associated [redacted] (Table 28).

Table 28 Changes in headache and migraine headache frequency in CONQUER trial: patients with episodic migraine who have a history of ≥3 prior preventive treatment failures

	CM patient with ≥3 prior treatment failures		EM patient with ≥3 prior treatment failures	
	Placebo (n=42)	**GMB(n=42)**	**Placebo (N=44)**	**GMB 120 mg (N=56)**
Change from baseline in the number of monthly headache days over 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]		[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in number of monthly migraine headache hours over 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in number of monthly migraine days with acute headache medication use over 3 months				
Baseline (SD)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE) from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in PG-I of Severity Rating until LOCF[c]				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ≥50% reduction from baseline in monthly MHDs over 3 months				

Overall responders, %	[redacted]	[redacted]	[redacted]	[redacted]
Odds Ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ≥30% reduction from baseline in monthly MHDs over 3 months				
Overall responders, %[a]	[redacted]	[redacted]	NA	NA
Odds Ratio (95% CI)	[redacted]	[redacted]	NA	NA
***P*-value vs. placebo**	[redacted]	[redacted]	NA	NA

Abbreviations: CI = confidence interval; diff = difference; ITT = intent-to-treat; LOCF = last observation carried forward; LS = Least Squares; N = number of intent-to-treat subjects with nonmissing baseline value and at least one nonmissing postbaseline value; PGI-S = Patient Global Impression of Severity; SD = standard deviation; SE = standard error; vs. = versus.

[a] Baseline mean values are for the entire the CM subpopulation with 3+ prior preventive medication failures ([redacted]

[b] This evaluated any day on which acute headache medication was taken, regardless of whether it was a migraine headache day. Note that a separate post hoc analysis was conducted to evaluate migraine headache days with acute headache medication use

[c] For the PGI-S, the number of patients with a baseline and postbaseline value was [redacted] in the chronic subpopulation with 3 or more medication failures; and [redacted] in the episodic subpopulation with 3 or more prior medication failures.

Health related quality of life outcomes

In the ITT CM subpopulation with a history of 3 or more prior preventive medication category failures, the mean change from baseline in MSQ Total Score at month 3 was [redacted] greater in the galcanezumab group compared with placebo [redacted]. In addition, compared with placebo, the mean change from baseline in MSQ Role Function-Restrictive, -Preventive and -Emotional, was also [redacted] greater for galcanezumab, indicating less functional impairment [redacted]. In the EM subpopulation with history of 3 or more prior preventive medication category failures, the mean change from baseline in [redacted] (Table 29).[redacted] (Table 29).

Table 29 Key quality of life endpoints in CM and EM subpopulations with 3 or more prior preventive medication category failures

	CM patient with ≥3 prior treatment failures		**EM patient with ≥3 prior treatment failures**	
Mean change from baseline in MSQ Total Score at 3 months				
	Placebo (N=41)	**GMB 120 mg (N=40)**	**Placebo (N=43)**	**GMB120 mg (N=54)**

Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]		[redacted]
Mean change from baseline in MSQ Role Function-Restrictive at 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in MSQ Role Function-Preventive at 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in MSQ Role Function-Emotional at 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in EQ-5D-5L health state index (UK) to LOCF endpoint				
	Placebo (N=43)	**GMB 120 mg (N=43)**	**Placebo (N=44)**	**GMB120 mg (N=56)**

Baseline based on US population (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value versus placebo**	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LS=least square; SE=standard error; SD=standard deviation; CI=confidence interval; Q=quarter

[a] Baseline mean values are for the entire the CM subpopulation with 3+ prior preventive medication failures ([redacted]

B.2.7.4 CONQUER HFEM and HFEM+CM subpopulations who failed ≥3 prior treatments

B.2.7.4.1 Primary outcome

In the ITT subpopulation of high frequency episodic migraine patients (HFEM) with ≥3 prior treatment failures, galcanezumab [redacted] reduced the number of monthly migraine headache days compared with placebo [redacted] (Table 30).

Compared with placebo, in the ITT subpopulation of high frequency episodic migraine or chronic migraine (HFEM + CM) with ≥3 prior treatment failures, galcanezumab also [redacted] reduced the number of monthly migraine headache days [redacted] (Table 30).

Table 30 Change from baseline in the number of monthly migraine headache days in HFEM and HFEM+CM patients with 3 or more prior preventive medication failures

	HFEM patient with ≥3 prior treatment failures		**HFEM or CM patient with ≥3 prior treatment failures**	
	Placebo (N=32)	**GMB 120 mg (N=48)**	**Placebo (N=74)**	**GMB 120 mg (N=90)**
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]		[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GMB=galcanezumab; HFEM= high frequency episodic migraine; CI = confidence interval; LS=lease square; SE= standard errors

[a] Baseline mean values are for the entire the CM subpopulation with 3+ prior preventive medication failures ([redacted])

B.2.7.4.2 Key Secondary outcome

Efficacy outcomes

In the ITT high frequency episodic migraine patients with ≥3 prior treatment failures [redacted] reduced the monthly headache days [redacted] and monthly migraine headache hours compared with placebo [redacted]. In addition, patients in the galcanezumab group achieved ≥30% and ≥50% [redacted] reduction in the monthly migraine headache hours [redacted] (Table 31)
In the pooled ITT high frequency episodic migraine and chronic migraine patients with ≥3 prior treatment failures, galcanezumab [redacted] the number of monthly headache days [redacted] and monthly migraine headache hours [redacted]. In addition, the proportion of patients who achieved ≥50% reduction in monthly migraine headache days was [redacted] greater in the galcanezumab group compared with placebo [redacted] (Table 31)

In both subpopulation analysis, galcanezumab was associated with [redacted] reduction in headache severity measured by the PG-I Severity Rating compared with placebo [redacted] (Table 31)

Table 31 Key secondary efficacy outcomes in HFEM and pooled HFEM + CM patients with 3 or more prior preventive medication category failure

	HFEM patient with ≥3 prior treatment failures		**HFEM + CM patient with ≥3 prior treatment failures**	
	Placebo (n=32)	**GMB (n=48)**	**Placebo (N=74)**	**GMB 120 mg (N=90)**
Change from baseline in the number of monthly headache days over 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]		[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in number of monthly migraine headache hours over 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI		[redacted]	[redacted]	[redacted]

***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in PG-I of Severity Rating until LOCF[b]				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ≥50% reduction from baseline in monthly MHDs in ITT population over 3 months				
Overall responders, %	[redacted]	[redacted]	[redacted]	[redacted]
Odds Ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with ≥30% reduction from baseline in monthly MHDs in ITT population over 3 months				
Overall responders, %	[redacted]	[redacted]	NA	NA
Odds Ratio (95% CI)	[redacted]	[redacted]	NA	NA
***P*-value vs. placebo**	[redacted]	[redacted]	NA	NA

Abbreviations: GMB=galcanezumab; ITT = intent-to-treat; CI = confidence interval; LOCF = last observation carried forward; LS = Least Squares; MHDs= Monthly Migraine Headache days; N = number of intent-to-treat subjects with non-missing baseline value and at least one non-missing post-baseline value; PGI-S = Patient Global Impression of Severity; SD = standard deviation; SE = standard error; vs. = versus.

[a] Baseline values are for the entire ITT population or episodic subpopulation.

[b] For the PGI-S, the number of patients with a baseline and postbaseline value was [redacted] in the HFEM patients with 3 or more prior medication fails; and [redacted] in HFEM and CM pooled patients with 3 or more prior medication failures.

Health related quality of life outcomes

In the ITT subpopulation of patients with high frequency episodic migraine with (Table 32). 3 or more prior treatment failures, the mean change from baseline in MSQ Total Score at month 3 was [redacted] greater in the galcanezumab group compared with placebo [redacted]). However, there was no [redacted] between the two treatment groups for EQ-5D-5L index change [redacted]

In addition, in the ITT subpopulation analysis of patients with high frequency episodic migraine and chronic migraine with 3 or more prior treatment failures, galcanezumab achieved a greater [redacted] mean change from baseline in MSQ Total Score at Month 3 compared with placebo [redacted]. However, the mean change was [redacted] for the MSQ function restrictive domain [redacted]) (Table 32).

Table 32 Key quality of life endpoints in HFEM and HFEM + CM subpopulations with 3 or more prior preventive medication category failures

	HFEM patient with ≥3 prior treatment failures		**HFEM +CM patient with ≥3 prior treatment failures**	
Mean change from baseline in MSQ Total Score at 3 months				
	Placebo (N=31)	**GMB 120 mg (N=46)**	**Placebo (N=43)**	**GMB 120 mg (N=54)**
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in MSQ Role Restrictive score at 3 months				
Baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

***P*-value vs. placebo**	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline in EQ-5D-5L health state index (UK) to LOCF endpoint				
	Placebo (N=32)	**GMB 120 mg (N=48)**	**Placebo (N=44)**	**GMB 120 mg (N=56)**
Baseline, US population based (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
***P*-value versus placebo**	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LS=least square; SE=standard error; SD=standard deviation; CI=confidence interval; Q=quarter

B.2.7.5 REGAIN subpopulation who failed ≥3 prior treatments

B.2.7.5.1 Primary outcome

In the post hoc analysis of REGAIN for the subpopulation of patients with ≥3 prior treatment failures, galcanezumab statistically significantly reduced the number of monthly migraine headache days compared with placebo (p<0.001) (Table 33).

Table 33 Change from baseline in the number of monthly migraine headache days in post-hoc REGAIN 3 or more prior preventive medication failures

	REGAIN ITT patient (CM) with ≥3 prior treatment failures	
	Placebo (N=102)	**GMB 120 mg (N=36)**
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	-0.39 (0.76)	-5.64 (0.97)
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI		[redacted]
***P*-value vs. placebo**	[redacted]	<0.001

Abbreviations: GMB=galcanezumab; ITT = intent-to-treat; CI = confidence interval; LS = Least Squares; MHDs= Monthly Migraine Headache days; N = number of intent-to-treat subjects with non-missing baseline value and at least one non-missing post-baseline value; SD = standard deviation; SE = standard error; vs. = versus.

[a] Baseline mean values are for the entire the CM subpopulation with 3+ prior preventive medication failures (REGAIN: placebo N=103, GMB N=36[redacted])

B.2.7.5.2 Key secondary and health outcomes

Post hoc analysis of REGAIN for patients with ≥3 prior treatment failures a significant improvement in the number of overall mean change of monthly days with acute headache medication use in the galcanezumab treatment arm compared to placebo (p<0.001) (Table 34).

In addition, post hoc analysis that that there was a [redacted] difference in the galcanezumab treatment arm compared to placebo that achieved [redacted] reduction in monthly MHDs for both the REGAIN subpopulation with ≥3 prior treatment failures [redacted], and improvements in MSQ Role Function Restrictive domain scores [redacted] (Table 34)

Table 34 Key secondary endpoints in post-hoc REGAIN patients with 3 or more prior preventive medication failures at month 3

	REGAIN ITT patient (CM) with ≥3 prior treatment failures	
	Placebo (N=102)	**GMB 120MG (N=36)**
Change from baseline in number of monthly days with acute headache medication use over 3 months[a]		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE) from baseline	-0.78 (0.75)	-6.01 (0.96)
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Proportion of patients with ≥50% reduction from baseline in monthly MHDs in ITT population over 3 months		
Overall responders, %	[redacted]	[redacted]
Odds Ratio (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]
Overall mean change of MSQ Function-Restrictive domain scores over 3 months[b]		
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE) from baseline	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: GMB=galcanezumab; ITT = intent-to-treat; CI = confidence interval; LS = Least Squares; N = number of intent-to-treat subjects with non-missing baseline value and at least one non-missing post-baseline value; SD = standard deviation; SE = standard error; vs. = versus.

[a] Baseline mean values are for the entire the subpopulation with 3+ prior preventive medication failures (REGAIN: placebo N=103, GMB N=36; [redacted])
[b] Subjects included for the MSQ measures included [redacted].

B.2.7.6 EVOLVE-1 and EVOLVE-2 pooled subpopulation who failed ≥3 prior treatments

One post hoc analysis for 50% response rate for pooled EVOLVE-1 and EVOLVE-2 subpopulation with episodic migraine who had a history of ≥3 prior treatments failures, and the results showed that that there was a [redacted] in the galcanezumab treatment arm compared to place that achieved ≥50% reduction in monthly MHDs for both the REGAIN subpopulation with ≥3 prior treatment failures [redacted] Table 35)

Table 35 Overall change of the proportion of patients with ≥50% reduction from baseline over 6 months

	Placebo (N=102)	**GMB 120 mg (N=36)**
Overall responders, %	[redacted]	[redacted]
Odds Ratio (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: GMB=galcanezumab; ITT = intent-to-treat; CI = confidence interval; LS = Least Squares; N = number of intent-to-treat subjects with non-missing baseline value and at least one non-missing post-baseline value; SD = standard deviation; SE = standard error; vs. = versus.

B.2.8 Indirect treatment comparisons

A systematic literature review (SLR) in patients with a history of prior preventive treatment failure was conducted to identify efficacy and safety data for galcanezumab 120 mg (with a 240 mg loading dose) in comparison with other therapies for the prevention of chronic migraine. In the absence of head-to-head comparisons, an indirect treatment comparison (ITC) was performed to assess the relative efficacy and safety of galcanezumab (120mg with a 240mg loading dose) compared to botulinum toxin A (Botox). In the SLR, as part of the HTA repository search, a CADTH assessment report for botulinum toxin A was identified, which reports clinical trial evidence from a post-hoc analysis of PREEMPT-1 and PREEMPT-2 in patients for whom at least 3 prior preventive treatments failed. The methods of the SLR are detailed in Appendix D. Summary of the trials used to carry out the ITC is shown in Table 36.

Table 36 Summary of the trials used to carry out the indirect treatment comparison

Intervention of interest	**Study name and acronym**	**Study acronym/ identifier**	**Reference**
Galcanezumab trials	Evaluation of Galcanezumab in the	I5Q-MC-CGAI NCT02614261	CGAI [100]
			Detke (2018) [103]

	Prevention of Chronic Migraine **(REGAIN)**		Ruff (2019) [108]
	A Study of Galcanezumab (LY2951742) in Adults With Treatment-Resistant Migraine (**CONQUER**)	I5Q-MC-CGAW NCT03559257	CGAW [107]
Botulinum toxin A trials	PREEMPT 1 and 2 clinical program	NCT00156910 NCT00168428	PREEMPT-1 PREEMPT-2 [126]
			Aurora (2010) [127]
			Diener (2010) [128]

The target population of interest in whom this comparison was deemed necessary was patients who had a history ≥3 failed prior preventative treatments. However, the feasibility assessment for the ITC revealed key outcomes (i.e. response rates) and baseline characteristics missing, and small numbers of patients available for the comparisons from the trials identified for botulinum toxin A in the target populations. Therefore, additional analyses were conducted in the total trial eligible population to support the estimates from the history ≥3 failed prior preventative treatments population:

- All-comers patient population defined as patients who are naïve to preventive migraine treatment and patients who have previously been unsuccessfully treated with prior preventive migraine treatment
- Difficult-to-treat (DTT-3) patient population defined as failure to at least 3 prior preventive treatments for all-cause reasons

The outcome measures included in the indirect comparison using the all-comers patient population and the treatment-resistant patient population are presented in Table 37. The monthly migraine headache days is the primary endpoint outcome for both the trials that evaluated galcanezumab and for trials that evaluated botulinum toxin A. The ≥50% response rate based on monthly migraine headache days was not included in the indirect comparison of the ≥3 treatment failure patient population, as the data was not available from the PREEMPT trials. Other response rates endpoints were not included due to limited data for standardised cut-off values (e.g. 25% response rate was evaluated for botulinum toxin A, but 30% for galcanezumab). The key secondary endpoint is the MSQ Role Function Restrictive Domain score as it is used in the cost-effectiveness model as the measure of QoL. All these outcomes were predefined in the galcanezumab studies for the ITT population.

Table 37 Outcomes considered in the ITC

Outcomes	All-comers population	Treatment-resistant population
50% or greater reduction in monthly Migraine Headache Days	X	NA
CFB in monthly Migraine Headache Days	X	X
CFB in monthly Headache Days	X	X
CFB in MSQ-RFR	X	X

CFB in MSQ-RFP	X	X
CFB in MSQ-EF	X	X

Abbreviations: CFB – change from baseline; MSQ-RFR - Migraine Specific Quality of life instrument Role Function-Restrictive; MSQ RFP- Migraine Specific Quality of life instrument Role Function-Preventive; MSQ -EF- Migraine Specific Quality of life instrument Emotional Function; NA – not available

The ITC followed the approach proposed by Bucher et al. (1997). The analysis was performed using the Cheetah-tool (Indirect Comparison on results from 2 Meta-Analyses version 1.1), a Lilly developed program based on R package. A key assumption required for the ITC is that homogeneity and transitivity hold across the trials included in the network (i.e. the studies must be similar enough to allow the treatment effects to be pooled. Note that ITC results may still hold when study characteristics differ if they are not treatment effect modifiers). A qualitative assessment of the comparability with respect to baseline characteristics between the limited numbers of studies included is presented in Table 38 below for the populations of interest. The results show that the baseline characteristics are generally comparable across the PREEMPT and REGAIN trials for the all-comers populations.

Table 38. Baseline disease characteristics for REGAIN, CONQUER and pooled PREEMPT trials

Characteristics	All-comers patient population				Patients with a history of at least 3 prior preventive treatment failures			
	REGAIN		Pooled PREEMPT		CONQUER		REGAIN	
	Galcanezumab 120mg [redacted]	Placebo [redacted]	Botulinum toxin A [redacted]	Placebo [redacted]	Galcanezumab 120mg [redacted]	Placebo [redacted]	Galcanezumab 120mg [redacted]	Placebo [redacted]
Duration of migraine illness, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Had migraine with aura at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of comorbidities, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of monthly MHDs, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of monthly headache days, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MHD with acute medication use, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of monthly migraine attacks, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean severity of monthly migraine headaches[b], mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior migraine preventive treatment, n (%)[d]								
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes and failed ≥1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes and failed ≥2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes and failed ≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MIDAS total score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSQ Role Function-Restrictive domain, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGI-S, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MHDs= Migraine Headache Days; MIDAS= Migraine Disability Assessment; MSQ= Migraine-Specific Quality of Life Questionnaire; N = number of patients; n = number of patients within each specific category; NR= not reported; PGI-S= Patient Global Impression of Severity; SD= standard deviation

The base case analyses used the estimates of the primary analyses as displayed in the publicly available information of each study. Note that:

- The clinical trial programs had different study durations. Galcanezumab estimates were assessed across the 3-month double-blind treatment period apart from the MSQ, which was estimated at month 3. The outcomes in PREEMPT were estimated at week 24.
- The botulinum toxin A trials calculated monthly estimates based on 28 days, whereas galcanezumab studies considered a month based on 30 days (and were used as reported in this base case analyses).
- The definitions for the continuous measurements from one study to another one considers data from different durations (e.g. mean change across month 1 to month 3)
- The 50% responder definition varied between the galcanezumab and botulinum toxin A development plans (continuous measurement in some studies and binary measurement in other studies)

Two sensitivity analyses were also conducted to assess the robustness of the base case results:

- **Sensitivity analysis 1 (SA1):** This sensitivity analysis was performed as per the base case except that continuous estimates from REGAIN and CONQUER were multiplied by 28/30 to assess the impact of defining a month in line with the PREEMPT program (28 vs 30 days). Note that the standard error (SE) associated with the estimates calculated on the 30 days were used (i.e. the same SE as in the base case). Given an SE calculated on 30 days is expected to be higher than an SE calculated on 28 days, taking the SE calculated on 30 days is assuming more variability for the galcanezumab and therefore is a conservative comparison.

- **Sensitivity analysis 2 (SA2):** This sensitivity analysis considers outcome results reported at Week 12, if available. This means that for galcanezumab the data for 50% or greater reduction in migraine headache days, change from baseline in migraine headache days and headache days are taken at week 12 instead of the average across month 1 to 3 as in the base case. The pre-specified analysis for MSQ was conducted at week 12. Estimates from the PREEMPT studies were taken at Week 12 as opposed to Week 24 in the base case. This sensitivity analysis was conducted to assess the impact of the different analysis's choices across studies.

Full details of the methodology for the indirect comparison or mixed treatment comparison should be presented in Appendix D.

B.2.8.1 Results

B2.8.2.1.1 All-comers population

[redacted] is seen between galcanezumab and botulinum toxin A for [redacted] (Table 39).

Table 39 50% or greater reduction in migraine headache days

Galcanezumab 120mg versus Botulinum toxin A	Odds Ratio (95%CI), p-value	Risk Ratio (95%CI), p-value	Risk difference (95%CI), p-value
Fixed effect model results			
≥50% Reduction in Migraine Headache Days	[redacted]	[redacted]	[redacted]
Random effect model results			
≥50% Reduction in Migraine Headache Days	[redacted]	[redacted]	[redacted]

Abbreviations: CFB= change from baseline; **CI=confidence interval**

Figure 7 Forest plot: Response reduction in Migraine Headache Days (Galcanezumab 120mg versus Botulinum toxin A via Placebo)

OR – Odds Ratio

[redacted] between galcanezumab and botulinum toxin A [redacted] (Table 40).

Table 40 : All-comer patients: change from baseline in the outcomes - Galcanezumab 120mg versus Botulinum toxin A

Outcomes	Mean difference (95%CI), p-value - Fixed effect model	Mean difference (95%CI), p-value – Random effect model
CFB in monthly Migraine Headache Days	[redacted]	[redacted]
CFB in monthly Headache Days	[redacted]	[redacted]
CFB in MSQ-Role Function Restrictive	[redacted]	[redacted]
CFB in MSQ- Role Function Preventive	[redacted]	[redacted]
CFB in MSQ- Emotional Function	[redacted]	[redacted]

Abbreviations: FE=Fix effects; RE=Random effects; CFB = change from baseline; CI = Confidence Interval; CM = Chronic Migraine; DTT=Difficult-to-Treat; MSQ RFR = Migraine Specific Quality of life instrument Role Function-Restrictive; MSQ RFP = Migraine Specific Quality of life instrument Role Function-Preventive; MSQ –EF=Migraine Specific Quality of life instrument Emotional Function; OR = Odds Ratio

B2.8.2.1.2 Difficult to treat-3-Chronic migraine (DTT-3-CM)

[redacted] (Table 41).

Table 41 DTT-3: change from baseline in the outcomes - Galcanezumab 120mg versus Botulinum toxin A

Galcanezumab 120mg versus Botulinum toxin A	Fixed effect model: Mean difference (95%CI), p-value	Random effect model: Mean difference (95%CI), p-value
CFB in monthly Migraine Headache Days	[redacted]	[redacted]
CFB in monthly Headache Days	[redacted]	[redacted]
CFB in MSQ-Role Function Restrictive	[redacted]	[redacted]
CFB in MSQ- Role Function Preventive	[redacted]	[redacted]
CFB in MSQ- Emotional Function	[redacted]	[redacted]

Abbreviations: FE=Fix effects; RE=Random effects; CFB = change from baseline; CI = Confidence Interval; CM = Chronic Migraine; DTT=Difficult-to-Treat; MSQ RFR = Migraine Specific Quality of life instrument Role Function-Restrictive; MSQ RFP = Migraine Specific Quality of life instrument Role Function-Preventive; MSQ –EF=Migraine Specific Quality of life instrument Emotional Function;

B.2.8.2 Sensitivity analysis

Table 42 provides further details on the sensitivity analyses conducted by population and outcome, where available.

Table 42. Summary of key pairwise ITC fix and random effects model results, Galcanezumab 120mg vs. Botox via Placebo

Outcomes	All-comers patient population		DTT-3-CM	
	Sensitivity 1	Sensitivity 2	Sensitivity 1	Sensitivity 2
	Galcanezumab 120mg vs Botulinum toxin A	Galcanezumab 120mg vs Botulinum toxin A	Galcanezumab 120mg vs Botulinum toxin A	Galcanezumab 120mg vs Botulinum toxin A
≥50% reduction in migraine headache days				
OR (95%CI); p-value	NA	NA	NA	NA
Change from baseline in migraine headache days				
FE, Mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
RE, Mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
Change from baseline in headache days				
FE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
RE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
Change from baseline in MSQ-RFR				
FE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
RE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
Change from baseline in MSQ-RFP				
FE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
RE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA
Change from baseline in MSQ-EF				
FE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA

RE, mean difference (95% CI); p-value	[redacted]	[redacted]	[redacted]	NA

Abbreviations: FE=Fix effects; RE=Random effects; CFB = change from baseline; CI = Confidence Interval; CM = Chronic Migraine; DTT=Difficult-to-Treat; MSQ RFR = Migraine Specific Quality of life instrument Role Function-Restrictive; MSQ RFP = Migraine Specific Quality of life instrument Role Function-Preventive; MSQ – EF=Migraine Specific Quality of life instrument Emotional Function; OR = Odds Ratio

Results of the sensitivity analyses were consistent with the base case in both populations of interest (Figure 8, Figure 9 and Figure 10) [redacted]

Figure 8. Forest plot: Change from baseline in monthly Migraine Headache Days and monthly Headache Days (Galcanezumab 120mg versus Botulinum toxin A via Placebo)

CI – Confidence Interval; DTT – Difficult-to-Treat; HD – Headache Days; MHD – Migraine Headache Days

Figure 9. Forest plot: Change from baseline in MSQ domain scores – All-comers patient population (Galcanezumab 120mg versus Botulinum toxin A via Placebo)

CI – Confidence Interval; MSQ-RFR - Migraine Specific Quality of life instrument Role Function-Restrictive; MSQ RFP- Migraine Specific Quality of life instrument Role Function-Preventive; MSQ -EF- Migraine Specific Quality of life instrument Emotional Function

Figure 10. Forest plot: Change from baseline in MSQ domain scores – DTT-3-CM patient population (Galcanezumab 120mg versus Botulinum toxin A via Placebo

CI – Confidence Interval; DTT – Difficult-to-Treat; MSQ-RFR - Migraine Specific Quality of life instrument Role Function-Restrictive; MSQ RFP- Migraine Specific Quality of life instrument Role Function-Preventive; MSQ -EF- Migraine Specific Quality of life instrument Emotional Function

B.2.8.3 Uncertainties in the indirect comparisons

One of the key weakness of this analysis was the low number of included studies. The ITC was based at most on two studies per direct comparison and up to four studies per network although only CONQUER was specifically conducted in patients with a history of prior treatment failures. The sample size of the individual study groups, particularly for the treatment resistant patient population was not considerably high. No baseline characteristics for the treatment-resistant patient population were reported for the PREEMPT trials, thus it is difficult to draw conclusions about the comparability between the galcanezumab patient populations and the PREEMPT subgroup population. In addition, no indirect comparisons of adverse events (AE) were considered appropriate between REGAIN and PREEMPT due to potential differences in AE reporting and imbalance in incidence rates of AEs due to the different duration of double-blind periods for REGAIN and CONQUER (3 months) and PREEMPT trials (24 weeks). Moreover, no data on AEs were identified for the patient population with a history of prior preventive treatment failure from PREEMPT.

Due to the limited number of studies, estimates of between study variability are difficult to estimate, and so results from the FE and RE models are similar. The wide confidence intervals reflect the uncertainty in the estimates. Also, the Q test statistics may perform poorly to detect the heterogeneity between studies. In those circumstances, heterogeneity between studies may only be assessed descriptively when comparing the study design and the estimates for each study treatment across studies, which is highlighted in the preceding paragraph. The ITC is based on the transitivity assumption, which implies that the treatment comparison within the indirect comparison do not differ with respect to the distribution of known treatment effect modifiers. For the ITC of galcanezumab versus botulinum toxin A, it must be noted that firstly, the definition of headache/migraine headache differs across the galcanezumab (≥30 minutes duration) and botulinum toxin A (≥4 continuous hours) clinical program. Secondly, the statistical methods varied between the trial programs (MMRM versus ANCOVA models). Thirdly, the placebo response in the PREEMPT trials is higher compared to REGAIN or CONQUER, which is to be expected due to the invasiveness of the multiple injections as highlighted by Diener et al. (2008)[129]. Higher

placebo response in patients in PREEMPT 1 and 2 study could partly be explained by the perception of stronger efficacy related to more invasive treatment/procedures (31-39 injections sites with botulinum toxin A administration)[130]. Fourthly, the study duration differed between the development programs with the double-blind treatment period of galcanezumab trials lasting 3 months whereas PREEMPT trials were 24 weeks in duration. For the PREEMPT trials limited evidence was available for outcomes at week 12. Given these limitations, the results of the ITC are highly uncertain and must therefore be interpreted with caution.

B.2.9 Adverse reactions

The summary of the safety results for CONQUER ITT population is demonstrated in B.2.9.2.1 Summary of safety data in CONQUER ITT safety population and the safety results for the patients with 3 or more prior preventive medication failures is demonstrated in B.2.9.2.2 Summary of safety data in CONQUER patients . The pooled safety results from pivotal trails including REGAIN, EVOLVE-1, EVOLVE-2, CGAJ and a Phase II trial CGAB are presented in B.2.9.1 Summary of pooled safety data from multiple trials

In addition, detailed safety results from all the pivotal trials including REGAIN, EVOLVE-1, EVOLVE-2, the 6 months safety results from the open-label treatment phase in CONQUER and the one year open-label study CGAJ are included in Appendix F.

B.2.9.1 Summary of pooled safety data from multiple trials

Based on a pooled analysis results in the UK, to date, over 2500 patients were exposed to galcanezumab in clinical studies in migraine prophylaxis.[131, 132] Over 1400 patients were exposed to galcanezumab during the double-blind treatment phase of the placebo-controlled phase 3 studies [1, 131, 132].

The reported adverse drug reactions from pooled safety population during the double blind treatment phase for 120 mg in the migraine clinical trials were injection site pain (10.1 %), injection site reactions (9.9 %), vertigo (0.7 %), constipation (1.0 %), pruritus (0.7 %) and urticaria (0.3 %).[131] Most of the reactions were mild or moderate in severity. Less than 2.5 % of patients in these studies discontinued due to adverse events.[1, 131]

Table 43 shows a list of adverse reactions in clinical studies and post-marketing reports as shown in the SmPC, where the frequency estimate is based on the following number of cases: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000).[1]

Table 43 List of adverse reactions in clinical studies and post-marketing reports

System Organ Class	Very common	Common	Uncommon	Rare
Immune system disorders				Anaphylaxis Angioedema
Ear and Labyrinth System		Vertigo		
Gastrointestinal System		Constipation		

Skin and Subcutaneous Tissue		Pruritus Rash	Urticaria	
General disorders and administration site conditions	Injection site pain Injection site reactions[a]			

[a.] Most frequently reported terms (⩾ 1 %) were: Injection site reaction, Injection site erythema, Injection site pruritus, Injection site bruising, Injection site swelling.

B.2.9.2 CONQUER exposure data

In the safety population (defined in Table 8), mean duration of exposure to investigational product during the double-blind treatment phase was similar between treatment groups [redacted]
Most patients received all 3 doses of investigational product. [redacted].

B.2.9.2.1 Summary of safety data in CONQUER ITT safety population

The percentage of patients that reported 1 or more treatment-emergent adverse events (TEAEs) was similar between the galcanezumab and placebo groups [redacted] (Table 44)
No individual TEAE was reported in a significantly higher percentage of patients in the galcanezumab group compared with placebo. Among patients who reported TEAEs, most reported them as mild or moderate in severity. [redacted]

Table 44 Summary of adverse events in CONQUER ITT safety population

Preferred Term	Placebo N=230, n (%)	GMB 120 mg N=232, n (%)
TEAEs	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Nausea	[redacted]	[redacted]

Oropharyngeal pain	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]
Behcet's syndrome	[redacted]	[redacted]
Lower limb fracture	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]
Death	[redacted]	[redacted]

B.2.9.2.2 Summary of safety data in CONQUER patients who have a history of ≥3 prior preventive treatment failures

Table 45 summarises the adverse events in the safety sub-population with ≥3 prior preventive medication failures. [redacted]

[redacted]

Table 45 Summary of Adverse Events in Safety Sub-population patients who have a history of ≥3 prior preventive treatment failures

Preferred Term	**Placebo N=87, n (%)**	**Galcanezumab 120 mg N=99, n (%)**
TEAEs	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]

Upper respiratory tract infection	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]
Behcet's syndrome	[redacted]	[redacted]
Discontinuation due to AE	[redacted]	[redacted]
Death	[redacted]	[redacted]

B.2.10 Ongoing studies

TRIUMPH is a two-year prospective, post-launch observational study of treatment patterns and outcomes in patients newly prescribed medications commonly used for the prevention of migraine. Patients may be included for reasons of prior failure to other preventative medications. The trial is currently being conducted in the US, Germany, France [redacted]. In addition, OVERCOME is a two-year, multi-wave prospective, web-based patient survey to understand the burden of migraine and the stigma experienced by people living with migraine, identify barriers to the use of preventive and acute treatments for migraine and to assess how the introduction of novel preventive and acute treatment options may influence delivery of migraine care and costs of care in real-world settings. The trial will be conducted in the US. Key details of the studies are summarized below in Table 46.

Table 46 also summarises the ongoing migraine clinical trials with galcanezumab, including countries, objectives and study designs. Two studies in Japanese patients (CGAN and CGAP - phase IIb and phase III, respectively) completed in 2019. There is one ongoing Phase III studies, CGAS (REBUILD) is a Phase III trial in paediatric migraine patients. In addition, one Phase I study in healthy patients (CGAY) and one phase III study in EM patients are currently ongoing in China.

Table 46 Ongoing and recently completed studies of galcanezumab for migraine patients

Study identifier	Countries	Population	Study design	Estimated enrolment	Study period
Recently completed controlled clinical studies in migraine prevention (adults)					
I5Q-JE-CGAN (NCT02959177)	Japan	Japanese patients with EM	Phase IIb, multicentre, randomised, double-blind, placebo-controlled, parallel-group study Following double-blind treatment, 4-month post-treatment (washout) period	N=451	Actual start: 9 November 2016 Completion: 2 February 2019
I5Q-JE-CGAP (NCT0959190)	Japan	Japanese patients with EM who completed the treatment period in CGAN	Phase III, multicentre, randomised, long-term, open-label safety study Following open-label treatment, 4-month post-treatment (washout) period	N=300	Actual start: 7 February 2017 Completion: 24 August 2019

Ongoing studies in controlled clinical studies in migraine prevention (paediatric)					
I5Q-MC-CGAS REBUILD (NCT0342286)	US, Puerto Rico	Patients aged 6–17 years with EM	Phase III, multicentre, randomised, double-blind, placebo-controlled trial	645	Actual start: 14 March 2018 Estimated completion: 25 May 2023
Ongoing studies in controlled clinical studies in migraine prevention (Adults)					
I5Q-MC-CGAX (NCT03963232)	China	Adults patients with EM	Phase 3, Randomized, Double-Blind, Placebo-Controlled	486	Actual start: 30 June 2019 Estimated completion: 29 Oct 2021
I5Q-MC-CGAY (NCT04085289)	China	Healthy	Phase 1, Randomized, Double-Blind, Placebo-Controlled	30	Actual start: 30 June 2019 Estimated completion: 15 May 2020
Observational studies					
TRIUMPH	US, France and Germany [redacted]	Adult patients with episodic or chronic migraine who are switching (or initiating) a preventive treatment	Prospective Observational Research Study, global, multisite, 2-stage: **Stage 1**: cross-sectional (N=6,000) assessment of treatment patterns and burden **Stage 2**: 24-month longitudinal assessment of those in stage 1 meeting	**Stage** 1: 6000 **Stage 2:** 2,850	[redacted]

			enrollment criteria (N= 2,500, with 1,250 galcanezumab and 1,250 on other preventive treatments)		
OVERCOME	US	Adults with migraine who reported having a headache or migraine attack in past 12 months	Prospective, Observational, multi-wave and web-based patient survey	20,000	Estimated start: August 2018 Estimated baseline data: 2019 Estimated completion: 2022

Abbreviations: EM= episodic migraine; CM=chronic migraine; US= United States; UK= United Kingdom

B.2.11 Innovation

Galcanezumab is among the first of a new group of monoclonal antibodies that inhibit the effects of calcitonin gene-related peptide (CGRP) with the aim of preventing migraine. This new therapeutic approach, with a novel mechanism of action specifically designed to target migraine pathophysiology, provides a needed addition for patients suffering from this disabling disease. In addition, Galcanezumab provides a convenient therapeutic option administered monthly as a subcutaneous injection via an auto-injector (pen device).

Patient-reported satisfaction (PSMQ-M) with galcanezumab was rated positively throughout the trials, ranging from 68.9% to 74.8% for overall study medication satisfaction, 73.5% to 85.3% for preference over prior treatments, and 71.2% to 81.2% for less impact from side effects over the 12-month treatment period [133] In addition, more than 90% of patients reported positive experiences when they used the autoinjector for the first time and this continued with subsequent use [134].

Efficacy results from the pivotal double-blind placebo-controlled studies demonstrated consistent evidence that galcanezumab treatment is associated with statistically significant, clinically meaningful effects on number of monthly MHDs, day-to-day functioning, and migraine-related disability among patients with EM and CM in the all-comers patient population and patients who had been unsuccessfully treated with prior preventive treatments previously. In addition, galcanezumab demonstrated a favourable safety profile in the phase III migraine studies including in the subpopulation with a history of 3 or more prior medication failures in CONQUER, with only mild or moderate treatment-emergent AEs reported. The safety profile of galcanezumab 120 mg/month in patients with treatment-resistant migraine was consistent with the known safety profile based on the Phase 3 migraine studies. No new safety concerns were identified [redacted] .In addition, CONQUER was the first trial to use the Work Productivity and Activity Impairment Questionnaire (WPAI) to determine the impact of treatment on work productivity and regular activities due to migraine. The results showed that patients with EM or CM and a history of prior failure with ≥3 preventive medication categories had a [redacted] mean change from baseline to month 3 of treatment if they received galcanezumab compared with placebo with respect to activity impairment, presenteeism (impairment while working), and overall work impairment ([redacted]).

B.2.12 Interpretation of clinical effectiveness and safety evidence

The primary objective was met in the CONQUER trial for patients who have a history of ≥3 prior preventive treatment failures.

The primary objective in the CONQUER trial was met for patients who have a history of ≥3 prior preventive treatment failures. Galcanezumab 120 mg [redacted] the [redacted]

- chronic migraine patients [redacted] and;
- episodic migraine patients [redacted].

In addition, at the end of the 6 months open-label treatment phase, both the prior galcanezumab group and the prior placebo group from the 3 month double blind phase demonstrated [redacted], indicating the durability of treatment effects (see B.2.6.3.5 Long-term effectiveness of galcanezumab in CONQUER CM and EM patients)

Key secondary objectives were met in the CONQUER patients who have a history of ≥3 prior preventive treatment failures

Galcanezumab [redacted] improved the clinical endpoints during the 3 month double-blind treatment phase compared with placebo in the overall mean number of:

monthly headache day: chronic population [redacted] monthly migraine headache hours: chronic population [redacted] monthly migraine days of acute medication use: chronic population [redacted]. In addition, there was an improvement in patients' global assessment of severity of their migraine disease as assessed by [redacted]

The mean percentage of patients with [redacted] in the galcanezumab group compared with placebo in the chronic population [redacted] In addition, the mean percentage of patients with [redacted] in the galcanezumab group compared with place in both the chronic [redacted] and the episodic population [redacted]

Impact on headache-related measures in HFEM patients and pooled HFEM and CM patients who have a history of ≥3 prior preventive treatment failures

As discussed in Section B.1 Decision problem, description of the technology and clinical care pathway, HFEM patients have similar disease burdens to chronic patients and there have been calls for a revision of the criteria for chronic migraine to include patients with HFEM. Until such time that chronic migraine is redefined, patients with HFEM failing three or more oral preventive treatments have limited treatment options and a substantial unmet need. A subgroup analysis was therefore conducted in CONQUER to assess the efficacy of galcanezumab in HFEM patients and pooled HFEM or chronic patients. The [redacted] results are summarised below:

Mean change from baseline in the number of MHD of galcanezumab vs placebo [redacted]. Monthly migraine headache hours [redacted] ≥50% reduction from baseline in monthly MHDs [redacted] ≥30% reduction from baseline in monthly MHDs in pooled HFEM and CM patients [redacted]

Health-related quality of life outcome measures in patients who have a history of ≥3 prior preventive treatment failures

The mean change from baseline in MSQ role total score, and the three separate domains including MSQ Role Function Restrictive, Function Preventive and Function Emotional scores at month 3 were [redacted] in the galcanezumab group compared with placebo in the ITT subgroup who had a history of ≥3 prior preventive treatments failures (see B.2.7.2.2 Key secondary outcomes) These improvement in MSQ domain scores were also consistent when evaluating the CM and EM subgroup who had a history of ≥3 prior preventive treatment failures, respectively (see B.2.7.3.2 Key secondary outcomes).

The ED-5D-5L was collected in the CGAW trial, and there were [redacted] A primary reason for this may be the insufficient recall period of the EQ-5D-5L in migraine. The EQ-5D-5L instrument collects information at a single point in time as it asks patients to complete the questionnaire based on how they feel 'today'. In addition, the instrument was administered at baseline and once again at 3 months at the end of the double-blind period of the study. In comparison, the MSQ questionnaire was administered monthly throughout the randomised and open-label phases of the trial and has a 4-week recall period. Therefore, the MSQ instrument was able to better capture more granular changes in health-related quality of life compared to EQ-5D-5L. This may explain the differing results seen between the two instruments, since some patients might have been asked to complete the EQ-5D-5L questionnaire when they were not experiencing a migraine attack on the day of the assessment.

Safety and tolerability profile of galcanezumab

The safety profile of galcanezumab is supported by four randomised controlled trials assessed for up to 6 months in CONQUER (

B.2.9 Adverse reactions, Appendix F), REGAIN, EVOLVE 1 and EVOLVE 2 (Appendix F). The pooled safety data from pivotal trials (excluding CONQUER) for up to 1 year reported adverse drug reactions for 120 mg in the migraine clinical trials were [redacted] [1].

In addition, the long-term safety data is supported by a 12 months open-label long-term study CGAJ[redacted]. Discontinuation due to adverse events (AEs) from CGAJ is consistent with that observed from RCTs (Table 47). The pooled analysis showed that the proportion of discontinuation due to AEs among galcanezumab 120mg treated patients was [redacted] during the double-blind treatment phase.[131] In conclusion, galcanezumab demonstrated a favourable safety and tolerability profile for up to 1 year of treatment for the prevention of migraine.

Table 47 Summary of discontinuation due to safety population adverse events

	CONQUER – 3 month double blind phase		**CONQUER – month 4-6 open-label phase**	**REGAIN – 3 month double blind phase**		**EVOLVE 1– 6 month double blind phase**		**EVOLVE 2 –– 6 month double blind phase**		**CGAJ - 12 month open-label treatment phase**
	Placebo N=230	GMB N=232	GMB N=457	Placebo N=558	GMB N=273	Placebo N=432	GMB N=206	Placebo N=431	GMB N=226	GMB N=457
Discontinuation due to AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE= adverse reactions; GMB= galcanezumab

Indirect comparison with botulinum toxin A in patients who have a history of ≥3 prior preventive treatment failures

Efficacy of galcanezumab 120mg was compared with botulinum toxin A in patients with chronic migraine. Key results include the followings:

- In the all-comer patient group, patients achieving a [redacted]; however, [redacted]),
- For the patient group who had failed 3 or more prior preventive treatments, the overall mean reduction of MHD from baseline over 3 months for Galcanezumab 120mg was compared to the mean reduction of MHD at month 3 for botulinum toxin A and the result showed a [redacted] (fixed effects model, [redacted].
- In addition, for the patient group who have a history of ≥3 prior preventive treatment failures, the mean change of MSQ-RFR from baseline was observed for Galcanezumab 120mg compared to botulinum toxin A [redacted] ([redacted]

Overall, across the base case and sensitivity analyses, no [redacted] were observed between Galcanezumab 120mg and for all the outcomes that were assessed in the populations of interests including the all-comers patient group and the subgroup with a history of 3 or more prior preventive treatment failures. Thus, the efficacy profile was found to be broadly similar. However, the limitations in the comparisons of the studies need to be taken into consideration and the results need to be interpreted with caution.

Strengths and limitations of evidence base

EVOLVE-1 and -2, REGAIN and CONQUER were all multi-centre double-blind randomised controlled trials dedicated to investigating the efficacy and safety of galcanezumab for preventing migraine. All the trials were of good quality and had good internal validity as conducted in line with the CONSORT quality checklist (B.2.5 and Appendix M-P). External validity was also good. CONQUER was specifically designed to study the efficacy and safety of galcanezumab in treatment-resistant patients (who have a history of 2-4 medication categories preventative treatment failures). The mean number of prior preventative treatments failed by patients who entered the CONQUER study was [redacted]. Therefore, the evidence base from the studies directly reflect the use of galcanezumab in clinical practice in the UK.

The primary and key secondary outcome measures included the studies captured important clinically meaningful changes in outcomes important for patients; change in monthly MHDs, response rates and HRQoL. In CONUQER all these endpoints were pre-specified for the target subgroup of patients that had a history of ≥3 failed preventative treatments; minimising bias and increasing robustness and confidence of the results in the target population.

Continued efficacy and safety data were also collected in the REGAIN open-label extension study and open-label CGAJ study, up to 52-weeks. These studies showed durability of effect and response up to one-year of use with galcanezumab and no indication of a waning effect. In addition, EVOLVE-1 and -2, and REGAIN had washout periods which showed treatment benefit is maintained up to 5 months after the last monthly dose of galcanezumab, indicating a steady trajectory towards baseline.

Limitations of the clinical evidence base for galcanezumab include the lack of double-blind treatment evaluation beyond 6 months lack of follow up beyond 1 year. In addition, the evidence lacks a direct comparison versus the key active comparator used in clinical practice (i.e. botulinum toxin A). Therefore, the indirect treatment comparison analysis was conducted to address this limitation (see B.2.8 Indirect treatment comparisons). The results of the ITC which should be interpreted with caution due to the lack of data for botulinum toxin A for the comparison for the target population who had a history of ≥3 failed prior preventative treatments.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

To understand the evidence base of economic models in episodic and chronic migraine a targeted literature review (TLR) of cost effectiveness models was conducted in 2017. The search aimed to conduct a combined review of economic model structures, utility values and costs used in existing cost effectiveness models. Given the recent launch of new treatments, the targeted review from 2017 was updated to identify relevant economic model structures and data sources published from 2017 through 2019. Databases were searched for using terms for migraine and economic evaluations. In addition, reference lists of recent economic evaluations and conference proceedings were hand searched. MEDLINE, EMBASE, EconLit and EBM Reviews Health Technology Assessment were searched from 2017 to 2 December 2019. Search terms developed for the initial literature review were used to capture the relevant treatments.

In addition, three conferences of interest were hand searched for the last 2 years:

- ISPOR Europe 2019
- Annual Scientific Meeting American Headache Society
- International Headache Congress

Details of the methodological approach used to identify the economic evaluations used is presented in Appendix G.

In total, sixteen publications were identified describing economic models for topiramate [135-138], botulinum toxin A [6, 139-144] erenumab [12, 45, 145, 146] and fremanezumab[147]..

B.3.2 Economic analysis

Based on the literature reviewed and feedback from health technology appraisal (HTA) bodies, a Markov model was deemed appropriate [148]. A cost-utility analysis was conducted, considering the UK NHS and Personal Social Services perspective, consistent with the NICE reference case.

The objectives of the model were:

1) to accurately reflect clinical practice in the UK
2) to accommodate all possible comparisons of treatment strategies within the target populations as defined by the NICE scope.

Although the TLR did not identify any economic analyses which compared galcanezumab to the required comparators, economic models describing the cost-effectiveness for erenumab and fremanezumab in migraine prevention were identified [145-147, 149]. Therefore, a *de novo* model with a similar structure was developed to determine the cost effectiveness of galcanezumab in migraine prevention. According to International Headache Society (IHS) clinical guidelines, the important outcomes in migraine prevention are change from baseline in MHDs and the proportion of responders to treatment, both assessed at three months of treatment [1, 80]. Economic evaluations published in prior HTAs (i.e. botulinum toxin A) were criticized for their complexity [6]. Grouping patients of differing MHD frequencies into a single health state resulted in a loss of information on differences in costs and HRQoL between individual MHD frequencies,

thereby compromising the reliability of the trial data. A number of the economic evaluations identified considered both response status and frequency of MHD [135-137, 145, 147].

It is essential to consider the distribution of patients by MHDs in the economic evaluations of migraine prophylaxis instead of implementing estimates of mean frequency or categorical health states in order to justify the cost and quality of life consequences of different frequencies of MHDs. To address these concerns, the modelling approach adopted in this economic evaluation for galcanezumab utilised patient distributions across individual monthly MHD frequencies for each treatment and time points taken from the clinical trial data. These frequencies were defined differently for responders and non-responders, which allows both MHD frequency and response status outcomes to be captured explicitly in the model. The model structure is described in detail in Section B.3.2.2 Model

Patients with episodic migraine are modelled separately from patients with chronic migraine, with input paramterers specific to the population of interest. As described in Section B.1, these patient populations can be evaluated in parallel to allow for an accurate reflection of UK clinical practice. In addition, the model is also designed to allow analyis of patients with HFEM. Model input parameters were informed using direct head-to-head trial data from the placebo-treatment group (which is considered a suitable proxy for BSC) or evidence sythesised from an indirect comparison when evaluating galcanezumab against the different active comparators and for the different population groups. Model comparators were deemed appropriate as related to the NICE guidelines for migraine prophylaxis [64].

The model utilises a number of assumptions to estimiate the relevant costs and QALYs over a patient's lifetime. The assumptions were guided by the NICE comitttee's preferences from similar economic analyses in appraisals for erenumab and fremanezumab [12, 150] and modified for relevance to the decision problem for galcanezumab in preventing migraine.

B.3.2.1 Patient populations

The target patient population consisted of adult patients aged ≥18 years who have ≥4 MHDs per month and who have a history of ≥3 prior preventive treatment failures. As discussed in Section B.1.1 this optimised population falls within the marketing authorisation for galcanezumab and at a position in the treatment pathway where speciality treatments, such as botulinum toxin A are used in NHS clinical practice.

Patients with episodic migraine and patients with chronic migraine were modelled separately to capture the differences in costs and QALYs per population. This also allows the model to reflect differences in treatment practices between episodic migraine and chronic migraine (i.e. use of botulinum toxin A as preventive treatment in patients with chronic migraine).

While the pivotal trials for galcanezumab in migraine prevention evaluated patients with episodic migraine (EVOLVE-1 and EVOLVE-2) and patients with chronic migraine (REGAIN), they provided limited post hoc evidence for the target population in this submission (i.e. for patients with a history of ≥3 prior preventive treatment failures). The evidence for the economic evaluation is based primarily on clinical data from CONQUER which was designed specifically to evaluate galcanezumab in patients who had a history of 2 – 4 prior medication category failures. The patient populations considered in this model are defined in Table 48.

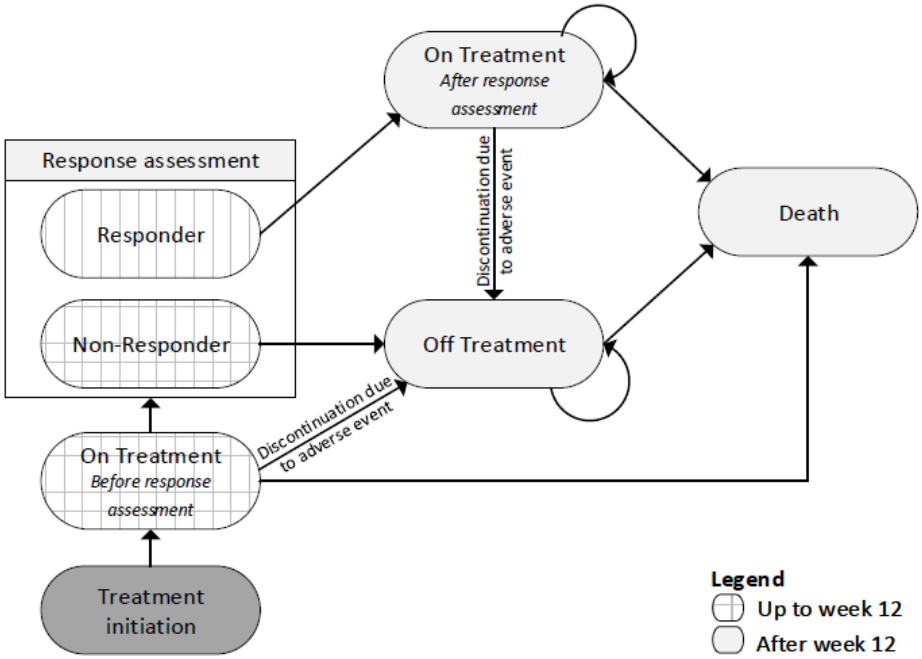
Table 48. Patient populations considered in the model

Treatment experience	Episodic migraine	High frequency episodic migraine	Chronic migraine
Patients with a history of at least 3 failed preventive treatments	<15 headache days, and <8 MHDs per 30-day period	<15 headache days and 8-14 MHDs per 30-day period	≥15 headache days and ≥8 MHDs per 30-day period for >3 months

B.3.2.2 Model overview

The economic model has a semi-Markov model structure comprised of four health states; on-treatment, off-treatment due to non-response, off-treatment due to adverse events and death (Figure 11). The model had an assessment period (month 1 – 3) and post-assessment period (month 4 onwards). Each of the health states is associated with a mean monthly MHD frequency, and the response assessment period allows differentiation between responders and non-responders.

Figure 11 Model structure



Assessment period

At the start of the model, patients initiate treatment for a period of 3 months, at which point there are two key transitions:

1. **Assessment of response**: Clinical trial data at month 3 were used to inform the proportion of patients who met a specific response criterion (defined as a ≥50% reduction from baseline in monthly MHDs for patients with episodic migraine or HFEM, and as a

≥30% reduction from baseline in monthly MHDs for patients with chronic migraine). Patients who experience the treatment effect at month 3 continue to respond for the remainder of the time horizon unless they discontinue due to AEs or death.

2. **Discontinuation due to non-response**: Patients who do not respond at month 3 discontinue treatment and would only incur costs of BSC and baseline utility associated with that MHD value for the remainder of the time horizon. This was applied once within the 3-month assessment period of the first part of the model

Post assessment period

Change from baseline (CFB) in monthly MHDs was analysed by responder status, which allowed to model the mean reduction in monthly MHDs for responders and non-responders separately, for comparisons to BSC only.

These data were not identified in the clinical SLR or economic TLR for other comparators, therefore the combined (responder and non-responder) mean reduction in monthly MHDs for the total population was applied for the comparison to botulinum toxin A in patients with chronic migraine.

Discontinuation due to AEs is a key transition point in the post assessment period. For patients who remain on-treatment after the assessment period, this is applied as a per cycle probability in the post assessment period and patient who discontinue would incur costs of BSC and baseline utility associated with the corresponding MHD value.

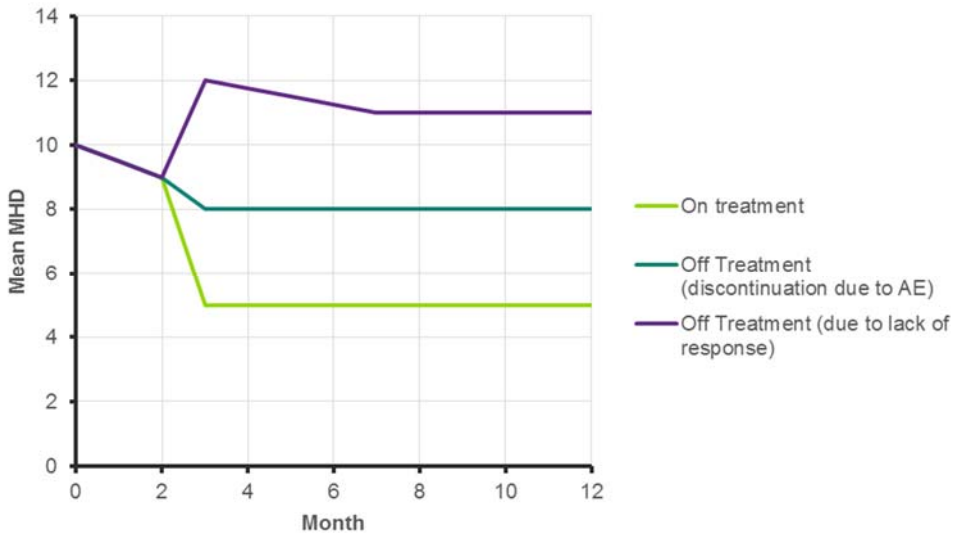
Patients could die from any health state and had an equal risk of death in all health states (i.e. no excess mortality was assumed).

Distribution approach

The model includes a second structure, whereby the mean change in monthly MHDs in each health state are used to estimate the number of patients experiencing each frequency of monthly MHDs. This is achieved by employing a statistical distribution to estimate the full range of monthly MHDs from the mean monthly MHDs (which are informed by the clinical trial data for galcanezumab). Since the mean change in monthly MHDs does not capture the full range and distribution around the mean of individual monthly MHD frequencies, this second aspect captures the non-linear impact on costs and QALYs due to the fluctuating nature of disease (month-to-month variation of MHDs experienced by patients). The number of patients experiencing each frequency of monthly MHDs is used to calculate the costs and QALYs.

Each of the health states is associated with a mean change in monthly MHDs based on the CFB in monthly MHDs from the clinical trials. A visual representation of how the mean change in monthly MHDs would look over time by health states is shown in Figure 12.

Figure 12 Illustrative example – Model MHD



B.3.2.2.1 Assessment of response

Three months of treatment is described as an appropriate time period to assess clinical effectiveness of treatment based on feedback from clinicians and headache specialists. It is also aligned with the SmPC for galcanezumab, which states that treatment benefit should be assessed within 3 months after initiation of treatment [1]. Base case assessment response rates are incorporated into the model as follows:

- **Episodic migraine and HFEM**: ≥50% reduction from baseline in monthly MHDs over 3 months
- **Chronic migraine**: ≥30% overall reduction from baseline in monthly MHDs during over 3 months

The assessment response rates chosen to apply to the separate populations are clinically meaningful endpoints for the prevention of migraine [69, 151] and were based on recent NICE technology appraisals for erenumab and fremanezumab [12, 150]. As such, these are applied as appropriate treatment continuation rules in the model.

Treatment responses was assessed at month 3 (90 days) for all treatments. However, the economic model from the company submission for botulinum toxin A for the treatment of chronic migraine was performed at week 24 (~day 180) [6]. Therefore, we also present a scenario in which the assessment period for botulinum toxin A was altered to day 180. No data has been published describing 30% response rates for patients with a history of ≥3 prior preventive treatment failures from the PREEMPT trials for botulinum toxin A. Therefore, an response rates were assumed to be equal for the 30% response rate. Where appropriate, data were taken directly from the pre-determined analyses from the CONQUER trial or the pooled post hoc analyses from the pivotal trials to inform the response rates of 50% (for episodic migraine and HFEM) and 30% (for chronic migraine).

For the comparison to BSC: patients who do not achieve a response over the first 3-months will transition to the off-treatment health state where they have the mean change in monthly MHDs of a non-responder and return to baseline monthly MHDs over time and return to baseline monthly MHDs (see section B.3.3). The same applies for patients who discontinue in the post-assessment period due to AEs where patients switch from their responder mean monthly MHDs to non-responder monthly MHDs. For patients in the BSC arm who respond to treatment, they are assumed to remain on-treatment and maintain their responder mean MHD change and return to baseline monthly MHDs over time (see section B.3.3.). Responders in the galcanezumab arm are assumed to maintain their mean change monthly MHDs until the end of the time horizon.

For the comparison to botulinum toxin A: patients who discontinue for lack of response or AEs are assumed to wane back to baseline MHDs from a combined response/non-responder mean monthly MHDs over time. Responders to either galcanezumab or botulinum toxin A are assumed to continue the combined mean change monthly MHDs in the post assessment period but may discontinue due to AEs.

The 3-month assessment period is informed directly from the double-blind treatment period of the clinical trials for galcanezumab (CONQUER, EVOLVE-1, EVOLVE-2 for patients with episodic migraine, CONQUER for patients with HFEM, CONQUER and REGAIN for patients with chronic migraine) where data was available when evaluating galcanezumab to BSC per population. A constant mean change in monthly MHDs is applied from the assessment point at month 3 for responders and the range of monthly MHDs around this mean is captured until the end of the time horizon, assuming the same constant mean change in monthly MHDs.

B.3.2.2.2. Discontinuation due to adverse events

Discontinuation due to adverse events is aligned with CONQUER and is assumed to happen prior to the assessment of response (i.e. within the assessment period – first 3 months of the model). This is applied as a one-off discontinuation probability. The patients who discontinue due to adverse events go to the off-treatment health state and are assumed to rebound to the baseline monthly MHDs, which occurs over a waning period attributed to each modelled active treatment. For galcanezumab, this was based on the observed MHDs during the washout period of the pivotal clinical trials (EVOLVE-2 for episodic migraine; REGAIN for chronic migraine). No such washout data was available for botulinum toxin A (i.e. patients who do not respond or discontinue treatment due to AEs and still have disease) therefore it was assumed that patients return to baseline monthly MHDs by the time they were expected to receive their usual administration of botulinum toxin A, at a further 3-months. This is also true in the model for patients discontinuing treatment due to non-response. The discontinuation rate for patients on BSC is assumed to be zero.

A second discontinuation due to AEs was included for those patients who respond to treatment at month 3. For galcanezumab, these values have been taken from the open-label study CGAJ to reflect the long-term discontinuation in the model and are applied at a per month probability for the duration of the post assessment period in the model. For active comparators, these are taken from appropriate trials attributed to that active treatment. When patients discontinue treatment, they are also assumed to rebound to the baseline monthly MHD in the base case and the same waning assumptions apply. The discontinuation rate for patients on BSC is assumed to be zero in the post assessment period.

A rebound back to baseline for discontinuers was chosen to align with the conclusions from the NICE technology appraisal for fremanezumab where it states that a placebo response of the magnitude seen in the clinical trials would not be observed in clinical practice [150].

Furthermore, aligned to the NICE committee's preferred assumptions from the NICE technology appraisal for fremanezumab, responders in the BSC arm in the model also wane back baseline monthly MHDs over 12 months [150]. Alternative scenarios are explored where the treatment arms wane at different rates to different mean change monthly MHD frequenciesfor patients who discontinue treatment for non-response or AE which includes a return to BSC non-responder mean change monthly MHDs. The impact of the placebo response is also included in a scenario analysis whereby patients in the BSC arm continue to receive further benefit from the mean change monthly MHDs for responders throughout the post-assessment period.

B.3.2.2.3. Model structure – Distribution approach

The second part of the model captures the range of monthly MHDs within the health states, capturing the distribution around the mean change in monthly MHDs, which is calculated as part of the first part of the model. The range of monthly MHDs is calculated using a statistical distribution as described in Section B.3.3.2.2. The distribution was calculated from the pivotal trial data, comparing the observed histogram with a fitted distribution. The statistical distribution has been calculated in a way by which it is estimated solely on the mean change MHD. By only using the mean monthly MHDs, the model can incorporate evidence from evidence synthesis (i.e. separate estimates for responder and non-responder mean monthly MHDs and mean monthly MHDs from the indirect treatment comparisons [ITC]) to estimate the full range of monthly MHDs a patient may experience. The range of monthly MHDs is captured separately for the different health states (excluding death).

Based on the assessment of appropriate distributions, the model includes two different distributions, the beta binomial and the negative binomial, and different distributions are applied to the model populations:

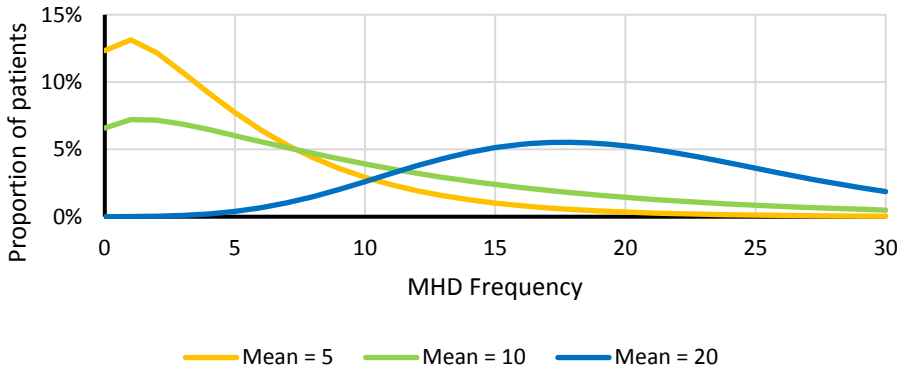
- **Episodic migraine and HFEM**: Negative binomial
- **Chronic migraine**: Beta binomial

The choice of distribution was based on goodness-of-fit analyses for the modelled populations. Alternative distributions were tested in scenario analyses.

A visual representation of how the distribution would look for different mean monthly MHDs is shown in

Figure 13 As can be seen the fluctuation and the likelihood around the chosen mean monthly MHD value can be incorporated in the model.

Figure 13 Illustrative example – Model monthly MHDs



B.3.2.2.4 Time horizon

The time horizon of the model is set to lifetime (defined as 25 years) in the base case. Previous models have used a variety of time horizons ranging from 2 years in the technology appraisal for botulinum toxin A [6] to 10 years in the appraisals for erenumab and fremanezumab [12, 150] The NICE committee has pointed out that a time horizon of 10 years is still not sufficiently long enough to capture all relevant costs and outcomes associated with the intervention and recommended a longer time horizon [12, 150]. In the base case analysis, a 25-year time horizon was selected since this period is expected to capture all appropriate material effects on benefits and costs. For longer time horizons, the uncertainty from short-term clinical trial data would inherently make any long-term estimates unreliable. Furthermore, migraine affects predominately women and the natural course of disease suggests that prevalence of migraine reduces significantly after menopause [44]. However, it should be noted that effect of the natural history of the disease was not modelled due to lack of evidence. Shorter and longer time-horizons will be explored in sensitivity analyses.

B.3.2.2.5 Cycle length

The model utilises monthly cycles (30 days) over which transitions are modelled and costs and outcomes accrued. This is convenient for modelling the treatment regimens and appropriate given the treatment cycle of galcanezumab and the trial definition of monthly MHDs applied in the phase 3 clinical trial programme of galcanezumab. Due to the short cycle length, a half cycle correction was not included in the model. Sometimes, half-cycle correction is implemented, reflecting that in a Markov cohort, it is assumed that transitions happen at the end of each cycle. In reality, however, patient transition is a continuous process, which may occur during any time in the cycle [152]. To address this, a half-cycle correction may be used, which assumes that state transitions occur, on average, halfway through the cycle. However, in this case, the cycle length (one month) is sufficiently short so that half-cycle corrections do not need to be applied.

Furthermore, it has been argued that half-cycle corrections do not affect estimated incremental costs and benefits and may therefore not be needed in economic evaluations [153].

B.3.2.2.6 Model perspective

The perspective was that of the UK National Health Service (NHS) and Personal Social Services (PSS) aligned with the NICE reference case. A societal perspective has been included as part of a sensitivity analysis and is presented in Appendix R.

B.3.2.2.7. Discount rate

Discount rates of 3.5% per annum were applied to both costs and benefits in the base case in line with the NICE reference case.

Differences between the current appraisal and previous appraisals in this therapy area are summarised in Table 49.

Table 49 Features of the economic analysis

	Previous appraisals	**Current appraisal**	
Factor	**TA260 Botulinum toxin [6]**	**Chosen values**	**Justification**
Model structure	Markov model	Semi-Markov model	Based on a review of literature and early scientific advice relating to a Markov model grouping categories of MHDs as employed in the Botulinum toxin A model (NICE TA260) being too complicated.
Cycle length	12 weeks	Monthly (30 days)	Cycle length is chosen to match the monthly duration in the Phase 3 trials of galcanezumab
Time horizon	2 years	Lifetime (25 years)	Long enough to capture all material effects on benefits and costs. Scenario analyses exploring alternative time horizons were conducted
Source of utilities	Patient-level MSQ data from clinical trials	Patient-level MSQ v.2.1 data from CONQUER (for patient with history of treatment failure) mapped onto EQ-5D-3L utility scores using an existing mapping function [154]	While EQ-5D is the preferred measure by NICE, it was administered at baseline and once again at 3 months at the end of the double-blind period of the study. The recall period of “today” is particularly insufficient in migraine as he EQ-5D was administered during the study visit and patients experiencing a migraine

			would have been unlikely to attend in person. Thus, the full impact of migraine on HRQoL may not have been captured when using the EQ-5D. In comparison, the MSQ questionnaire was administered monthly throughout the randomised and open-label phases of the trial and has a 4-week recall period. Therefore, the MSQ instrument was able to better capture more granular changes in health-related quality of life compared to EQ-5D-5L.
Source of drug costs	Based on one 200IU vial of botulinum toxin at £276.40, and an administration cost of £116.00, leading to a total cost of £392.40 per 12-week cycle.	Based on one 200IU vial of botulinum toxin at £276.40, and an administration cost of £116.00, leading to a total cost of £392.40 per 12-week cycle. The net price of galcanezumab after application of the confidential discount is [redacted]	Established sources of drug costs within the NHS Galcanezumab and Botulinum toxin costs were taken from the BNF [155] and MIMS [156, 157] A full hour of outpatient clinic time was assumed based on the conclusions from the NICE technology appraisal for botulinum toxin A which states a half-hour administration is an underestimate [6]
Source of other costs	International Burden of Migraine study, PSSRU, NHS reference costs, Annual Survey on Hours and Earnings and International Burden of Migraine study (IBMS)	BNF, NHS Tariff and PPRSU	Established sources of resource use costs within the NHS
Resource use	International Burden of Migraine study (IBMS)	Trial-specific data and Lipton et al 2018 [145]	Provided the granularity of use as it applied to each MHD for which costs could be applied to
Health effects measure	QALYs	QALYs	NICE reference case
Discount rate for costs and benefits	3.5% per year	3.5% per year	NICE reference case
Perspective	NHS	NHS/PSS	NICE reference case

Half cycle correction applied	Yes	No	The cycle length (one month) is sufficiently short so that half-cycle corrections do not need to be applied. Furthermore, it has been argued that half-cycle corrections do not affect estimated incremental costs and benefits and may therefore not be needed in economic evaluations [153]

Abbreviations: BNF: British National Formulary; EQ-5D: EuroQol Five-Dimensions; IBMS: Institute of Biomedical Science; MHD: monthly headache day; MMD, monthly migraine day; MSQ, Migraine-Specific Quality-of-Life Questionnaire; NICE: National Institute for Health and Care Excellence; NHWS: National Health and Wellness Survey; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life year.

B.3.2.2 Intervention technology and comparators

Intervention

The intervention of interest in all modelled populations is galcanezumab, a humanised monoclonal antibody that potently and selectively binds to and inhibits calcitonin-gene-related peptide (CGRP). Galcanezumab is indicated for the prophylaxis of migraine in adults who have ≥4 migraine days per month. The licensed dose is 120 mg injected subcutaneously (SC) once monthly, with a 240-mg loading dose as the initial dose. In the base case and all scenarios, the posology was modelled in combination with BSC, which is defined as continued treatment with acute medication and healthcare resource use associated with the MHD frequency experienced. Galcanezumab was assumed to be self-administered continuously with no treatment breaks. Patients stop treatment only for reasons of discontinuation due to adverse events and lack of response.

Efficacy and safety data on galcanezumab (120 mg with an initial dose of 240mg) implemented in this model were taken from the following key clinical trials which involved different patient populations: post hoc analysis of EVOLVE-1 and 2 (episodic migraine), post hoc analysis of REGAIN (chronic migraine), CONQUER (episodic and chronic migraine) and CGAJ (open-label safety study in episodic and chronic migraine).

Comparators

The comparators included in the model have been informed based on the current standard of care for the different populations of interest along with the available literature identified from the clinical SLR. Also, the selection of comparators was informed by the NICE technology appraisals for erenumab and fremanezumab for preventing migraine [12]. Most patients with migraine who have a history of ≥3 prior preventive treatment failures would either use botulinum toxin A (patients with chronic migraine only) or BSC. A fourth oral preventive treatment is unlikely to have a clinically meaningful benefit [12]. For episodic migraine and HFEM, BSC was the comparator of choice, while for chronic migraine, BSC and botulinum toxin A were considered comparators in the model. As discussed in Section B.1.1, data from the placebo-controlled group from the galcanezumab clinical trial programme was used to represent BSC.

BSC is the most relevant comparator for the base case modelled populations and all sensitivity analyses in this submission. As per NICE guidance, the BSC for management of migraine includes acute treatments that can alleviate symptoms within ~2 hours of the attack [64]. Unless contraindicated, these may include simple analgesics (i.e. ibuprofen, aspirin or paracetamol) or a triptan with or without paracetamol or an NSAID. Oral triptans (e.g. sumatriptan) are recommended unless vomiting restricts treatment [64]. Anti-emetics (e.g. metoclopramide or prochlorperazine) should be considered even in the absence of vomiting [64]. BASH guidelines recommend use of a stratified approach based on severity of attack versus a stepped approach based on evidence supporting better health related outcomes and lower indirect costs [66]. Clinical trials evaluating galcanezumab in migraine were designed using placebo as a comparator. The placebo arm of the CONQUER study serves as a suitable proxy for BSC comparator arm in the model for responder / non-responder analyses. Throughout the study patients in both arms were permitted to take acute medication to treat migraine attacks if needed. The list of permitted medications included triptans, NSAIDs, paracetamol or paracetamol combinations (e.g. Migraleve) with some restrictions to the use of opioids and barbiturates [107]. Data collected from the CONQUER trial reveals that the acute treatments most used by patients in the study (by decreasing percentage) were sumatriptan and ibuprofen, paracetamol, eletriptan, rizatriptan, naproxen among others [107]. These represent acute treatments that would normally be prescribed in NHS clinical practice for the management of migraine symptoms [64].

Botulinum toxin A has been recommended in patients with chronic migraine with a history of ≥3 prior oral prophylactic treatment failures [6]. The use of botulinum toxin A in this patient group is restricted as administration must be performed by trained physicians. However, botulinum toxin A is also considered a relevant comparator for this population because it is available to some patients and was included as comparator in the technology appraisals for erenumab and fremanezumab [12, 150]

The model adopted a dynamic approach where comparators will be considered in the model if the required efficacy parameters have been populated. The comparators considered for this submission are summarised in Table 50.

Table 50 Galcanezumab comparators by population

	Galcanezumab	Botulinum toxin type A	BSC
Episodic – history of ≥3 failed preventive treatments	✓		✓
High frequency episodic migraine (HFEM) - history of ≥3 failed preventive treatments	✓		✓
Chronic - history of ≥3 failed preventive treatments	✓	✓	✓

B.3.3 Clinical parameters and variables

Clinical parameters were derived from the subgroup of patients that had a history of ≥3 prior preventive treatment failures from the CONQUER trial (patients with chronic migraine and patients with episodic migraine), pivotal trials; REGAIN (patients with chronic migraine) and,

EVOLVE-1 and EVOLE-2 (patients with episodic migraine), and from the long-term open-label study CGAJ (patients with episodic and chronic migraine). Where feasible, data was pooled.

- Mean CFB in the monthly number of MHDs over 3-months
    - **Galcanezumab and botulinum toxin A** – pooled data from CONQUER and REGAIN from the ITC to botulinum toxin A
- Responder and non-responder mean CFB in the monthly number of MHDs over 3-months
    - **Galcanezumab and BSC** – CONQUER only
- 30% reduction from baseline in the monthly number of MHDs over 3-months (chronic migraine only)
    - **Galcanezumab and botulinum toxin A** – CONQUER only
- 50% reduction from baseline in the monthly number of MHDs over 3-months (episodic migraine and HFEM)
    - **Galcanezumab and BSC, episodic**– pooled data from CONQUER and EVOLVE-1 and -2
    - **Galcanezumab and BSC, HFEM** – CONQUER

B.3.3.1 Baseline patient characteristics

The baseline patient characteristics used in the model are from the CONQUER study and are specific to the population of interest shown in Table 51. No differences in population characteristics are assumed between interventions. The age and gender parameters are used to calculate background mortality. The mean monthly MHD shown in Table 51 is required to model the CFB in MHD over the assessment period.

Table 51 Baseline patient characteristics

	Age (years)	Gender (% Female)	Mean MHD	Reference
Episodic - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]	CONQUER CSR: table CGAW.14.153[107] CONQUER CSR: table CGAW.14.154[107]
High frequency episodic migraine (HFEM) - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]	CONQUER CSR: table CGAW.14.155[107] CONQUER CSR: table CGAW.14.156[107]
Chronic - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]	CONQUER CSR: table CGAW.14.157[107] CONQUER CSR: table CGAW.14.158[107]

B.3.3.2 Treatment efficacy

The treatment efficacy is captured through two aspects in the model: mean CFB over 3 months in monthly MHDs and discontinuation due to AEs. The mean change from baseline in monthly MHDs was taken from the galcanezumab trials and the ITC of galcanezumab compared to botulinum toxin A. Discontinuation rates were informed from the clinical trial programmes for galcanezumab and botulinum toxin A separately, an ITC of discontinuation due to AE's was not feasible (See Section B.2.8).

B.3.3.2.1 Distribution parameters

To approximate the distribution of monthly MHDs around the mean monthly MHD in the post assessment period (second part of the model), statistical distributions for count data were chosen and applied. The Poisson, negative binomial, binomial, beta-binomial and zero-inflated negative distributions were explored for fit against the observed mean MHDs data from the trials. The negative binomial and beta binomial were chosen based on goodness of fit statistics and applied to the episodic and chronic populations, respectively. The distributions were fitted to the whole naïve and treatment experienced trial population MHDs from EVOLVE-1, EVOLVE-2 and REGAIN, and checked against the treatment-resistant populations from REGAIN and CONQUER. Table 52 presents the results from the regression analysis, associated with the negative binomial and beta-binomial distributions, to estimate the dispersion parameter around the mean MHDs. Full methodology for the choice of distributions are provided in Appendix S.

Table 52 Distribution parameters

	Episodic migraine	Chronic migraine
Negative binomial		
Intercept	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Mean Square	[redacted]	[redacted]
Source	Based on a fitted distribution to the observed data from EVOLVE-1 and -2* [158], [159]	Based on a fitted distribution to the observed data from REGAIN* [158], [159]
Beta-binomial		
Intercept	[redacted]	[redacted]
Mean	[redacted]	[redacted]
Mean Square	[redacted]	[redacted]
Source	Based on a fitted distribution to the observed data from EVOLVE-1 and -2* [158], [159]	Based on a fitted distribution to the observed data from REGAIN* [158], [159]

*validated against the CGAW trial which supported the same parameters could be used

B.3.3.2.2 Mean change from baseline in MHD

The CFB in MHD is dependent upon population and treatment and assessed over the first 3 months. The analysis has parameters for 3 months (90 days) that aligns with the assessment of

response. The change from baseline is applied to the population specific baseline MHD. The MHD is limited in the model between the bounds of 0 and 30, based on the number of days in a treatment cycle from the galcanezumab trials. The mean CFB in MHDs is applied to each health state in the model and used in the distribution to calculate the number of patients experiencing each frequency of MHD. The model considers two options to apply the mean change MHDs: either by response known as the responder criteria (i.e. mean change monthly MHDs for responders and non-responders separately, defined either by a 30% or 50% mean reduction in monthly MHD from baseline) or by combined population known as the combined criteria (i.e. responder and non-responder mean change monthly MHDs combined).

Beyond the trial data, mean change in monthly MHDs is assumed to remain constant until the end of the time horizon. This is supported by long-term follow-up data from REGAIN (chronic only) and CGAJ and is aligned with other economic models [12, 150].

In summary, the base case assumes the following:

- **Galcanezumab vs BSC in episodic migraine (and HFEM):** responder criteria
- **Galcanezumab vs BSC in chronic migraine:** responder criteria
- **Galcanezumab vs botulin toxin A:** combined criteria

Mean change from baseline (combined criteria)

The mean change was populated from the ITC compared to botulinum toxin A. The ITC estimated the CFB directly for galcanezumab compared to botulinum toxin A. Since the model splits the population by responders and non-responders at the point of assessment of response, the mean change is thus applied to both groups when looking at a combined population of responders and non-responders for the comparison to botulinum toxin A. The response assessment still takes place to account for the negative discontinuation rule at 3 months. It is important to highlight that the ITC to botulinum toxin A was based on evidence from two 3-month Phase 3, multicentre, randomised, double-blind, placebo-controlled studies of galcanezumab (REGAIN and CONQUER), and two 24-week Phase 3, multicentre, double-blind, placebo-controlled studies, (PREEMPT 1 and PREEMPT 2) in patients suffering from chronic migraine. The shorter randomised double-blind trial duration of REGAIN and CONQUER is likely underestimating the treatment effect as the open-label extension data of REGAIN show a further [redacted]

Table 53 shows the mean change from baseline for the different populations considered in the model.

Table 53 Mean change – month 3

	Chronic - Failed at least 3 preventive treatments	Reference
Galcanezumab	[redacted]	Indirect comparison of galcanezumab versus Botox, pooled data from REGAIN and CONQUER: Section [redacted] B.2.8.1, Table 40

Botulinum toxin type A	[redacted]	Indirect comparison of galcanezumab versus Botox: Section 2.8.1, Table 40 mean difference of -2.30 (fixed effects model)

B.3.3.2.3 Response based mean change

For the analysis compared to BSC that considers direct head-to-head data from the trial, the mean CFB in monthly MHD is linked to the response criteria (50% for episodic migraines and HFEM. or 30% for chronic migraines)

Individual patient level data from CONQUER in the patient populations of interest were analysed and results are, shown in Table 54 for a 50% definition of response Table 55 for a 30% definition of response. As with the combined population, the CFB in MHD at 3 months has been analysed. The results of this analysis show that responders have a comparable mean change when stratified by response status, regardless of treatment. It is important to note that the proportion of patients achieving this CFB in MHD is greater in patients receiving galcanezumab compared to BSC in CONQUQER which suggests that the differences in treatment is driven by differences in response rates.

Table 54 Change from baseline in Migraine Headache Days for responders and non-responders at month 3 (50% response rate)

	Responders		**Non-responders**		**Source**
	N	**Mean CFB in MHD**	**N**	**Mean CFB in MHD**	
Episodic - Failed at least 3 preventive treatments					
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	CONQUER [160]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
High frequency episodic migraine (HFEM)					
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	CONQUER [160]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	

Table 55 Change from baseline in Migraine Headache Days for responders and non-responders at month 3 (30% response rate)

	Responders		**Non-responders**		**Source**
	N	**Mean CFB in MHD**	**N**	**Mean CFB in MHD**	
Chronic - Failed at least 3 preventives					
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	CONQUER [160]
BSC					

As data for the mean change by response for botulinum toxin A could not be identified in the clinical SLR, it is not possible to compare the values for galcanezumab to botulinum toxin A. A scenario analysis is explored using the estimated responder and non-responder MHDs for botulinum toxin A. It was possible to estimate the CFB for responders by assuming that the non-responders had the same mean MHD change as the BSC patients which is taken from the population specific inputs. However, this should be used with caution as it is only an estimation. Methodology for this approximation is provided in Appendix T.

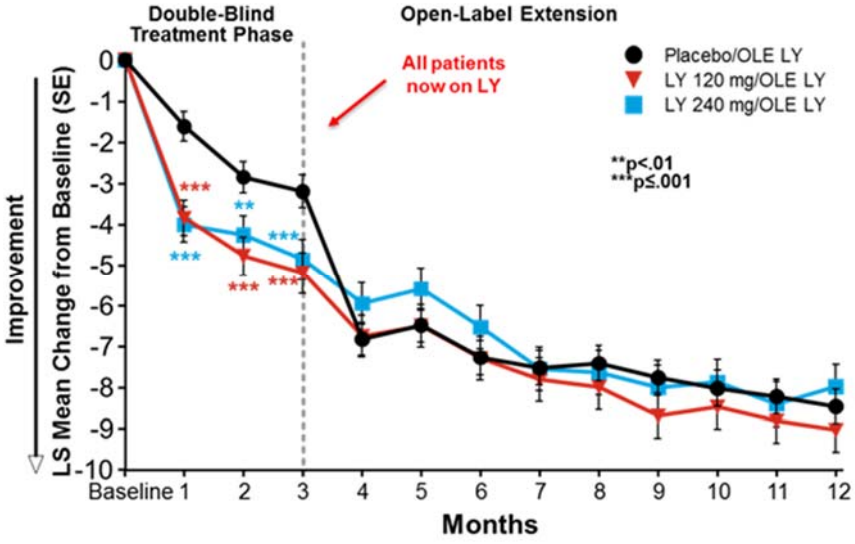
B.3.3.2.4 Mean change extrapolation

The mean monthly MHDs are extrapolated over a 25- year time horizon, beyond the 3- month clinical trial data. The base case assumes the mean change in monthly MHD (and number of MHDs experienced) is constant for patients remaining on treatment after the response assessment and is applied from the third cycle until the end of the time horizon. Treatment waning effects were not explored. This assumption is aligned with data collected from OLE/REGAIN (chronic migraine patients), CGAJ (episodic and chronic patients), and additional economic models for migraine [139]

REGAIN open-label period

Of the 1,037 patients who completed the double-blind treatment phase of REGAIN, 1,022 (98.6%) entered the open-label treatment phase; 259 of whom received galcanezumab 120mg previously and 78.8% of these completed the OLE phase. Results across the full nine months of the open-label treatment phase indicated overall durability of treatment effect, with the previous 120 mg group generally improving upon their gains from the double-blinded treatment phase. Mean change from double-blind baseline (Month 0) to Month 12 in the previous galcanezumab 120 mg group was -9.0 MHDs (Figure 14). The results for 50% improvement over

Figure 14 LS Mean Change from Baseline in REGAIN (open-label extension phase)



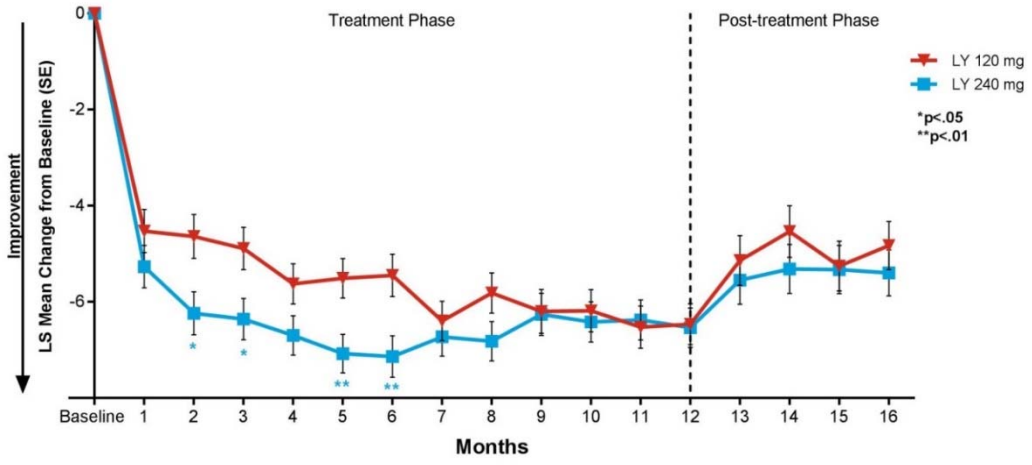
CGAJ open-label study

341 patients entered the study and 270 patients were randomized. All randomized patients received at least 1 dose of galcanezumab and were included in the ITT population, including 135 patients who received galcanezumab 120 mg. Overall, 210 patients (77.8%) completed the open-label treatment phase, including 97 patients (71.9%) in the galcanezumab 120 mg treatment group. The overall mean reduction from baseline, in the number of monthly MHDs over the 12-month open-label treatment phase was 5.6 days for the galcanezumab 120 mg population. From the end of the 12 month open-label treatment period to the end of the post-treatment washout period at month 16, the mean CFB in monthly MHDs for the galcanezumab 120 mg population increased by an average rate of 0.9 MHD. The mean percentage of patients with a ≥30% and

≥50% reduction in the number of monthly MHDs during the 12-month treatment phase was 76.1%, respectively 65.6% in the galcanezumab 120 mg treatment group (

Figure 15)

Figure 15 LS Mean Change from Baseline in Study CGAJ



Furthermore, tests for immunogenicity reveal only a small percentage of patients develop anti-drug antibodies (ADA). At baseline, ADAs were prevalent in 6.9% and 10.1% of patients in the galcanezumab 120-mg and 240-mg arm respectively. Treatment-emergent ADAs were greater in

patients in the galcanezumab 120-mg arm (26.7%) compared to the galcanezumab 240-mg arm (12.8%). During the post-treatment phase, 19 patients became treatment-emergent ADA.

Pharmacokinetic/pharmacodynamic analyses of galcanezumab revealed that galcanezumab serum concentrations appeared to increase proportionally with dose. Galcanezumab or CGRP concentrations were similar when compared across various ADA titer categories suggesting that ADA has no appreciable effect on the PK of galcanezumab nor does it interfere with the binding of the CGRP ligand to the galcanezumab antibody. The PK and PD results in the 1-year open label study were consistent with shorter-duration studies having 6-month and 3-month treatment phases in patients with episodic migraine and patients with chronic migraine, respectively (See Appendix C – EPAR).

B.3.3.2.5 Response rates

Assessment of response has been included in the model in line with the marketing authorisation of galcanezumab to inform the negative discontinuation rule [1]. Response to treatment is assessed at day 90. To identify the proportion of patients continuing treatment beyond month 3, the base case assumes a response rate as a reduction in monthly MHD of 50% or greater from baseline for patients with episodic migraine and patients with HFEM and 30% or greater for patients with chronic migraine. Both are considered clinical meaningful in its respective patient population [12, 69, 151] The proportion of chronic migraine patients with a history of at least 3 prior preventive treatment failures experiencing a 30% or greater reduction in MHD response rate was informed by CONQUER only . For patients with episodic migraine who have a history of ≥3 prior preventive treatment failures, pooled data from CONQUER and EVOLVE-1 and EVOLVE-2 were considered. Given the very low patient numbers of HFEM patients with a history of at least ≥3 prior preventive treatment failures in EVOLVE-1 and EVOLVE-2, only data from CONQUER were considered.

The response rate is taken from evidence synthesis where evidence is available. Table 56 shows the 50% response rates used in the model. Table 57 shows the response rates used for 30%, which is only used for chronic migraine. There was no data for ≥30 response rate for botulinum toxin A in patients who have experienced ≥3 prior failures identified in the clinical SLR. Therefore, the response rate for botulinum toxin A is assumed to be equal to galcanezumab based on [redacted] between galcanezumab and botulinum toxin A for the 50% response rate in the all-comers population (see section 2.8.1, table 40).

Table 56 Response rates at 50%

	Galcanezumab	Botulinum toxin type A	BSC	Reference
Episodic - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]	Pooled data from CONQUER, EVOLVE-1, and EVOVLE-2[161]
High frequency episodic migraine (HFEM) - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]	CONQUER CSR, table CGAW.14.172 [107]

Chronic - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]	Indirect comparison of galcanezumab versus Botox, pooled data from REGAIN and CONQUER: Section B.2.8.1

NA, not applicable

Table 57 Response rates at 30%

	Galcanezumab	Botulinum toxin type A	BSC	Reference
Chronic - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]	CONQUER CSR, table CGAW.14.174 [107]

B.3.2.2.6 Discontinuation

Patients can discontinue from treatment in one of three ways:

1. Discontinuation due to lack of response (50% response rate for episodic migraine and HFEM, and 30% response rate for chronic migraine patients) at the end of the assessment period (month 3) – See Section B.3.2.2.6.1

2. Discontinuation due to adverse events during the first 90 days – See Section B.3.2.2.6.2

3. Long-term discontinuation in the post-assessment period (month 4 onwards) – See Section B.3.2.2.6.3

B.3.2.2.6.1 Discontinuation due to lack of response (50% response rate for patients with episodic migraine and patients with HFEM and 30% response rate for patients with chronic migraine) at the end of the assessment period

All patients considered to be non-responders at month 3 transition to an off-treatment health state where they receive BSC. The proportion of patients who discontinue due to lack of response is informed directly by the clinical trials for galcanezumab and BSC and, assumed equal for galcanezumab and botulinum toxin A due to the lack of data identified from the clinical SLR so evidence could not be synthesised (see section B.3.3.2.5)

B.3.2.2.6.2 Discontinuation due to adverse events during the first 12 weeks

Patients could discontinue due to adverse events during the first 3 months of the model (assessment period). The values used in the model are based on CONQUER for the respective treatments. The discontinuation due to adverse events is assumed to happen at the same time as the assessment of response, and after discontinuing active treatment patients go back to baseline monthly MHDs. Table 58 summarises the discontinuation rate for the assessment period.

Table 58 Probability of discontinuation due to adverse events across the first 3 months

	Probability of discontinuation	Reference
Episodic migraine – patients, for whom prior preventive treatments failed		
Galcanezumab	[redacted]	CONQUER CSR [107]
BSC	[redacted]	CONQUER CSR [107]
High-frequency episodic migraine – patients, for whom prior preventive treatments failed		
Galcanezumab	[redacted]	CONQUER CSR [107]
BSC	[redacted]	CONQUER CSR [107]
Chronic migraine – patients, for whom prior preventive treatments failed		
Galcanezumab	[redacted]	CONQUER CSR [107]
Botox*	[redacted]	Diener et al. 2014 [96]
BSC	[redacted]	CONQUER CSR [107]

* only applicable for chronic migraine patients with a history of at least 3 prior treatment failures

B.3.2.2.6.3 Long-term discontinuation due to adverse events (after 90 days)

After the initial 3 months of treatment, patients who did respond to treatment could further discontinue galcanezumab due to adverse events. CGAJ, a phase III, multicentre, randomised, open-label study assessing the long-term (12-month) safety and tolerability of galcanezumab in patients with episodic migraine or chronic migraine was used to inform this discontinuation rate [106]. A total of [redacted] the open-label phase due to an adverse event. The discontinuation rate was further adjusted to match a monthly cycle rate resulting in a discontinuation rate of [redacted] per cycle. The discontinuation rate is based on the full trial population that entered CGAJ as the number of patients with a history of ≥3 prior preventives treatment failures were too few. For comparison, during the OLE period of CONQUER, [redacted] galcanezumab-treated patients ([redacted] discontinued the study due to an AE resulting in a discontinuation rate of 0.37% [107]. Given the short follow up period in CONQUER, it was decided to use the long-term data of CGAJ.

The model only incorporates a discontinuation rate for dropouts due to AEs from the clinical trials. This is because no positive discontinuation rule was applied in the model for patient and physician decision to stop treatment due to long-term stability of treatment response. All-cause discontinuation was included in an exploratory analysis.

Table 59 Rate of discontinuation beyond assessment period (after 90 days)

	Probability of discontinuation	Reference
Discontinuation due to AEs		
Galcanezumab	[redacted]	Study CGAJ [106]
Botulinum toxin A*	[redacted]	COMPEL trial [162]
BSC	[redacted]	Study CGAJ [106]
Discontinuation for all-cause reason		
Galcanezumab	[redacted]	Study CGAJ [106]
Botulinum toxin A*	[redacted]	REPOSE trial [163]
BSC	[redacted]	Study CGAJ [106]

* only applicable for patients with chronic migraine with a history of at least 3 prior preventive treatment failures

B.3.3.2.6.5 Mean change after discontinuation

Mean change for the BSC arm

For patients on BSC who discontinue, either for non-response or due to adverse events the mean change monthly MHDs returns to the baseline value based on patients losing their placebo effect immediately in the next cycle. For patients on BSC who respond at the point of assessment at month 3 it is assumed that these patients return to baseline monthly MHDs over a period of 1-year. A return to baseline monthly MHDs for both BSC responders and non-responders means that the placebo effects encountered in the trial are negligible in the model. This assumption is based on the NICE committee's preferred assumptions from NICE technology appraisal of fremanezumab [150] where it states that the placebo response observed during the clinical trial would not be seen in clinical practice. The base case assumptions for the BSC arm is applied to both the episodic and chronic analyses, as well as for the HFEM subgroup.

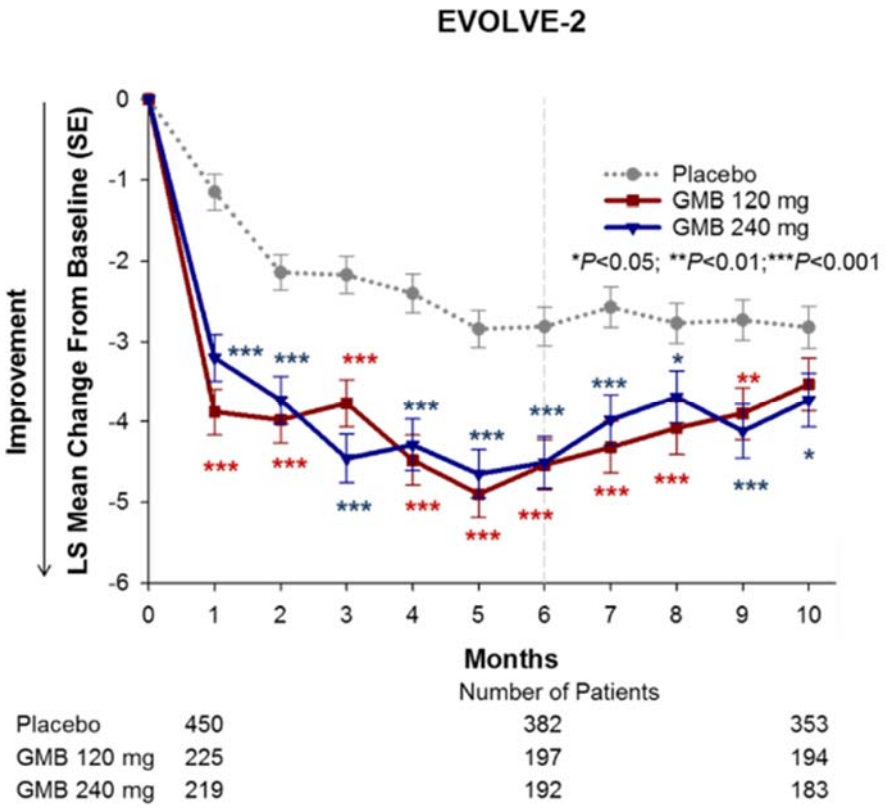
An alternative scenario has been included in the model where the placebo effect is continued for the remainder of the time horizon. BSC-responder mean change monthly MHDs from the assessment point at month 3 is modelled throughout without any post-assessment period discontinuers returning to baseline monthly MHD (as a 0% discontinuation rate is used in the post assessment period for the BSC arm). This is a conservative assumption considering patients who discontinue due to lack of response and AEs in the galcanezumab arm also go back to baseline monthly MHDs.

An additional scenario is explored, in which patients transition over 13 months (episodic) or at a rate of [redacted] migraine headache days per cycle (chronic) to the mean change monthly MHDs of BSC non-responders, to explore the impact of incorporating a lesser placebo effect.

Mean change for the galcanezumab arm

For patients who discontinue galcanezumab, either due to non-response or adverse events, transition to the off-treatment health state, go back to baseline monthly MHD and are assumed to receive BSC only. These patients are assigned the non-responder mean change monthly MHDs and return to baseline monthly MHDs values over time. The wane back to baseline monthly MHDs occurs at different rates for patients with episodic and chronic migraine. For patients in the galcanezumab arm with episodic migraine in the base case, patients who discontinue treatment return to baseline over [redacted] based on data observed from the episodic trial wash out periods. A simple quadratic function was fitted to the wash out data from EVOLVE-2 (shown in Figure 16) to predict the time required when MHDs return to baseline. Analysis of the pooled individual patient level data from EVOLVE-1 and EVOLVE-2 was conducted but the regression models produced implausible predictions. In addition, the assumption of treatment waning effect is closely aligned with the assumption on placebo treatment waning effect.

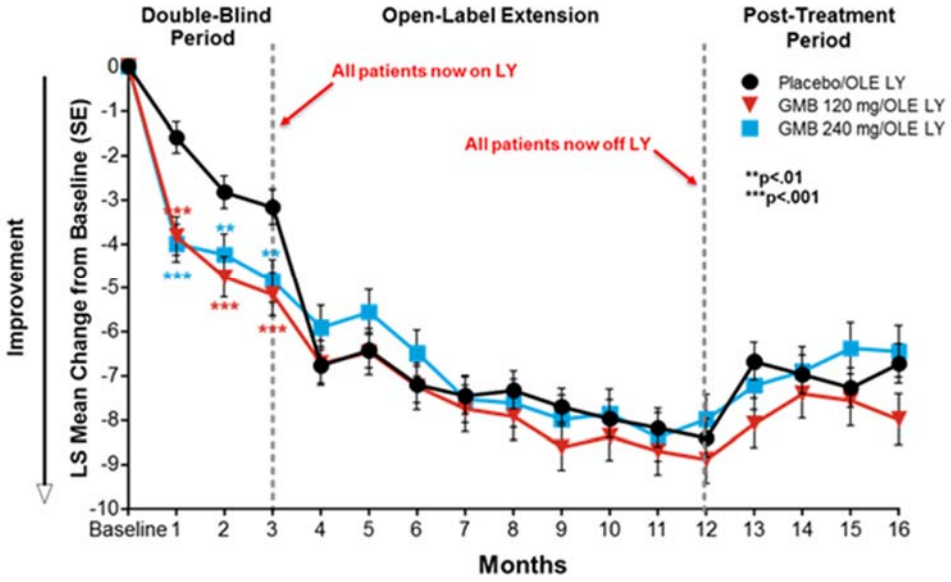
Figure 16 Washout data –EVOLVE-2 [99]



For the patients with chronic migraine, the REGAIN trial (shown in

Figure 17) had an open label extension which meant that all patients received galcanezumab from month 3 to month 12, meaning it is not possible to compare galcanezumab discontinuation to placebo. Due to this, the rate of mean change in monthly MHD decline has been calculated from the wash out period from [redacted]. A rate of decline of [redacted] per cycle was applied to the chronic population based on this data.

Figure 17 Washout data – REGAIN



A conservative exploratory analysis was conducted where patients with episodic or patients with chronic migraine who discontinue galcanezumab return to baseline MHDs over 5 cycles, based solely on the observed data (after patients receive their last dose in the trials) shown in Figure 16 and

Figure 17.

To note, the estimated rate of treatment waning after discontinuation for the galcanezumab arms is based on the total population enrolled in the pivotal trials. It was not feasible to conduct an analysis for the subgroup of patients what have a history of ≥3 prior preventive treatment failures due to small numbers.

B.3.3.2.6.3 Summary mean change

A summary of the mean change and the data sources over time has been provided in Table 60.

Table 60 Summary of mean change assumptions in the model

Model treatment arm	Discontinuation due to AE – assessment period	Responders	Non-responders	Discontinuation due to AE – post assessment

Galcanezumab	One-off rate of 0.43% applied for the first 3 cycles Discontinue active treatment and switch to BSC Switch to non-responder MHDs and wane back to baseline MHDs over time (over 13 cycles for episodic and at rate of 0.23 MHDs per cycle for chronic) Baseline MHDs maintained until end of time horizon	Continue with active treatment Maintain responder MHDs until end of time horizon (comparison to BSC) Maintain combined (responder and non-responder) MHDs until end of time horizon (comparison to botulinum toxin A)	Active treatment until day 90 then switch to BSC Non-responder stratified mean change MHDs from baseline applied from month 3 and effect wanes back to baseline MHDs over time (over 13 cycles for episodic and at rate of 0.23 per cycle for chronic) Baseline MHDs maintained until end of time horizon	Per cycle discontinuation rate of 0.44% applied until end of time horizon Switch to non-responder stratified mean change MHDs from baseline applied from month 3 and effect wanes back to baseline MHDs over time (over 13 cycles for episodic and at rate of 0.23 per cycle for chronic) Baseline MHDs maintained until end of time horizon
BSC	0% discontinue due to AEs within trial period.	BSC until day 90 response assessment BSC responder mean change MHDs waned back to baseline MHDs over 12 cycles Baseline MHDs from cycle 15 maintained until end of time horizon	BSC treatment until day 90 Mean change from baseline until month 3 MHDs until day 90 then switch to baseline MHDs immediately in the next cycle	0% per cycle discontinuation No patients remain on BSC mean change MHDs in the post assessment period after 15 cycles
Botox	One-off rate of 3.4% applied for the first 3 cycles Discontinue active treatment and switch to BSC Combined population (responder and non-responder) MHDs wanes	Continue with active treatment Maintain combined population (responder and non-responder) MHDs until end of time horizon	Active treatment until day 90 then switch to BSC Switch to combined population (responder and non-responder) MHDs and wane back to baseline mean change MHDs over 3 cycles.	Per cycle discontinuation rate of 0.1% applied until end of time horizon Switch to combined population (responder and non-responder) MHDs and wane back to baseline

	back to baseline MHDs over 3 cycles Baseline MHDs maintained until end of time horizon		Baseline MHDs maintained until end of time horizon	MHDs over 3 cycles. Baseline MHDs maintained until end of time horizon

B.3.3.2.7 Adverse events

Adverse events have not been explicitly modelled due to the small number of patients experiencing serious adverse events, their transient nature, the limited impact these would have on resource use and subsequently on the overall results, and to avoid double counting since discontinuation due to adverse events has been included in the model.

The impact of the adverse events on the utility values from the trial is still included in the model by modelling discontinuation due to AEs, therefore explicitly capturing the impact of adverse events on HRQoL would lead to double counting.

B.3.3.2.8 Mortality

In the cost-effectiveness analysis only all-cause mortality, based on the Office for National Statistics National life tables, is considered. Applying the population specific characteristics (see Table 51) to the life tables, allows the calculation of a monthly (cycle) mortality rate.

Given conflicting evidence shown in the literature regarding migraine-specific mortality, no additional mortality rate was considered in the model [164, 165].

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

EVOLVE-1, EVOLVE-2, REAGIN and CONQUER studies all collected the migraine-specific quality of life questionnaire (MSQ v2.1). The EQ-5D-5L quality-of-life instrument was administered in the CONQUER study only. The results are presented in section B.2.6.3.3.

The NICE reference case stipulates a preference for utility values derived directly from the clinical trials for the intervention using the EQ-5D instrument of quality-of-life, and that the valuation of health-related quality of life should reflect the preferences of a representative sample of the UK population.

Focus was on the results from HRQoL instruments used in the CONQUER study since it included patients who were treatment-resistant which directly relates to galcanezumab decision problem for this appraisal. Trial results for MSQ v2.1 and EQ-5D-5L (mapped to the EQ-5D-3L) were compared to assess which instrument produced reliable results for the economic analysis. Past appraisals for botulinum toxin A, erenumab and fremanezumab [6, 12, 150] for preventing migraine have preferred the MSQ over the EQ-5D stating the EQ-5D may not be sensitive and does not capture all the important symptoms of disease that impact patient's quality-of-life. A reason for this may be the insufficient recall period of "today" for the EQ-5D in migraine and the

frequency of administration in the clinical trials. The EQ-5D-5L instrument collects HRQoL information at a single point in time as it asks patients to complete the questionnaire based on how they feel 'today'. In addition, the instrument was administered at baseline and once again at study visit at 3 months at the end of the double-blind period of the study. Patients who experienced a migraine were unlikely to attend a study visit on that specific day. Given the recall period being today, it is therefore more likely to capture utility results similar to that of the population norm (see Figure 18). This may explain the differing results seen between the two instruments since patient's were asked to complete the questionnaire when they may not have been experiencing a migraine attack. In contrast, the MSQ was administered monthly throughout the randomised and open-label phases of the trial. The MSQ has a 4-week recall period therefore it may have the ability to capture the interictal burden, or impairment between attacks [166], as well as capturing more granular changes in HRQoL due to attacks in the preceding 4-weeks, which the EQ-5D is not able to do given the short 'one point in time' recall period.

A visual assessment of the individual patient utility values, the observed mean and the estimated mean utility values as a function of MHD are shown in Figure 18. This shows that there is minimal change in utility when measured using the EQ-5D compared to the MSQ with increasing monthly MHDs.

Figure 18 Utilities derived from the MSQ and from the EQ-5D-3L estimates, for each number of MHD, at Month 3 using CONQUER data

B.3.4.2 Mapping

MSQ utility data were mapped to the EQ-5D-3L to estimate the quality of life of patients, for the purpose of the economic model. The use of the EQ-5D-3L was chosen as per NICE guidance [167]. Utility values were estimated for each MHD frequency ranging from 0 to 30. Utilities were derived using a previously published mapping algorithm by Gillard et al [154]. which presents a

function which allows to map the results of the MSQ collected at each month for episodic and chronic migraine patients to the EQ-5D-3L using UK country-specific tariffs [154]. The utility models specified by Gillard et al. were used to further investigate: (i) whether episodic and chronic patients should be modeled independently or together, (ii) the functional form of the relationship between utilities and MHD, and (iii) whether the treatment effect variable should be included into the regression. Full details regarding the methodological approach associated with mapping MSQ to the EQ-5D-3L can be found in Appendix U.

B.3.4.3 Health-related quality-of-life studies

Full details for the methodology for the literature review can be found in Appendix H. The literature search yielded no results related to utility data while on galcanezumab treatment. As such, mapped values from the MSQ v.2.1, to the EQ-5D-3L, collected directly from the treatment-resistant population from the CONQUER study was applied in the base case.

B.3.4.4 Adverse reactions

Adverse reactions were not considered in the cost-effectiveness model of galcanezumab. See section B.3.3.2.7.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values estimated from mapping MSQ values to the EQ-5D-3L were deemed most appropriate for the economic model and adhered closest to the NICE reference case.

The on-treatment (pooled) utilities were selected for use in the economic model using MHD as the only covariate in the model (see Table 61). The final specified model is displayed below.

[redacted]

Even though including a treatment effect modifier was statistically significant, single pooled values were chosen based on recent NICE committee preferences from NICE technology appraisal for fremanezumab [150]. This conservative approach assumes utility values do not differ between model treatment arms; galcanezumab, BSC or botulinum toxin A. Differences in HRQoL is purely captured through differences in the efficacy parameters applied to the model.

Table 61 Utility values from us the economic model

MHD	On treatment (pooled)
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]

12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]
17	[redacted]
18	[redacted]
19	[redacted]
20	[redacted]
21	[redacted]
22	[redacted]
23	[redacted]
24	[redacted]
25	[redacted]
26	[redacted]
27	[redacted]
28	[redacted]
29	[redacted]
30	[redacted]

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The details of studies found in the literature review are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs are calculated by combining the cost per unit and the required number of units per cycle. The drug costs per pack are presented in

Table 62. The dosing and frequency of dose administration is shown in Table 63. Drug costs were sourced from British National Formulary (BNF) [155] and database of prescription and generic drugs, clinical guidelines (MIMS) [168]. Allowing a unit per cycle costing gives detailed reflections of the annual costs associated with each treatment.

The most relevant comparators are BSC for episodic migraine patients which comprises of self-administration of acute medications and resource use associated with the specific mean change MHDs. BSC was not associated with additional costs as both galcanezumab and active comparators are assumed to be given with the same acute medication received in BSC. For chronic migraine patients the most relevant comparator is botulinum toxin A. Botulinum toxin type A has a list price of £276.40 as per the dose recommended in the SmPC for chronic migraine (total dose range of 155 to 195 units) and we assume the costs of a 200IU vial applied every 12-weeks which also assumes no vial sharing. Costs were taken from the BNF [155] and applied only to the chronic migraine model where botulinum toxin type A is included as a comparator.

One-off administration and patient training costs for galcanezumab are applied in the first cycle only and assumed to be one hour of working time for a Band 5 hospital nurse which is £39.68.

Botulinum toxin A requires a trained specialist to perform each administration, which comprises of over 30 injections every 12 weeks. This is associated with a considerably greater administrative burden, incurring a cost per dose of £116.00, based on the cost of attending one follow-up neurologist outpatient appointment.

Table 62 Drug costs

	Pack size (Units)	mg per unit	Pack cost	Cost per Unit	Initial administration costs	Administration costs - ongoing	Reference
Galcanezumab 120mg	1	120	List price: £386.50 PAS Price: [redacted]	List price: £386.50 PAS Price: [redacted]	£39.68	£0.00	MIMS 2019 [168], NHS Tariff 19/20 [169] Assumed to be one hour of working time for a Band 5 hospital nurse which is £39.68
Botulinum toxin type A	1	200	£276.40	£276.40	£0.00	£116.00	BNF 2019 [155], NHS Tariff 19/20 [169] Assumed to be the tariff "WF01A Follow Up Attendance - Single Professional (code 400)" in the non-mandatory prices worksheet of the 2017/2018 tariffs [170] which aligns with the NICE costing template [6]

The model allows for a loading dose and different dosing cycles based on the product characteristics for the treatment. For the loading dose, this is applied in the first cycle of treatment and is applied in addition to the maintenance dose.

Table 63 Drug dosing

	Type of dose	Dose (mg)	Administration per cycle	Frequency	Dose per cycle (mg)	References
Galcanezumab		120	1	30	120	SmPC Galcanezumab [1]

Galcanezumab	Loading dose	120	1			SmPC Galcanezumab [1]
Botulinum toxin type A		200	1	84	71.43	SmPC Botulinum toxin type A [171]

B.3.5.2 Health-state unit costs and resource use

The model considers resource use by each MHD, an approach identified from the literature review by Lipton et al [145]. The paper took annual average medical resource use for physician visits (GP visits), emergency room visits (A&E visits), hospitalisations, and specialist neurologist consultation (neurologist visits) from a US-specific survey of migraine patients [172]. Resource use per MHD was estimated by dividing the annual average use by the annual number of headache days reported by patients. Table 64 shows the costs used per resource and the average use per year, and the associated use per migraine headache day. Clinical feedback suggested that nurse specialist visits was also an important direct medical resource, therefore, it was assumed to be equal to the rate of GP visits since this data was unavailable from the Lipton et al. paper.

Using published resource use by Lipton et al. had several limitations: (i) it was not specific to the target population who had a history of ≥3 prior preventative treatment failures, (ii) it used headache days to estimate resource use per MHD, and (iii) it did not include UK-specific patients. These estimates were compared to the recent values used in the NICE technology for Erenumab and fremanezumab for validity[12, 150]. However, one of the strengths of the approach taken by Lipton et al. is that it does provide the rate of resource use associated with each MHD frequency, which is aligned with our model structure More details are presented in Appendix I.1.

Table 64 Resource costs

Medical resource	Unit cost	Average use per year	Use per migraine day	References
GP visits	£37.40	0.72	0.0379	PSSRU 2018 [173] Based on contact lasting 9.22 minutes
A & E visits	£155.00	0.167	0.0088	NHS Tariff 19/20 [169]. A&E worksheet. 'VB08Z' Emergency Medicine, Category 2 Investigation with Category 1 Treatment
Hospitalisation	£582.00	0.075	0.0039	NHS Tariff 19/20 [169]. Non-elective tariff for code AA31E (Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0–6) in worksheet “1 APC & OPROC” HRG code: AA31E
Nurse specialist visits	£37.00	0.72	0.0379	NHS Tariff 19/20 [169]. Assumed be the cost of an hour of a nurse

Neurologist visit	£125.00	0.221	0.012	NHS Tariff 18/19 [170]. Latest tariff did not include costs for neurology outpatient therefore assumed to be a Follow Up Attendance - Single Professional (WF01A)" for a Neurology outpatient visits (code 400) in non-mandatory prices.

The economic analysis also captures acute medication use per MHD frequency by applying a statistical distribution to predict the frequency of acute medication use with triptans, acetaminophen (paracetamol and containing products) and NSAIDs, with each MHD frequency. Full methodology for estimating acute medication costs can be found in Appendix I.2 and statistical distribution method can be found in Appendix V.

A summary of frequencies of resource use by category and the resultant total management costs by MHD frequency is provided in Table 65.

Table 65 Summary of resource use frequency and total cost by MHD frequency

MHD	Hospitalisations	A&E Visits	GP Visits	Nurse Practitioner Visits	Neurologist Visits	Paracetamol use	NSAID use	Triptan use	Total cost
0	0	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
1	0.0039	0.0088	0.0379	0.0379	0.0116	[redacted]	[redacted]	[redacted]	[redacted]
2	0.0078	0.0176	0.0758	0.0758	0.0232	[redacted]	[redacted]	[redacted]	[redacted]
3	0.0117	0.0264	0.1137	0.1137	0.0348	[redacted]	[redacted]	[redacted]	[redacted]
4	0.0156	0.0352	0.1516	0.1516	0.0464	[redacted]	[redacted]	[redacted]	[redacted]
5	0.0195	0.0440	0.1895	0.1895	0.0580	[redacted]	[redacted]	[redacted]	[redacted]
6	0.0234	0.0528	0.2274	0.2274	0.0696	[redacted]	[redacted]	[redacted]	[redacted]
7	0.0273	0.0616	0.2653	0.2653	0.0812	[redacted]	[redacted]	[redacted]	[redacted]
8	0.0312	0.0704	0.3032	0.3032	0.0928	[redacted]	[redacted]	[redacted]	[redacted]
9	0.0351	0.0792	0.3411	0.3411	0.1044	[redacted]	[redacted]	[redacted]	[redacted]
10	0.0390	0.0880	0.3790	0.3790	0.1160	[redacted]	[redacted]	[redacted]	[redacted]
11	0.0429	0.0968	0.4169	0.4169	0.1276	[redacted]	[redacted]	[redacted]	[redacted]
12	0.0468	0.1056	0.4548	0.4548	0.1392	[redacted]	[redacted]	[redacted]	[redacted]
13	0.0507	0.1144	0.4927	0.4927	0.1508	[redacted]	[redacted]	[redacted]	[redacted]
14	0.0546	0.1232	0.5306	0.5306	0.1624	[redacted]	[redacted]	[redacted]	[redacted]
15	0.0585	0.132	0.5685	0.5685	0.1740	[redacted]	[redacted]	[redacted]	[redacted]
16	0.0624	0.1408	0.6064	0.6064	0.1856	[redacted]	[redacted]	[redacted]	[redacted]
17	0.0663	0.1496	0.6443	0.6443	0.1972	[redacted]	[redacted]	[redacted]	[redacted]

18	0.0702	0.1584	0.6822	0.6822	0.2088	[redacted]	[redacted]	[redacted]	[redacted]
19	0.0741	0.1672	0.7201	0.7201	0.2204	[redacted]	[redacted]	[redacted]	[redacted]
20	0.0780	0.1760	0.7580	0.7580	0.2320	[redacted]	[redacted]	[redacted]	[redacted]
21	0.0819	0.1848	0.7959	0.7959	0.2436	[redacted]	[redacted]	[redacted]	[redacted]
22	0.0858	0.1936	0.8338	0.8338	0.2552	[redacted]	[redacted]	[redacted]	[redacted]
23	0.0897	0.2024	0.8717	0.8717	0.2668	[redacted]	[redacted]	[redacted]	[redacted]
24	0.0936	0.2112	0.9096	0.9096	0.2784	[redacted]	[redacted]	[redacted]	[redacted]
25	0.0975	0.2200	0.9475	0.9475	0.2900	[redacted]	[redacted]	[redacted]	[redacted]
26	0.1014	0.2288	0.9854	0.9854	0.3016	[redacted]	[redacted]	[redacted]	[redacted]
27	0.1053	0.2376	1.0233	1.0233	0.3132	[redacted]	[redacted]	[redacted]	[redacted]
28	0.1092	0.2464	1.0612	1.0612	0.3248	[redacted]	[redacted]	[redacted]	[redacted]
29	0.1131	0.2552	1.0991	1.0991	0.3364	[redacted]	[redacted]	[redacted]	[redacted]
30	0.1170	0.2640	1.1370	1.1370	0.3480	[redacted]	[redacted]	[redacted]	[redacted]

B.3.5.5 Adverse reaction unit costs and resource use

Adverse reactions were not considered in this model.

B.3.5.3 Miscellaneous unit costs and resource use

To examine the impact of migraine from a societal perspective, the costs of both absenteeism and presenteeism were incorporated into the model as a scenario analysis. The findings from this scenario analysis are presented in Section B.3.8 and further details on the methodology are presented in Appendix R.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 66 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Mean Age	Episodic – failed at least 3 preventives – [redacted] Chronic – failed at least 3 preventives – [redacted]	Normal distribution	Section B.3.2.1 Patient population
Gender (percentage female patients)	Episodic – failed at least 3 preventives – [redacted] Chronic – failed at least 3 preventives – [redacted]	Beta distribution	Section B.3.2.1 Patient population
Baseline MHD	Episodic – failed at least 3 preventives –[redacted] Chronic – failed at least 3 preventives – [redacted]	Normal	Section B.3.2.1 Patient population
Mean change (month 3) with galcanezumab	Chronic – failed at least 3 preventives – [redacted]	Normal distribution	Section B.3.3.2 Treatment efficacy
Responder mean change (month 3) with galcanezumab	Episodic – failed at least 3 preventives – [redacted]	Normal distribution	

<table>
<tr><td>Response rate (galcanezumab)</td><td>Episodic (50%) – failed at least 3 preventives – [redacted]
Chronic (30%) – failed at least 3 preventives – [redacted]</td><td>Beta distribution</td><td>Section B.3.3.2.5 Response rates</td></tr>
<tr><td>Drug costs (cost per unit)</td><td>Galcanezumab 120mg - [redacted]
Botulinum toxin type A – £276.40</td><td>Normal distribution</td><td>Section B.3.5.1 Intervention and comparators' costs and resource use</td></tr>
<tr><td>Resource costs (unit cost)</td><td>Physician visits - £37.40
Emergency room visits -£155.00
Hospitalization - £582.00
Nurse visits - £37.00
Specialist consultations - £125.00</td><td>Gamma distribution</td><td>Section B.3.5.1 Intervention and comparators' costs and resource use</td></tr>
<tr><td>Resource use</td><td><table><tr><th>Average use per year</th><th>Use per migraine day</th></tr><tr><td>0.72</td><td>0.0379</td></tr><tr><td>0.167</td><td>0.0088</td></tr><tr><td>0.075</td><td>0.0039</td></tr><tr><td>0.72</td><td>0.0379</td></tr><tr><td>0.221</td><td>0.0116</td></tr></table></td><td>Normal distribution</td><td>Section B.3.5.1 Intervention and comparators' costs and resource use</td></tr>
<tr><td>Discontinuation</td><td>Episodic – failed at least 3 preventives – [redacted]
Chronic – failed at least 3 preventives – [redacted]</td><td>Beta distribution</td><td>Section B.3.2.2.6 Discontinuation</td></tr>
<tr><td>Utility values</td><td></td><td>Normal distribution</td><td>SectionB.3.5.2 Health-state unit costs and resource use</td></tr>
</table>

B.3.6.2 Assumptions

The model contains some key assumptions that will be tested in scenario analysis. The key assumption is the use of a negative binomial distribution and validity of the regression model used to estimate the dispersion parameter. This approach assumes that the entire treatment effect is captured through the MHD. This is a required assumption to accurately model the effect of comparator treatments and is tested by testing a second distribution. Another key assumption of the model pertains to the extrapolation of the MHD after the trial data, the base case assumes that it is sustained from the point of assessment of response until the end of the time horizon.

The model made several other key assumptions, which are outlined in Table 67.

Table 67 Summary of assumptions applied in the economic model

Assumptions	Justification
Cycle length	The model utilised monthly cycles (30 days) over which transitions are modelled and costs and outcomes accrued. This is both

	convenient for modelling the treatment regimens and appropriate given the treatment cycle of galcanezumab and the trial definition of migraine headache days per month applied in the Phase 3 RCT programme of galcanezumab.
Responder, non-responder MHDs derived separately based on galcanezumab trials and applied to the galcanezumab and BSC arms of the model. A combined criterion was applied to non-responder and responder mean change MHDs was applied to galcanezumab and botulinum toxin A	The marketing authorisation of galcanezumab [1] states that doctors should review treatment after 3 months and only continue it if patients benefit from it. To reflect these criteria in the model, change from baseline in monthly MHDs was analysed by responder status applying the clinical meaningful response criteria of 30% or greater reduction in MHD for CM and 50% or greater reduction in MHD for EM and HFEM patients. This allows to model the mean reduction in monthly MHDs for responders and non-responders separately. This analysis is only considered for the comparison to BSC, for which individual patient level data are available from CONQUER. Since no publicly available information by responder/non-responder status could be identified in the SLR for botulinum toxin A, the combined efficacy results as observed in CONQUER for galcanezumab are modelled.
Treatment responders remain on treatment and are assumed to maintain responder, or combined mean change MHDs, until the end of the time horizon	Efficacy data for galcanezumab are available for up to one year. Results from CGAJ, the 12-month open-label safety study in patients with episodic or chronic migraine support galcanezumab's durability of effect for up to a year [106]. A decrease in the number of monthly MHDs was observed at month 1 (decreases of 4.5 days for the 120 mg dose, with an initial 240mg dose for the first month), with plateauing of effect several months later and maintenance of effect throughout 12 months (with decreases of 6.4 days at Month 12). Data from the 9-month, open-label extension phase of REGAIN in patients with chronic migraine indicated that reductions in MHD during the 3 –month double blind period were sustained during the OLE phase, and the percentages of patients with clinically meaningful reductions in MHDs increased from the rates observed in the double-blind period [104, 174]. Galcanezumab or CGRP concentrations were similar when compared across various ADA titer categories suggesting that ADA has no appreciable effect on the PK of galcanezumab nor does it interfere with the

	binding of the CGRP ligand to the galcanezumab antibody [105]. Consequently, no treatment waning is expected while on treatment.
Patients who discontinue active treatment due to non-response or AEs switch to BSC treatment only and revert to baseline monthly MHDs for the remainder of the time horizon	This assumption is consistent with the NICE committee's conclusions for the appraisals of erenumab and fremanezumab [12, 150] In the assessment of erenumab, NICE highlighted that patients must have experienced an insufficient response to at least 3 oral preventive treatments before more specialist treatment options are considered generally in NHS practice [12]. The target patient population in this submission reflects this patient population. Hence, for patients who discontinue active treatment, no alternative treatment is considered available as fremanezumab or erenumab are currently not reimbursed in NHS England and the other specialist treatment botulinum toxin A is considered a comparator in the model for chronic migraine.
Patient who discontinue active treatment are assumed to wane back to baseline monthly MHDs at different rates based on available data for the respective modelled treatments	The waning period attributed to each modelled active treatment is informed by the observed MHDs during the washout period of the pivotal clinical trials (EVOLVE-2 for episodic migraine; REGAIN for chronic migraine). No such washout data was available for botulinum toxin A, therefore it was assumed that patients return to baseline monthly MHDs by the time they were expected to receive their usual administration of botulinum toxin A, at a further 3-months.
There is no placebo response modelled. BSC responder, non-responders discontinue treatment after the assessment period at different rates back the baseline monthly MHDs. Non-responders, immediately in the next cycle. Responders, wane back over 12 months	Aligned with the NICE committee's preferred assumptions from the NICE technology appraisal for fremanezumab, responders in the BSC arm in the model wane back to baseline MHDs over 12 months [150].
No excess mortality in the model	Given conflicting evidence in the literature regarding migraine-specific mortality, no excess mortality was considered in the model [164, 165]. Therefore, patients from the on-treatment and off-treatment health state had an equal probability of transitioning to the health state 'death'. The background mortality risk does not differ by treatment. This is also consistent with past NICE technology appraisals in migraine [6]
Discontinuation is purely captured through the assessment of response and due to AEs	No positive discontinuation rule was applied in the model for patient and physician decision to stop treatment due to long-term stability of treatment response. This is

	consistent with the NICE committee's conclusions for the appraisal for erenumab and fremanezumab [12, 150].
Assessment of response for botulinum toxin A is assumed to take place at 90-days	Based on clinical feedback that assessment takes place between 90 and 180 days. 90 days was chosen to keep the assessment of response consistent to galcanezumab.
Placebo arms from the trial assumed as a proxy for BSC in the model	It is assumed appropriate that the placebo arm in the randomised controlled trials of galcanezumab is representative of best supportive care in patients who experienced at least 3 prior preventive treatment failures. Patients in the placebo group of the clinical trials were allowed acute medication to manage their symptoms when preventive medication had failed. Under current NHS practice, these patients are not receiving further preventive treatment as highlighted in the NICE technology appraisal for erenumab [12] and would manage their symptoms with acute medication only.
25-year lifetime horizon	In the assessment of erenumab and fremanezumab, the NICE committee has pointed out that a time horizon of 10 years is not sufficiently long enough to capture all relevant costs and outcomes associated with the intervention and recommended a longer time horizon [12, 150].In addition, migraine affects predominately women and the natural course of disease suggests that prevalence of migraine reduces significantly after menopause [44]. Therefore, the time horizon of the model is set to lifetime (defined as 25 years) in the base case. 25-years was deemed appropriate to capture all material effects on benefits and costs while considering the natural course of the disease. Any longer time horizons would result to propagate the uncertainty of short-term clinical trial data though the model and inherently make any longer-term estimates unreliable.
Pooled treatment utilities	Pooled utility values were chosen based on recent NICE committee preferences from NICE technology appraisal for fremanezumab [150]. This approach is conservative as it assumes that utility values do not differ between model treatment arms despite an observed [redacted] effect between galcanezumab and BSC in CONQUER and pivotal trials. Differences in HRQoL is therefore only captured through differences in the efficacy parameters applied to the model.

B.3.6.3 Model settings

A summary of the base case settings for episodic migraine, chronic migraine (comparing Galcanezumab to BSC) and chronic migraine (comparing Galcanezumab to botulinum toxin A), is provided in Table 68.

Table 68 Base-case model settings

Parameter	**Episodic vs BSC**	**Chronic vs BSC**	**Chronic vs botulinum toxin A**
Perspective	Health payer	Health payer	Health payer
Discount rate, costs and benefits	3.5%	3.5%	3.5%
Responder rate	50%	30%	30%
Negative discontinuation rule at 3 months	Yes	Yes	Yes
Statistical distribution	Negative Binomial	Beta Binomial	Beta Binomial
Responder criteria	Yes	Yes	No, mean change MHDs from ITC applied to responders and non-responders combined
Placebo effect modelled	No. BSC-responders return to baseline MHDs after 1-year	No. BSC-responders return to baseline MHDs after 1-year	NA
Mean change MHDs applied to discontinuers and non-responders	Switch to non-responder mean change MHDs and return to baseline MHDs	Switch to non-responder mean change MHDs and return to baseline MHDs	Stay on combined mean change MHDs and return to baseline MHDs
Wane rate after discontinuation	Galcanezumab – [redacted] BSC – immediately after the next cycle	Galcanezumab – [redacted] BSC – immediately after the next cycle	Galcanezumab – [redacted] Botulinum toxin A – 3 cycles
Discontinuation rate in the post-assessment period	AEs only Galcanezumab [redacted] BSC – [redacted]	AEs only Galcanezumab - [redacted] BSC – [redacted]	AEs only Galcanezumab [redacted] Botulinum toxin A – 0.1%

Utility values	Pooled utilities from CONQUER	Pooled utilities from CONQUER	Pooled utilities from CONQUER
Acute medication use	CONQUER separate acute medication categories	CONQUER separate acute medication categories	CONQUER separate acute medication categories

Abbreviations: MHD: Migraine Headache Days; ITC: Indirect Treatment Comparison

B.3.7 Base-case incremental cost-effectiveness analysis results

A summary of the base-case results for the episodic, chronic and HFEM are presented in Table 69, Table 70, and Table 71. At the confidential PAS price all the ICERs in base case populations are within a range normally considered cost effective for routine commissioning. The ICER of the base case shows galcanezumab falls within NICEs' WTP threshold of £20,000 to £30,000 for the episodic population modelled, whereas the ICERs for the chronic populations falls below the lower threshold of £20,000, as defined by NICE guidelines. Sensitivity analyses in the form of deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were undertaken to examine the level of uncertainty surrounding the model parameters. Furthermore, scenario analyses were also undertaken to explore the uncertainty surrounding the model assumptions. The findings of the sensitivity analyses are presented below. Clinical outcomes modelled and disaggregated results of the base case ICER analyses are presented in Appendix J.

Table 69 Base-case results: Episodic (vs BSC)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,230

Table 70 Base-case results: Chronic (vs BSC)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,077

Table 71 Base-case results: Chronic (vs Botulinum toxin type A)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,595

Subgroup analysis: HFEM

A subgroup analysis was undertaken on the HFEM population, and base-case results are presented in Table 72. At the confidential PAS price all the ICERs in base case populations are within a range normally considered cost effective for routine commissioning. The ICERs derived from this analysis indicate the additional cost per QALY for galcanezumab, for the HFEM population, falls within NICEs' WTP threshold of £20,000 to £30,000, as defined by NICE guidelines.

Table 72 Base-case results: HFEM

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,351

B.3.8 Sensitivity analyses

B.3.8.1 Deterministic sensitivity analysis

Figure 19 DSA: Episodic (vs BSC)

, Figure 19, and Error! Reference source not found. show the findings from the DSA for each population modelled. The most impactful parameter for each population modelled was the mean change responders for Galcanezumab at a 50% and 30% response rate. In each case, the upper bound value for this specific DSA let to large increases in the ICER relative to the base-case analysis.

Figure 19 DSA: Episodic (vs BSC)

[redacted]

Figure 19 DSA: Chronic (vs BSC)

Figure 20 DSA: Chronic (vs Botulinum toxin type A)

B.3.8.2 Probabilistic sensitivity analysis

A PSA was undertaken to examine the uncertainty surrounding model parameters. A Monte Carlo approach, with 1,000 iterations, was undertaken. A summary of the distributions chosen for the probabilistic parameters in the model is provided in
Table 73 for both episodic and chronic migraine populations.

Table 73: Model parameter summary

Parameter	Distribution	Justification
Age	Normal distribution	Based on the information available from the trial data
Gender	Beta distribution	Based on natural limit between 0 and 100%.
Baseline MHD	Normal distribution	Based on the information available from the trial data
Distribution parameters	Variance covariance matrix	Used to account for uncertainty in regression parameters
Mean change	Normal distribution	Aligned with the ITC output
Response rate	Beta distribution	Based on natural limit between 0 and 100%.
Drug costs	Normal distribution	Assumption of uncertainty around the mean
Resource costs	Gamma distribution	Based on an anticipated skewed distribution
Resource use	Normal distribution	Based on the information available from the trial data
Discontinuation	Beta distribution	Based on natural limit between 0 and 100%.
Utility values	Normal distribution	Variance taken from trial analysis

Table 74, Table 75,

Figure 21 and Figure 22 show the findings from the PSA for the episodic migraine group. The ICERs derived from the PSA (Table 74) do not change significantly compared to the base case analysis, especially given the ICER values remain below the upper WTP threshold of £30,000, as defined by NICE guidelines.

Figure 21 shows the cost-effectives plane from the PSA, and therefore the level of uncertainty surrounding model parameters. The findings for the chronic migraine population show all iterations fall within the north-east quadrant for the cost-effectives plane, this finding suggested that galcanezumab will result in both incremental cost and QALY gain compared to BSC. Table 75 and Figure 22 show the probability of galcanezumab being cost-effectiveness at various WTP

thresholds. In general, when the WTP threshold increases, so does the probability of cost-effectiveness for galcanezumab.

Table 74 PSA: Episodic (vs BSC)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,866

Figure 21 PSA Scatterplot: Episodic (vs BSC)

Table 75 PSA WTP: Episodic (vs BSC)

WTP	% Cost effective
£20,000	[redacted]
£30,000	[redacted]
£40,000	[redacted]
£50,000	[redacted]

Figure 22 PSA CEAC: Episodic (vs BSC)

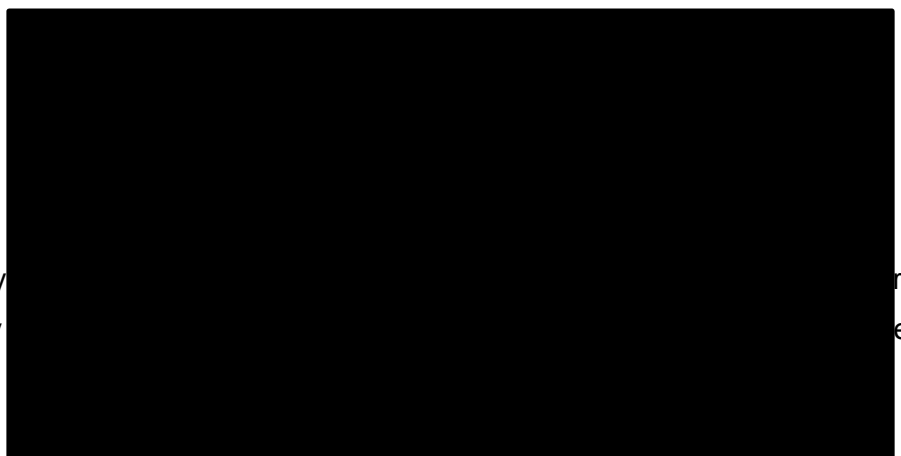


Table 76, Table 77, Figure 23 and Figure 24 show the findings from the PSA for the chronic migraine group (galcanezumab compared to BSC). The ICERs derived from the PSA (Table 76) do not change significantly compared to the base case analysis, especially given the ICER values remain below the lower WTP threshold of £20,000, as defined by NICE guidelines. Figure 23 shows the cost-effectives plane from the PSA, and therefore the level of uncertainty surrounding model parameters. The findings from the plane show some uncertainty around the parameters included in the model for this population, given that the iterations spread across all four quadrants. However, in general, the findings suggest that in the majority of cases, galcanezumab will lead to QALY gains. Table 77, and Figure 24 show the probability of galcanezumab being cost-effectiveness at various WTP thresholds. The findings indicate that at the lower threshold of £20,000, galcanezumab has a [redacted] of being cost-effective compared to BSC.

Table 76 PSA: Chronic (vs BSC)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,216

Figure 23 PSA Scatterplot: Chronic (vs BSC)

Company [redacted] aine

Table 77 PSA WTP: Chronic (vs BSC)

WTP	% Cost effective
£20,000	
£30,000	
£40,000	
£50,000	

Figure 24 PSA CEAC: Chronic (vs BSC)

Table 78, Table 79,

Figure 25 and Figure 26 shows the findings from the PSA for the chronic migraine group (galcanezumab compared to Botulinum toxin type A). The ICERs derived from the PSA (Table 78) do not change significantly compared to the base case analysis, especially given the ICER values remain below the lower WTP threshold of £20,000, as defined by NICE guidelines.

Figure 25 shows the cost-effectives plane from the PSA, and therefore the level of uncertainty surrounding model parameters. The findings from the plane show some uncertainty around the parameters included in the model for this population, given that the iterations spread across all four quadrants. However, in general, the findings suggest that in the majority of cases, galcanezumab will lead to QALY gains. Table 79, and Figure 26 show the probability of galcanezumab being cost-effectiveness at various WTP thresholds. The findings indicate that at the lower threshold of £20,000, galcanezumab has a high [redacted] of being cost-effective compared to Botulinum toxin type A.

Table 78 PSA: Chronic (vs Botulinum toxin type A)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]			
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,230

Figure 25 PSA Scatterplot: Chronic (vs Botulinum toxin type A)

Table 79 PSA WTP: Chronic (vs Botulinum toxin type A)

WTP	% Cost effective
£20,000	[redacted]
£30,000	[redacted]

£40,000	[redacted]
£50,000	[redacted]

Figure 26 PSA CEAC: Chronic (vs Botulinum toxin type A)

B.3.8.3 Scenario analysis

Table 80, Table 81, and Table 82 show the ICERs derived from the scenario analyses for the episodic and chronic migraine populations modelled. The scenario analysis assessing the mean MHD improvement for comparison in BSC, for each population, appeared to have the most significant impact on the ICER.

Table 80 Scenario Analyses: Episodic (vs BSC)

Scenario	Scenario Details	ICER
Discount rates (costs, benefits)	0%	£28,174
Discount rates (costs, benefits)	6%	£30,030
Time horizon	10 Years	£31,470
Time horizon	45 Years	£28,929
Clinical outcomes		
Mean Migraine Headache Days improvement for comparison in BSC	Combined population	£59,851
Mean monthly MHDs change after discontinuing therapy	BSC - Non responder	£24,629
Time of treatment waning after discontinuation, Galcanezumab	5 Cycles	£29,723
Remove time of treatment waning, BSC-responders	Model the placebo response	£100,373
Discontinuation rate, all-cause CONQUER	2.34%	£32,451
Distribution around Migraine Headache Days, episodic	Beta-Binomial	£29,221

Utilities		
Utilities by treatment	Treatment specific	£8,174
Perspective	Societal	£5,025

Table 81 Scenario Analyses: Chronic (vs BSC)

Scenario	Scenario Details	ICER
Discount rates (costs, benefits)	0%	£7,554
Discount rates (costs, benefits)	6%	£8,117
Time horizon	10 Years	£8,474
Time horizon	45 Years	£7,917
Clinical outcomes		
Response rate, CM	50%	£5,252
Mean Migraine Headache Days improvement for comparison in BSC	Combined population	£24,197
Mean monthly MHDs change after discontinuing therapy	BSC - Non responder	£7,246
Time of treatment waning after discontinuation, Galcanezumab	5 cycles	£9,934
Remove time of treatment waning, BSC-responders	Model the placebo response	£22,337
Discontinuation rate, all-cause CONQUER	2.34%	£4,281
Distribution around Migraine Headache Days, chronic	Negative binomial	£8,583
Utilities		
Utilities by treatment	Treatment specific	£3,927
Perspective	Societal	Galcanezumab Dominates

Table 82 Scenario Analyses: Chronic (vs Botulinum toxin type A)

Scenario	Scenario Details	ICER
Discount rates (costs, benefits)	0%	Galcanezumab Dominates
Discount rates (costs, benefits)	6%	£5,091
Time horizon	10 Years	£10,697
Time horizon	45 Years	Galcanezumab Dominates
Clinical outcomes		
Response assessment vs. Botox, chronic	180 Days for Botox	£2,004
Response rate, CM	50%	£3,310
Mean Migraine Headache Days improvement for comparison to active treatments	Responder criteria	Galcanezumab Dominates
Mean monthly MHDs change after discontinuing therapy	BSC - Non responder	£3,938
Time of treatment waning after discontinuation, Galcanezumab	5 Cycles	£35,898

Time of treatment waning after discontinuation, Botulinum toxin A	[redacted] MHDs per cycle	£4,715
Discontinuation rate, all-cause	2.34% for galcanezumab and 0.94% for Botox	Galcanezumab Dominates
Distribution around Migraine Headache Days, chronic	Negative binomial	£2,504
Perspective	Societal	Galcanezumab Dominates

B.3.9 Model Validation

Validation of cost-effectiveness analysis

Model development was undertaken with clinical and health economic experts. The model validation was undertaken by an independent third party who were not involved any stage of the model development process. The validation investigated the following attributes of the model: the scope, ease of use, model inputs, accuracy, survival analyses, sensitivity analyses, VBA coding, and results. In general, the model was deemed suitable, although some discrepancies were identified. These minor discrepancies did not have a significant impact on the model results and were rectified.

Model predictions are compared to trial results in Appendix J

B.3.10 Interpretation and conclusions of economic evidence

Summary of the economic evidence for galcanezumab

The ICER for episodic migraine patients with ≥4 MHDs per month and less than 15 headache days per month currently being treated with BSC was £29,230, which is within the range normally considered a cost-effective use of NHS resources. The ICERs for chronic migraine patients with ⩾15 headache days per month, with ⩾8 being MHDs currently treated with BSC or botulinum toxin A was £8,077 and £2,595, respectively. Finally, a subgroup analysis took place where the ICER in a distinct subgroup of patients in episodic migraine with high-frequency episodic migraine who experience between 8-14 MHDs per month and <15 headache days per month was £25,351.

Galcanezumab compared to botulinum toxin A in chronic migraine

An ICER of £2,595 is below the accepted threshold considered to be a cost-effective use of NHS resources. Sensitivity analyses showed that the biggest drivers of the ICER was the response rates and the mean change in MHDs from baseline incorporated into the model from the ITC. However, these analyses show the ICERs still remained below a threshold of £30,000 per QALY gained when varied to the lower or upper bound.

The low ICER is likely driven by the difference in acquisition costs and the granularity of model to capture resource use, costs and utilities by each MHD frequency. Changes in costs and QALY are driven purely by the mean change in monthly MHD as response rates are held equal. Similar low discontinuation rates also explain the base case ICERs as when using trial-based estimates for all-cause discontinuation, the ICER reduce dramatically to the point where galcanezumab dominates.

The base case generally took a conservative approach due to uncertainties from the indirect comparisons to botulinum toxin A and from the lack of long-term clinical data beyond 1-year:

- Response rates were assumed equal for botulinum toxin A and galcanezumab due to the lack of data for botulinum toxin A
- Combined population (responder and non-responder) estimates were used for the comparison to botulinum toxin A due to the lack of data for botulinum toxin A
- Discontinuation was only captured through AEs, resulting in higher costs for both arms of the model for the duration of the time horizon.

The economic analysis relied on several assumptions stemming from the requirement to extrapolate from the short-term estimates of mean change in monthly MHDs and response rates from the double-blind periods of the trials to a lifetime horizon. One being the application of a distribution to measure the dispersion around the mean MHDs when extrapolating beyond the assessment period. Most of the other assumptions were generally guided by the NICE committee's conclusions from past or ongoing appraisals for erenumab and fremanezumab. As a result, patients on the active treatment arms were assumed to maintain their effect from the point of assessment of response and assumed to rebound to baseline monthly MHDs once patients discontinue treatment for either lack of response or due to AEs. A further assumption was applied to patients discontinuing active treatment where efficacy returned to baseline over time rather than immediately in the next cycle. The rate at which patients waned back to baseline was different for galcanezumab compared to botulinum toxin A, which was driven by the wash-out period data from galcanezumab's pivotal trials and the lack thereof for botulinum toxin A. These assumptions were tested in scenario analyses and showed that the ICERs were highly sensitive to the waning assumptions. The ICER increased to £35,898 when the wane period for galcanezumab was reduced to only 5-cycles to match the observed period in the pivotal trials. However, this is a conservative scenario since the washout data was only for 5 months after the last dose of galcanezumab and show that patients may still receive benefit long after stopping treatment.

Galcanezumab compared to BSC in chronic and episodic migraine

The chronic migraine ICER of £8,077 was below the accepted threshold considered to be a cost-effective use of NHS resources. Sensitivity analyses showed the key drivers for the ICER were the response rates and the mean change in monthly MHDs for responders. However, all analyses were still under the accepted threshold of £20,000 per QALY gained.

The episodic migraine ICER of £29,230 is within the range normally considered cost effective for the use of NHS resources. Sensitivity analyses showed the key drivers of the ICERs were the mean change MHDs for responders, the discount rate and utility values. the upper bound for the estimate for mean change MHDs for responders raise the ICER to an approximately £40,000 per QALY gained.

The comparison to BSC employed alternative assumptions to the comparison to botulinum toxin A which is driven partially by the NICE committee's conclusions by past appraisals of erenumab and fremanezumab. Key assumptions include using pooled utilities values from the treatment arms informed by the CONQUER trial. This was a conservative assumption employed in the model since regression analysis showed a [redacted] when including treatment effect as a covariate.

Another key assumption was the dissipation of the placebo over 12 months after the assessment of response (after the double-blind RCT trial data). This was the biggest driver of the ICERs in both populations, more than doubling the ICERs in both cases.

Strengths of the economic analysis

In general, the economic model reflected the decision problem, clinical practice (assessment of response and the negative discontinuation rule at 3 months) and to the target population in which galcanezumab will be used in NHS practice. It was able to incorporate two important clinically meaningful endpoints from high quality RCTs for galcanezumab which impact on the health-related quality of life for migraineurs; the number who respond to treatment and mean change in monthly MHDs. The ability of the second part of the model to capture the fluctuation around the mean MHDs by applying a distribution to model the full range of MHDs experienced by patients was important as costs and QALYs are not expected to linearly increase or decrease over time because migraine is a naturally fluctuating disease. This avoids the unnecessary grouping of MHDs into arbitrary categories seen in past models in migraine and attributes costs and QALYs to each MHD frequency to accurately capture the QALYs lost (or gained) and the cost increase (or decreased) with a change in MHD.

Limitations of the economic analysis

A limitation of the model was its inability to capture the natural progression of disease and the impact of menopause as there was lack of data to inform this in the model. Migraine chronification is known to occur over time for patients with episodic migraine who eventually convert to chronic migraine. The inability of the model to capture this natural progression or chronification potentially leads to an underestimation of the mean MHD change over time for patients on BSC and consequently leads to an underestimation of the lifetime costs and QALYs. However, without robust data for the ability of galcanezumab to prevent chronification it was appropriate to not model the natural progression of disease. The model also relied on indirect estimates from the ITC to botulinum toxin A. Limited data were available from the PREEMPT trials for patients who had a history of ≥3 prior preventive treatments. Therefore, a conservative assumptions regarding response rates were employed which may have underestimated the ICER. Finally, the model only captured mean change monthly MHDs over 3 months from the double-blind treatment period of the galcanezumab trials, but OLE periods of REGAIN and CONQUER show that patients continue to improve the longer they receive treatment.

B.4 References

1. Eli Lilly and Company. *EMGALITY Summary of Product Characteristics*. 2019 January 22, 2020]; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/emgality.
2. Mulleners, W.K., B. Lainez, M. et al. , *A Randomized, Placebo-Controlled Study of Galcanezumab in Patients with TreatmentResistant Migraine: Double-Blind Results from the CONQUER Study (International Headache Society Abstract: IHC-OR-042).* Celphalalgia, 2019. **39**(IS): p. 366.
3. Ford, J.H., et al., *Cycling Through Migraine Preventive Treatments: Implications for All-Cause Total Direct Costs and Disease-Specific Costs.* J Manag Care Spec Pharm, 2019. **25**(1): p. 46-59.
4. Martelletti, P., et al., *My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed.* J Headache Pain, 2018. **19**(1): p. 115.
5. Headache Classification Committee of the International Headache, S., *The International Classification of Headache Disorders, 3rd edition (beta version).* Cephalalgia, 2013. **33**(9): p. 629-808.
6. National Institute for Health and Care Excellence., *Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. Technology Appraisal Guidance [TA260]*. 2012.
7. Pozo-Rosich, P., et al., *EHMTI-0288. A clinical comparison demonstratessimilarities between chronic and high frequencyepisodic migraine*, in *4th European Headache and Migraine Trust International Congress*. 2014: Copenhagen, Denmark. p. E28.
8. Barbanti, P., et al., *Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study.* J Headache Pain, 2015. **16**: p. 61.
9. National Institute for Health and Care Excellence, *Erenumab for preventing migraine: Appraisal Consultation Document*. 2018.
10. Chalmer, M.A., et al., *Proposed new diagnostic criteria for chronic migraine.* Cephalalgia, 2019: p. 333102419877171.
11. Guglielmetti, M., et al., *The clinical and public health implications and risks of widening the definition of chronic migraine.* Cephalalgia, 2019: p. 333102419895777.

12. National Institute for Health and Care Excellence, *Erenumab for preventing migraine: Final Appraisal Document*. 2019.
13. Dodick, D.W., *Migraine.* Lancet, 2018. **391**(10127): p. 1315-1330.
14. The International Headache Society, *Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.* Cephalalgia, 2018. **38**(1): p. 1-211.
15. Weatherall, M.W., *The diagnosis and treatment of chronic migraine.* Ther Adv Chronic Dis, 2015. **6**(3): p. 115-23.
16. Lipton, R.B. and S.D. Silberstein, *Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention.* Headache, 2015. **55 Suppl 2**: p. 103-22; quiz 123-6.
17. Charles, A., *The evolution of a migraine attack - a review of recent evidence.* Headache, 2013. **53**(2): p. 413-9.
18. Charles, A., *The pathophysiology of migraine: implications for clinical management.* Lancet Neurol, 2018. **17**(2): p. 174-182.
19. Kelman, L., *The postdrome of the acute migraine attack.* Cephalalgia, 2006. **26**(2): p. 214-20.
20. Giffin, N.J., et al., *The migraine postdrome: An electronic diary study.* Neurology, 2016. **87**(3): p. 309-13.
21. Steiner, T.J., et al., *The impact of headache in Europe: principal results of the Eurolight project.* J Headache Pain, 2014. **15**: p. 31.
22. Lampl, C., et al., *Interictal burden attributable to episodic headache: findings from the Eurolight project.* J Headache Pain, 2016. **17**: p. 9.
23. Stovner, L.J., et al., *The methodology of population surveys of headache prevalence, burden and cost: principles and recommendations from the Global Campaign against Headache.* J Headache Pain, 2014. **15**: p. 5.
24. Gil-Gouveia, R., A.G. Oliveira, and I.P. Martins, *Assessment of cognitive dysfunction during migraine attacks: a systematic review.* J Neurol, 2015. **262**(3): p. 654-65.
25. Goadsby, P.J., et al., *Pathophysiology of Migraine: A Disorder of Sensory Processing.* Physiol Rev, 2017. **97**(2): p. 553-622.
26. Akerman, S., M. Romero-Reyes, and P.R. Holland, *Current and novel insights into the neurophysiology of migraine and its implications for therapeutics.* Pharmacol Ther, 2017. **172**: p. 151-170.
27. Burstein, R., R. Noseda, and D. Borsook, *Migraine: multiple processes, complex pathophysiology.* J Neurosci, 2015. **35**(17): p. 6619-29.
28. Iyengar, S., M.H. Ossipov, and K.W. Johnson, *The role of calcitonin gene-related peptide in peripheral and central pain mechanisms including migraine.* Pain, 2017. **158**(4): p. 543-559.
29. Edvinsson, L., et al., *CGRP as the target of new migraine therapies - successful translation from bench to clinic.* Nat Rev Neurol, 2018. **14**(6): p. 338-350.
30. Lassen, L.H., et al., *CGRP may play a causative role in migraine.* Cephalalgia, 2002. **22**(1): p. 54-61.
31. Hansen, J.M., et al., *Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura.* Cephalalgia, 2010. **30**(10): p. 1179-86.
32. Villalon, C.M. and J. Olesen, *The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs.* Pharmacol Ther, 2009. **124**(3): p. 309-23.
33. Schwedt, T.J., *Chronic migraine.* BMJ, 2014. **348**: p. g1416.
34. Aurora, S.K. and M.F. Brin, *Chronic Migraine: An Update on Physiology, Imaging, and the Mechanism of Action of Two Available Pharmacologic Therapies.* Headache, 2017. **57**(1): p. 109-125.
35. Katsarava, Z., et al., *Defining the differences between episodic migraine and chronic migraine.* Curr Pain Headache Rep, 2012. **16**(1): p. 86-92.
36. Katsarava, Z., et al., *Chronic migraine: classification and comparisons.* Cephalalgia, 2011. **31**(5): p. 520-9.

37. Maleki, N., et al., *Concurrent functional and structural cortical alterations in migraine.* Cephalalgia, 2012. **32**(8): p. 607-20.
38. Torres-Ferrus, M., et al., *When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month.* Cephalalgia, 2017. **37**(2): p. 104-113.
39. Data on File, *Migraine VI DSP - UK Overview*. 2018.
40. Bigal, M.E. and R.B. Lipton, *Concepts and mechanisms of migraine chronification.* Headache, 2008. **48**(1): p. 7-15.
41. Bigal, M.E., et al., *Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study.* Headache, 2008. **48**(8): p. 1157-68.
42. Katsarava, Z., et al., *Incidence and predictors for chronicity of headache in patients with episodic migraine.* Neurology, 2004. **62**(5): p. 788-90.
43. Carod-Artal, F.J., *Tackling chronic migraine: current perspectives.* J Pain Res, 2014. **7**: p. 185-94.
44. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1789-1858.
45. Blumenfeld, A.M., et al., *Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS).* Cephalalgia, 2011. **31**(3): p. 301-15.
46. Steiner, T.J., et al., *Migraine is first cause of disability in under 50s: will health politicians now take notice?* J Headache Pain, 2018. **19**(1): p. 17.
47. Hareendran, A., et al., *EHMTI-0236. A qualitative study of the functional impact of symptoms on migraine patients.* J Headache Pain, 2014. **15**: p. D53.
48. Steiner, T.J., et al., *The Prevalence and Disability Burden of Adult Migraine in England and their Relationships to Age, Gender and Ethnicity.* Cephalalgia, 2003. **23**(7): p. 519-527.
49. Ruiz de Velasco, I., et al., *Quality of life in migraine patients: a qualitative study.* Cephalalgia, 2003. **23**(9): p. 892-900.
50. Walters, A.B., J.D. Hamer, and T.A. Smitherman, *Sleep disturbance and affective comorbidity among episodic migraineurs.* Headache, 2014. **54**(1): p. 116-24.
51. Pike, J., et al., *Factors associated with a history of failure and switching migraine prophylaxis treatment: an analysis of clinical practice data from the United States, Germany, France, and Japan.* Value Health. , 2016. **19**(3): p. A68.
52. Buse, D., et al., *Headache impact of chronic and episodic migraine: results from the American Migraine Prevalence and Prevention study.* Headache, 2012. **52**(1): p. 3-17.
53. Ford, J.H., et al., *A Real-World Analysis of Migraine: A Cross-Sectional Study of Disease Burden and Treatment Patterns.* Headache, 2017. **57**(10): p. 1532-1544.
54. Brown, J.S., et al., *Migraine frequency and health utilities: findings from a multisite survey.* Value Health, 2008. **11**(2): p. 315-21.
55. Rencz, F., et al., *Health state utilities for migraine based on attack frequency: a time trade-off study.* Neurol Sci, 2015. **36**(2): p. 197-202.
56. Buse, D.C., et al., *Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study.* Headache, 2012. **52**(10): p. 1456-70.
57. The Work Foundation, *Society's Headache: The socioeconomic impact of migraine*. 2018.
58. Linde, M., et al., *The cost of headache disorders in Europe: the Eurolight project.* Eur J Neurol, 2012. **19**(5): p. 703-11.
59. National Institute for Health and Care Excellence (NICE). *Headaches - NICE Pathway*. 2017; Available from: https://pathways.nice.org.uk/pathways/headaches.
60. British Association for the Study of Headache. *National headache management system for adults* 2019; Available from: http://www.bash.org.uk/guidelines/.
61. Worthington, I., et al., *Canadian Headache Society Guideline: acute drug therapy for migraine headache.* Can J Neurol Sci, 2013. **40**(5 Suppl 3): p. S1-S80.

62. Freitag, F.G. and F. Schloemer, *Medical management of adult headache.* Otolaryngol Clin North Am, 2014. **47**(2): p. 221-37.
63. Estemalik, E. and S. Tepper, *Preventive treatment in migraine and the new US guidelines.* Neuropsychiatr Dis Treat, 2013. **9**: p. 709-20.
64. National Institute for Health and Care Excellence, *Headaches in over 12s: diagnosis and management (CG150)*. 2015.
65. Edmeads, J., *Defining response in migraine: which endpoints are important?* Eur Neurol, 2005. **53 Suppl 1**: p. 22-8.
66. Lipton, R.B., et al., *Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial.* JAMA, 2000. **284**(20): p. 2599-605.
67. Sculpher, M., et al., *Cost-effectiveness analysis of stratified versus stepped care strategies for acute treatment of migraine: The Disability in Strategies for Care (DISC) Study.* Pharmacoeconomics, 2002. **20**(2): p. 91-100.
68. Hepp, Z., L.M. Bloudek, and S.F. Varon, *Systematic review of migraine prophylaxis adherence and persistence.* J Manag Care Pharm, 2014. **20**(1): p. 22-33.
69. Tfelt-Hansen, P., et al., *Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators.* Cephalalgia, 2012. **32**(1): p. 6-38.
70. Adelman, J., et al., *Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials.* Pain Med, 2008. **9**(2): p. 175-85.
71. Silberstein, S.D., *Topiramate in Migraine Prevention: A 2016 Perspective.* Headache, 2017. **57**(1): p. 165-178.
72. Antonaci, F., et al., *Recent advances in migraine therapy.* Springerplus, 2016. **5**: p. 637.
73. Starling, A.J. and D.W. Dodick, *Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care.* Mayo Clin Proc, 2015. **90**(3): p. 408-14.
74. Jackson, J.L., et al., *A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache.* PLoS One, 2015. **10**(7): p. e0130733.
75. Ansari, H. and S. Ziad, *Drug-Drug Interactions in Headache Medicine.* Headache, 2016. **56**(7): p. 1241-8.
76. Blumenfeld, A.M., et al., *Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II).* Headache, 2013. **53**(4): p. 644-55.
77. Hepp, Z., et al., *Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis.* Cephalalgia, 2017. **37**(5): p. 470-485.
78. Matza, L.S., et al., *Health state utilities associated with attributes of migraine preventive treatments based on patient and general population preferences.* Qual Life Res, 2019. **28**(9): p. 2359-2372.
79. Moriarty, M. and T. Mallick-Searle, *Diagnosis and treatment for chronic migraine.* Nurse Pract, 2016. **41**(6): p. 18-32.
80. Lanteri-Minet, M., et al., *Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review.* Cephalalgia, 2011. **31**(7): p. 837-50.
81. Bagley, C.L., et al., *Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine.* Headache, 2012. **52**(3): p. 409-21.
82. Abu Bakar, N., et al., *Quality of life in primary headache disorders: A review.* Cephalalgia, 2016. **36**(1): p. 67-91.
83. Kristoffersen, E.S., et al., *Disability, anxiety and depression in patients with medication-overuse headache in primary care - the BIMOH study.* Eur J Neurol, 2016. **23 Suppl 1**: p. 28-35.
84. Shah, A.M., et al., *Reduction of medication costs after detoxification for medication-overuse headache.* Headache, 2013. **53**(4): p. 665-72.
85. Messali, A., et al., *Direct and Indirect Costs of Chronic and Episodic Migraine in the United States: A Web-Based Survey.* Headache, 2016. **56**(2): p. 306-22.
86. Lanteri-Minet, M., *Economic burden and costs of chronic migraine.* Curr Pain Headache Rep, 2014. **18**(1): p. 385.

87. Bonafede, M., et al., *Direct costs associated with migraine in the US.* Neurology, 2017. **88**: p. 1.180.
88. Raval, A.D. and A. Shah, *National Trends in Direct Health Care Expenditures Among US Adults With Migraine: 2004 to 2013.* J Pain, 2017. **18**(1): p. 96-107.
89. Burch, R.C., et al., *The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies.* Headache, 2015. **55**(1): p. 21-34.
90. Young, N., et al., *Multicenter prevalence of opioid medication use as abortive therapy in the ED treatment of migraine headaches.* Am J Emerg Med, 2017. **35**(12): p. 1845-1849.
91. Wu, J., et al., *Antimigraine medication use and associated health care costs in employed patients.* J Headache Pain, 2012. **13**(2): p. 121-7.
92. Lipton, R.B., et al., *Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study.* Headache, 2013. **53**(8): p. 1300-11.
93. Lipton, R.B., et al., *Impact of NSAID and Triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study.* Headache, 2013. **53**(10): p. 1548-63.
94. Silberstein, S.D., *Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology.* Neurology, 2000. **55**(6): p. 754-62.
95. Goadsby, P.J., *Therapeutic prospects for migraine: can paradise be regained?* Ann Neurol, 2013. **74**(3): p. 423-34.
96. Diener, H.C., et al., *New therapeutic approaches for the prevention and treatment of migraine.* Lancet Neurol, 2015. **14**(10): p. 1010-22.
97. Silva-Neto, R.P., K.J. Almeida, and S.N. Bernardino, *Analysis of the duration of migraine prophylaxis.* J Neurol Sci, 2014. **337**(1-2): p. 38-41.
98. Freitag, F.G. and D. Shumate, *Current and investigational drugs for the prevention of migraine in adults and children.* CNS Drugs, 2014. **28**(10): p. 921-7.
99. Stauffer, V.L., et al., *Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial.* JAMA Neurol, 2018. **75**(9): p. 1080-1088.
100. Data on File, *Eli Lilly and Co.: I5Q-MC-CGAG Clinical Study Report* 2017.
101. Skljarevski, V., et al., *Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial.* Cephalalgia, 2018. **38**(8): p. 1442-1454.
102. Data on File, *Eli Lilly and Co.: I5Q-MC-CGAH Clinical Study Report* 2017.
103. Detke, H.C., et al., *Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study.* Neurology, 2018. **91**(24): p. e2211-e2221.
104. Data on File, *Eli Lilly and Co.: I5Q-MC-CGAI Clinical Study Report* 2017.
105. Data on File, *Eli Lilly and Co.: I5Q-MC-CGAJ Clinical Study Report* 2017.
106. Camporeale, A., et al., *A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine.* BMC Neurol, 2018. **18**(1): p. 188.
107. Data on File, *Eli Lilly and Co.: I5Q-MC-CGAW Clinical Study Report*. 2019.
108. Ruff, D.D., et al., *Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure.* Cephalalgia, 2019. **39**(8): p. 931-944.
109. Stauffer, V.L., et al., *Effect of Galcanezumab Following Treatment Cessation in Patients With Migraine: Results From 2 Randomized Phase 3 Trials.* Headache, 2019. **59**(6): p. 834-847.
110. Silberstein, S.D., et al., *Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society.* Neurology, 2012. **78**(17): p. 1337-45.
111. Naumann, M.S., Y. Argoff, C. et al. , *Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Subcommittee of the American Academy of Neurology.* Neurology, 2008. **70** p. 1707–1714

112. Jhingran, P., et al., *Development and validation of the Migraine-Specific Quality of Life Questionnaire.* Headache, 1998. **38**(4): p. 295-302.
113. Martin, B.P.D., Sharfman MI, , *Validity and reliability of the Migraine-Specific Quality of Life Questionnaire (MSQ Version 2.1).* Headache. , 2000. **40**(3): p. 204-215.
114. Jhingran, P.D., SM. LaVange, LM. Miller, DW. Helms, RW. , *MSQ: Migraine-Specific Quality-of-Life Questionnaire. Further investigation of the factor structure.* Pharmacoeconomics, 1998a. **13**(6): p. 707-717.
115. Stewart, W.F., et al., *Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability.* Neurology, 2001. **56**(6 Suppl 1): p. S20-8.
116. Stewart, W.F., et al., *Reliability of the migraine disability assessment score in a population-based sample of headache sufferers.* Cephalalgia, 1999. **19**(2): p. 107-14; discussion 74.
117. Buse, D.C., et al., *Development and validation of the Migraine Interictal Burden Scale (MIBS): a self-administered instrument for measuring the burden of migraine between attacks.* Neurology 2007. **68**: p. A89.
118. Buse, D.C., M.F. Rupnow, and R.B. Lipton, *Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life.* Mayo Clin Proc, 2009. **84**(5): p. 422-35.
119. EuroQol, G., *EuroQol--a new facility for the measurement of health-related quality of life.* Health Policy, 1990. **16**(3): p. 199-208.
120. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Qual Life Res, 2011. **20**(10): p. 1727-36.
121. Reilly, M.C., A.S. Zbrozek, and E.M. Dukes, *The validity and reproducibility of a work productivity and activity impairment instrument.* Pharmacoeconomics, 1993. **4**(5): p. 353-65.
122. Spitzer, R.L., et al., *A brief measure for assessing generalized anxiety disorder: the GAD-7.* Arch Intern Med, 2006. **166**(10): p. 1092-7.
123. Kruskal, W.H. and W.A. Wallis, *Use of ranks in one-criterion variance analysis.* J Am Stat Assoc, 1952. **47**(260): p. 583-621.
124. Wilcoxon, F., *Individual comparisons by ranking methods.* Biometrics Bulletin, 1945. **1**(6): p. 80-83.
125. Finniss, D.G. and F. Benedetti, *Mechanisms of the placebo response and their impact on clinical trials and clinical practice.* Pain, 2005. **114**(1-2): p. 3-6.
126. Health., C.A.f.D.a.T.i., *Common Drug Review Clinical Review Report for Botox. Retrieved from: https://www.cadth.ca/sites/default/files/cdr/clinical/SR0345_Botox_Migraine_CL_Report_e.pdf* 2015.
127. Aurora SK, D.D., Turkel CC, DeGryse RE, Silberstein SD, Lipton RB, Diener HC, Brin MF, *OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial.* Cephalalgia. , 2010. **30**(7): p. 793-803.
128. Diener HC, D.D., Aurora SK, Turkel CC, DeGryse RE, Lipton RB, Silberstein SD, Brin MF, P. C., M. S. Group, *OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. .* Cephalalgia, 2010 **30**(7): p. 804-814.
129. Diener HC, S.C., Bingel U, Dodick DW *The importance of placebo in headache research. .* Cephalalgia 2008. **28**(10): p. 1003-1011.
130. Diederich NJ, G.C., *The placebo treatments in neurosciences: New insights from clinical and neuroimaging studies. .* Neurology, 2008. **71**(9): p. 677-684.
131. Bangs, M.E., Kudrow, D., Wang, S. et al. , *afety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies.* BMC Neurol, 2020. **20**(25).
132. Oakes TM, K.R., Rosen N, et al., *Evaluation of Cardiovascular Outcomes in Adult Patients With Episodic or Chronic Migraine Treated With Galcanezumab: Data From Three Phase 3, Randomized, Double-Blind, Placebo-Controlled EVOLVE-1, EVOLVE-2, and REGAIN Studies.* Headache, 2020. **60**(1): p. 110-123.

133. Ford, J.H., et al., *Patient satisfaction, health care resource utilization, and acute headache medication use with galcanezumab: results from a 12-month open-label study in patients with migraine.* Patient Prefer Adherence, 2018. **12**: p. 2413-2424.
134. Stauffer, V.L., et al., *Comparison between prefilled syringe and autoinjector devices on patient-reported experiences and pharmacokinetics in galcanezumab studies.* Patient Prefer Adherence, 2018. **12**: p. 1785-1795.
135. Brown, J.S., et al., *Cost-effectiveness of topiramate in migraine prevention: results from a pharmacoeconomic model of topiramate treatment.* Headache, 2005. **45**(8): p. 1012-22.
136. Brown, J.S., et al., *Cost effectiveness of topiramate in the prevention of migraines in the United States: an update.* Manag Care Interface, 2006. **19**(12): p. 31-8.
137. Brown, J.S., et al., *Cost-effectiveness of migraine prevention: the case of topiramate in the UK.* Cephalalgia, 2006. **26**(12): p. 1473-82.
138. Giannouchos, T.O., R., *PND42: COST-EFFECTIVENESS ANALYSIS OF ERENUMAB VERSUS TOPIRAMATE FOR PATIENTS WITH CHRONIC MIGRAINES TO IDENTIFY THE COST-EFFECTIVE PRICE THRESHOLD IN GREECE.* Value in Health, 2019. **22**(S2).
139. Batty, A.J., et al., *The cost-effectiveness of onabotulinumtoxinA for the prophylaxis of headache in adults with chronic migraine in the UK.* J Med Econ, 2013. **16**(7): p. 877-87.
140. Ruggeri, M., *The cost effectiveness of Botox in Italian patients with chronic migraine.* Neurol Sci, 2014. **35 Suppl 1**: p. 45-7.
141. Kelley, K., A. Schoenbrunner, and J. Murphy, *Cost-Effectiveness of Initial Prophylactic Treatment of Chronic Migraine: Oral Medications versus OnabotulinumtoxinA (P2.198).* 2016. **86**(16 Supplement): p. P2.198.
142. Canadian Agency for Drugs and Technologies in Health, *Common Drug Review Clinical Review Report for Botox*. 2015.
143. Pharmaceutical Benefits Advisory Committee, *Botulinum toxin type A for chronic migraine*. 2017.
144. Giannouchos, T.V., et al., *Cost-Effectiveness Analysis of Erenumab Versus OnabotulinumtoxinA for Patients with Chronic Migraine Attacks in Greece.* Clin Drug Investig, 2019. **39**(10): p. 979-990.
145. Lipton, R.B., et al., *Estimating the clinical effectiveness and value-based price range of erenumab for the prevention of migraine in patients with prior treatment failures: a US societal perspective.* J Med Econ, 2018. **21**(7): p. 666-675.
146. Sussman, M., et al., *Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: Results from the US societal and payer perspectives.* Cephalalgia, 2018. **38**(10): p. 1644-1657.
147. Smolen L, G.S., Klein T., *10-year cost-effectiveness analyses of fremanezumab as preventive treatment in chronic and episodic migraine. PND21.* Value in Health, 2019. **22**(S2): p. S273.
148. Data on File, *Eli Lilly and Co: Company's minutes of EMA/HTA Parallel Scientific Advice Meeting 02 December 2014*. 2014.
149. Porter, J.K., et al., *Parametric Modelling of Migraine Day Frequency In Migraine Prevention: A Case Study Of Erenumab Clinical Trial Data.* Value in Health, 2017. **20**(9): p. A733.
150. National Institute for Health and Care Excellence (NICE). *Fremanezumab for preventing migraine [ID1368]*. 2019; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10339.
151. Silberstein, S., et al., *Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults.* Cephalalgia, 2008. **28**(5): p. 484-95.
152. Sun, X. and T. Faunce, *Decision-analytical modelling in health-care economic evaluations.* Eur J Health Econ, 2008. **9**(4): p. 313-23.
153. Briggs, A. and M. Sculpher, *An introduction to Markov modelling for economic evaluation.* Pharmacoeconomics, 1998. **13**(4): p. 397-409.
154. Gillard, P.J., et al., *Mapping from disease-specific measures to health-state utility values in individuals with migraine.* Value Health, 2012. **15**(3): p. 485-94.

155. British National Formulary. *Drugs*. 2019 24 January 2020]; Available from: https://bnf.nice.org.uk/drug/.
156. Monthly Index of Medical Specialities. *Botox*. 2020 February 7, 2020]; Available from: https://www.mims.co.uk/drugs/pain/migraine/botox.
157. Monthly Index of Medical Specialities. *Emgality*. 2020 February 07, 2020]; Available from: https://www.mims.co.uk/drugs/pain/migraine/emgality.
158. Paget M, T.-H.A., *Evaluating Previous Migraine Headache Frequency Statistical Modelling Approaches.* Value in Health, 2017. **21**.
159. Paget MA PW, T.-H.A., *Using a Parametric Approach to Simulate the Frequency of Migraine Headache Days in Patients with Chronic Migraine with Data from the REGAIN Study.* Value in Health, 2017: p. 398.
160. Data on File, *Eli Lilly and Co.: Additional data tables from CONQUER study*. 2019.
161. Data on File, *Eli Lilly and Co.; Indirect Treatment Comparison Report of Galcanezumab compared to Erenumab* 2019.
162. Blumenfeld, A.M., et al., *Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study.* The journal of headache and pain, 2018. **19**(1): p. 13-13.
163. Ahmed, F., et al., *An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study.* J Headache Pain, 2019. **20**(1): p. 26.
164. Gudmundsson, L.S., et al., *Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study.* Bmj, 2010. **341**: p. c3966.
165. Asberg, A.N., et al., *Migraine as a predictor of mortality: The HUNT study.* Cephalalgia, 2016. **36**(4): p. 351-7.
166. Speck, R.M., et al., *Content validity of the Migraine-Specific Quality of Life Questionnaire version 2.1 electronic patient-reported outcome.* J Patient Rep Outcomes, 2019. **3**(1): p. 39.
167. National Institute for Health and Care Excellence. *Position statement on use of the EQ-5D-5L value set for England* 2019; Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.
168. MIMS. *Database of prescription and generic drugs, clinical guidelines (MIMS).* . 2019 February 7, 2020]; Available from: https://www.mims.co.uk/.
169. National Health Service Improvement. *2019/20 National Tariff Payment System*. 2020 February 6, 2020]; Available from: https://www.england.nhs.uk/pay-syst/national-tariff/2019-20-payment-reform-proposals/.
170. National Health Service Improvement. *National tariff payment system 2017/18 and 2018/19*. 2019 January 24, 2020]; Available from: https://improvement.nhs.uk/resources/national-tariff-1719/.
171. Allergan Ltd. *BOTOX Summary of Product Characteristics*. 2019 February 6, 2020]; Available from: https://www.medicines.org.uk/emc/product/859/smpc.
172. Munakata, J., et al., *Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study.* Headache, 2009. **49**(4): p. 498-508.
173. Personal Social Services Research Unit. *Unit Costs of Health and Social Care 2019*. 2019; Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/.
174. Detke, H.C.L., L.Q.; Wang, S.; Aurora, S.K. . *One-year treatment with galcanezumab in patients with chronic migraine: results from the open-label phase of the REGAIN study. Poster presented at 17th Biennial Migraine Trust International Symposium (MTIS); September 6-9, 2018; London, United Kingdom*. 2018.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Galcanezumab for preventing migraine

[ID 1372]

Clarification questions

March 2020

File name	Version	Contains confidential information	Date
ID1372_ Emgality NICE clarification response_170320 [ACIC]	Final	Redacted	25/06/2020

Section A: Clarification on effectiveness data

Galcanezumab trial data

A1. The flowchart (company submission Figure 4) and Table 13 report the Intention to treat (ITT) population for CONQUER as [redacted] for placebo and galcanezumab respectively. However, the number of patients with 2, 3 and 4 medication failures and the number of patients in different race categories in Table 13 do not add up to these values. In addition, subsequent tables give different numbers of patients for the same ITT population (including subgroup tables Section B.2.7).

a) Please clarify how many patients contribute to each row in Table 13 and subsequent tables.

b) Please clarify the size of the ITT population and reason for discrepant values across tables. Please also make reference to the subgroups of episodic and chronic migraine populations and the ITT population in each subgroup.

c) If discrepancies are due to missing data please clarify which outcomes have had data imputed (detailing imputation methods), which have not and why.

Company Response:

a) Table 13 in the submission document is missing the data described below. Regarding the data presented in subsequent tables please see response c)

   1) For the variable “Qualifying preventive medication category failures in past 10 years”, the submission Document B is missing data for “1 medication failure” and “5 medication failures”. These data are described in Table 1.

   2) Baseline demographic data was available for all variables except “Race” for XXX patients in the placebo arm and XXX patients in the galcanezumab arm. At baseline, data on race was available only for XXX subjects in the placebo arm and XXX of the subjects in the galcanezumab arm. An additional footnote “b” has been added to highlight the reasons for the difference in sample size.

Table 1 Amendments to Table 13 in submission (Summary of demographic characteristics in ITT population)

Characteristic	Placebo (N=230)	GMB 120 mg (N=232)	Total (N=462)
Disease characteristics			
Qualifying preventive medication category failures in past 10 years[a], n (%)			
1 medication failures	XXX	XXX	XXX
2 medication failures	XXX	XXX	XXX
3 medication failures	XXX	XXX	XXX
4 medication failures	XXX	XXX	XXX
5 medication failures	XXX	XXX	XXX
Race[b], n (%)			
American Indian or Alaska Native	XXX	XXX	XXX
Asian	XXX	XXX	XXX
Black or African American	XXX	XXX	XXX
Native Hawaiian or Other Pacific Islander	XXX	XXX	XXX
White	XXX	XXX	XXX
Multiple	XXX	XXX	XXX

Abbreviations: GMB, galcanezumab; ITT, intent-to-treat

[a]Based on any medications taken for migraine prevention in the patient's lifetime; not limited to standard-of-care treatments from inclusion criterion. Failure defined as discontinuation due to no response/inadequate response, or medical history event (safety/tolerability). Contraindications did not count as treatment failures.

[b]Data was available for XXX patients in the placebo arm and for XXX patients in the galcanezumab arm

Source: Eli Lilly data on file, CGAW Clinical Study Report Table CGAW.14.152

a) A total of 462 patients were randomized and included in the ITT population of CONQUER, including 230 and 232 patients in the placebo arm and galcanezumab arm, respectively.

Of the 462 patients in the ITT population, XXX patients comprised the episodic subpopulation. Of these, a total of XXX patients (XXX with episodic migraine completed the double-blind treatment phase, including

- XXX in the galcanezumab group, and
- XXX in the placebo group.

A total of XXX patients in the ITT population had chronic migraine, among which a total of XXX patients (XXX) completed the double-blind treatment phase, including

- XXX in the galcanezumab group, and
- XXX in the placebo group.

b) Discrepancies between the baseline sample size and the sample size for individual endpoints were due to discontinuation of treatment during the double-blind phase. A total of 451 patients (97.6%) completed the 3-month double-blind treatment phase, including:

   - 225 (97.0%) in the galcanezumab group, and
   - 226 (98.3%) in the placebo group.

   The most frequent reason for discontinuing from the double-blind treatment phase was protocol deviation (1.7% galcanezumab, 0.4% placebo). Other reasons for dropouts in the ITT population are shown in Table 2

Table 2 Reasons for Discontinuation from Double-Blind Treatment Phase ITT Population

Reason for Discontinuation	Placebo (N=230)	Galcanezumab (N=232)
	n (%)	n (%)
Discontinued Double-Blind Treatment Phase Due to Any Reason	4 (1.74)	7 (3.02)
Protocol Deviation	1 (0.43)	4 (1.72)
Patient Decision	2 (0.87)	1 (0.43)
Scheduling Conflicts	0	1 (0.43)
Subject is Moving or has Moved	1 (0.43)	0
Other	1 (0.43)	0
Lack of Efficacy	1 (0.43)	1 (0.43)
Adverse Event	0	1 (0.43)

Abbreviations: ITT, intent-to-treat.

Source: Eli Lilly data on file, CGAW Clinical Study Report Table CGAW.10.1

Handling of dropouts or missing data

The primary measure of the number of monthly MHDs was summarized from the daily electronic patient reported outcomes (ePRO), which included daily data from the baseline period prior to randomisation, and 3 months of daily data during the double-blind treatment phase. In calculating the number of MHDs for each monthly interval, the number of MHDs was normalized to a 30-day period by multiplying the number of MHDs by (30/x) where 'x' was the total number of non-missing diary days in the monthly interval.

This approach to missing ePRO diary data assumed that the rate of migraine headache per day was the same for days with missing and non-missing ePRO diary days. The same approach was also applied to secondary and exploratory efficacy measures that were derived from ePRO data.

Clarification questions

Two statistical approaches to handling missing data were used as appropriate:

- repeated measures analyses, and
- ANCOVA/ANOVA model using change from baseline to last-observation-carried-forward (LOCF) endpoint.

For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when data are missing at random.

A2. Please provide a measure of uncertainty for the values in Tables 21 and 22 (company submission page 63-65).

Company Response:

The 95% confidence interval values are added to the mean change values presented in Tables 21 and 22 of the original submission as shown in Table 3 and Table 4, respectively.

Table 3 Addition of 95% confidence intervals to Table 21. Key headache related efficacy outcomes in ITT population, chronic subpopulation and episodic subpopulations at month 6

	ITT population		CM population		EM population	
	Prior placebo (n=211)	Prior GMB (n=215)	Prior Placebo (n=88)	Prior GMB (n=84)	Prior Placebo (n=123)	Prior GMB (n=131)
Change from baseline in the number of monthly headache days						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Change from Baseline in Number of Monthly Migraine Headache Hours						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX

95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Change from Baseline in Number of Monthly Days with Acute Headache Medication Use[b]						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Change from Baseline in Patient Global Impression (PG-I) of Severity Rating until LOCF						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Proportion of patients with ≥50% reduction from baseline in monthly MHDs						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Proportion of patients with ≥30% reduction from baseline in monthly MHDs						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: CM, chronic migraine; EM, episodic migraine; GMB, Galcanezumab; ITT, Intent-to-treat; LOCF, last observation carried forward; LS, Least Squares; MHDs, Monthly Migraine Headache days; N, number of intent-to-treat subjects with non-missing baseline value and at least one non-missing postbaseline value; NA, Not available; PGI-S, Patient Global Impression of Severity

[a] This evaluated any day on which acute headache medication was taken, regardless of whether it was a migraine headache day. Note that a separate post hoc analysis was conducted to evaluate migraine headache days with acute headache medication use

[b] For the PGI-S, the number of patients with a baseline and postbaseline value was XXX, and XXX in the episodic subpopulation:

Table 4 Addition of 95% confidence intervals to Table 22 Key quality of life outcomes of the ITT chronic and episodic subpopulations at Month 6

	ITT		CM		EM	
	Placebo (n=211)	GMB (n=215)	Placebo (n=88)	GMB (n=84)	Placebo (n=123)	GMB (n=131)
Mean change from baseline in MSQ Total Score						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Mean change from baseline to LOCF endpoint in EQ-5D-5L health state index (UK)						
Month 3 (double-blind phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX
Month 6 (open-label phase)	XXX	XXX	XXX	XXX	XXX	XXX
95% CI	XXX	XXX	XXX	XXX	XXX	XXX

Abbreviations: CM, chronic migraine; EQ-5D-5L, EuroQol 5 Dimension 5 Level questionnaire; EM, episodic migraine; GMB, Galcanezumab; ITT, Intent-to-treat; LOCF, last observation carried forward; MSQ, Migraine-specific quality of life questionnaire; N, number of intent-to-treat subjects with non-missing baseline value and at least one non-missing postbaseline value; NA, Not available; UK, United Kingdom

A3. PRIORITY: Please clarify whether the subpopulation of patients who have failed ≥3 previous therapies includes patients who have failed botulinum toxin type A? If so, can the company please present effectiveness data excluding botulinum toxin type A failures from the analysis.

Company response:

The subpopulation of patients who have a history of ≥3 prior preventative medication category failures did not exclude those patients for whom botulinum toxin A failed. Presented below is effectiveness data for all CONQUER patients with a history of ⩾3 prior preventive medication category failures (in the last 10 years) for efficacy or safety/tolerability reasons excluding the botulinum toxin A or B category.

The statistical methods followed the same principles defined in the Clinical Study Report for CONQUER (section 9.3.7). However, no multiplicity adjustment was done on the requested post-hoc analyses.

At baseline there were XXX patients in the placebo group and XXX patients in the galcanezumab group. No statistical differences between galcanezumab and placebo for each continuous or categorical baseline characteristics were observed except for medication overuse (p-value = XXX) with a higher number of patients with medication overuse in the galcanezumab group than the placebo group at baseline.

Table 5 Baseline characteristics, Patients with a history of ⩾3 prior preventative medication category failures excluding prior botulinum toxin A failures, CONQUER

Characteristic	Placebo (XXX)	GMB 120 mg (XXX)	Total (XXX)	p-value*
Age (years)				
Mean (±SD)	XXX	XXX	XXX	XXX
Sex, n (%)				
Female	XXX	XXX	XXX	XXX
Male	XXX	XXX	XXX	
Race, n (%)[1]				
American Indian or Alaska Native	XXX	XXX	XXX	XXX
Asian	XXX	XXX	XXX	
Black or African American	XXX	XXX	XXX	
Native Hawaiian or Other Pacific Islander	XXX	XXX	XXX	
White	XXX	XXX	XXX	

Multiple	XXX	XXX	XXX	
Body Mass Index (kg/m2)				
Mean (±SD)	XXX	XXX	XXX	XXX
Region, n (%)				
North America	XXX	XXX	XXX	XXX
Europe	XXX	XXX	XXX	
Asia	XXX	XXX	XXX	
Baseline Migraine Frequency Category				
Low frequency episodic	XXX	XXX	XXX	XXX
High frequency episodic	XXX	XXX	XXX	
Chronic	XXX	XXX	XXX	
Patient global impressions - severity				
Normal, not at all ill	XXX	XXX	XXX	XXX
Borderline ill	XXX	XXX	XXX	
Mildly ill	XXX	XXX	XXX	
Moderately ill	XXX	XXX	XXX	
Markedly ill	XXX	XXX	XXX	
Severely ill	XXX	XXX	XXX	
Extremely ill	XXX	XXX	XXX	
Qualifying preventive medication failures in the past 10 years, n (%)[2]				
1 medication failures	XXX	XXX	XXX	
2 medication failures	XXX	XXX	XXX	
3 medication failures	XXX	XXX	XXX	
4 medication failures	XXX	XXX	XXX	
5 medication failures	XXX	XXX	XXX	
6 medication failures	XXX	XXX	XXX	
7 medication failures	XXX	XXX	XXX	
>8 medication failures	XXX	XXX	XXX	
Acute medication overuse				
Yes	XXX	XXX	XXX	XXX
No	XXX	XXX	XXX	
Total number of failed individual preventive meds lifetime, mean (±SD)	XXX	XXX	XXX	XXX
Total number of failed individual preventive meds past 10 years, mean (±SD)	XXX	XXX	XXX	XXX
Number of monthly headache days, mean (±SD)	XXX	XXX	XXX	XXX

Number of monthly MHDs, mean (±SD)	XXX	XXX	XXX	XXX
Number of monthly migraine attacks, mean (±SD)	XXX	XXX	XXX	XXX
MSQ Role Function-Restrictive domain, mean (±SD)	XXX	XXX	XXX	XXX
MIDAS total score, mean (±SD)	XXX	XXX	XXX	XXX
Duration of migraine illness, years, mean (±SD)	XXX	XXX	XXX	XXX
PGI-S, mean (±SD)	XXX	XXX	XXX	XXX

Abbreviations: ITT, intent-to-treat; GMB, galcanezumab; PGI-S, Patient Global Impression – Severity; ITT, intention-to-treat; meds, medications; MHDs, migraine headache days; MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality of Life Questionnaire; N, number of ITT patients; n, number of patients within each specific category; SD, standard deviation; yrs, years.

The total number of subject reported race was XXX, including XXX for the placebo arm and XXX for the galcanezumab arm

Prior migraine preventive medications includes any migraine preventive medications that were discontinued in the past 10 years due to Medical History Event, Inadequate Response, or No Response

Source: Eli Lilly data on file, smedemocat_prev3_nobtx, smedemocon_prev3_nobtx and smmedov_prev3_nobtx

The efficacy data showed that the mean change from baseline for MHD over 3 months in CONQUER was XXX in the galcanezumab arm compared with the placebo arm (difference in the mean change from baseline XXX). The odds of patients who achieved 30% and 50% response were also XXX in the galcanezumab arm than the placebo arm XXX (30% responder: XXX; 50% responder: XXX). The detailed clinical efficacy results are shown in Table 6.

Table 6 Efficacy outcomes, Patients with a history of ⩾3 prior preventative medication category failures excluding prior botulinum toxin A failures, CONQUER

	Placebo (XXX)	**GMB 120 mg (XXX)**
Change from Baseline in the Number of Monthly Migraine Headache Days		
LSMean change from baseline	XXX	XXX
95% CI	XXX	XXX
Within group p-value	XXX	XXX
LSMean change difference between groups	XXX	XXX
95% CI	XXX	XXX
Within group p-value	XXX	XXX
Estimated Proportion of 30% Responders for Migraine Headache Days		
Model estimated rate (SE)[1]	XXX	XXX

Clarification questions

95% CI	[redacted]	[redacted]
Odd ratio	[redacted]	[redacted]
95% CI for odds ratio	[redacted]	[redacted]
Within group p-value	[redacted]	[redacted]
Estimated Proportion of 50% Responders for Migraine Headache Days		
Model estimated rate (SE)[1]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Odd ratio	[redacted]	[redacted]
95% CI for odds ratio	[redacted]	[redacted]
p-value	[redacted]	[redacted]

Abbreviations: ITT, intent-to-treat; GMB, galcanezumab; LSMean, least square mean; SE, standard error; CI, confidence interval

Categorical pseudo likelihood-based repeated measures model for binary outcome: Responder indicator = treatment, month, treatment*month, and baseline monthly MHD.
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: Eli Lilly data on file, rmmhd14_prev3_nobtx, remresp30_prev3_nobtx and rmresp50_prev3_nobtx

A4. For patients who have failed ≥3 treatments, please could you state how many of these patients failed on treatments not used in clinical practice in the UK.

Company Response:

A summary of the medication categories failed in the past 10 years for the ITT population from CONQUER is provided in Table 7. A complete table with reasons for discontinuations is provided in the Clinical Study Report for CONQUER (Table CGAW14.24).

Table 7 Summary of medication categories failures in the past 10 years

Medication category – prevention therapy	Placebo (n=230) N (%)	GMB 120mg (n=232) N (%)	p-value*a
Topiramate	[redacted]	[redacted]	[redacted]
Amitriptyline	[redacted]	[redacted]	[redacted]
Propranolol or Metoprolol	[redacted]	[redacted]	[redacted]
Valproate	[redacted]	[redacted]	[redacted]
Medication locally approved for prevention of migraine	[redacted]	[redacted]	[redacted]

Botulinum toxin A	XXX	XXX	XXX
Flunarizine	XXX	XXX	XXX
Candesartan	XXX	XXX	XXX

Abbreviations: GMB, galcanezumab; N, number of subjects in the analysis population; n, number of subjects within each specific response category.
*a, Fisher's exact p-value comparing treatment groups for 3 non-missing reasons

Source: Eli Lilly Data on file, CGAW Clinical Study Report Table CGAW14.24

The medication categories failed largely represents clinical practice in the UK as outlined in NICE clinical guideline 150, Headaches in over 12s: diagnosis and management (2015) and in the British Association for the Study of Headache guidelines (2019). Topiramate (XXX), amitriptyline (XXX and propranolol (XXX make up the majority of medication category failures and are directly relevant to UK clinical practice.

Medication category failures that are not relevant to UK clinical practice and may potentially impact generalisability include flunarizine XXX valproate XXX and medications locally approved for the prevention of migraine XXX; lomerizine, cinnarizine, oxetorone, iprazochrome and nadolol, excluding pizotifen which is licensed in UK for preventing migraine) but these make up relatively low numbers. These other categories were included as a necessity to accommodate a global trial design for galcanezumab.

Botulinum toxin A XXX is also represented in low numbers but we acknowledge that this would not be used in patients that have a history of less than 3 prior preventative therapies in the UK. A supplementary analysis with these patients excluded in the target patient group is presented in A.3.

Table 8 presents a summary of patients that have failed at least one medication category failure not used in the UK at baseline for patients with a history of failure to ≥3 prior preventative medication categories. The medication categories are defined according to the CONQUER protocol and reported in the CONQUER Clinical Study Report inclusion criteria (section 9.3.1). The medication categories are as follows:

a. propranolol or metoprolol
b. topiramate
c. valproate or divalproex
d. amitriptyline
e. flunarizine
f. candesartan
g. botulinum toxin A or B (if documented that botulinum toxin was taken for chronic migraine)
h. medication locally approved for prevention of migraine

Table 8 Summary of prior preventive medication category failures, patients who have failed at least one treatment not used in UK clinical practice.
Intent-to-Treat Population with ≥3 prior preventive medication category failures within the last 10 years (with MHD data), CONQUER

Period	Treatment	N	n (%)
Baseline	Placebo	XXX	XXX
	GMB 120mg	XXX	XXX
Month 1	Placebo	XXX	XXX
	GMB 120mg	XXX	XXX
Month 2	Placebo	XXX	XXX
	GMB 120mg	XXX	XXX
Month 3	Placebo	XXX	XXX
	GMB 120mg	XXX	XXX

Abbreviations: GMB, galcanezumab; N, patients who are flagged to have failed at least 3 preventive treatment categories in the last 10 years and have MHD data; n, patients failed at least one treatment not used in UK clinical practice (i.e. flunarizine, valproic acid, lomerizine, cinnarzine, oxetorone, iprazochrome, nadolol).

Source: Eli Lilly data on file, smprev3_trt

At baseline, XXX out of XXX placebo and XXX XXX out of XXX galcanezumab patients had a medication category not used in the UK market among the CONQUER patients who had failed ≥3 preventative medication categories of preventive treatments.

However, when using a modified definition of medication categories which included only mediations used in UK clinical practice and excluded those not used in UK clinical practice (i.e. flunarizine, valproic acid, lomerizine, cinnarzine, oxetorone, iprazochrome and nadolol), [redacted] patients in the placebo group and [redacted] patients in the galcanezumab groups had at least one treatment in the modified medication category not used in UK clinical practice. The modified medication categories defined for this analysis are as follows:

a) propranolol or metoprolol
b) topiramate
c) amitriptyline
d) candesartan
e) botulinum toxin A or B (if documented that botulinum toxin was taken for chronic migraine)
f) medication locally approved for prevention of migraine
    i. Note that none of the patients received “clonidine” or “timodol” so the f) category corresponds to only “pizotifen”

Table 9 Summary of prior preventive medication modified category failures Intent-to-Treat Population with ≥3 prior preventive medication modified category failures last 10 years, CONQUER

Period	Treatment	N
Baseline	Placebo	XXX
	GMB 120mg	XXX
Month 1	Placebo	XXX
	GMB 120mg	XXX
Month 2	Placebo	XXX
	GMB 120mg	XXX
Month 3	Placebo	XXX
	GMB 120mg	XXX

Abbreviations: GMB, galcanezumab; N, patients who are flagged to have failed at least 3 preventive treatment modified categories in the last 10 years and have MHD data.

Source: Eli Data on file, smprev3_notrt

A5. REGAIN subpopulation who have failed ≥3 treatments (section B.2.7.5, company submission page 79): Please could you explain some of the discrepancies in tables for this subpopulation:

a) The galcanezumab 120 mg group is [redacted] the size of the placebo group (REGAIN CSR, Figure CGAI.10.1, page 87). However, Table 33 shows for patients with ≥3 prior treatments, the galcanezumab 120mg group is [redacted] the size of the placebo group.

b) Table 38 includes an additional patient in the placebo group ([redacted]) compared with Table 33 ([redacted]).

Company Response

a) REGAIN ITT population included three treatment arms: placebo (N=558), galcanezumab 120mg (N=278), galcanezumab 240mg (N=277). In Section B.2.7.5.1, the results presented are a post hoc analysis of REGAIN for the subpopulation who had a history of ≥3 prior preventive treatment failures, and only included patients receiving placebo or galcanezumab 120mg. The discrepancy observed is due to the natural differences between the number of patients who had ≥3 prior treatments in the respective arms.

b) Table 38 (placebo XXX) describes the baseline characteristics of the subpopulation. However, one patient dropped out during the double-blind treatment phase and was not assessed for the primary endpoint. Therefore, data is presented only for XXX patients in the placebo arm in Table 33.

A6. PRIORITY: Company submission Table 34, there is a lack of clarity about time-points for data:

a) **The title states data are reported at month 6. However, subheadings within the table suggest data were assessed over 3 months (e.g. 'change from baseline in number of monthly days with acute headache medication use over 3 months'). Please could you clarify this discrepancy.**

b) **Please provide a revised version of Table 34 with data at both 3 and 6 months for all trials?**

Company Response:

a) The title for Table 34 in the submission is incorrect and should be revised to: "Key secondary endpoints in post-hoc REGAIN patients with 3 or more prior preventive medication failures at month 3".

Month 6 results for the pooled EVOLVE -1 and EVOLVE-2 studies are provided in Table 35 in the submission.

b) Revised Table 34 is shown below as Table 10.

Table 10 Amendment to the title and footnote of Table 34. Key secondary endpoints in post-hoc REGAIN patients with 3 or more prior preventive medication failures

	REGAIN ITT patient (CM) with ⩾3 prior treatment failures	
	Placebo (N=102)	**GMB 120MG (N=36)**
Change from baseline in number of monthly days with acute headache medication use over 3 months[a]		
Baseline (SD)[a]	XXX	XXX
Overall LS Mean (SE) from baseline	-0.78 (0.75)	-6.01 (0.96)
Difference vs. placebo (SE)	XXX	XXX
95% CI	XXX	XXX
***P*-value vs. placebo**	XXX	XXX
Proportion of patients with ⩾50% reduction from baseline in monthly MHDs in ITT population over 3 months		
Overall responders, %	XXX	XXX

Odds Ratio (95% CI)	XXX	XXX
***P*-value vs. placebo**	XXX	XXX
Overall mean change of MSQ Function-Restrictive domain scores over 3 months[b]		
Baseline (SD)[a]	XXX	XXX
Overall LS Mean (SE) from baseline	XXX	XXX
Difference vs. placebo (SE)	XXX	XXX
95% CI	XXX	XXX
***P*-value vs. placebo**	XXX	XXX

Abbreviations: GMB, galcanezumab; ITT, intent-to-treat; CI, confidence interval; LS = Least Squares; N = number of intent-to-treat subjects with non-missing baseline value and at least one non-missing post-baseline value; SD = standard deviation; SE = standard error; vs. = versus.[a] Baseline mean values are for the entire the subpopulation with 3+ prior preventive medication failures (placebo N=103, GMB 120mg: N=36)[b] Subjects included for the MSQ measures included XXX.

A7. Patients in Tables 33-35: There is a lack of clarity about patients included in Tables 33-35 and inconsistency of table and section headings.

Section B.2.7.5 and company submission Table 33 state that these data are from a subpopulation of REGAIN (but footnote of this table suggests patients from EVOLVE-1 and EVOLVE-2 were included). Table 34 states in the heading that it includes a post-hoc analysis of patients from REGAIN, EVOLVE-1 and EVOLVE-2. Table 35 and section B.2.7.6 are presented as a post-hoc analysis of only EVOLVE-1 and EVOLVE-2. However, the sample sizes in Tables 33, 34 and 35 are identical. Please could you clarify:

a) Are patients from EVOLVE-1 and EVOLVE-2 included in Tables 33 and 34?

b) Are patients from the REGAIN trial included in Table 35? If the data are only from EVOLVE-1 and EVOLVE-2, why are more patients included from these trials in Table 35 ([redacted]) compared with Tables 33 and 34 ([redacted] from EVOLVE-1 and EVOLVE-2)?

c) If Table 35 includes data from REGAIN were they taken at month 6 as reported in Table 35 or at month 3 (end of double-blind phase)? Please provide a revised table with data at both time points.

Company Response:

a) Patients from EVOLVE-1 and EVOLVE-2 were not included in tables 33 and 34. Please see the company response to question A6 for the clarification and correction of the mistake in the title of Table 34.

b) The REGAIN trial was not included in Table 35. Please see the company responses to question A6.a) and question A5.

c) Table 35 did not include data from REGAIN.

Risk of bias assessments for indirect treatment comparison and systematic review

A8. Please clarify why PREEMPT 1 and PREEMPT 2 studies were judged to be at high risk of selective reporting (Appendix D, Table 12 and Table 14).

Company response:

The SLR was conducted specifically for the difficult-to-treat population. The inclusion criteria specified that patients must have had at least one prior treatment failure (Appendix D, Table 8). The PREEMPT studies included in the indirect treatment comparison to botulinum toxin A only included publicly available information for patients with a history of ≥3 prior preventative failures (DDT-3). Evidence for this target patient population was only picked up from the HTA repository search, particularly in the CADTH assessment report (3). Publicly available information was limited in this report; no baseline characteristics were reported and only data for a selected number of outcomes are displayed, hence the PREEMPT trials (for this subgroup) were judged to have a high risk of selective reporting bias.

A9. It is stated that risk of bias for the CONQUER study is unclear (Appendix D, Table 12, page 33). Can this be clarified by referencing the company's protocol, CSR and other documents detailing the trial design and conduct?

Company Response:

The SLR only included publicly available studies or abstracts. At the time of the update in October 2019 the CONQUER manuscript was not publicly availably therefore only the abstract was included in the results. Hence, the risk of bias was unclear as it was judged only on this abstract (Mulleners, W. M. K., B. Láinez, M.J. Lanteri-Minet, M. Aurora, S.K. Nichols, R.M. Wang, S. Tockhorn-Heidenreich, A. Detke, H.C. (2019). A Randomized, Placebo-Controlled Study of Galcanezumab in Patients with Treatment-Resistant Migraine: Double-Blind Results from the CONQUER Study. Paper presented at the International Headache Congress 2019) (4).

The quality assessment of the CONQUER trial as provided in the submission (section B.2.5, Table 12), from the Clinical Study Report, indicates a low risk of bias, and states:

'The accuracy and reliability of the CONQUER clinical trial data were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the sponsor. In addition, an independent Data Monitoring Committee

(DMC) was established with the responsibility of safeguarding the interests of study participants.'

Randomisation in the trial was successfully carried out such that baseline characteristics of patients randomised were well balanced across treatment groups. Patient withdrawals during the study period were accounted for with pre-defined, standard censoring methods. Patients and investigators remained blinded throughout the trial, and all outcome assessments were conducted in accordance with trial validated methodology and were based on the ITT principle.'

Indirect treatment comparison

A10. PRIORITY: Please provide the full report on the indirect treatment comparison (ITC) and all the files required to reproduce all the ITC performed, including details of:

a) **data sources used (include raw data extraction tables if possible);**
b) **calculations to transform extracted data to useable data (e.g. from follow-up measures to change from baseline);**
c) **data pooling within comparisons (e.g. for multiple studies of galcanezumab or comparators) and justification for fixed or random effects models;**
d) **the R script used to run the ITC (and any functions required), the R data and results files – so that results can be reproduced.**

Full details should also be provided for any additional ITC or meta-analyses carried out in response to other questions.

Company Response:

The full report on the ITC between galcanezumab and botulinum toxin A has been provided with this document (5)

a) Data tables and sources to run each meta-analysis for the base case and sensitivity analysis 2 (section B.2.8.1 and B.2.8.2) are provided in the ITC report between galcanezumab and botulinum toxin (5) with this document. Each .csv file allowing to run the analyses are provided (how & where) has the name of the corresponding table and there is one file per meta-analysis

b) Please see Table 11 for details on the source of the data and the calculations that were performed (e.g. for the %). Please note that all change from baseline values were publicly available and no transformations were done

Table 11 Data sources used in the ITC to botulinum toxin A and details of the transformation calculations

Population	Analysis	Endpoint	Study	Source	Comment*
ITT	Base case	50% reduction of MHD	REGAIN	Detke et al 2018	Number of responders calculated as percentage of total patients
			PREEMPT1	CADTH Report	Table 24
			PREEMPT2	CADTH Report	Table 24
		MHD change from BL	REGAIN	Detke et al 2018	Table 2
			PREEMPT1	CADTH Report	Table 24, N is calculated with mLOCF
			PREEMPT2	CADTH Report	Table 24 N is calculated with mLOCF
		HD change from BL	REGAIN	Detke et al 2018	Table 2
			PREEMPT1	CADTH Report	Table 24, N is calculated with mLOCF
			PREEMPT2	CADTH Report	Table 24 N is calculated with mLOCF
		MSQ-RFR	REGAIN	Detke et al 2018	Table 2
			PREEMPT1	CADTH Report	Table 14, N is calculated with observed cases. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 14, N is calculated with observed cases. Data are transformed in positive.

		MSQ-RFP	REGAIN	Detke et al 2018	Table 2
			PREEMPT1	CADTH Report	Table 14, N is calculated with observed cases. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 14, N is calculated with observed cases. Data are transformed in positive.
		MSQ-EF	REGAIN	Detke et al 2018	Table 2
			PREEMPT1	CADTH Report	Table 14, N is calculated with observed cases. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 14, N is calculated with observed cases. Data are transformed in positive.
	Sensitivity analysis 2	MHD change from BL	REGAIN	Internal data	
			PREEMPT1	CADTH Report	Table 16, N and SD as per overall analysis
			PREEMPT2	CADTH Report	Table 16, N and SD as per overall analysis
		HD change from BL	REGAIN	Internal data	
			PREEMPT1	Aurora et al 2010	Figure 3 digitized
			PREEMPT2	Diener et al 2010	Figure 3 digitized
		MSQ-RFR	REGAIN	Detke et al 2018	Table 2

			PREEMPT1	CADTH Report	Table 14, N is calculated with observed cases at week 12. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 14, N is calculated with observed cases at week 12. Data are transformed in positive.
		MSQ-RFP	REGAIN	Detke et al 2018	Table 2
			PREEMPT1	CADTH Report	Table 14, N is calculated with observed cases at week 12. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 14, N is calculated with observed cases at week 12. Data are transformed in positive.
		MSQ-EF	REGAIN	Detke et al 2018	Table 2
			PREEMPT1	CADTH Report	Table 14, N is calculated with observed cases at week 12. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 14, N is calculated with observed cases at week 12. Data are transformed in positive.
DTT3	Base case	MHD change from BL	REGAIN	Ruff et al 2019	
			CONQUER	Internal data	
			PREEMPT1	CADTH Report	Table 26
			PREEMPT2	CADTH Report	Table 26
		HD change from BL	REGAIN	Internal data	
			CONQUER	Internal data	
			PREEMPT1	CADTH Report	Table 25

			PREEMPT2	CADTH Report	Table 25
		MSQ-RFP	REGAIN	Ruff et al 2019	
			CONQUER	Internal data	
			PREEMPT1	CADTH Report	Table 15, N is calculated with cases at week 24. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 15, N is calculated with cases at week 24. Data are transformed in positive.
		MSQ-RFP	CONQUER	Internal data	
			PREEMPT1	CADTH Report	Table 15, N is calculated with cases at week 24. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 15, N is calculated with cases at week 24. Data are transformed in positive.
		MSQ-EF	CONQUER	Internal data	
			PREEMPT1	CADTH Report	Table 15, N is calculated with cases at week 24. Data are transformed in positive.
			PREEMPT2	CADTH Report	Table 15, N is calculated with cases at week 24. Data are transformed in positive.

*Table numbers refer to the table in the source document

Abbreviations: ITC, indirect treatment comparison; MHD, migraine headache days; HD, headache days; BL, baseline; MSQ, Migraine-Specific Quality of Life Questionnaire version 2.1; RFR, role function preventive; EF, emotional function; CADTH, The Canadian Agency for Drug and Technologies in Health

Source: Eli Lilly data on file, 2016-4893 Indirect comparison of galcanezumab compared to Botox_V4

c) Please see full ITC report between galcanezumab and botulinum toxin A for data tables that include pooled results when more than one study was available for an individual treatment (5).

Fixed and random effects model results are provided in section 8 of the ITC report between galcanezumab and botulinum toxin A. The ITC only included two studies for botulinum toxin A (PREEMPT-1 and 2) and were judged to be very similar based on tests for heterogeneity (I^2 = XXX and two studies on galcanezumab (I^2 = XXX). The fixed and random treatment effects results were also very similar for the change from baseline in MHD:

- Fixed effects model result; Mean Difference (95% CI); XXX.
- Random-effects model result; Mean Difference (95% CI); XXX.

Source: Eli Lilly data on file, 2016-4893 Indirect comparison of galcanezumab compared to Botox_V4 Table 13

Therefore, the fixed effect model was chosen. To note, in the absence of substantial or considerable heterogeneity, the results of fixed effects and random effects models are expected to be identical.

The impact of using the random effects estimates in the cost effectiveness model is presented below.

Table 12 Scenario analysis, ≥3 prior preventative failure subgroup, Chronic vs Botox (Random-effects model)

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	XXX	XXX	XXX	XXX	XXX	£2,366
Botulinum toxin type A	XXX	XXX	XXX			

Analysis conducted using combined efficacy criterion

d) R-scripts are provided with this document (6).

A11. PRIORITY: Company submission top of page 82: Additional ITCs are detailed in the two bullet points. Please clarify if the definition of these populations were used for both galcanezumab and botulinum toxin type A studies. Please also provide full details of the ITC, as requested in A10.

Company Response:

The ITCs for the all-comers populations and difficult-to-treat failed 3 or more prior preventatives (DTT-3) are contained within the submission and results are outlined in section B.2.8.1.

The definitions for these populations are assumed to be consistent for both the galcanezumab and botulinum toxin A trial programmes. Differences in trial inclusion criteria between the PREEMPT trials and the CONQUER and REGAIN trials may impact the similarity assumption for the all-comers (including patients naïve to preventive treatment and those with a history of prior preventive treatment failure) and DDT-3 (defined as failure to at least 3 prior preventive treatments for efficacy and safety/tolerability reasons). The definition of headache/migraine headache differs across the galcanezumab (≥30 minutes duration) and botulinum toxin A (≥4 continuous hours) trial programmes.

The definition of migraine headache used in the galcanezumab trials was adapted from the definition provided in the ICHD classification. It should be noted that this classification was designed to assist with the appropriate diagnosis of different types of primary and secondary headaches, including migraine. As such, it specifies the presence of headache characteristics and other symptoms that are typical of migraine, and further specifies that a migraine headache must persist for at least 4 hours untreated. This specification is meant as an aid to differential diagnosis, as other headache types might sometimes have characteristics similar to migraine, but not last as long.

However, once a patient has a migraine diagnosis clinical practice guideline recommend that acute treatments be taken immediately upon onset of any migraine symptoms. For example, guidelines from the European Federation of Neurological Societies (Evers et al. 2009) note that the earlier triptans are taken, the better their efficacy, and that they may be less efficacious if taken too late (7). Similarly, American Academy of Neurology guidelines (Silberstein 2000) specify that migraine attacks should be treated rapidly and consistently, and that “failure to use an effective treatment promptly may increase pain, disability, and the impact of the headache” (8) Based on these conventions, it was considered appropriate in the galcanezumab studies to designate headaches of durations as short as 30 minutes as migraine headaches if they meet the other necessary criteria.

Using the 4-hour duration specified in ICHD criteria to define MHDs for purposes of clinical study is therefore not consistent with clinical practice (9). Nevertheless, sensitivity analyses using the ICHD definition for migraine headache and shown in terms of duration of the migraine headache episode were conducted on REGAIN.

These analyses of change from baseline in number of ICHD MHDs are provided for the ITT population of REGAIN below. The results of these analyses were consistent with the primary efficacy analyses. Given these consistencies observed for the primary efficacy analyses, we would anticipate to also find consistent results for the response rate outcomes.

Table 13 Change from Baseline in Number of ICHD Migraine Headache Days per Month, ITT population REGAIN

	Original CFB in Monthly MHDs		Modified with Migraine Headache Episodes ≥4 hours	
	Placebo	Galcanezumab 120mg	Placebo	Galcanezumab 120mg
N	538	273	[redacted]	[redacted]
LSMean Change	-2.27	-4.56	[redacted]	[redacted]
Diff. vs Placebo	-	-2.29	[redacted]	[redacted]
P-value vs placebo	-	<.001	[redacted]	[redacted]

Abbreviations: LS= least square. **Source:** Eli Lilly data on file, CGAI Clinical Study Report Table CGAI.11.5

The full ITC report to botulinum toxin A is provided with this response (5).

A12. PRIORITY: Feasibility of ITC (Appendix D): Table 11 (outcomes considered in the ITC) shows 5 outcomes, whereas at the end of page 31-32, 10 efficacy and 2 safety outcomes are mentioned as being assessed for ITC. Please clarify this discrepancy and update Table 11 to include all outcomes for which ITC were assessed or conducted. Please provide full details of all ITC conducted, as requested in A10.

Company Response:

The protocol plan for the ITC to botulinum toxin A pre-defined 10 efficacy and 2 safety outcomes. However, after the SLR in the difficult to treat patient population was conducted, it became evident in the feasibility assessment that publicly available data for botulinum toxin A in the patient population of interest (patient with a history of ≥3 prior preventative treatments) were only available for 5 outcomes. The evidence base identified for botulinum toxin A is limited to data reported in the CADTH assessment (10), which focused on PREEMPT-1 and 2 only. Hence, only these were considered in the ITC, shown in Table 37 in the submission.

A13. PRIORITY: Company submission Section B.2.8 on the ITC uses the subpopulation from the REGAIN trial who failed ≥3 treatments. Does the ITC include within these data patients from EVOLVE-1 and EVOLVE-2 in the same way as reported in Company submission section B.2.7.5 and Tables 33 and 34

above? If so, please could you clarify at which time points all data were collected and provide full details of the ITC, as requested in A10.

Company Response:

The ITC in question (i.e. the galcanezumab compared to botulinum toxin A) did not include patients from EVOLVE-1 and EVOLVE-2. As stated in A.6, the title for Table 34 in the submission is incorrect and should be revised to: "Key secondary endpoints in post-hoc REGAIN patients with 3 or more prior preventive medication failures at month 3". Month 6 results for the pooled EVOLVE -1 and EVOLVE-2 studies are provided in Table 35 in the submission. The ITC between galcanezumab and botulinum toxin A did not include patients from EVOLVE-1 and EVOLVE-2.

Systematic review

A14. Appendix D searches: Appendix D reports the conduct of four systematic reviews (SLR1, SLR2, SLR3, and SLR4).

a) Please could you clarify if these were four separate systematic reviews or one systematic review updated three times?

b) Search strategies in Tables 2-5, Appendix D, are provided only for the year 2019 (i.e. SLR4). Please could you clarify if the search strategies, and all other methods for the systematic review, were the same (with the exception of search date) for SLRs 1-3 as SLR4. If not, please clarify any differences in methods.

c) Please provide a PRISMA diagram that illustrates the number of records identified, included and excluded, and the reasons for exclusions for the SLRs described in Appendix D1.1 and Appendix G.

Company response:

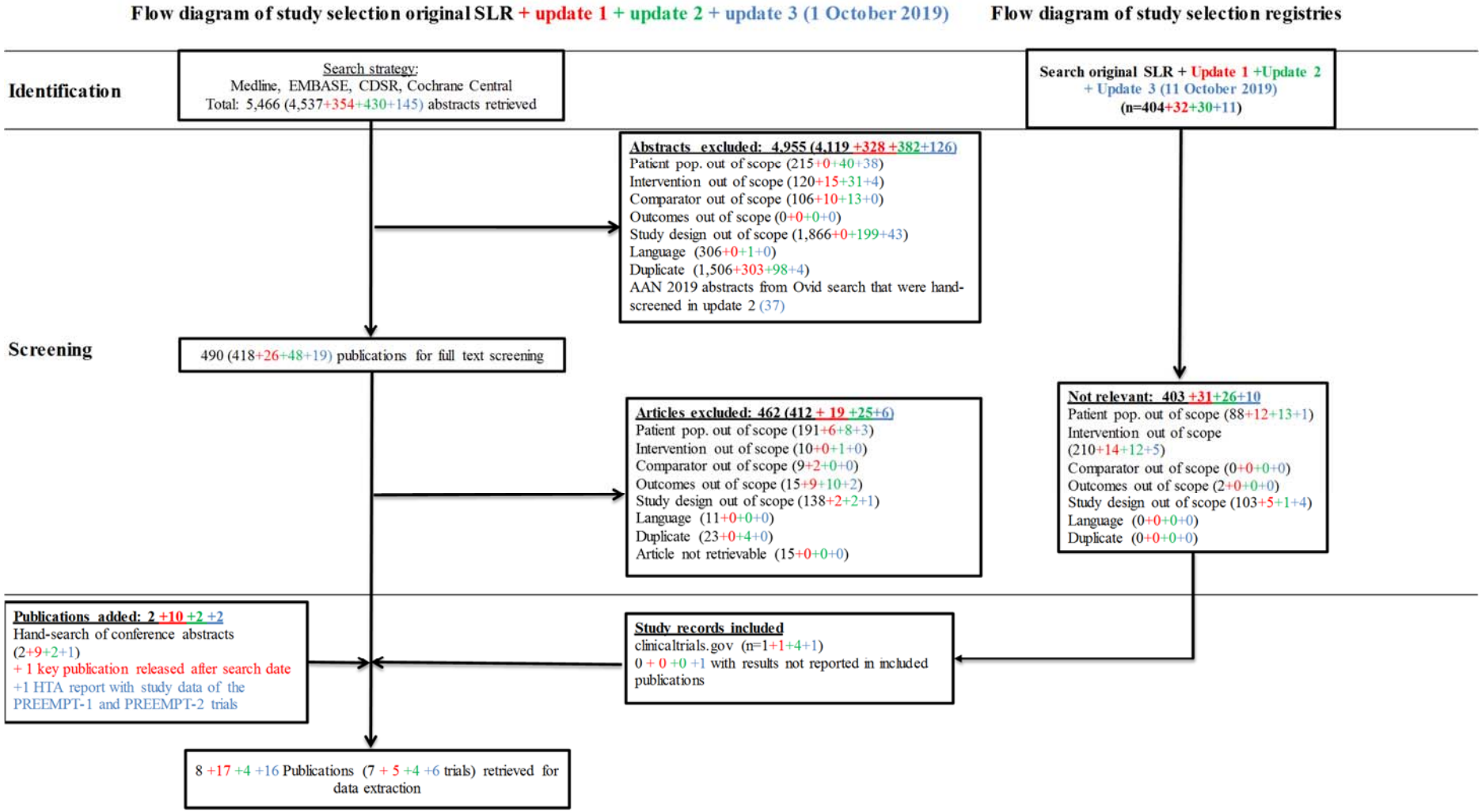
a) One SLR was conducted and updated three times. The initial search was conducted on December 13rd, 2017, first updated on October 20th, 2018, secondly updated from June 11th to August 2nd, 2019 and updated for the third time on October 1st, 2019.

b) The search strategy remained the same in each of the 3 updates. A search strategy combining disease terms (MeSH and text) with study design and intervention terms was used. Validated search filters by Cochrane were used to identify randomised controlled trials (RCTs) in MEDLINE and EMBASE. Searches were performed per database, which is in line with HTA guidelines (11). The original SLR search was conducted with no time limit until December 2017 and the first update was performed from December 2017 to October 2018. The second update was performed from October 2018 to August 2019 and the current update was performed from August

2019 to October 2019. The updated search was conducted from the beginning of 2019, as limiting to portions of years in OVID is complex, since the “Date of Publication” field in OVID databases consist of non-standard values supplied by publishers (e.g. Jan–Feb 2019, Winter 2018 etc.). Therefore, dates more precise than the “Publication Year” are unsuitable for searches across multiple databases. Duplicates from the time frame of August 2019 to October 2019 were removed and documented as duplicates.

The current update applied new search strings, containing the generic names for interventions fremanezumab and eptinezumab. These generic names were not included in the original search strings and lead to an additional search for studies on these interventions during the second update of this SLR. An additional update included the search in HTA repositories which was only done in the latter searches.

c) Study flow diagram for RCT study selection (PRISMA diagram)



A15. Appendix D, page 27 has a subsection titled ‘Complete reference lists for included studies and excluded studies’.

a) Table 9 includes a list of included studies but does not appear to provide a list of excluded studies. Please could you provide a table of excluded studies with reasons for exclusion.

b) The note at the bottom of Table 8 states that some Cochrane reviews were used to cross-check references. Please could you clarify which Cochrane reviews were used for cross-checking. Was the following Cochrane review on botulinum toxins checked? https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011616.pub2/full#CD011616-sec1-0005

c) The above cited Cochrane review includes a number of studies potentially relevant for your systematic review and ITC analyses. Please clarify:

   i) If they were picked up elsewhere in your searches of MEDLINE, Embase, CENTRAL

   ii) If they were excluded, and reasons for exclusion

   iii) If they met your inclusion criteria, why they were not included in ITC analyses

Company response:

a) Please see separate excel file for screening criteria and excluded studies (12).

b) The SLR (Appendix D) explains that up to five meta-analysis and systematic reviews (for example Cochrane reviews) were cross-checked. The following five studies were cross-checked:

- Hong, P., Wu, X., & Liu, Y. (2017). Calcitonin gene-related peptide monoclonal antibody for preventive treatment of episodic migraine: A meta-analysis. Clin Neurol Neurosurg, 154, 74-78. doi:10.1016/j.clineuro.2017.01.009
- Jackson, J. L., Cogbill, E., Santana-Davila, R., Eldredge, C., Collier, W., Gradall, A., . . . Kuester, J. (2015). A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLoS One, 10(7), e0130733. doi:10.1371/journal.pone.0130733
- Linde, M., Mulleners, W. M., Chronicle, E. P., & McCrory, D. C. (2013a). Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev(6), CD010609. doi:10.1002/14651858.CD010609

- Linde, M., Mulleners, W. M., Chronicle, E. P., & McCrory, D. C. (2013b). Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev(6), CD010610. doi:10.1002/14651858.CD010610
- Linde, M., Mulleners, W. M., Chronicle, E. P., & McCrory, D. C. (2013c). Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev(6), CD010611. doi:10.1002/14651858.CD010611

  The cross-check applies to both the all-comers population SLR and the prior treatment failure SLR. Herd CP et al, (2018). Botulinum toxins for the prevention of migraine in adults. Cochrane Database Syst Rev. was not included in the cross-check

c) The objective of the ITC to botulinum toxin A was to synthesise clinical data and parameters for the economic model in the target population relevant to the decision problem, i.e. in patients with a history of ≥3 prior preventative failures (DDT-3). The SLR did not define how many previous treatments patients must have failed in the inclusion criteria other than at least one, therefore hits were generated for more trials for botulinum toxin A than just the PREEMPT-1 and -2 trials. Cady & Schreiber, 2008 and Chankrachang et al., 2011 were two other trials in botulinum toxin A but the feasibility assessment revealed that data did not exist for patients with a hisotry of ≥3 prior preventative failures therefore these trials were not included in the ITC. Apart from PREEMPT-1 and 2, no additional Botox trials were included in the all-comers analyses to ensure consistency as this was only a supportive analysis to strengthen the confidence in the DTT-3 ITC to botulinum toxin A, e.g. comparison of baseline characterisitcs.

Clinical inputs to the economic model

A16. Description of the model: company submission page 108 states change from baseline (CFB) in monthly migraine days was analysed by responder status and results are provided in the References folder (‘Lilly data on file’). Please provide a description of the statistical analyses conducted on the response subgroups.

Company response:

The statistical models used to analyse responder and non-responder subgroups were conducted in line with the statistical analysis plan outlined for the primary analysis set in the Clinical Study Protocol for CONQUER, Section 9.7.1

A17. PRIORITY: Company submission p111 states “the model can incorporate evidence from evidence synthesis i.e. separate estimates for responder and non-responder mean monthly MHDs and mean monthly MHDs from the indirect treatment comparisons [ITC])”. Please clarify what data from the

evidence synthesis were incorporated into the economic model. Please make clear where you present these data in the clinical section of the company submission (cross-referencing tables and/or text) or alternatively provide the data if not reported elsewhere. Please also provide full details of any synthesis or ITC carried out, as requested in A10.

Company response:

Data only from the ITC to botulinum toxin A in the DDT-3 population for the mean change from baseline in monthly migraine headache days (section B2.8.2.1.2, Table 41) is incorporated. These estimates are not split by responder and non-responder and the fixed effect model estimates are used in the cost effectiveness analysis.

Table 14 Mean change form baseline in monthly MHDs used in the model

Galcanezumab 120mg versus Botulinum toxin A	Fixed effect model: Mean difference (95%CI), p-value
CFB in monthly Migraine Headache Days	XXX

Abbreviations: CFB, change from baseline; CI, confidence interval

Source: Eli Lilly data on file, 2016-4893 Indirect comparison of galcanezumab compared to Botox_V4 Table 13

A18. PRIORITY: Table 53 provides mean change from baseline data for galcanezumab ([redacted]) and botulinum toxin type A ([redacted]) with a cross-reference to Table 40. Please clarify how you used data from Table 40 to inform these values and if any additional data were used.

Company response:

The "Reference" column in Table 53 of the submission should read "Indirect comparison of galcanezumab versus Botox, pooled data from REGAIN and CONQUER: Section B2.8.2.1.2, Table 41 mean difference of XXX (fixed effects model)".

Table 15 Revised Table 53 for mean change in MHDs

	Chronic - Failed at least 3 preventive treatments	Reference
Galcanezumab	XXX	Indirect comparison of galcanezumab versus Botox, pooled data from REGAIN and CONQUER: Section B2.8.2.1.2, Table 41
Botulinum toxin type A	XXX	Indirect comparison of galcanezumab versus Botox: Section B2.8.2.1.2, Table 41 mean difference of XXX (fixed effects model)

A19. PRIORITY: Whilst Table 53 uses data synthesised from REGAIN and CONQUER trials for chronic migraine, Tables 54 and 55 use data only from the CONQUER trial. This leads to inconsistencies in how the data is analysed (i.e. some inputs are a synthesis of data from different trials, but other inputs are from a single trial where data from other trials are available).

a) **Please could you justify the discrepancy in approach.**

b) **Please provide revised versions of Tables 53 and 54 based on data:**

   i) **only from the CONQUER trial**

   ii) **synthesised data from EVOLVE-1, EVOLVE-2 and the CONQUER trial for episodic migraine (EM) and high frequency episodic migraine (HFEM) patients. For chronic migraine (CM) patients please use synthesised data from REGAIN and CONQUER trials.**

Company response:

a) The approach taken was to use the totality of the evidence available for galcanezumab in the target population, where it was feasible and available in the form of synthesised evidence from the indirect comparison to botulinum toxin A. However, it was not possible to provide pooled results for the relevant response rates for the chronic population (30% reduction in MHDs) since data was not available from the botulinum toxin A studies used in the ITC for the DTT-3 population (PREEPT 1 and 2). Hence these data were taken directly from the CONQUER study to incorporate into the model.

b) i) An updated Table 53 excluding the REGAIN study from the ITC to botulinum toxin A is provided in Table . These are calculated from:

   - Fixed effects model result; Mean Difference (95% CI); XXX.
   - Random-effects model result; Mean Difference (95% CI); XXX.

   Tables 54 and 55 from the main submission remain unchanged. Removing REGAIN from the analysis has a minor impact on the results but the confidence intervals are wider. This is an artefact from the reduced sample size available for the analysis. The impact on the cost effectiveness results are presented in B.9.

Table 16 Mean change from baseline in MHDs – overall in the chronic DDT-3 population (Fixed-effect model)

	Chronic - Failed at least 3 preventive treatments	Reference
Galcanezumab	XXX	Eli Lilly data on file (13)
Botulinum toxin type A	XXX	Eli Lilly data on file (13)

Source: Eli Lilly data on file, IC_vs_Botox_ITT_DTT3_Sens.without.CGAI_tfls.rtf

Table 17 Mean change from baseline in MHDs – overall in the chronic DDT-3 population (Random-effects model)

	Chronic - Failed at least 3 preventive treatments	Reference
Galcanezumab	XXX	Eli Lilly data on file (13)
Botulinum toxin type A	XXX	Eli Lilly data on file (13)

Source: Eli Lilly data on file, IC_vs_Botox_ITT_DTT3_Sens.without.CGAI_tfls.rtf

ii) For brevity it was not possible to pool the pivotal trials EVOLVE-1 and -2 and REGAIN with CONQUER to estimate responder and non-responders mean change in MHDs separately for the economic model. However, a scenario analysis is provided in B.9 using consistent data sources. (i.e. only CONQUER data for clinical parameters and variables - mean change from baseline in MHDs and responder rates).

Section B: Clarification on cost-effectiveness data

Important note: any scenario analyses provided in this clarification response incorporates the technical amendments identified in B.18 – B.19.

Provided with this document are updated cost effectiveness models including:

- **Technical amendments, updated utility estimates and placebo response functionality using original base case data sources**
- **Technical amendments, updated utility estimates and placebo response functionality using CONQUER data sources**

Utilities

B1. PRIORITY: Utility values used in the model were mapped from the Migraine-Specific Quality of Life Questionnaire (MSQ) data collected in the CONQUER trial. Was this restricted to patients who have failed ≥3 prior

therapies? If required, please provide supplemental analysis in which only patients who have failed ≥3 prior therapies are modelled. Please incorporate the functionality in the model to allow the ERG to replicate and verify the scenario.

Company response:

Utility values mapped for the model were not specific to patients with a history of ≥3 prior preventative failures. You will find below the utility estimates modelled on subpopulations of patients with a history of ≥3 prior preventative failures from CONQUER (14, 15).

- Table 18 displays the estimates obtained with all CONQUER patients as presented in the original submission.
- Table 19 displays the estimates obtained with all CONQUER patients who have failed at least 3 categories of preventive treatments (to be consistent with all other analysis in this subpopulation).

A mixed model for repeated measures, with migraine headache days and study treatment as covariates, an unstructured variance covariance matrix and using month 1 to month 3 data, was used to model the post-treatment data.

Table 20, Table 21 and Table 22 displays the estimated utility values as well as the number of observations that contributed to the models in Table 19

Table 18 Estimates and goodness of fit of the tested mixed models for the MSQ utility values with repeated measurements (except at baseline) using all patients from CONQUER (original submission)

Candidate Model	df	AIC	DIC	Model estimates	Data
MHD at baseline	NC	NC	NC	XXX	Baseline data
MHD only	4	-2345	-2324	XXX	M1 to M3 data
MHD and treatment	5	-2368	-2337	XXX	M1 to M3 data

*0 if treatment = galcanezumab, 1 if treatment= placebo; NC: not comparable

Table 19 Estimates and goodness of fit of the tested mixed models for the MSQ utility values with repeated measurements (except at baseline) for the patients having failed at least 3 categories of treatments using CONQUER (new analysis)

Candidate Model	df	AIC	DIC	Model estimates	Data
MHD at baseline	NC	NC	NC	XXX	Baseline data

MHD only	4	-850	-833	[redacted]	M1 to M3 data
MHD and treatment	5	-850	-829	[redacted]	M1 to M3 data

*0 if treatment = galcanezumab, 1 if treatment= placebo; NC: not comparable; DTT-3: subpopulation of patients having failed at least 3 categories of preventive treatments as defined in the CONQUER protocol.

Table 20 Results of a linear regression including only baseline and MHD as covariate for failed ≥3 medication categories in CONQUER :

MHD	Observed	Predicted	N
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]

Table 21 Predictions from a linear mixed model including MHD as covariate for failed ≥3 medication categories (month 1 to 3) in CONQUER

MHD	Observed	Predicted	N

Clarification questions

0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]

Table 22 Predictions from a linear mixed model including MHD and treatment as covariates for failed ≥3 medication categories (month 1 to 3) in CONQUER :

MHD	PBO	Treatment	Prediction PBO	Prediction treatment	N (PBO)	N (Treatment)	N (all)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario analyses using the utility values estimated specifically from the CONQUER failed ≥3 population are presented in Table , Table 24 and Table 25

Table 23 Scenario analysis using utility values from CONQUER in the failed ≥3 prior preventative treatment subpopulation, Episodic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,847
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 24 Scenario analysis using utility values from CONQUER in the failed ≥3 prior preventative treatment subpopulation, Chronic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,421
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 25 Scenario analysis using utility values from CONQUER in the failed ≥3 prior preventative treatment subpopulation (pooled treatment arms), Chronic vs Botox

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,352
Botulinum toxin type A	[redacted]	[redacted]	[redacted]			

Analysis conducted using combined efficacy criterion

B2. Quality of life data were collected using MSQ in the REGAIN, EVOLVE 1 and EVOLVE 2 trials. Please justify why these data were not used to estimate the utilities. Please also provide the following supplemental analysis in which utilities are modelled using all available trial evidence. Please incorporate the functionality in the model to allow the ERG to replicate and verify the scenario.

Company Response:

Modelled utility values used in the original cost effectiveness analysis were not specific to patients with a history of ≥3 prior preventative failures. Data from REGAIN and EVOLVE studies were not used for the utility estimations as they included naïve patients. CONQUER alone was deemed most appropriate as it included patients that better represented the target population of difficult to treat patients.

You will find below the utility estimates modelled for the subpopulation of patients with a history of ≥3 prior preventative failures from CONQUER pooled with REGAIN, EVOLVE-1 and 2 (14, 15). Note, this analysis was conducted on patients with ≥3 prior individual treatment failures rather than categories.

- Table 26 displays the estimates obtained with all CONQUER, REGAIN and EVOLVE 1 and 2 patients who have failed at least 3 preventive treatments

A linear model was used to estimate monthly migraine headache at baseline model. Only patients with non-missing MHD and MSQ data was used at baseline. However, out of the 507 intention-to-treat patients having at least failed 3 preventive treatments from the 4 studies (CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2), only 6 patients didn't have MHD and MSQ data.

A mixed model for repeated measures, with migraine headache days and study treatment as covariates, an unstructured variance covariance matrix and using month 1 to month 3 data, was used to model the post-treatment data.

Table ,
Table ,

Clarification questions

Table , Table 30 and Table 31 display the estimated utility values as well as the number of observations that contributed to the models in Table 19. Note analysis was conducted on patients with ≥3 prior individual treatment failures rather than categories.

Table 26 Estimates and goodness of fit of the tested mixed models for the MSQ utility values with repeated measurements (except at baseline) for the patients having failed at least 3 preventive treatments using CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2

Candidate Model	df	AIC	DIC	Model estimates	Data
MHD at baseline	NC	NC	NC	XXX	Baseline data
MHD only	4	-2521	-2500	XXX	M1 to M3 data
MHD and treatment	5	-2536	-2510	XXX	M1 to M3 data

*0 if treatment = galcanezumab, 1 if treatment= placebo; NC: not comparable; DTT-3m: subpopulation of patients having failed at least 3 preventive treatments as defined in the CONQUER protocol

Table 27 Number of observations by study and period for failed ≥3 treatments in CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2:

	Period			
Study ID	**Baseline**	**Month 1**	**Month 2**	**Month 3**
I5Q-MC-CGAG	XXX	XXX	XXX	XXX
I5Q-MC-CGAH	XXX	XXX	XXX	XXX
I5Q-MC-CGAI	XXX	XXX	XXX	XXX
I5Q-MC-CGAW	XXX	XXX	XXX	XXX

Table 28 Number of observations with MHD and MSQ data by study and period for failed ≥3 treatments in CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2:

	Period			
Study ID	**Baseline**	**Month 1**	**Month 2**	**Month 3**
I5Q-MC-CGAG	XXX	XXX	XXX	XXX
I5Q-MC-CGAH	XXX	XXX	XXX	XXX
I5Q-MC-CGAI	XXX	XXX	XXX	XXX
I5Q-MC-CGAW	XXX	XXX	XXX	XXX

Table 29 Predictions from a linear regression including only baseline and MHD as covariate for failed ≥3 treatments in CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2:

MHD	Observed	Predicted	N_baseline_all
0	XXX	XXX	XXX
1	XXX	XXX	XXX
2	XXX	XXX	XXX
3	XXX	XXX	XXX

Clarification questions

MHD	Observed	Predicted	N_baseline_all
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]

Table 30 Predictions from a linear mixed model including MHD as covariate for failed ≥3 treatments (month 1 to 3) in CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2:

MHD	Observed	Predicted	N
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]

MHD	Observed	Predicted	N
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]

Table 31 Predictions from a linear mixed model including MHD and treatment as covariates for failed ≥3 treatments (month 1 to 3) in CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2:

MHD	Placebo	GMB120mg	Predict placebo	Predict GMB120mg	N (Placebo)	N (GMB120mg)	N (all)
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clarification questions

MHD	Placebo	GMB120mg	Predict placebo	Predict GMB120mg	N (Placebo)	N (GMB120mg)	N (all)
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario analyses using the utility values from the pooled studies specifically in the failed ≥3 subpopulation are presented in Table , Table and Table .

Table 32 Scenario analysis using CONQUER pooled with REGAIN and EVOLVE studies failed ≥3 utility values (pooled treatment arms), Episodic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,149
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 33 Scenario analysis using CONQUER pooled with REGAIN and EVOLVE studies failed ≥3 utility values (pooled treatment arms), Chronic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,269
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 34 Scenario analysis using CONQUER pooled with REGAIN and EVOLVE studies failed ≥3 utility values (pooled treatment arms), Chronic vs Botox

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,254
Botulinum toxin type A	[redacted]	[redacted]	[redacted]			

Analysis conducted using combined efficacy criterion

B3. It appears from the description of the regression analysis undertaken that only data recorded at 3 months were used. Please justify this decision. Please present supplemental analyses using data from all time points using appropriate methods to

account for repeated measures. Please implement this for all trials reporting utility data and for the subpopulation who have failed 3 prior therapies.

Company response:

Independently, MSQ data as observed in month 1 to 3 were modeled using a mixed model for repeated measures with MHD and study treatment as covariates and an unstructured variance covariance matrix. This included all observations from month 1, month 2 and month 3.

Exploratory work to model utilities was done at month 3 only to investigate the impact of covariates such as gender and age (allowing easier visualization as one observation per patient), but the modeled utilities included in the cost effectiveness analysis used all data from month 1, month 2 and month 3.

B4. Please provide further information on the patients that contributed quality of life data including baseline characteristics and the number of patients. Please also provide the number of observations included in analyses, stratified by trial and migraine headache day (MHD) frequency.

Company Response:

The number of observations that contributed to the utility analyses are provided in Table 35. There was no MSQ missing data (and no MHD missing data) at baseline. Therefore, the baseline characteristics as displayed in the Appendix L, Table 36 are relevant. From month 1 to month 3, a total of XXX observations were used to model the post-treatment utilities. Therefore, there were only XXX missing data points (out of XXX patients and XXX time points) which were handle within the MMRM model.

Table 12 Number of observations by number of migraine headache days

No. of migraine headache days	No. of patients Contributing to the baseline model	No. of obs. contributing to Galcanezumab (M1 to M3)	No. of obs. contributing to Placebo (M1 to M3)
0		XXX	XXX
1		XXX	XXX
2		XXX	XXX
3		XXX	XXX
4	XXX	XXX	XXX
5	XXX	XXX	XXX
6	XXX	XXX	XXX
7	XXX	XXX	XXX
8	XXX	XXX	XXX
9	XXX	XXX	XXX
10	XXX	XXX	XXX
11	XXX	XXX	XXX
12	XXX	XXX	XXX

No. of migraine headache days	No. of patients Contributing to the baseline model	No. of obs. contributing to Galcanezumab (M1 to M3)	No. of obs. contributing to Placebo (M1 to M3)
13	XXX	XXX	XXX
14	XXX	XXX	XXX
15	XXX	XXX	XXX
16	XXX	XXX	XXX
17	XXX	XXX	XXX
18	XXX	XXX	XXX
19	XXX	XXX	XXX
20	XXX	XXX	XXX
21	XXX	XXX	XXX
22	XXX	XXX	XXX
23	XXX	XXX	XXX
24	XXX	XXX	XXX
25	XXX	XXX	XXX
26	XXX	XXX	XXX
27	XXX	XXX	XXX
28	XXX	XXX	XXX
29	XXX	XXX	XXX
30		XXX	XXX

Source: Eli Lilly Data on file, T_number_observations_utility_MHD_ap

The baseline characteristics of patients having at least failed 3 preventive treatments presented in Appendix L.1 is shown in Table 13 again.

Table 13 Baseline characteristics of patients CONQUER ITT sub-population with ≥3 prior preventive treatment failures

Characteristic	Placebo (XXX)	Galcanezumab 120 mg (XXX)	Total (XXX)
Age (years)			
Mean (±SD)	XXX	XXX	XXX
Sex, n (%)			
Female	XXX	XXX	XXX
Male	XXX	XXX	XXX
Race, n (%)			
American Indian or Alaska Native	XXX	XXX	XXX
Asian	XXX	XXX	XXX
Black or African American	XXX	XXX	XXX
Native Hawaiian or Other Pacific Islander	XXX	XXX	XXX
White	XXX	XXX	XXX
Multiple	XXX	XXX	XXX

Clarification questions

Body Mass Index (kg/m2)			
Mean (±SD)	XXX	XXX	XXX
Region, n (%)			
North America	XXX	XXX	XXX
Europe	XXX	XXX	XXX
Asia	XXX	XXX	XXX
Qualifying preventive medication failures in past 10 years, n (%)			
3 medication failures	XXX	XXX	XXX
4 medication failures	XXX	XXX	XXX
5 medication failures	XXX	XXX	XXX
6 medication failures	XXX	XXX	XXX
7 medication failures	XXX	XXX	XXX
Total number of failed individual preventive meds lifetime, mean (±SD)	XXX	XXX	XXX
Total number of failed individual preventive meds past 10 years, mean (±SD)	XXX	XXX	XXX
Number of monthly headache days, mean (±SD)	XXX	XXX	XXX
Number of monthly MHDs, mean (±SD)	XXX	XXX	XXX
Number of monthly migraine attacks, mean (±SD)	XXX	XXX	XXX
MSQ Role Function-Restrictive domain, mean (±SD)	XXX	XXX	XXX
MIDAS total score, mean (±SD)	XXX	XXX	XXX
Duration of migraine illness, years, mean (±SD)	XXX	XXX	XXX
Number of comorbidities, mean (±SD)	XXX	XXX	XXX
PGI-S, mean (±SD)	XXX	XXX	XXX

Abbreviations: PGI-S, Patient Global Impression – Severity; ITT, intention-to-treat; meds, medications; MHDs, migraine headache days; MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality of Life Questionnaire; N, number of ITT patients; n, number of patients within each specific category; SD, standard deviation; yrs, years.

Source: Eli Lilly Data on file, CGAW Clinical Study Report Table Table CGAW.0.14 and Table CGAW.0.15

B5. Please provide information on the number of missing observations in the health-related quality of life analyses, (Section B.2.6.3.3, company submission page 56) and how these were handled.

Company Response:

Health outcome measures including MSQ v2.1 were self-reported by the patient and were collected upon study site visit. The differences in the data collection methods for the migraine/headache related endpoints and the healthcare outcome endpoints resulted in a difference in the missing observations.

A summary of the data collection methods is described in **Error! Reference source not found.**

Table 37 Data collection tools used in this study.

Data Collection Tool	Description and Use
ePRO diary	Used daily by the patient to collect migraine/headache-related information and whether any acute headache medication was taken
Headache medication log	Used by the patient to record the name, dose, and date of any acute headache medication taken and returned to site staff at each study visit
Slate device	Used by the patient at the site to enter responses on • the Patient Global Impression of Severity and • all health outcomes measures with the exception of the Health Care Resource Utilization
Electronic case report form	Used by the investigator or study site personnel to record entries on all other measures, including safety and Health Care Resource Utilization

Abbreviation: ePRO= electronic patient-reported outcome

As stated in the response to B.6, the number of missing observations that contributed to the utility estimations was small. Out of the 507 intention to treat patients from the pooled analysis considering CONQUER, REGAIN, EVOLVE-1 and 2 who have failed ≥3 preventive treatments from the 4 studies, only 6 patients had missing MHD and MSQ data.

The analysis for MSQ v2.1 was defined as the number of patients in the ITT population with non-missing baseline value and non-missing value at month 3. 445 patients contributed to the MSQ analyses (vs 462 to primary endpoint) which represent 3.7% missing MSQ data. In contrast, the EQ-5D-5L analysis was reported as the last observation carried forward (LOCF), therefore it captured the entire ITT population.

Treatment effect

B6. Please elaborate on the expected impact of not fully incorporating the natural progression of migraine on the estimated cost effectiveness analysis. Please

incorporate scenario analyses exploring the impact of different plausible scenarios regarding the natural progression of migraine.

Company Response:

Due to lack of data on the chronification of migraine or progression of migraine (increase in severity and frequency), particularly for active comparators, it was not possible to incorporate this impact. No analysis was undertaken to assess whether galcanezumab treatment would impact disease progression or chronification due to short length of the trials. As a result, the cost effectiveness of galcanezumab in the episodic population may be underestimated since additional resource use and costs are incurred in the model for patients that may otherwise have had chronification prevented, particularly for younger patients. Migraine chronification happens over time where some patients with episodic or high frequency episodic migraine, MHDs or HDs increase over time until they have more than 15 HDs per months and their disease becomes chronic. Migraine chronification is reported to occur in 2.5 to 3.0% of patients with episodic migraine (although rates as high as 14% have been reported).

B7. Table 56 row 1 suggests that pooled data from REGAIN, EVOLVE-1 and EVOLVE-2 were used to generate the response rates. Please provide further information of the methods of synthesis used to pool these studies along with all the files required to reproduce synthesis. In particular, please refer to steps a) to d) outlined in Question A10 when providing this information.

Company Response:

The response rates were calculated based on analyses conducted as part of the ITC between galcanezumab and erenumab. Full details of the analysis are provided in the full report for the ITC between galcanezumab and erenumab (16) with this document.

This ITC analysis supported the submission as it conducted a pooled analysis from CONQUER, EVOLVE-1 and EVOLVE-2 for galcanezumab, and the 50% response rate was used in the cost-effectives model for the episodic migraine patients who failed ≥3 prior medication treatments.

The included studies for galcanezumab and erenumab in difficult-to-treat patients (defined as those who had at least 2 prior treatment failures) who had episodic migraine are shown in Table 16. The analysis method followed the standard procedure of ITC as outlined in the full report for the galcanezumab vs. erenumab. The summary table of the pooled result for episodic patients with 3 or more treatment failures for 50% reduction in MHD is shown in Table 17.

Table 16 Base case DTT-3-EM: 50% or greater reduction in Migraine Headache Days overall - Galcanezumab 120mg vs. Erenumab 140mg via Placebo.

Trial	Comparison	Test	Control	Odds Ratio	Risk Ratio	Risk Difference

		n/N (%)	n/N (%)	(95% CI)	(95% CI)	(95% CI)
CGAG (EVOLVE-1)	Galcanezumab_ 120 vs. Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CGAH (EVOLVE-2)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CGAW (EVOLVE-3)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled data		[redacted]	[redacted]			

Table 17 Included studies and source in the ITC comparing galcanezumab and erenumab difficult-to-treat (DTT) episodic patients

	Study name and acronym	Study acronym/ identifier	ITC alias	Full reference
Galcanezumab	Evaluation of Galcanezumab in the Prevention of Episodic Migraine- the EVOLVE-1 Study (Evolve-1)	I5Q-MC-CGAG NCT02614183	CGAG	Eli Lilly and Company (2018a). Galcanezumab Clinical Health Technology Assessment Toolkit. Assessment of Clinical Efficacy and Safety for Galcanezumab—Pooled Studies.
	Evaluation of Galcanezumab in the Prevention of Episodic Migraine- the EVOLVE-2 Study (Evolve-2)	I5Q-MC-CGAH NCT02614196	CGAH	Eli Lilly and Company (2018a). Galcanezumab Clinical Health Technology Assessment Toolkit. Assessment of Clinical Efficacy and Safety for Galcanezumab—Pooled Studies.
	A Study of Galcanezumab (LY2951742) in Adults With Treatment-Resistant Migraine (CONQUER)	I5Q-MC-CGAW NCT03559257	CGAW	Eli Lilly and Company (2019c). CGAW Clinical study report. A randomized, double-blind, placebo-controlled study of galcanezumab in adults with treatment-resistant migraine – the CONQUER study: final results from the double-blind treatment phase and interim results from the open-label treatment phase. 27 Sep 2019.
Erenumab	A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies (Liberty)	NCT03096834	Reuter (2018)	Reuter U., Goadsby PJ., Lanteri-Minet M., Wen S., Hours-Zesiger P., Ferrari MD., Klatt J. (2018). Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. Lancet. pii: S0140-6736(18)32534-0. doi: 10.1016/S0140-6736(18)32534-0. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30360965
	Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) in Migraine Prevention (Strive)	NCT02456740	Goadsby (2019)	Goadsby P., Paemeleire K., Broessner G., Brandes J., Klatt J., Zhang F., Picard H., Lenz R., Mikol D (2019). Efficacy and safety of erenumab (AMG334) in episodic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. Cephalalgia, 39(7):817-826. doi: 10.1177/0333102419835459. Epub 2019 Apr 13 https://www.ncbi.nlm.nih.gov/pubmed/30982348

B8. The response rates used in the model for the HFEM and CM populations (see Tables 56 and 57) appear not to match with the figures reported in Table 30 and Table 28. Please clarify the reason for the discrepancy and update the economic analysis as necessary.

Company Response:

The differences in the rates of 50% and 30% responders between Table 56, 57 and Table 28, 30 in the original submission were due the difference between the reports of the raw rate of responders at months 3 (presented in the clinical section of the submission) and the model estimated rate of responders at month 3, (which were used in the development of the cost-effectiveness model).

The model estimated rates were analysed using generalized linear mixed model as pseudo-likelihood-based mixed effects repeated measures analysis. The model adjusted for the fixed, categorical effects of treatment, month, including treatment, month, baseline migraine headache days and treatment-by-month interaction.

The differences are summarised in Table 18.

Table 18 Summary of the differences between the raw rate and the model estimated rate for the response rate

	Galcanezumab	**Placebo**	**Galcanezumab**	**Placebo**
	Raw rate	Raw rate	Model estimated rate (SE, 95% CI)	Model estimated rate (SE, 95% CI)
50% response rate				
High frequency episodic migraine (HFEM) - ⩾3 prior preventive treatment failures	XXX	XXX	XXX	XXX
30% response rate				
Chronic migraine (CM) - ⩾ 3 prior preventive treatment failures	XXX	XXX	XXX	XXX

Abbreviations: SE = standard error, CI = confidence interval

B9. The 50% response rate used for the CM population (Table 56) appears to be based on a pooled analysis of REGAIN and CONQUER, while the 30% response rate (Table 57) was based on the CONQUER trial alone. Please justify this

discrepancy. Please provide an appropriate pooled analysis of REGAIN and CONQUER for the 30% response rate.

Company Response:

The approach taken was to use the totality of the evidence available for galcanezumab in the target population, where it was feasible and available in the form of synthesised evidence from the ITC to botulinum toxin A. However, it was not possible to provide pooled results for the relevant response rates for the chronic population (30% reduction in monthly MHDs) since data was not available from the botulinum toxin A studies used in the ITC for the DTT-3 population (PREEPT 1 and 2). Hence these data were taken directly from the CONQUER study and incorporated into the cost effectiveness analysis and held constant for the response rate for galcanezumab and botulinum toxin A. However, an updated scenario analysis is provided below using consistent data sources data for clinical parameters and variables (i.e. mean change from baseline in MHDs and response rates from CONQUER only). Please note, 50% reduction in monthly MHDs is not a clinically relevant outcome for chronic patients (19, 20). There are minimal differences in the cost effectiveness results when only CONQUER data is used in the model.

Table 19 Clinical variables used in model from CONQUER

Mean change MHDs – Month 3	**Chronic - Failed at least 3 preventive treatments**	
Galcanezumab	XXX	Indirect comparison of galcanezumab versus Botox, excluding REGAIN. Lilly data on file (13)
Botulinum toxin type A (fixed-effects model)	XXX	Indirect comparison of galcanezumab versus Botox, excluding REGAIN. Lilly data on file (13)
Botulinum toxin type A (random-effect model)	XXX	Indirect comparison of galcanezumab versus Botox, excluding REGAIN. Lilly data on file (13)
Responder mean change MHDs 50%	**Episodic - Failed at least 3 preventive treatments**	
Galcanezumab	XXX	CONQUER
BSC	XXX	CONQUER
Responder mean change MHDs 30%	**Chronic - Failed at least 3 preventive treatments**	
Galcanezumab	XXX	CONQUER
BSC	XXX	CONQUER
50% Response rate	**Episodic - Failed at least 3 preventive treatments**	
Galcanezumab	XXX	CONQUER
BSC	XXX	CONQUER
30% Response rate	**Chronic - Failed at least 3 preventive treatments**	
Galcanezumab	XXX	CONQUER
BSC	XXX	CONQUER
Botulinum toxin type A	XXX	Equal to Galcanezumab

Clarification questions

Table 20 Scenario analysis using CONQUER inputs only, Episodic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,412
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 21 Scenario analysis using CONQUER inputs only, Chronic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,080
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 22 Scenario analysis using CONQUER inputs only, Chronic vs Botox, fixed-effect model

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,965
Botulinum toxin type A	[redacted]	[redacted]	[redacted]			

Analysis conducted using combined efficacy criterion

Table 23 Scenario analysis using CONQUER inputs only, Chronic vs Botox, random-effect model

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	XXX	XXX	XXX	XXX	XXX	£2,828
Botulinum toxin type A	XXX	XXX	XXX			

Analysis conducted using combined efficacy criterion

B10. Please provide justification for why patient-level data from EVOLVE-1, EVOLVE-2 and REGAIN were used to populate the monthly MHD distributions rather than data from CONQUER?

Company response:

The patient level data from four phase III randomized, placebo-controlled clinical trials and one phase III, long-term, open-label safety study were used to estimate the distribution of monthly migraine headache days in episodic and chronic migraine patients separately. The study evidence considered included data from CONQUER. However, given that CONQUER was ongoing at the time the work on the cost-effectiveness model started, the distributions of monthly migraine headache days were initially estimated using the observed mean migraine headache days from the pivotal trials separately for chronic and episodic migraine. As soon as the data from CONQUER became available, the estimated parametric distributions were tested for the CONQUER subpopulation of patients who had failed ≥3 prior preventive medication categories. This patient population is of particular interest to this submission (see r.

Figure 1). Based on visual assessment, the estimated and fitted binomial and beta-binomial distribution are similar.

Clarification questions

Figure 1 Observed, fitted and estimated parametric migraine headache days distributions at Month 1, 2 and 3 for chronic migraine patients with a treatment history of at least 3 prior failures to migraine medication categories (Placebo group of CONQUER)

As shown in

Figure 2, the residuals from the fitted and estimated distributions in CONQUER for chronic migraine population are very similar, indicating that the estimated distributions using the observed mean monthly migraine headache days are very similar to the fitted distributions.

Figure 2 Residual errors versus observed migraine headache days for estimated and fitted negative binomial and beta-binomial for chronic migraine patients with a treatment history of at least 3 prior failures to migraine medication categories at Month 1, 2 and 3 (CONQUER)

Figure 3 below displays the observed, fitted and estimated distribution of the negative binomial and the beta-binomial at month 1, 2 and 3 for the placebo cohort of patients with a history of at least 3 prior preventive medication category failures from CONQUER.

Figure 3 Observed, fitted and estimated distributions of migraine headache days at Month 1, 2 and 3 for the episodic migraine patient population with a history of failure to at least 3 prior preventive medication categories (placebo group of CONQUER)

Clarification questions

Figure 4 displays the corresponding residuals. The beta-binomial with the fixed intra-class correlation of 0.01 doesn't perfectly fit the observed data and provides wider residuals. However, residuals remain within a 10% margin and the impact of this choice was tested in the cost-effectiveness model with very little impact on overall results.

Figure 4. Residual errors versus observed migraine headache days by treatment and Month 1, 2 and 3 for the estimated and fitted negative binomial and beta-binomial distribution in episodic migraine patients with a treatment history of at least 3 prior failures to medication categories (CONQUER)

B11. Regarding the modelled monthly MHD distributions outlined in B.3.3.2.1, company submission page 117 and Appendix S:

a) Please provide justification for why monthly MHD distributions were fitted to the whole trial populations rather than stratifying patients into responder and non-responder groups and fitting separate distributions to those groups.

b) Please provide supplemental analysis in which separate MHD distributions are fitted to responder and non-responder patient data for episodic and chronic migraine.

c) Please incorporate scenario analyses exploring the impact of including separate MHD distributions for responders and non-responders. Please incorporate the functionality in the model to allow the ERG to replicate and verify the scenario.

Company response:

a) As stated in the response to B.10, analyses were undertaken at a time when the CONQUER study was still ongoing and at a time when the model structure was not yet finalised. There was also a concern that low patient numbers, particularly in the non-responder subgroup, would not allow a robust assessment of distribution fits.

b) Assessment of the estimated distributions fitted to responders and non-responder MHDs was undertaken. Please note, the estimation of the negative binomial and beta binomial were not re-estimated but the estimated and fitted negative binomial and beta-binomial distributions based on mean MHDs, where the estimated distributions were derived from the REGAIN population for chronic patients and from the EVOLVE

1 & 2 population for episodic patients, were plotted and visually assessed with the corresponding fitted distributions of MHD for the responders and the non-responders (similar method of validation was done for the response to B.10). The difference between the observed and estimated/fitted proportion of patients for a given number of MHDs was bound from 10 to 30 days, encompassing high frequency episodic migraine (HFEM) and chronic migraine.

For the populations assessed, two graphs are displayed to assess visually how the estimated distribution is compares to the fitted distribution:

I. Chronic patients who have failed at least 3 categories of preventive treatments using CONQUER per responder status based on a reduction from baseline of at least 30% in MHD

Figure 5 Distribution of MHD for Chronic, CGAW, DTT-3 categories, 30% responders, galcanezumab 120 mg

Figure 6 Residual errors for Chronic, CGAW, DTT-3 categories, 30% responders, galcanezumab 120 mg

II. Chronic patients who have failed at least 3 preventive treatments using CONQUER and REAGAIN per responder status based on a reduction from baseline of at least 30% in MHD

Figure 7 Distribution of MHD for Chronic, CGAW and REGAIN, DTT-3 treatments, 30% responders, galcanezumab 120 mg

Figure 8 Residual errors for Chronic, CGAW and REGAIN, DTT-3 treatments, 30% responders, galcanezumab 120 mg

III. HFEM patients who have failed at least 3 categories of preventive treatments using CONQUER per responder status based on a reduction from baseline of at least 50% in MHD

Figure 9 Distribution of MHD for HFEM, CGAW, DTT-3 categories, 50% responders, galcanezumab 120 mg

Figure 10 Residual errors for HFEM, CGAW, DTT-3 categories, 50% responders, galcanezumab 120 mg

IV. HFEM patients who have failed at least 3 categories of preventive treatments using CONQUER and EVOLVE 1 & 2 per responder status based on a reduction from baseline of at least 50% in MHD

Figure 11 Distribution of MHD for HFEM, CGAW and EVOLVE-1, -2, DTT-3 treatments, 50% responders, galcanezumab 120 mg

Figure 12 Residual errors for HFEM, CGAW and EVOLVE-1, -2, DTT-3 treatments, 50% responders, galcanezumab 120 mg

For I. and III., the numbers of patients are small. Nevertheless, the estimated distributions are relatively close to the fitted corresponding distributions. For II. and IV., where the graphs are based on the pooled CONQUER and pivotal studies and where the treatments are counted individually rather than counted as grouped medication categories, the number of patients is higher, and the estimated distributions are close to the corresponding fitted distributions.

c) Responder and non-responder specific distributions were not included in the cost effectiveness model. Visual assessment of the estimated distributions fitted to the responder and non-responder mean MHDs reveals that the fit is similar to the overall

Clarification questions

mean MHDs fitted from the pivotal trial and shown in Appendix S. This suggests that the estimated beta-binomial and negative binomial distributions based on the mean using the pivotal studies are relevant to estimate the MHD distributions of the responders and non-responders of the patients having failed ≥3 treatments or categories of treatments.

Comparison with botulinum toxin type A

B12. The comparison with botulinum toxin type A assumes a different change in monthly migraine days for responder to the comparison with best supportive care (BSC). Please justify this approach commenting on the face-validity of the models predictions.

Company Response:

The SLR did not find any find any data for the change form baseline in mean MHDs for responders and non-responders separately for botulinum toxin A. Therefore, it was not possible to synthesise data for responders and non-responders separately to incorporate into the cost effectiveness analysis. Outcomes could only be estimated from the ITC for mean change from baseline in monthly MHDs which is not split by responder and non-responders but since the model splits the population by responders and non-responders at the point of assessment of response, the mean change is thus applied to both groups when looking at a combined population of responders and non-responders for the comparison to botulinum toxin A. Taking this conservative approach may underestimate the cost effectiveness of galcanezumab compared to botulinum toxin A, particularly when assuming response rates are equal for the two arms. It is not possible to synthesise the mean change from baseline in monthly MHDs for responders and non-responders separately but a scenario analysis is provided in the main submission with response rates estimated for botulinum toxin A so that the responder criteria applied to the comparison to BSC can be applied to the comparison to botulinum toxin A.

When comparing the model outcomes for the overall mean change from baseline in monthly MHDs at 3 months (Table 46) we can see that there is an underestimation of the mean monthly MHDs predicted by the model when using the combined criteria in the chronic model. This is because the predicted results are taken across the health states as an average. (please see response to B.20 for further explanation).

Table 24 Comparison between the pooled clinical trial results from ITC and model estimations for the monthly MHD and 30% response rate outcomes

Outcome (at month 3)	Treatment	Clinical Trial Result	Model Result
Overall mean change from BL in monthly MHD	Galcanezumab 120mg	[redacted]	[redacted]
	Botulinum toxin type A	[redacted]	[redacted]
Response rate - 30%	Galcanezumab 120mg	[redacted]	[redacted]
	Botulinum toxin type A	[redacted]	[redacted]

B13. Please present a comparison with botulinum toxin type A using the same modelling approaching adopted for the comparison of galcanezumab with BSC.

Company Response:

Please see response to question B.12. It was not possible to estimate responder and non-responder mean change from baseline in monthly MHDs separately and to apply the responder criteria for this comparison. However, an approximation can be applied to the botulinum toxin A responders by assuming that the non-responders had the same mean MHD change as the BSC patients which is taken from the population specific inputs. Further details on this approximation are provided in Appendix T. Cost effectiveness results are presented below but these should be interpreted with caution since no empirical evidence is informing the approximation for botulinum toxin A.

Table 25 Scenario analysis, approximated responder and non-responder MHDs for botulinum toxin A , Chronic vs Botox

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Galcanezumab Dominates
Botulinum toxin type A	[redacted]	[redacted]	[redacted]			

Analysis conducted using the 'estimated' responder efficacy criterion

Discontinuation

B14. Currently patients who respond to BSC are assumed to wane back to baseline after a period of 12 months. Please justify this assumption and why you consider that any placebo effect would not impact on both galcanezumab and BSC. Please provide a scenario where patients responding to BSC maintain their initial response. Please incorporate the functionality in the model to allow the ERG to replicate and verify the scenario.

Company Response:

A scenario analysis is provided in the main submission in section B.3.8.3 and presented again below. The functionality is provided in the excel file under the 'Discontinuation' tab, cell F31, where this assumption can be switched off or set to alternative wane assumptions.

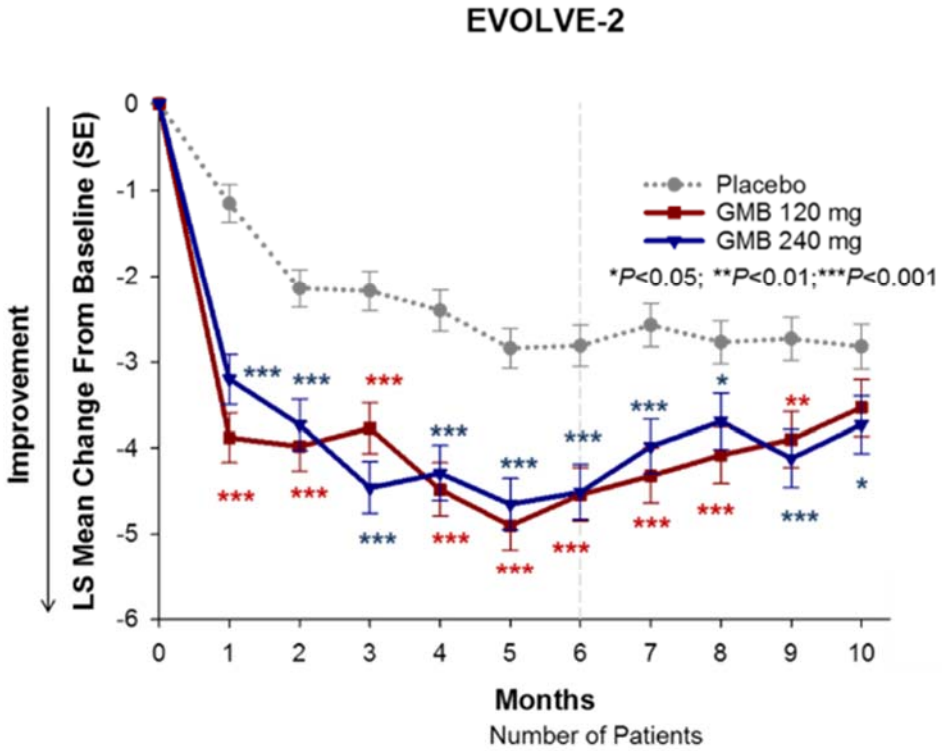
The dissipation of the placebo effect was included after assessing the committees preferred assumptions which were included in the Appraisal Consultation Document (ACD) for fremanezumab (17), where it states: *'..people reverted to baseline migraine days after fremanezumab all-cause discontinuation, and the* ***treatment effect for people who responded to best supportive care diminished to baseline over 1 year****. The committee agreed that this scenario was more in line with how the clinical experts expected treatment effectiveness could change after stopping treatment'*.

Clarification questions

When modelling the placebo response, it is a key driver for the cost effectiveness of galcanezumab in the episodic model but without long-term observational data it is unclear whether the placebo effect seen in the trial truly translates into clinical practice.

Observing the placebo arm in the EVOLVE studies, a consistent response is still seen for the placebo group in the washout period.

Figure 13 Washout Data of EVOLVE-2 Double-Blind Period & Follow-up, ITT Population



It is unclear why this persistent of effect occurs off-treatment for the placebo group in the ITT population. It should be noted that these patients are still in a controlled environment where regular data is still being collected, even after the double-blind period and sham injections have stopped, which may explain the trend in the placebo arm.

A scenario analysis is presented below where the placebo effect does not dissipate but continues after the assessment of response. It is then appropriate to attribute a part of the placebo response to patients who discontinue galcanezumab where it is assumed patients return to BSC non-responder mean change in monthly MHDs rather than baseline MHDs. It is not appropriate to model baseline MHDs after discontinuation if the placebo response does not dissipate. Another scenario is also provided where the dissipation of the placebo effect for BSC-responders happens over 60 months. Please note this scenario is only applicable to the comparison to BSC since this has no impact to the comparison to botulinum toxin A.

Clarification questions

Table 26 Scenario analysis, no dissipation of the placebo effect and a return to BSC non-responder MHDs after discontinuation, Episodic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,282
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 27 Scenario analysis, no dissipation of the placebo effect and a return to BSC non-responder MHDs after discontinuation, Chronic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,578
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 28 Scenario analysis, dissipation of the placebo effect over 60 months and a return baseline MHDs after discontinuation, Episodic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,918
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 29 Scenario analysis, dissipation of the placebo effect over 60 months and a return baseline MHDs after discontinuation, Chronic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,239
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

B15. Please provide full details of the analysis used to generate the 0.23 figure used to model the waning of the treatment effect in the CM population.

Company Response:

For the chronic population, the post treatment per data from the REGAIN trial was used. The analysis focused on the galcanezumab 120mg dose. Based on the observed data at 12 months and the change to Month 16 an overall change on MHD of [redacted] was converted to a per month change of [redacted].

Figure 14 Washout data – REGAIN

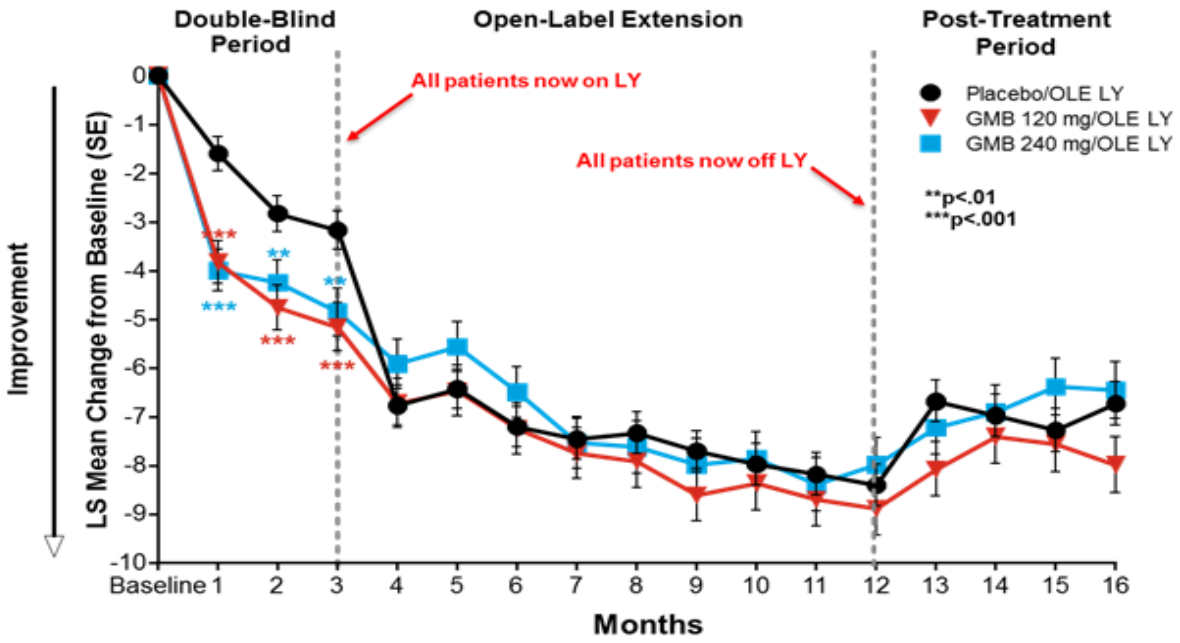


Table 52 mean MHD reduction at months 12 and 16 from the REGAIN washout period

	Month 12	Month 16	Difference
Placebo	XXX	XXX	XXX
LY120mg	XXX	XXX	XXX
LY240mg	XXX	XXX	XXX

B16. Please comment on why the waning period following discontinuation for galcanezumab would be substantially different for EM and CM patients. The waning period is currently modelled as XXX for EM patients and XXX for CM.

Company Response:

The waning effect uses the available evidence for the available populations and any differences should be considered within the context of the heterogeneity of the trials.

When the trial data was analysed for the distribution fitting, the two populations were determined to show different trends that separate distributions were fit to the data. With the model utilising a beta binomial distribution for the chronic population and negative binomial distribution for the episodic population.

Within the model, the main difference between the two populations is the baseline MHD and the size of effect. For example, the mean change in responders in the chronic population is twice that of episodic patients (XXX for galcanezumab at 30% response rate and XXX for galcanezumab at 50% response rate) meaning that if the populations had the same rate of change, there would differences between the populations. Secondly, the difference in response rate used for the populations means it is hard to compare between the populations directly.

B17. Please justify the use of a differential waning period for galcanezumab compared with BSC and botulinum toxin type A.

Company Response:

As stated in the responses to B.15 and B.16. Both the EVOLVE and REGAIN washout periods show a persistent of effect for patients in the galcanezumab arms. From these periods a rate of dissipation of effect was calculated for the chronic and episodic populations separately.

To Lilly's knowledge there are no data on the persistence of effect for patient's discontinuing botulinum toxin A for non-response or due to adverse events. Hence, we assume patients return to their baseline monthly MHDs by the time they were expected to receive their next dose of botulinum toxin a (i.e. over 3 months). A scenario analysis is provided below where the waning period is assumed to return to baseline monthly MHDs at the same rate to galcanezumab in chronic migraine, XX cycles. Please note the return to baseline monthly

MHDs for patients in the BSC arm is held fixed to immediately return in the following cycle since we assume a dissipation of the placebo effect for BSC-responders therefore the same dissipation cannot be assumed for BSC non-responders.

Table 53 Scenario analysis where patients who discontinue galcanezumab and botulinum toxin A return to baseline MHDs over XX cycles

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	XXX	XXX	XXX	XXX	XXX	£10,903
Botulinum toxin type A	XXX	XXX	XXX			

Analysis conducted using combined efficacy criterion

B18. There appears to be an error in Column DB on the Calc TX1 sheet – patients do not return to base-line monthly migraine days, but to a slightly higher value. Please check and amend as necessary.

Company Response: Having reviewed the model, we can see a difference between XXX at baseline and XXX the value returned to, showing a difference of XXX. This was observed for galcanezumab arm in the chronic patient population only. The has been corrected in the model.

B19. Columns DB and BK on the Calc TX1 and Calc TX2 sheets appear to contain redundant code in cells referring MC_ROC/RAC. Please remove as part of a revised model.

Company Response:

This has been removed from the model, the base case results were only minimally impacted.

Updated base case analyses are presented below using the amended model (incorporating B.18 and B.19). Results show these amendments had a minimal impact on the cost effectiveness results.

Table 30 Updated base case results: Episodic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	XXX	XXX	XXX	XXX	XXX	£29,230
BSC	XXX	XXX	XXX			

Analysis conducted using responder and non-responder efficacy criterion

Clarification questions

Table 31 Updated base case results: Chronic vs BSC

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,080
BSC	[redacted]	[redacted]	[redacted]			

Analysis conducted using responder and non-responder efficacy criterion

Table 32 Updated base case results: Chronic (vs Botulinum toxin type A)

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,560
Botulinum toxin type A	[redacted]	[redacted]	[redacted]			

Analysis conducted using combined efficacy criterion

B20. Can you explain (a) the modelled impact of discontinuation on mean MHD and (b) why the mean MHD for chronic migraine patients discontinuing galcanezumab initially goes up immediately after discontinuation, then falls to a low of 9.1 and remains below 18.81 (Column BK, Calc – tx1) Please check the calculations and revise as necessary. Note, the ERG considers it acceptable for all waning of treatment effects to be removed if this cannot be corrected appropriately.

Company Response:

a) The discontinuation of patients after the trial happens every cycle, therefore within each cycle a proportion of patients transition from 'on-treatment' to 'off-treatment' health states due to discontinuation. For discontinued patients the mean MHD is calculated based on a weighted average of the patients who discontinue after the initial response assessment and the discontinuation per cycle. Over time, the weighting between the two groups switches from initially being all patients who discontinue from the initial assessment to eventually being all patients who responded initially.

b) The mean change in MHD for non-responders is positive, hence for the chronic migraine population initially goes up.

Clarification questions

After 3 months, patients start to discontinue from the response health state, where they had a lower MHD, hence lowering the average MHD.

For example, at 5 months, the MHD is based on a weighted average of one patient cohort which discontinued at month 3. At month 6, there are now two patient cohorts, the previously mentioned cohort that initially discontinued with a small increase in MHD and a second cohort who discontinue in month 6, this cohort has a low MHD because they received the treatment effect. Hence the weighted average is mix of the two. After this cycle there is a continuous increase in the patients who discontinue from the response health state based on discontinuation due to AE, meaning the MHD remains low. Eventually these patients return to baseline in line with the treatment waning assumption, meaning there is a trend towards the respective baseline MHD

To demonstrate how this works, an illustrative example is provided in the tables below. A separate table is shown for cycle 5, 6, 7. This is an example that closely aligns with the model, however based on rounding there are some differences, hence this should only be considered an illustrative example

Table 56 Illustrative example at month 5

Cycle	Patients	MHD	Notes
Discontinued month 5	0.40%	19.415	Based on an increase from baseline for non-responders
Average		19.415	

Table 57 Illustrative example at month 6

Cycle	Patients	MHD	Notes
Discontinued month 5	0.39%	19.40	As table above with return to baseline
Discontinued month 6	0.25%	6.47	Aligned with responders
Average		14.39	

Table 58 Illustrative example at month 7

Cycle	Patients	MHD	Notes
Discontinued month 5	0.39%	19.39	As table above with return to baseline
Discontinued month 6	0.25%	6.695	Aligned with responders with some waning
Discontinued month 7	0.25%	6.47	Aligned with responders
Average		12.20	

Clarification questions

Other

B21. Erenumab and fremenazumab are currently being appraised by NICE and potentially would represent comparator treatments if approved. Can the company comment on the potential implications of erenumab and fremenazumab being comparator treatments?

Company Response:

Lilly believes erenumab is not a valid comparator for galcanezumab. There remains considerable uncertainty around the data in the chronic population which was evident from the appraisal documentation by NICE (18, 19). Following an appeal, the data in the 4th line population was substantiated by an independent appeal panel which upheld only the point for a 5th line post-Botox consideration. Galcanezumab is positioned as a 4th line treatment, hence, erenumab is not a valid comparator for galcanezumab.

Lilly agrees fremanezumab is a potential comparator for chronic migraine patients with a history of ≥3 prior preventative treatment failures. It has recently been recommended by NICE in a Final Appraisal Determination (20) and guidance is expected 15th April pending appeal. However, the SLR revealed no published data in the target population of patients with a history of ≥3 prior preventative treatment failure, therefore, an ITC to fremanezumab was not feasible. Furthermore, this guidance is expected to be released after galcanezumab received its Invitation to Participate and was not standard of care at the time of submission.

B22. Please provide justification for excluding migraine severity from the economic model despite identifying the incorporation of migraine severity as a strength of the ICER study identified in the targeted literature review (TLR).

Company Response:

Lilly undertook the cost effectiveness model development in conjunction with clinical experts and advice from health economics experts and health technology agencies (21). Lilly agrees that severity is an important patient outcome and has an impact on patient's HRQoL, however, this is a considerable increase in model complexity and there is a lack of data to inform the granularity that would be required to incorporate severity within the current health states of the model, particularly to combine with the current individual MHDs distribution structure. Severity is also difficult to capture accurately as it is a subjective measure and differs from person to person. Furthermore, it was not deemed feasible to synthesis such clinical inputs indirectly for active comparators (i.e. botulinum toxin A) given the lack of evidence identified in the SLR.

The model incorporates important clinical outcomes as defined by the IHS (9) and directly relates to the marketing authorisation for galcanezumab, that is, reducing the number of monthly migraine attacks – preventing migraine. Also, models in migraine seen in past NICE Technology Appraisals have not included severity as and were deemed appropriate for decision making (19, 20, 22).

B23. Please provide migraine severity distributions of patients from the clinical evidence at baseline and at 3 months for chronic, episodic and HFEM.

Please see response to B.22

B24. Please provide mean utility values for the patient populations in each of the migraine severity classifications defined by the company in question B23.

Please see response to B.22

B25. Please comment on the relevance of the subgroup of patients who have previously failed botulinum toxin type A, specifically referring to patients failing botulinum toxin type A used in the a) 3rd line and b) 4th line settings.

Company Response:

At the 3rd line and 4th line setting the subgroup of patients that have a history of failed botulinum toxin A is not relevant to UK clinical practice. For patients with chronic migraine, patients cycle through 3 oral preventative medications before specialist treatments are tried (1, 2). Therefore, botulinum toxin A would be used for patients with chronic migraine at 4th line – aligned to the recommendation in NICE Technology Appraisal guidance for botulinum toxin type A for the prevention of headaches in adults with chronic migraine (TA260) (22). Patient who have a history of failed botulinum toxin A is only applicable to the 5th line setting.

B26. With reference to Question A4, can the company please incorporate scenario analyses exploring the impact of excluding botulinum toxin type A failures from the economic model. Please can the company also reproduce the supplementary analyses and scenarios outlined in Questions B1, B2, B3, B14, B23, B24, making sure to exclude botulinum toxin type A failures. Please incorporate the functionality in the model to allow the ERG to replicate and verify the scenario.

Company response:

Due to time restrictions, Lilly was unable to conduct the efficacy analyses with the aim to exclude botulinum toxin A failures for the subgroup of patients with either chronic or episodic migraine with a history of ≥3 prior preventative failures. Therefore, it was not possible to conduct a cost effectiveness analysis for this population

Section C: Textual clarification and additional points

C1. Please clarify the sentence in the third bullet point, company submission page 87: “The definitions for the continuous measurements from one study to another one

considers data from different durations (e.g. mean change across month 1 to month 3)”

Company Response:

Responder rates (50%) were analysed differently in the Botox and galcanezumab development plans and therefore reported differently in disclosures and source documents. In the galcanezumab studies, the responder outcomes correspond to the average of the monthly responder rates calculated across the double-blind study duration and is therefore a continuous measure, whereas the Botox analyses are based on the number of patients. Hence, to be able to indirectly compare to the Botox studies, the number of responders in the galcanezumab studies were re-calculated from the average of the response rates and the number of patients contributing to the analyses. Therefore, the percentage displayed in the indirect comparison analyses might slightly differ from the average percentage reported in the disclosures or in internal study reports.

C2. Table 46 (company submission page 97-99) please provide details of interventions being compared or used in all studies e.g. state doses used and whether any other active arms are being studied.

Company Response:

Table 46 in the submission has been revised to include an additional column describing the interventions as shown in Table .

Table 59 Amendment to Table 46 Ongoing and recently completed studies of galcanezumab for migraine patients

Study identifier	Countries	Population	Interventions	Study design	Estimated enrolment	Study period
Recently completed controlled clinical studies in migraine prevention (adults)						
I5Q-JE-CGAN (NCT02959177)	Japan	Japanese patients with EM	Galcanezumab 120 mg, 240mg Placebo	Phase IIb, multicentre, randomised, double-blind, placebo-controlled, parallel-group study Following double-blind treatment, 4-month post-treatment (washout) period	N=451	Actual start: 9 November 2016 Completion: 2 February 2019
I5Q-JE-CGAP (NCT02959190)	Japan	Japanese patients with EM who completed the treatment period in CGAN	Galcanezumab 120 mg, 240mg	Phase III, multicentre, randomised, long-term, open-label safety study Following open-label treatment, 4-month post-treatment (washout) period	N=300	Actual start: 7 February 2017 Completion: 24 August 2019
Ongoing studies in controlled clinical studies in migraine prevention (paediatric)						
I5Q-MC-CGAS REBUILD (NCT03432286)	US, Puerto Rico	Patients aged 6–17 years with EM	Galcanezumab 120 mg, 240mg Placebo	Phase III, multicentre, randomised, double-blind, placebo-controlled trial	645	Actual start: 14 March 2018 Estimated completion: 25 May 2023
Ongoing studies in controlled clinical studies in migraine prevention (Adults)						
I5Q-MC-CGAX (NCT03963232)	China	Adults patients with EM	Galcanezumab 120 mg Placebo	Phase 3, Randomized, Double-Blind, Placebo-Controlled	486	Actual start: 30 June 2019 Estimated completion: 29 Oct 2021

I5Q-MC-CGAY (NCT04085289)	China	Healthy	Galcanezumab 120 mg, 240mg	Phase 1, Randomized, Double-Blind, Placebo-Controlled	30	Actual start: 30 June 2019 Estimated completion: 15 May 2020
Observational studies						
TRIUMPH	US, France and Germany XXX	Adult patients with episodic or chronic migraine who are switching (or initiating) a preventive treatment	Galcanezumab 120 mg with 240 loading dose	Prospective Observational Research Study, global, multisite, 2-stage: **Stage 1**: cross-sectional (N=6,000) assessment of treatment patterns and burden **Stage 2**: 24-month longitudinal assessment of those in stage 1 meeting enrolment criteria (N= 2,500, with 1,250 galcanezumab and 1,250 on other preventive treatments)	**Stage** 1: 6000 **Stage 2:** XXX	XXX
OVERCOME	US XXX	Adults with migraine who reported having a headache or migraine attack in past 12 months	Galcanezumab 120 mg with 240 loading dose	Prospective, Observational, multi-wave and web-based patient survey	20,000 XXX	Estimated start: August 2018 Estimated completion: 2022

Abbreviations: EM, episodic migraine; CM, chronic migraine; SC, subcutaneous; US, United States; UK, United Kingdom

References

1. National Institute for Health and Care Excellence. Headaches in over 12s: diagnosis and management (CG150). 2015.
2. British Association for the Study of Headache. National headache management system for adults 2019 [Available from: http://www.bash.org.uk/guidelines/.
3. Data on File. Eli Lilly and Co.: A third update to a systematic literature review of clinical evidence of comparator treatments in migraine in adults with Prior Treatment Failures 2019.
4. Mulleners WK, B. Lainez, M. et al. . A Randomized, Placebo-Controlled Study of Galcanezumab in Patients with TreatmentResistant Migraine: Double-Blind Results from the CONQUER Study (International Headache Society Abstract: IHC-OR-042). Celphalalgia. 2019;39(IS):366.
5. Data on file. Eli Lilly and Co.; Indirect Treatment Comparison Report of Galcanezumab compared to Botulinum Toxin A 2020.
6. Data on File. Eli Lilly: NICE Request to provide data and scripts. 2020.
7. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009;16(9):968-81.
8. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;55(6):754-62.
9. The International Headache Society. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia : an international journal of headache. 2018;38(1):1-211.
10. Canadian Agency for Drugs and Technologies in Health. Common Drug Review Clinical Review Report for Botox. 2015.
11. EUnetHTA. Guideline. Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness. 2016 December 2016.
12. Data on File. Eli Lilly & Co. Ltd: Clinial SLR prior failures screening file v2. 2020.
13. Data on File. Eli Lilly: Indirect comparison between galcanezumab 120 mg vs. Botox (excluding CGAI). 2020.
14. Data on file. Eli Lilly: Results_failed3plus_treatment_All_studies. 2020.
15. Data on File. Eli Lilly: Results_failed3plus_Categories_CGAW. 2020.
16. Data on File. Eli Lilly and Co.; Indirect Treatment Comparison Report of Galcanezumab compared to Erenumab 2019.
17. National Institute for Health and Care Excellence (NICE). Fremanezumab for preventing migraine [ID1368] Appraisal Consultation Document 2019 [cited 2019 April]. Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/129-2.
18. National Institute for Health and Care Excellence. Erenumab for preventing migraine: Appraisal Consultation Document. 2018.
19. National Institute for Health and Care Excellence. Erenumab for preventing migraine: Final Appraisal Document. 2019.
20. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [ID1368]: Final Appraisal Document 2020 [Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/final-appraisal-determination-document.
21. Data on File. Eli Lilly and Co: Company's minutes of EMA/HTA Parallel Scientific Advice Meeting 02 December 2014. 2014.
22. National Institute for Health and Care Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. Technology Appraisal Guidance [TA260]. 2012.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Galcanezumab for preventing migraine [ID1372]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Migraine Trust
3. Job title or position	Policy and Research Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Migraine Trust is the largest research and support charity for people affected by migraine in the UK. Our role is to fund and promote new research into migraine, provide day-to-day support for people affected by migraine, and campaign for change. Since we were founded in 1965, we have funded over 130 medical research projects that have improved our understanding of migraine and encouraged new researchers into the field. We hold an international symposium every two years, bringing together the world's leading experts on migraine and headache to share latest research findings and discuss current trends in treatment and prevention. The next Migraine Trust International Symposium (MTIS) will be in London on 10-13 September 2020. We also provide evidence-based information and support on all aspects of migraine and help for people with migraine experiencing difficulties at work, in education, or in accessing healthcare services via our website and our information and advocacy helplines. Every year over two million people visit our website and over 2,300 people receive support through our helplines. We campaign for national policy change to improve the lives of people affected by migraine. We are currently developing a 'State of the Migraine Nation' report that aims to explore the challenges and opportunities facing the migraine community today and identify priorities for future change across the UK. We are funded through legacies, individual donations, community and event fundraising, corporate partnerships, trusts and foundations, and industry. We are not a membership organisation, but we do have over 24,000 people signed up to receive our monthly e-bulletin.
4b. Has the organisation received any funding from the	Yes **Eli Lilly** – We received £24,200 from Eli Lilly towards the production of our 'State of the Migraine Nation' policy report

manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**Allergan** – We received £15,000 for our Information & Support Services team nurse specialist role **Amgen/Novartis** – We received £10,507 for our Information & Support Services team nurse specialist role
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We ran three surveys of people affected by migraine and migraine health professionals to help inform this submission. They are: **1. Migraine community survey** – This was the largest survey of the UK's migraine population that we've ever done in our nearly 55-year history. It was completed by over 1,800 people affected by migraine, including patients, their carers, and friends and family. It asked respondees about all aspects of their migraine, including: their experience of care and treatment, their main symptoms, and the impact that their migraine has had on their quality of life, family, education and/or career, and mental health and wellbeing. It ran from 7 October 2019 to 19 November 2019.

	2. CGRP Patient Experience Survey – We surveyed 203 patients between 14 October 2019 and 19 November 2019 who are currently taking (or had recently taken) a CGRP drug for the prevention of their migraine. The survey asked a variety of questions about the patient experience of using CGRP inhibitors, including about effectiveness, tolerability, and comparisons with Botox. **3. Snap poll of neurologists and headache nurses** – There are currently 60 headache nurses and 38 neurologists with a special interest in headache, according to the Association of British Neurologists (ABN). We surveyed 5 headache nurses and 11 neurologists between 22 November and 5 December 2019 about the experiences of their chronic migraine patients with Botox and CGRP drugs. In total, the snap poll results speak to the experience of 9,490 chronic migraine patients across the UK. We would be happy to share the full results of all three surveys with the committee if that would be helpful.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**What is migraine?** Migraine is a complex brain disease that greatly impacts individuals, their families, and society as a whole. It is the third most common disease in the world, affecting around 1 in 7 of the global population. According to NHS England, in the UK there are around 10 million people living with migraine. It is three times more common in women compared to men and around 10% of school children will experience a migraine every year. If you have migraine, you are likely to experience regular migraine 'attacks' that can last for up to four days. More than 75% of people living with migraine experience at least one attack every month, but the number of attacks varies considerably. People with migraine can experience an incredible range of debilitating symptoms. According to our recent survey of people affected by migraine, the ten most common symptoms are fatigue, severe head pain, light sensitivity, difficulty concentrating, nausea, stiff neck or back, feeling down, sound sensitivity, 'background' headache, and visual aura. But people affected by migraine cited more than 30 different symptoms in total.

	People with ‘chronic migraine’ have at least eight migraine attacks per month. It is estimated that between 660,000 and 1.3 million people in the UK are living with chronic migraine right now. The World Health Organization (WHO) categorises chronic migraine as causing the same level of disability as dementia and quadriplegia. At the moment, there is no cure. **What is it like to live with the condition?** Migraine exacts a large personal toll on people’s lives. People with migraine most commonly report that migraine has significantly impacted the following aspects of their life: work and career, family relationships, social life, and mental health and wellbeing. **a. Work and career** – Migraine is the leading cause of disability for people aged 15-49 and the second most disabling medical condition in the world. Our Migraine Community Survey found that nearly half (47%) of respondees consider themselves to have a disability as defined by the Equality Act 2020 because of their migraine. Our CGRP Patient Experience Survey found that for chronic migraine patients who have failed three other preventives, the percentage of respondees who identify as having a disability as defined by the Equality Act 2010 rises to 84%. This can create challenges in the workplace as people with migraine try to access the support they need to stay in work, develop, and progress. Our Migraine Community Survey found that 41% of eligible respondees ‘definitely agree’ that migraine has significantly impacted their career. People with migraine told us: “I lost my job because of migraine.” “My migraine has been the reason for taking early retirement.”

	"The lack of understanding of what migraine is…means that I was recently threatened with a level 3 disciplinary. I may lose my job despite 35 years of experience. It made me feel undervalued and discriminated against." **b. Family relationships** Over half (54%) of respondees to our CGRP Patient Experience Survey strongly agree that migraine has had a significant impact on their relationship with their partner or spouse and one-third (35%) strongly agree that migraine has significantly impacted their relationship with their children. People with migraine told us: "My family have suffered in helplessness for decades, unable to ease my pain…While they have lived their lives together I have been alone in a dark room isolated by my disease." "Migraine has stolen years of my life. I have missed so many events and missed out on so much of my son's life because of it." "I am not able to look after my child." **c. Social life** Migraine can be a very isolating condition, with 83% of respondees to our CGRP Patient Experience Survey strongly agreeing that migraine has significantly impacted their social life. The unpredictable nature of migraine, both episodic and chronic, can prevent people from being able to make plans or commit fully to family or leisure activities. People with migraine told us: "My friends have disappeared. This condition has ruined my existence." "My whole life revolves around migraine. I never see my friends or make any plans because migraine rules everything."

	d. Mental health and wellbeing People with migraine are three times more likely than people without migraine to have depression. 70% of respondees to our CGRP Patient Experience Survey strongly agree that migraine has significantly impacted their mental health and wellbeing.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**What options are currently available to patients and which are patients using?** While migraine cannot be cured, there are numerous acute and preventive treatments currently available to patients on the NHS in England and Wales to help them work with their clinician to manage this condition. Our Migraine Community Survey found that patients are most likely to be using the following types of treatments to help them manage their migraine: triptans (58%), lifestyle modifications (56%), over the counter painkillers (51%), and preventives (39%). However, it is important to emphasise that patients often have to try numerous different medicines before they find something that may work for them. Our Migraine Community Survey found that only around one-third of patients are satisfied with the care they receive for their migraine and only 31% believe they are effective at self-managing their migraine. **What do patients think of current acute options?** Acute treatments include pain-relief medicine, such as codeine, triptans, and paracetamol. People with migraine can experience adverse side effects from acute treatments, including fatigue, nausea, medication overuse headache, confusion and anxiety. For many, this limits the number of treatment options available to them. **What do patients think of current preventive options?**

	For the prevention of migraine, NICE clinical guideline 150 recommends a suite of different drugs that can be considered by patients and their clinician, including anticonvulsants and betablockers. However, many of these were developed for other conditions and have been repurposed for migraine. They often have severe and unwanted side-effects. For example, topiramate is very poorly tolerated in greater than 50% of patients and the Medicines and Healthcare products Regulatory Agency (MHRA) warns that sodium valproate causes learning disability in approximately 40% of babies born to mothers using it. Our CGRP Patient Experience Survey found that 90% of respondees had experienced adverse side-effects from migraine preventives, excluding CGRP. They told us: ““Propranolol side-effects were so bad that I had to take a month off of work.” “Low blood pressure from beta blockers and horrendous brain fog from Topamax. It was so intense that I had to come off the drug.” “I tried Botox and had a reaction to it. My throat swelled and I had a hard time breathing.” “Some preventives have caused me to have brain fog, taste changes, musculoskeletal pain, and sleepiness during the day.” Regardless of these side-effects, it is also important to stress that these ‘first line’ preventives also don’t work for everyone with migraine or they can stop working relatively quickly. Our CGRP Patient Experience Survey shows that 78% of respondees had tried more than five different preventives and 70% had also failed to respond to more than five different preventives. Patients told us: “No preventives have been successful, apart from topiramate which works for a couple of months and then stops completely.”

	"I have tried everything there is to try! Anti-depressants, anti-convulsants, HRT, etc. I experienced unpleasant side-effects to a greater or lesser extent from everything and no relief from migraine at all." **What do patients think of botulinum toxin type A (Botox) for the prevention of migraine?** NICE technology appraisal guidance 260 also recommends botulinum toxin type A (Botox) for preventing migraine for adults with chronic migraine who have not responded to at least three prior preventives. Botox is an effective preventive, but is hugely demanding of healthcare professional time and resource and, for some patients, difficult to access (see more below). While uncertainty remains over whether galcanezumab is more clinically effective than Botox, our findings from patients who have taken both a CGRP inhibitor for their migraine and Botox can shed some light on the real-world patient experience of comparative effectiveness and tolerability. Our CGRP Patient Experience Survey shows that for patients who have received both Botox and a CGRP inhibitor for their chronic migraine, 78% agree or strongly agree that the CGRP drug that they are currently taking (or have taken in the past) is more effective at managing their migraine than Botox, 76% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) has improved their quality of life more than Botox, and 95% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) is easier to administer than Botox. Our snap poll of neurologists and headache nurses shows that 62% of those surveyed believe that CGRP drugs are as or more effective than Botox based on their real-world experience of treating migraine patients. None of the neurologists or headache nurses we surveyed believed that CGRP drugs are less effective than Botox. 75% of those surveyed agree that their patients would prefer to receive CGRP drugs for their migraine over Botox.
8. Is there an unmet need for patients with this condition?	As referenced above, there is an unmet need for patients who experience intolerable side-effects from the preventives currently available.

	There is also a considerable unmet need for patients with migraine who will fail to respond to oral preventives and botulinum toxin type A (Botox). These chronic migraine patients currently have no preventive option that works for them. We are not aware of the total size of the UK Botox non-responder population for migraine and our understanding is that no one else knows with certainty either. However, our snap poll of neurologists and headache nurses sheds some light on the size of this population. Of the 9,490 chronic migraine patients the health professionals polled have seen in their clinic in the past year, 5,085 patients have also received Botox injections. Of those 5,085 patients, an estimated 801 (15.7%) failed to respond to that therapy. This means that an estimated 8.4% of chronic migraine patients are not having their treatment needs met by current treatment options. Our CGRP Patient Experience Survey shows that CGRP drugs are answering a significant unmet need in this sub-group, delivering an effective and well-tolerated treatment that many report as 'life changing.' For example, of the patients we surveyed who had failed to respond to Botox, 76% agree or strongly agree that the CGRP drug they are currently taking (or have taken in the past) has improved their quality of life. There is also an unmet need for patients who experience difficulties in accessing Botox injections, which must be administered at a specialist centre by a trained healthcare professional on a quarterly basis. Our snap poll of neurologists and headache specialists shows that over the past year, 9% of their patients receiving Botox (437) have been forced to skip or delay a course of Botox injections due to access, availability, or capacity issues. These findings chime with the results of our CGRP Patient Experience Survey, which shows that 12% of eligible respondees had to wait over one year to receive their first course of injections from the time they were first prescribed it. This survey also found that 27% of respondees who had received Botox injections had to pay privately in order to do so.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Galcanezumab is a specific preventive treatment designed for migraine that has a very tolerable side-effect profile and can be administered in the patient's own home. 80% of respondees to our CGRP Patient Experience Survey agree or strongly agree that using a CGRP drug has improved their quality of life. Their reasons for saying this varied, but most have referenced reduced frequency of migraine attacks, reduced severity of attacks, being able to break the cycle of medication overuse headache, less stress, improved performance at work, being able to spend time with family, and improved mental health. It was not unusual for respondees to report that taking a CGRP drug like galcanezumab has been 'life changing' for them. Respondees told us: "My number of migraine days has reduced from up to 20 days per month to 5 days. Plus the migraines I still have are less severe and more responsive to triptans. My quality of life has returned to near normal for the first time in 14 years….I could weep with the relief of my life now." "I have gone from 20 plus migraines a month to 3-4. This has been life-changing for me. I was able to start driving a car again. All aspects of my life have improved after having this treatment: work, life, mental health, social life, home life, etc." "My quality of life is transformed." "My life has changed beyond recognition. I have been given the opportunity to live again. I can make plans, go places, do things, see people; none of this was possible before. For 45 years my life has been controlled by migraines, my personality, my identity…has been defined by this illness. Now I am free to find out who I am and how I should live."

	"I am able to leave my house for the first time in over 20 years with no fear of being stranded somewhere, possibly with a migraine attack so bad that I would be unable to open my eyes, walk, or even talk to anyone coherently. I can look after my grandchildren on my own for the first time ever." "Yesterday, for the first time in 15 months I felt well enough to drive my car and take my little boy out." "One injection and my life has improved massively. My mood is better, daily life is better, I've started being involved in physical activity again because my pain is managed effectively." "For the first time in 12 years, I am having pain free days, out of my darkened quiet bedroom." "It has changed my life beyond recognition. I no longer feel isolated. I have a new full time job that I can travel to on public transport and with confidence. I am not spending my life lying in a quiet, dark room. My migraines have gone from 17 per month to 3…AMAZING." "This is life-changing; a resurrection. I can see better, have clarity of thought, can make decisions and have fun again. I now have hope that I can resume work again." "I see friends, I can eat and enjoy food, spend time with family, appreciate my home, go outside!!!! Just to be in daylight and not see the inside of a toilet bowl hour after hour with no end in sight - I cannot tell you what that means to me." "Since taking the CGRP drug, I have not once been sick. I have not had to go into A&E to stop intractable migraine….Previously, I had to give up work because I could not function….Now my migraine episodes are much less frequent." "I have been given my life back, after suffering for over 20 years. I actually feel human again." "I have my life back. I still get headaches, but they are nothing compared. I can plan things now, help with my grandchildren, meet up with friends, work again. It's miraculous."

	Overwhelmingly, respondees to our CGRP Patient Experience Survey indicate that taking a CGRP drug for their migraine has had a positive impact on their family and/or carers. Respondees report that they are able to spend more time with their children, spouse/partner, or grandchildren. They say that their mood has dramatically improved, which in turn has led to a happier life at home. They also report that family members no longer need to act as carers. Respondees wrote: "My husband and I no longer live our lives completely dictated by migraine. We do things together and make plans. My family no longer have to see me in the depths of depression and with no hope that life will ever get better again." "The hope for my husband is palpable. He's seen me disabled and in pain for so long that he's overjoyed to see his former wife back." "Since starting the CGRP drug, my 80-year-old parents have not had to come and take care of me and my son. They have not had to carry me to the doctor or to A&E." "It has had an immeasurable effect. I can be fully present for my family. I can help support my siblings with their numerous small children. My own 16-year-old child can rely on me to be able to do stuff/support her without her having to feel guilty about asking me when I'm clearly struggling." "My parents are much happier as they don't have to worry about me so much. They don't have to do so much for me anymore, like cooking for me, going shopping for me, or driving me to various appointments."

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There are few disadvantages when compared to current standard treatments, although it's important to highlight that not all patients will respond to CGRP drugs. Some people with migraine may have a needle phobia which could be a problem as the drug is administered via an injection. Respondees to our CGRP Patient Experience Survey confirm these few disadvantages, with most indicating in the free text commentary for our survey that there are no disadvantages when compared to standard treatment. A small minority of respondees did indicate that there were disadvantages, which includes: the cost, injection site rashes, constipation, and needing to keep the drug refrigerated (which can make travelling difficult).
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As detailed above, patients who have failed to respond to three oral preventives and also failed to respond to Botox may benefit more from this therapy than others.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The Migraine Trust would like to raise the following key points: 1. Migraine can be classed as a disability under the Equality Act 2010 2. The Scottish Medicines Consortium (SMC) has recently approved two other CGRP drugs (erenumab and fremanezumab) for use in Scotland for the prevention of migraine. This has created a 'post code lottery' where migraine patients in Scotland now have more treatment options for migraine than patients living elsewhere in the UK.
Other issues	
13. Are there any other issues that you would like the committee to consider?	As a fast, effective, and well-tolerated preventive, galcanezumab is able to not only reduce the number of headache days that patients experience, but also their use of acute treatments. This will help prevent the onset of medication overuse headache and also save resources elsewhere. 73% of respondees to our CGRP Patient Experience Survey report that they were able to stop or reduce their use of other migraine treatments while they were taking the CGRP medicine. The most common treatments respondees were able to reduce or stop include: triptans, codeine, and anti-sickness medicines. Respondees told us: "Before having the CGRP drug I was taking either triptans or painkillers for approximately 6 days of the week. I now generally have only needed medication for migraines approximately once a week." "I now only use only sumatriptan and cyclizine for the sickness. I use no other drugs which is wonderful. My triptan use has gone from the max allowed of 10 per month to max of 3 per month."

	"I managed to stop taking triptans and I drastically reduced my intake of over the counter medications."
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission:	

- Migraine is a complex brain disease that greatly impacts the day-to-day lives of people who live with the condition. In particular, people with migraine say it impacts their ability to work or progress in their career, spend time with their family, socialise with friends, and live up to their potential. It also has a significant detrimental impact on mental health and wellbeing.
- While there are many acute and preventive treatments currently available on the NHS in England and Wales, all of them have been developed for other conditions and repurposed for migraine. They can have extremely adverse side-effects.
- Galcanezumab is a specific preventive treatment designed for migraine that has a very tolerable side-effect profile. An overwhelming majority of patients who have used CGRP drugs who we surveyed (80%) report that the drug has improved their quality of life. Many say using this kind of drug has been 'life changing.' Patients report very few disadvantages.
- There is significant unmet need for patients who cannot tolerate currently available oral preventives and/or who have failed to respond to Botox therapy. According to our research, this sub-group of patients represents 8.4% of all chronic migraine patients. Additionally, there is an unmet need for patients who cannot access Botox injections due to capacity, resource, or travel issues.
- Patients we surveyed have been able to reduce or stop their use of other treatments (both acute and preventive) while they have been using CGRP drugs like galcanezumab.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Galcanezumab for preventing migraine [ID1372]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists headache and pain advisory group
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is the professional body that represents neurologists in the UK to 'promote excellent standards of care and champion high-quality education and world-class research in neurology'. It is funded by subscriptions from members. The advisory group members are self-nominated and selected by the elected council members, the Chair is nominated from the members by ABN council
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months. If so, please state the name of manufacturer, amount, and purpose of funding.	no
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• To reduce the impairment and improve disability caused by migraine and improve associated disease-related quality of life • Reduce the frequency and severity of headache in migraine sufferers • To have a positive impact in patients' work life and in other activities of daily living • To provide a preventative treatment that is well tolerated and safer than existing therapies • To reduce the need for additional acute medications to treat acute attacks
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In patients with **episodic** migraine (< 15 days of headaches per month) a **50%** reduction either in the severity or frequency of headache is regarded as a meaningful response. Many studies report on average headache day reduction in comparison to placebo that does not reflect on actual therapeutic gain of the drug. In patients with **chronic** migraine (> 15 days of headache per month for at least three months) a **30%** reduction either in the severity or frequency of headache is shown to have a positive impact on patients' disability. Improvement in quality of life measures such as Headache Impact Test (HIT-6), EQ5D or MIDAS often reflect considerable improvement in patients' disability particularly when headache frequency and severity is difficult to quantify in patients with poor headache record keeping.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	As a group, we strongly believe there is a very significant unmet need • Migraine affects 15% of the general population (22% women and 8% men) and has impact similar to arthritis, diabetes and worse than asthma. Migraine along with other headache disorders have more years lived with disability worldwide than epilepsy. The condition is recognised as the seventh disabler in a recent publication by the Global Burden group. Around 1.5-4% patients have chronic migraine that is extremely disabling. The indirect cost to the economy run in billions with 20 million lost days a year in addition to direct cost to the NHS. Still the condition is under-recognised, under-diagnosed and under-resourced.

	• There is a massive unmet need in both research and education on the disorder. There is a major need for education on headache disorder in primary and secondary care as well as in the general public. • As a result many patients with headache disorders do not receive the right diagnosis and treatment. 50% of patients do not bother consulting as they feel their condition do not receive appropriate attention. Many continue to treat themselves with over the counter medication resulting in analgesic overuse problem. • Lack of appropriate resources to manage headache despite high cost to society, the NHS and the individual with greatest costs being indirect and largely discounted in health budget decision making
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Low frequency episodic migraine is usually self-managed in the community or through primary care. Patients with disabling or high frequency migraine are often referred to secondary care; those with refractory migraine may be are seen in specialist services which are limited in number and location Treatment is through: 1. Lifestyle, behavioural and psychological modification and education is helpful but time consuming and are often delivered by the specialist headache nurses, although there are only around 50 nurses in the UK. Psychology services linked with headache clinics are rare in the UK 2. A range of acute and preventative pharmacological options. The preventative options being mostly re-purposed (betablockers, anti-epileptics, tricyclic anti-depressants and angiotensin converting enzyme inhibitors) they are not been designed to target the underlying migraine biology and have a range of side effects that are often limiting

	3. For refractory chronic migraine the use of injectable techniques such as cranial nerve blocks and botulinum toxin A is an option. Neuromodulation devices e.g. vagal nerve stimulators and transcranial magnetic stimulation, have been appraised positively by NICE but are not funded on the NHS unless pursued through exceptional treatment requests 4. Around 20% of migraine patients are refractory to all available options and may be referred for intravenous dihydroergotamine or invasive procedures that are only available in one or two centres in London as very little in-patient headache services exist in the remainder of the UK. These are expensive options with huge cost-implications to the CCG.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Clinical Guideline 150 (2012 & updates) https://www.nice.org.uk/guidance/cg150 SIGN Guideline 155 - Pharmacological management of Migraine (Feb 2018) http://www.sign.ac.uk/sign-155-migraine.html British Association of Headache (BASH) National Management System for adults 2019 https://www.bash.org.uk/guidelines/
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Significant variations in headache care occur across the country and in part are determined by access to specialist services. In general, there is lack of expertise among many primary care healthcare professionals and many general neurologists lack detailed understanding on the disorder. Hence services vary from being extremely good to very poor based on the availability of special headache services. Whilst guidelines exist, they are often not applied as there is a lack of expertise in making a proper diagnosis and management plan; for example many patients who should be accessing triptan therapy remaining triptan naïve. Most episodic migraineurs remain within the community or are managed by primary care.
• What impact would the technology have on the current pathway of care?	• Galcanezumab would bring a novel, easily self-administered, once monthly, well tolerated treatment to the migraine pathway. This would improve patient compliance, empower the patient to manage his/her own care and potentially reduce the need for frequent GP review to titrate treatments doses and monitor for side effects associated with other preventative treatments

	• Preventing need for emergency care, where patients with headache represent a high proportion of patients presenting at Accident and Emergency • Galcanezumab opens up a new option for patients with migraine who have previously failed to find suitable treatments in secondary care. Public knowledge of CGRP Monoclonal Antibody treatments makes it likely that patients who have previously failed other treatments will be asking their general practitioners for referrals to secondary care. This will need resources and investment both in terms of drug cost and manpower to be able to deliver the service.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be a further tool to use within the current pathway, offering the appeal of increased compliance, ease of use and tolerability
• How does healthcare resource use differ between the technology and current care?	The treatment pathway needs to be specifically defined for the new technology including: • Who will be eligible for the treatment? • What would be the starting and stopping criteria for the treatment? • Who would initially train the patient for injection? • How long the treatment be continued? • How and when the treatment is re-initiated once stopped? • How the treatment response will be monitored? • What follow up arrangement will be required considering the drug is self-administered? However once treatment is established, Galcanezumab is self-administered and is likely to require less frequent follow up as opposed to treatments such as botulinum toxin therapy which requires specialist appointments every 3 months.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment will be best suited to be initiated in the specialist headache centre (primary or secondary care) although once stabilised could be followed up via telephone or by primary care physician
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Injection training for patients, perhaps through headache specialist nurses • Specialist clinic expansion to triage referrals
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, especially for those patients intolerant of, or with poor compliance to, current treatment. The new technology will provide a better option even if the responder rate remains similar to the existing treatments. This will need to be revisited once a real life data is available.
• Do you expect the technology to increase length of life more than current care?	Improve quality rather than length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes with far better tolerability and infrequent treatments
12. Are there any groups of people for whom the technology would be more or less effective (or	In our opinion the treatment will be equally effective in both episodic and chronic migraine. However, there is more clinical need for better treatment in chronic migraine considering many patients are refractory to standard care and chronic migraine carries a very high disability and severely compromises quality of life, hence it is likely Galcanezumab will be used more in chronic than episodic migraine.

appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Easier: Galcanezumab is a monthly subcutaneous injection that can be self-administered and has side effect comparable to placebo. This will be more acceptable to the patient and would empower self-care compared to botulinum toxin which requires 31 injections by doctor or nurse and toxin disposal every 3 months
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do	Starting and stopping criteria would be advisable as this will be a high cost drug. Its placement with the current treatment will really be based on the cost of the technology. If similar to Botulinum Toxin (for example) we suggest: **Starting criteria**: i) failed 3 standard prophylactic mediations (at sufficient dose and for at least 2 months) ii) medication overuse addressed

these include any additional testing?	We feel with home treatment, self-administration and lack of frequent follow up it will be potentially cost savings when compared to Botulinum Toxin treatment. Careful monitoring for compliance, therapeutic response and adverse events will be required. **Stopping criteria:** ***'Negative':*** assessment 3 months after initiating treatment and stopping if there is lack of therapeutic response (50% in episodic and 30% in chronic migraine), ***'Positive':*** if effective in achieving the desired level of response consider discontinuing treatment after 6-12 months
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes: Episodic Migraine: Data from two Phase 3 studies (Skljarevski et al Cephalalgia 2018- Evolve 2 N=915) (Stauffer et al JAMA 2018 – Evolve 1 N=1671) have shown a therapeutic gain of 21% and 24% respectively for 50% reduction in monthly migraine days. The 75% reduction was 33-39% compared to 15% in the placebo group. Chronic Migraine: Data from Phase 3 study (Regain – Detke et al Neurology 2018) showed a therapeutic gain of 12.5% for 50% reduction in monthly migraine days. (27.5% Galcanezumab versus Placebo 15%) Chronic and Episodic treatment resistant migraine Phase 3 study (CONQUER Mulleners Cephalalgia. 2019;39(1S):366 N=462) patients who had previously failed 2-4 preventative treatments in last 10 years showed a reduction in average monthly migraine days of 4.1 Galcanezumab versus 1 day for Placebo
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits	Yes: It is one of the CGRP monoclonal antibodies that are the first ever migraine specific preventive treatment for migraine (both episodic and chronic) which targets the underlying biology of migraine.

and how might it improve the way that current need is met?	It offers preventative treatment with a side effect profile is better, and a dosing regimen that is far more attractive than existing treatments which will improve compliance, drop-out rates and quality of life.
• Is the technology a 'step-change' in the management of the condition?	Potentially yes: Galcanezumab is a migraine specific preventive treatment. All drugs currently used for migraine prevention were found by chance and were developed for other conditions such as depression, hypertension or epilepsy
• Does the use of the technology address any particular unmet need of the patient population?	Yes, empowering patients, improving compliance, better side effect profile
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The trials (short term treatment) have shown the side effect profile to be similar to placebo.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Not entirely – the largest Phase 3 clinical trial of episodic and chronic migraine patients were excluded if they had failed treatment on 3 or more classes of migraine preventative treatments. In the phase 3 trial of chronic migraine (REGAIN) only 78% had used other preventative treatments in the past 5 years and only 29% had failed at least 2 standard preventative treatments in the last 5 years.

	Only the CONQUER Phase 3 study (Mulleners Cephalalgia. 2019;39(1S):366 N=462) was designed to study those who had previously failed 2-4 preventative treatments in last 10years In UK clinical practice such high cost treatments would not be a 1st line treatment option.
• If not, how could the results be extrapolated to the UK setting?	The trial results are likely still to be applicable although treatment response may be reduced as in UK practise Galcanezumab would be used in patients refractory to first line treatments (at least three)
• What, in your view, are the most important outcomes, and were they measured in the trials?	• Reduction in frequency and severity of headache (50% in episodic and 30% in chronic) • Percentage of patients with sustained headache response • % of patients with 75% and 100% response rate • Significant reported change in patient quality of life measures e.g. o HIT6, MIDAS, EQ5D, MSQ (validated quality of life measure in migraine) The trials for Galcanezumab (REGAIN, EVOLVE 1 & 2, CONQUER) were based on monthly migraine days. We emphasise that response based on the frequency and severity of headache attacks are more meaningful and have major impact on ability to function. The current data is only for three months (chronic migraine) and six months (episodic migraine) and long term follow up is awaited.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in	Not to our knowledge

clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real life data and long term treatment efficacy and safety profile
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No
21. How do data on real-world experience compare with the trial data?	No real world data yet available
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is more common in women (22%) compared to men (8%).
22b. Consider whether these issues are different from issues with current care and why.	no
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an unmet need for patients with episodic and chronic migraine, conditions that result in very high levels of disability across the UK patient population
- Novel mode of action targeting underlying pathogenesis of migraine
- The treatment is involves monthly injections that are self-administered and reduce need for hospital visits
- Better compliance than existing treatment because of better tolerability and monthly injections
- Side effects of Galcanezumab are similar to placebo and are much less than with current preventative treatments

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Galcanezumab for preventing migraine [ID1372]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Association for the Study of Headache (BASH)
3. Job title or position	Consultant Neurologist, Educational Officer BASH

4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ A specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Association for the Study of Headache (BASH) is a professional body that represents Neurologists and Primary Care Physicians with interest in headache disorders. The organisation is funded through membership and is heavily involved in education and research in headache disorders all over the UK. BASH is a member of the International Headache Society (IHS) and European Headache Federation (EHF) representing views of the UK members in research, education at a global level.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	BASH has received unrestricted educational grant of £ 20,000 from Novartis for educational meeting on headache disorders in Cardiff and Penrith.

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of this treatment is to: a) Reduce the frequency and severity of headache in migraine sufferers. b) Improve the quality of life to help migraine sufferers have less disability. c) To have a positive impact in patients' work life and in other activities of daily living. d) To reduce the need of acute medications as a result of reduction in the frequency and severity of a migraine attack. e) Provide a preventive treatment with better tolerance and fewer side effects.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In patients with episodic migraine (< 15 days of headaches per month) a 50% reduction either in the severity or frequency of headache is regarded as a meaningful response. Many studies report on average headache day reduction in comparison to placebo that does not reflect on actual therapeutic gain of the drug. In patients with Chronic Migraine (> 15 days of headache per month for at least three months) a 30% reduction either in the severity or frequency of headache is shown to have a positive impact on patients' disability. Improvement in quality of life measures (Qi) such as Headache Impact Test (HIT-6), EQ5D or MIDAS often reflect considerable improvement in patients' disability particularly when headache frequency and severity is difficult to quantify in patients with poor headache record keeping.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Migraine affects 15% of the general population (22% women and 8% men) and has impact similar to arthritis, diabetes and worse than asthma. Migraine along with other headache disorders have more years lived with disability worldwide than epilepsy. The condition is recognised as the seventh disabler in a recent publication by the Global Burden group. Around 1.5-4% of the population has chronic migraine that is extremely disabling. The indirect cost to the economy run in billions with 20 million lost days a year in addition to direct cost to the NHS. Still the condition is under-recognised, under-diagnosed and under-resourced. There is a massive unmet need in both research and education on the disorder. There is a major need for education on headache disorder in primary and secondary care as well as in the general public. The research in headache disorders is massively under-resourced. As a result many patients with headache disorders do not receive the right diagnosis and treatment. 50% of patients do not bother consulting as they feel their condition do not receive appropriate attention. Many continue to treat themselves with over the counter medication resulting in analgesic overuse problem.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Many patients with infrequent migraines do not consult and those seen in primary care are managed with simple analgesics. Those with frequent and disabling attacks are often referred to secondary care managed by a general neurologist with little understanding on headache disorders. The dedicated headache services are few and patchy in the UK and have a very long waiting time. There are handful of General Practitioners with interest in headache

	disorders (GPwSI) overwhelmed with the referrals. Those that are lucky to receive appropriate attention may get early diagnosis and treatment advice, although vast majority do not have access to headache specialist. The pharmacological options for both acute and preventive treatment are limited. There is no migraine-specific preventive treatment and medications currently used include antidepressants, anti-hypertensive and anti-convulsants. Many are either less effective or poorly tolerated with range of side effects often worse than the migraine itself. For Chronic Migraine there are injectable treatments such as Botox that are expensive and are only available to those that have failed to respond to three other treatments. Neuromodulation devices such as gammacore, cephaly, transcranial magnetic stimulation have been appraised positively by NICE but are not funded on the NHS unless pursued through exceptional treatment requests. Around 20% of migraine patients are refractory to all available options and are referred for intravenous dihydroergotamine or invasive procedures that are only available in one or two centres in London as very little in-patient headache services exist in the remainder of the UK. These are expensive options with huge cost-implications to the CCG. Lifestyle and general advice is helpful but time consuming and are often delivered by the specialist headache nurses, although there are only around 50 nurses in the UK. Behaviour and cognitive therapy are often helpful although psychology services linked with headache clinics do not exist in the UK.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a range of guidelines available for management of migraine including those from American Headache Society, International Headache Society, European Headache Federation, European Federation of Neurological Sciences etc. However, in the UK many healthcare professionals follow NICE Clinical Guideline 150 (2012 & updates) https://www.nice.org.uk/guidance/cg150 SIGN Guideline 155 - Pharmacological management of Migraine (Feb 2018) http://www.sign.ac.uk/sign-155-migraine.html British Association of Headache (BASH) National Management System for adults 2019 https://www.bash.org.uk/guidelines/
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The care on headache and migraine varies across the country determined by the availability of either primary or secondary healthcare professional with interest in headache disorders. In general there is lack of expertise among many primary care healthcare professionals and many general neurologists lack detailed understanding on the disorder. Hence they vary from being extremely good to very poor based on the availability of special headache services. The approach to management of migraine depends whether you are a GP, Neurologist or headache specialist. The availability of guidelines is of little use if there is lack of expertise in making a proper diagnosis and management plan. Most of the infrequent and episodic headaches remain in the primary care.

• What impact would the technology have on the current pathway of care?	Galcanezumab is one of the CGRP Monoclonal antibodies that are migraine-specific preventive treatment for both episodic and chronic migraine. The side effect profile of the drug is very similar to placebo. The drug can be self-administered by the patient subcutaneously once a month that empower the patient to manage his/her own care. This will have positive impact on compliance and will potentially reduce the need for frequent GP or specialist consultation and treatment visits, and the number of acute attendance to the Accident and Emergency Department. Studies involving CGRP Monoclonal Antibodies and availability of some of the earlier agents (Scotland) many patients will be asking their general practitioners for the treatment that is likely to sit best with the specialised headache services considering not everyone will be suitable or responsive to the treatment. This will need resources and investment both in terms of drug cost and manpower to be able to deliver the service.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The treatment will be a valuable addition to the currently available preventative agents. There are few patients with episodic migraines and many with chronic migraines who fail to respond to the first line agents would welcome this additional option.
• How does healthcare resource use differ between the technology and current care?	The treatment pathway needs to be specifically defined for the new technology including: • Who will be eligible for the treatment? • What would be the start and stop criteria for the treatment? • How long the treatment be continued? • How and when the treatment is re-initiated once stopped? • How the treatment response will be monitored? • What follow up arrangement will be required considering the drug is self-administered?

	• How frequently the patient will need to be followed up? • Who would initially train the patient for injection?
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment will be best suited to be initiated in the specialist headache centre (primary or secondary care) although once stabilised could be followed up via telephone or by primary care physician.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Depending on where the new treatment would sit in the current pathway, there may be need for additional resources such as nurses training the injections and triaging referrals as to their suitability for the treatment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The main advantage with current treatment is tolerability and side effects. The new technology will provide a better option even if the responder rate remains similar to the existing treatments. This will need to be revisited once a real life data is available.
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	Yes – Due to better tolerability and less side effects experienced on this treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In our opinion the treatment will be equally effective in both episodic and chronic migraine. Currently there is more clinical need for better treatment in chronic migraine considering many patients refractory to the first line are treated with Botox. The fact that chronic migraine carries a very high disability and severely compromise the quality of life, it will be used more in chronic than episodic migraine.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Galcanezumab is a monthly subcutaneous injection that can be self-administered and has side effect comparable to placebo. This will be more acceptable to the patient and would empower self-care. For example comparing this with three monthly visits for Botulinum Toxin treatment that involves 31 injections by a physician/nurse.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As this is likely to be a high cost technology, appropriate start and stop criteria will need to be established. Its placement with the current treatment will really be based on the cost of the technology. If similar to Botulinum Toxin (for example) a suggestion to use the technology following failure of the first line drugs (three preventive treatments) will be reasonable. We feel with home treatment, self-administration and lack of frequent follow up will be potentially cost savings when compared to Botulinum Toxin treatment. Careful monitoring for compliance, therapeutic response and adverse events will be required. As with other preventive treatment, treatment be given for three months and stopped if there is lack of therapeutic response (Negative Stopping Rule). If effective, it will be reasonable to continue for 6-12 months following which attempts be made to withdraw the treatment or when a desired level of response (50% in episodic and 30% in chronic Migraineurs) is achieved. Medication overuse need to be evaluated as this may blur the response rate.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Episodic Migraine: Data from two Phase 3 studies (Skljarevski et al Cephalalgia 2018- Evolve 2 N=915) (Stauffer et al JAMA 2018 – Evolve 1 N=1671) have shown a therapeutic gain of 21% and 24% respectively for 50% reduction in monthly migraine days. The 75% reduction was 33-39% compared to 15% in the placebo group. Chronic Migraine: Data from Phase 3 study (Regain – Detke et al Neurology 2018) showed a therapeutic gain of 12.5% for 50% reduction in monthly migraine days. (27.5% Galcanezumab versus Placebo 15%)

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Galcanezumab is one of the CGRP monoclonal antibodies that is first ever migraine specific preventive treatment for migraine (both episodic and chronic). The treatment after an initial consultation and training is self-administered through monthly subcutaneous injection that may only need an infrequent telephone or email consultation by a specialist headache nurse. This certainly will reduce cost of care to the patient and the hospital/primary care. The side effect profile is better than existing treatment improving compliance, drop-out rates and quality of life.
• Is the technology a 'step-change' in the management of the condition?	Yes. Galcanezumab is a migraine specific preventive treatment. All drugs currently used for migraine prevention were found by chance and were developed for other conditions such as depression, hypertension or epilepsy.
• Does the use of the technology address any particular unmet need of the patient population?	Empowering patients, improving compliance, better side effect profile

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The trials have shown the side effect profile to be similar to placebo.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Patients with episodic and chronic migraine were excluded from the trials if they had failed treatment on 3 or more classes of migraine preventive treatments. Considering potential cost of the new technology the unmet need is for patients that are refractory to first line treatments. In REGAIN study for Chronic Migraine (Phase 3) only 29% had failed two first line treatments in the last 5 years. Conquer study (Mulleners et al, Cephalalgia 2019) showed superiority of Galacanezumab to Placebo in patients previously failed 2-4 preventive medications. The monthly migraine days reduced by 4.1 days in Galcanezumab group compared to 1.0 days in placebo arm.
• If not, how could the results be extrapolated to the UK setting?	Considering high cost of the new technology, patients refractory to first line treatments (at least three) would be more suitable for Galcanezumab.
• What, in your view, are the most important outcomes, and were they measured in the trials?	• Reduction in frequency and severity of headache (50% in episodic and 30% in chronic) • Improvement in quality of life as measured by validated tools like HIT6, MIDAS, EQ5D, MSQ • Percentage of patients with sustained headache response. • Percentage of patients with 75% and 100% response.

	The trials for Galcanezumab (Regain, Evolve 1 & 2) were based on monthly migraine days. We emphasise that response based on the frequency and severity of headache attacks are more meaningful and have major impact on ability to function. The current data is only for three months (chronic migraine) and six months (episodic migraine) and long term follow up is awaited.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	We are not aware of any reports.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real life data and long term follow up on patients receiving Galcanezumab
20. Are you aware of any new evidence for the comparator treatment(s) since the	No NICE guidance exist on this treatment

publication of NICE technology appraisal guidance [TAXXX]	
21. How do data on real-world experience compare with the trial data?	No real world data currently available for Galcanezumab
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is more common in women (22%) compared to men (8%). Women are mostly affected during fertile age of 18-45 when they have responsibility for work and / or childcare.
22b. Consider whether these issues are different from issues with current care and why.	No
Topic-specific questions	

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Galcanezumab is one of the CGRP monoclonal antibodies that is first ever migraine specific preventive treatment.
- The side effect profile of the drug is similar to placebo and much better than currently available treatments.
- The treatment is involves monthly injections that are self-administered and reduce need for hospital visits.
- Novel mode of action
- Better compliance than existing treatment because of better tolerability.

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Evidence Review Group's Report

Galcanezumab for preventing migraine

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Nick Meader and Sofia Dias wrote the clinical effectiveness sections of the report. Peter Murphy and Robert Hodgson wrote the cost effectiveness sections and conducted the ERG economic analyses. Kath Wright wrote the search strategy sections. Sofia Dias took overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Copyright statement

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List of abbreviations

AE	Adverse events
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analysis
CFB	Change from baseline
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence interval
CM	Chronic migraine
CMU	Commercial medicine unit
CS	Company submission
CSR	Clinical study report
CV	Cardiovascular
DSA	Deterministic sensitivity analysis
EM	Episodic migraine
EMA	European Medicines Agency
ERG	Evidence review group
GMB	Galcanezumab
HD	Headache days
HFEM	High frequency episodic migraine
HRQoL	Health related quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
MHD	Migraine headache days
MSQ	Migraine-Specific Quality of Life Questionnaire
NA	Not applicable
NHS	National Health Service
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient access scheme

PFC	Points for clarification
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life-year
RCT	Randomised Controlled Trial
SAE	Serious adverse events
SmPC	Summary of Product Characteristics
SR	Systematic Review
TLR	Targeted literature review

Glossary

'All-comers' population	Patients included in the trial regardless of how many previous preventive treatments received for migraine.
DTT-3 population	Difficult to treat population of patients who have failed ≥ 3 previous preventive treatments for migraine.
Intention-to-treat (ITT)	ITT technically requires all data from randomized patients to be included in the analyses whether they completed the trial or not. The company used a modified definition to include all randomized patients who received at least one dose. In addition, patients are analysed according to the group they were randomized whether they received the treatment or not.
Responders	Patients who experienced a predefined (≥ 30% or ≥ 50%) magnitude of reduction from baseline in migraine headache days.

1 EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's decision problem largely matched the NICE scope. The company is positioning galcanezumab as 4th line therapy for patients who have previously failed at least three preventive treatments. The key population of interest is therefore, patients with episodic or chronic migraine who have had at least 3 prior preventive treatment failures (i.e. the difficult to treat, failed three therapies, [DTT-3] population).

Evidence is presented separately for patients with episodic and chronic migraine. Evidence on patients with high frequency episodic migraine (HFEM, a subgroup of episodic migraine) is also presented. However, the Evidence Review Group (ERG) noted some uncertainties:

- Clinical meaningfulness of the HFEM category: there is debate in the literature regarding whether this a clinically distinct patient subgroup (see section 2.2.1 for further details).
- Combining chronic migraine (CM) and HFEM groups in some analyses: the ERG noted that in some analyses data from both groups were combined. This is inconsistent with the decision problem (see section 2.3). However, the ERG is aware that there is significant debate in the literature regarding the distinctiveness of HFEM in comparison with CM and episodic migraine (EM) (see section 2.2.1 for further detail).
- The natural history of the condition is not included in the economic evaluation. This has potential implications for evaluating long-term treatment benefits (see section 2.2.1 for further detail).

1.2 Summary of the key issues in the clinical effectiveness evidence

The key clinical evidence is based on the results of four randomized controlled trials (RCTs) comparing galcanezumab to placebo. The ERG noted three main limitations with the clinical effectiveness data:

- Only limited available data are available for all outcomes on the DTT-3 population: most company trial data for this population was based on small samples sizes and unplanned subgroup analyses (see section 3.2).
- Evidence on long-term efficacy and treatment effect waning after discontinuation covers only a limited time-period (see sections 2.2.1 and 3.2.1).
- Lack of consistency in data synthesis throughout submission: estimates used in the economic model were not always based on all available relevant data (see section 3.1.4).

- Concerns about generalisability of the DTT-3 patients included: approximately 50% of the participants included in the CONQUER trial had failed at least one treatment not used in the UK including botulinum toxin A, normally only available as 4th line treatment in the National Health Service (NHS, see section 3.2.1).
- Validity of the indirect treatment comparisons (ITC) between galcanezumab and botulinum toxin A is highly uncertain (see sections 3.3 and 3.4 for further discussion).
- Although galcanezumab appears to be well tolerated, safety in pregnancy and for those at risk of cardiovascular events in unknown (see section 3.2.1).

1.3 Summary of the key issues in the cost effectiveness evidence

Model structure

Outcomes used to drive clinical effectiveness

The economic analysis presented by the company adopted an approach based around frequency of migraine headache, which was assumed to drive all differences in both health related quality of life (HRQoL) and costs. While consistent with the previous appraisals of Calcitonin Gene-Related Peptide (CGRP) therapies, the focus on migraine frequency to the exclusion of other trial outcomes, represents a limitation of the present economic analysis (see section 4.2.2).

Long-term treatment efficacy

The economic analysis makes strong assumptions about the durability of the treatment effect extrapolating short-term effects observed over a period of 3 months to a 25-year time horizon. This together with the lack of modelling of the effects of natural history means there is substantial uncertainty regarding the long-term benefits of galcanezumab treatment. The ERG considers that there is significant scope for the benefits of galcanezumab treatment to decline with time, either as a result of acquired resistance to the drug or because of the natural reductions in the severity and frequency of migraine. This is particularly problematic when considered in the context of the modelled assumption of lifetime treatment (see section 4.2.2).

Comparison with botulinum toxin A for chronic migraine

While high quality trial evidence is available to support the comparisons to best supportive care (BSC), the comparison of galcanezumab with botulinum toxin A is drawn from an ITC, with significant concerns regarding the validity of the resulting effect estimates. Therefore, the results of the economic analysis for this comparison should be interpreted with caution and are subject to uncertainty not expressed in the probabilistic analysis (see section 4.2.6).

Treatment sequencing

The economic analysis presented by the company has the significant limitation of only evaluating the cost-effectiveness of specific treatments rather than evaluating alternative treatment sequences. This is an important omission, as the positioning of galcanezumab within the treatment pathway may have important implications for its cost-effectiveness. It is also inconsistent with clinical practice where it is anticipated that galcanezumab would be used as part of a treatment sequence for chronic migraine patients (see sections 2.2.2 and 4.2.4).

Inputs and assumptions

The ERG also identified several issues relating to the inputs and assumption used in the economic analysis. These are outlined in brief below.

Source of utility data

The company base-case uses the utility values from the whole population of the CONQUER trial. This population is broader than the modelled population as it includes patients who have failed fewer than three preventative treatments. It also ignores available HRQoL data from the other pivotal trials. It is the ERG's view that the utility data should align with the modelled population i.e. patients who have failed > 3 preventative treatments and should make maximum use of the available trial data (see section 4.2.7).

Treatment specific utilities

The company's base-case analysis takes the conservative position that utility estimates are the same across treatment groups. This aligns with committee preferences in previous appraisals. However, there is a case for implementing treatment specific utilities. The company presented an analysis showing a strong statistically significant difference in utility values between galcanezumab and placebo. Furthermore, the limitations of the model structure mean there is clinical rationale for such a difference, which would reflect the impact of treatment on migraine severity and the number of non-migraine headache days prevented (see section 4.2.7).

Age related disutility

The utilities used in the company's economic analysis are assumed to remain constant over the 25-year time horizon of the model. There is, however, significant scope for natural history to impact on the underlying severity of headache and migraine, as well as for the effects of aging to impact upon quality-of-life. While the impact of these factors is unknown, it is likely that they will act to moderate the benefits of reducing migraine days reducing the absolute HRQoL benefits of treatment (see section 4.2.7).

Source of effectiveness data

For both response and the mean change in migraine headache days (MHDs), the company does not use all the available trial evidence, instead relying primarily on the CONQUER trial. This creates several inconsistencies such that pooled values are used in some comparisons, but not in others. The ERG does not consider this selective approach appropriate and considers that, where possible, the company should have sought to use all the available data (see sections 3.1.4 and 4.2.6).

Estimation of treatment effect between galcanezumab and botulinum toxin A

Due to limited data on change in monthly MHDs in a responder population, the company adopts a different model structure from the comparison with BSC. This approach, referred to as the combined population approach, uses data from the ITC of MHDs (DTT-3 population) to approximate the difference in MHDs in responders to galcanezumab and botulinum toxin A. The ERG accepts the need for assumptions to be made for this comparison. However, the company's approach relies on assumptions that cannot hold, and which cause the model to make predictions that do not align with the results of the ITC. Importantly, where the response rate is < 100% the company's approach leads the model to predict a difference in MHDs that are lower than that estimated by the ITC, therefore biasing the ICER in favour of botulinum toxin A (see Section 1.1.1.3).

Furthermore, the use of different model structure means that an incremental analysis in which the cost-effectiveness of galcanezumab, BSC and botulinum toxin A are jointly assessed, cannot be conducted (see section 4.2.2).

Duration of waning period

The company model assumes patients discontinuing treatment will wane back to baseline MHDs. The ERG considers the application of a waning period reasonable in principle, but notes that the data used to model this waning is of very short duration and is not from patients who have discontinued due to adverse events. The ERG is also concerned about the plausibility of the predicted waning periods, noting that very different waning periods are applied in the EM and CM populations. The waning period for galcanezumab is also modelled as being considerably longer than that applied for BSC and botulinum toxin A, without any evidence to justify this assumption (see Section 4.2.6).

Waning of treatment effect in responders to BSC

The company's economic analysis assumes that responses to placebo will not be durable. As such, responders to BSC are assumed to wane back to baseline MHDs. The ERG considers it plausible that responses to placebo will be durable, representing factor such as regression to the mean, natural history and response to tertiary treatment that constitute BSC. Further, the ERG considers the unilateral application of waning unfair, as placebo effects will also be part of the observed response to

galcanezumab. The application of waning also means that the modelled benefit of treatment is, in effect, larger than the one observed in the trial (see Section 4.2.6).

Administration costs for galcanezumab

The company's economic analysis assumes all patients will be able to self-administer galcanezumab and as such, no administration costs are included after the first cycle. A proportion of patients may, however, not be able to self-administer due to comorbid physical or mental disabilities. In line with this, the ERG also notes previous committee preference for administration costs to be included for 10% of patients (see Section 4.2.8).

Resource use consumption rates

In contrast to the recent appraisals of erenumab and fremanezumab the company base-case uses a US survey of resource consumption rates to populate the model. The ERG preference is to use the same source as used in previous appraisals which is also more likely to reflect resource use in the NHS (see Section 4.2.8).

1.4 Summary of exploratory and sensitivity analyses undertaken by the ERG

The scenario analysis run by the ERG are summarised in Table 1.

Table 1 Summary of ERG scenario analysis

Scenario 1	Addition of administration cost in 10% of patients
Scenario 2	Resource consumptions rates revised to align with those used in previous appraisals of CGRP's.
Scenario 3	EVOLVE 1, EVOLVE 2, REGAIN and CONQUER used as the source of utility data (DDT3 population only)
Scenario 4	Differential utilities applied for active therapies relative to BSC.
Scenario 5	Age related disutilies applied.
Scenario 6	Waning period in the chronic migraine population set to 13 months, consistent with the episodic populations.
Scenario 7	Waning period for botulinum toxin A set equal to galcanezumab.
Scenario 8	All waning removed – patients revert to baseline after 1 cycle.
Scenario 9	BSC responders assumed to retain response for duration of model time horizon.
Scenario 10a	Patients discontinuing treatment assumed to wane back from responder MHDs
Scenario 10b	10 a, but also assuming rates of discontinuation are common across active treatments.
Scenario 11a	Galcanezumab and botulinum toxin A assumed equally effective.*
Scenario 11b	Response rate modelled using ITC, responder MHD assumed equal.*
Scenario 11c	Response rate assumed equal, responder MHDs estimated from ITC.*
Scenario 11d	11c and 11d combined.

*Response model structure used for both BSC and botulinum toxin A.

Results of the ERG's scenario analysis are presented in Table 2 for the episodic population. Results for chronic population are presented in Table 3 and Table 4. These results are presented inclusive of the patient access scheme (PAS) available for galcaneuzmab, but exclude the commercial medicine unit (CMU) discount for botulinum toxin A. Results including the CMU discount are presented in a confidential Appendix.

Table 2 Exploratory ERG analyses (episodic migraine)

Analysis	Discounted costs		Discounted QALYs		ICER	Change from company base case ICER
	Galcanezumab	BSC	Galcanezumab	BSC		
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	£29,230	-
ERG correction of model errors	[redacted]	[redacted]	[redacted]	[redacted]	£29,313	£83
1) Galcanezumab administration cost for 10% of patients	[redacted]	[redacted]	[redacted]	[redacted]	£29,563	£334
2) Alternative resource consumption rates	[redacted]	[redacted]	[redacted]	[redacted]	£36,049	£6,820
3) Alternative source used to generate HRQoL	[redacted]	[redacted]	[redacted]	[redacted]	£37,149	£7,919
4) Differential utilities for galcanezumab and comparator	[redacted]	[redacted]	[redacted]	[redacted]	£13,232	-£15,998
5) Age-related disutility	[redacted]	[redacted]	[redacted]	[redacted]	£30,247	£1,017
8) Removal of treatment waning	[redacted]	[redacted]	[redacted]	[redacted]	£29,976	£747
9) Dissipation of placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	£36,918	£7,689

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

Table 3 Exploratory ERG analyses - Chronic migraine pairwise analyses (separate models for comparison to BSC and botulinum toxin)

Analysis	Comparator	Discounted Costs		Discounted QALYs		Pairwise	
		Galcanezumab	Comparator	Galcanezumab	Comparator	ICER	Change from company base case
Company base case	**BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£8,080**	-
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	**£2,560**	-
ERG correction of model errors	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,053	-£27
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£4,203	£1,643

1) Galcanezumab administration cost for 10% of patients	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,243	£163
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,255	£694
2) Alternative resource consumption rates	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,892	£6,813
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£9,534	£6,974
3) Alternative source used to generate HRQoL	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,269	£2,189
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,254	£694
4) Differential utilities for galcanezumab and comparator	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£4,456	-£3,624
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£1,185	-£1,375
5) Age-related disutility	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,347	£268
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£2,622	£61
6) Consistent waning period between episodic and chronic migraine populations	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£9,602	£1,522
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£25,168	£22,608
7) Consistent waning period between galcanezumab and botulinum toxin A	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£5,464	£2,904
8) Removal of treatment waning	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,068	£1,988
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£42,566	£40,006
9) Dissipation of placebo effect	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,239	£2,160
	Botulinum toxin A	n/a	n/a	n/a	n/a	n/a	n/a
10a) Alternative MHDs for patients discontinuing galcanezumab (vs. Botulinum toxin type A)	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£27,615	£25,054
	BSC	n/a	n/a	n/a	n/a	n/a	n/a

10b) Equivalent long-term discontinuation rate for galcanezumab and botulinum toxin (0.44%)	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£11,742	£9,181

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

Table 4 Exploratory ERG analysis - Scenario 11 (chronic migraine)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
11a) Equal effectiveness (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,281
11b) Response rate differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,167
11c) CFB in MHD differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,454
11d) 11b and 11c combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,734

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

1.5 Summary of ERG's preferred assumptions and resulting ICER

The ERG's base case for the episodic population included scenarios 1,2, 3, 4, 5 and 9. Additional scenario analysis was also conducted on the ERG's base case incorporating natural history effects. Results are presented in Table 5. These results are presented inclusive of the PAS available for galcaneuzmab, but exclude the CMU discount for botulinum toxin A. Results including the CMU discount are presented in a confidential Appendix.

Table 5 ERG Base-case and exploratory analysis (Episodic population)

Analysis	Discounted costs		Discounted QALYs		ICER
	Galcanezumab	BSC	Galcanezumab	BSC	
ERG base case (1, 2, 3, 4, 5, 9)	[redacted]	[redacted]	[redacted]	[redacted]	£28,014
Base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	£66,583

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year
Note: Results based on probabilistic analysis

The ERG's base case in the chronic population included scenarios (1, 2, 3, 4, 5, 6, 7, 10a, 10b, and 11d. Additional scenario analysis was conducted exploring:

- Alternative assumptions regarding the relative treatment effect between galcanezumab and botulinum toxin A.
- The effects of natural history.

Results of these analyses are presented in Table 6. As above these results only include the PAS discount for galcanezumab not the CMU discount for botulinum toxin A.

Table 6 ERG Base-case and exploratory analysis (Chronic population)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
ERG base case 4 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,830
ERG exploratory analysis							
ERG base case 1 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11a)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£190,641
ERG base case 2 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,840
ERG base case 3 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11c)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,539
ERG preferred base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,721

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year
Note: Note: Results based on probabilistic analysis

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

2.2 Background

The company proposes galcanezumab (GMB) as fourth-line therapy for patients with episodic and chronic migraine, after failure of three other preventive therapies, which is appropriate and in line with ERG's clinical advice. However, for patients with chronic migraine who have failed on three previous preventive treatments, botulinum toxin A is an option, so it is possible that some patients might receive GMB as a fifth-line treatment, having previously failed on botulinum toxin A. This option is not considered in the company's submission (CS).

2.2.1 Disease Background

The description of the underlying health problem in the company's submission was appropriate and relevant to the decision problem.

The company focused the disease overview appropriately on the impact of migraine headaches. However, our clinical advisor pointed out that migraine patients often experience headaches that do not meet criteria for migraine which additionally impacts on their quality of life.

The CS rightly distinguishes between patients with episodic (<15 headache days per month) or chronic migraine (≥ 15 headache days with ≥ 8 migraine headache days) as distinct clinical populations based on standard clinical criteria. The CS does not mention the group of patients with ≥ 15 headache days but < 8 migraine headache days. However, the ERG's clinical advisor suggested these patients would usually be treated as CM patients in common clinical practice.

There is debate in the clinical community about the company's claim that HFEM represents a distinct subgroup of patients. Advice from two Consultant Neurologists specialising in migraine treatment, suggested these patients were a neglected and important clinical subgroup. However, it should also be noted that previous appraisals[1, 2] have judged that HFEM was not a clinically meaningful category. This uncertainty was reflected in the clinical advice received by the ERG. One of our clinical advisors considered little difference between HFEM and CM patients in terms of quality of life impact and disease burden, while another suggested that HFEM and CM patients were clinically distinct.

The CS correctly states that migraine is associated with a number of social and demographic variables (such as age, gender etc.). For example, prevalence of migraine is highest between ages 25-55 years before declining in middle age. Prevalence of migraine is higher in women than in men (28% vs 15%) and women are more likely to experience longer duration and greater intensity of migraines, with the exception of during pregnancy and after menopause when migraine attacks are less common.[3] However, there was limited discussion of stability of migraine symptoms over time. The CS estimates 2-3% of EM patients go on to meet criteria for chronic migraine annually, although this 'migraine chronification' may partly be accounted for by measurement error.[4]

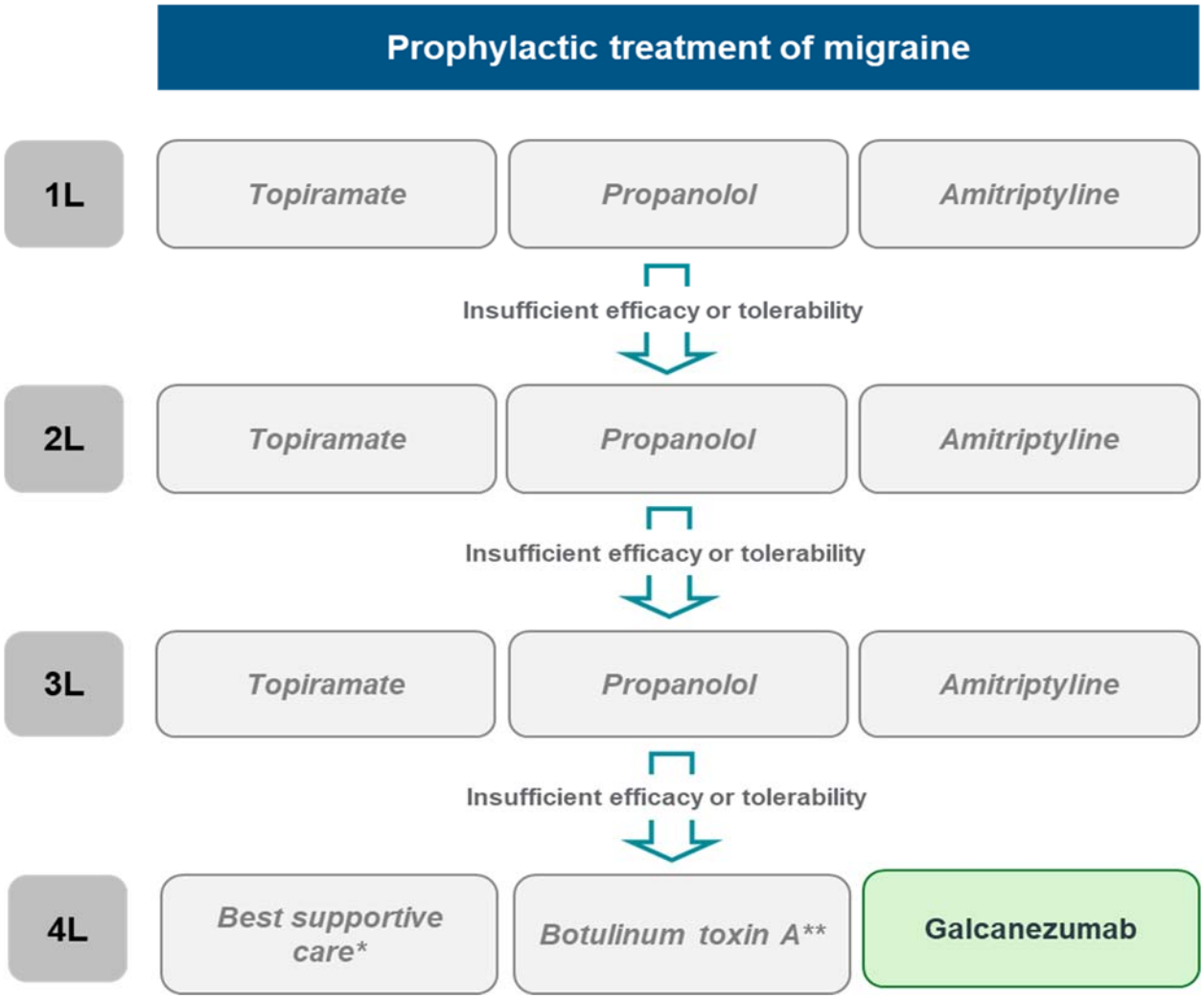
The CS did not completely capture the relapsing and remitting nature of migraine over time in the background. For example, a 30-year Swiss prospective study[5] found that most patients continued to experience migraine symptoms over the course of the study (86.7% of migraine with aura patients, 75.6% of migraine without aura patients). However, most did not experience migraines continually, only 20% of patients reported migraines for more than half of the follow up period with symptoms remitting and returning over time. On average, migraine with aura patients reported 27.4 migraine MHDs per year and migraine without aura patients reported 33.7 MHDs per year.[5]

Although available evidence on the natural history of chronic and episodic migraine is sparse, these data have implications for assumptions made about long-term efficacy and potential discontinuation.

2.2.2 The technology and the company's anticipated positioning of galcanezumab

Figure 1 summarizes the clinical care pathway for the prophylaxis of migraine (reproduced from Figure 2 in the CS).

Figure 1 The Company's anticipated positioning of galcanezumab (reproduced from CS, Figure 2)



*includes acute treatments such as triptans, analgesics and antiemetics **licensed for the treatment of chronic migraine only

The CS correctly stated that NICE guidance recommends topiramate, propranolol, and amitriptyline as first-, second-, and third-line preventive options. Sequencing is based on patient preference, comorbidities and risk of adverse events. For patients with CM who have failed ≥ 3 oral treatments, botulinum toxin A is recommended as a fourth-line treatment. Since the company submission, fremanezumab has also been recommended by NICE as a fourth-line treatment. Galcanezumab is positioned by the company as an additional fourth-line option. Our clinical advisors agreed this was appropriate. However, they noted that there is a potentially large prevalent population of CM patients who have already received botulinum toxin A as a failed preventive treatment. Therefore, GMB would represent a fifth-line option for these patients. In addition, the clinical advisors suggested there are potentially a range of other sequences that clinicians may consider for prescribing galcanezumab,

botulinum toxin A, and fremanezumab based on availability, service capacity and costs, and individual preference.

For patients with EM, botulinum toxin A and fremanezumab have not been recommended. Therefore, if recommended, GMB would be the only fourth line treatment option for this patient group.

2.3 Critique of company's definition of decision problem

Table 7 Summary of company's decision problem (adapted from CS, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with migraine	Adults with migraine who have ≥4 migraine headache days (MHDs) per month, who have a history of ≥3 prior preventive treatment failures. Two populations considered: • Patients with chronic migraine (≥15 headache days per 30-day period, of which ≥8 are MHDs) • Patients with episodic migraine (4-14 MHDs and <15 headache days per 30-day period)	The population is aligned to the marketing authorisation granted to galcanezumab in the UK, which restricts its use as prophylaxis of migraine in adults who have at least 4 MHDs per month. In addition, current clinical practice within the NHS, and feedback from clinicians suggests that galcanezumab is most suitable for use in patients who have a history of ≥3 prior preventive treatment failures.	The clinical evidence submitted largely matches the patient population. However, clinical parameters are used in the economic model which are informed by data on patient populations falling outside of the described populations. The ERG also notes analyses are conducted in which HFEM and chronic migraine are combined. This is a deviation from the two distinct patient populations outlined in the scope.
Intervention	Galcanezumab	Galcanezumab	NA	NA
Comparator(s)	Oral preventive treatments;	The following comparators are considered:	Comparators selected were based on final appraisal	Based on clinical advice and given the proposed positioning,

	botulinum toxin A; erenumab (subject to ongoing NICE appraisal); fremanezumab (subject to ongoing NICE appraisal); and best supportive care (BSC)	• Episodic migraine: BSC (represented by placebo) • Chronic migraine: BSC (placebo) and botulinum toxin A.	document of erenumab for preventing migraine.[6] Most people with migraine who have a history of ≥3 prior preventive treatment failures would either use botulinum toxin A or BSC. Clinical trials compared galcanezumab to placebo (used to represent BSC in CS) At the time of submission, erenumab and fremanezumab were not recommended as preventive treatment by NICE. As a result, they are not relevant comparators within the scope of this appraisal.	the ERG is satisfied with the selected comparators and the reason for the exclusion of fremanezumab and erenumab from any analyses.
Outcomes	The outcome measures to be considered include: • frequency of headache days per month • frequency of migraine days per month	The outcome measures to be considered include: • frequency of headache days per month	The outcome measures to be considered include: • frequency of headache days per month • frequency of migraine days per month	The outcomes considered in the clinical evidence submission are: • Improvement in MHDs • Improvement in HDs

	• severity of headaches and migraines • number of cumulative hours of headache or migraine on headache or migraine days • reduction in acute pharmacological medication • adverse effects of treatment • health-related quality of life	- overall mean change from baseline in mean monthly headache days • frequency of MHDs per month - overall mean change from baseline in mean monthly MHDs - percentage of patients with episodic migraine with ≥50% reduction from baseline in mean monthly MHDs - percentage of patients with chronic migraine with ≥30% reduction from baseline in mean monthly MHDs • number of cumulative hours of headache or migraine on headache or migraine headache days - Overall mean change from baseline in number of monthly migraine headache hours	• severity of headaches and migraines • number of cumulative hours of headache or migraine on headache or migraine days • reduction in acute pharmacological medication • adverse effects of treatment • health-related quality of life	• Response to treatment • Adverse events • Health related quality of life (captured by MSQ) • Acute medication use The economic model limits the outcomes considered to change in monthly MHD rather than both MHDs and HDs. The economic model does not consider adverse events, rather it captures discontinuation. The ERG notes that the severity of MHDs and HDs is not captured in the economic model.

		• reduction in acute pharmacological medication - Overall mean change from baseline in the number of monthly migraine headache days with acute headache medication use • Analysis of treatment-emergent adverse events • health-related quality of life Changes from baseline to month 3 in: • MSQ v2.1 total score, Role Function-Restrictive, Role Function-Preventive and Emotional Function domain scores • EQ-5D-5L		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	As per scope	NA	NA

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.			
Subgroups	If the evidence allows, subgroups considered: • People with chronic or episodic migraine • Number of previous preventive treatments • Frequency of episodic migraine.	The following subgroups are considered in the CS: • People with HFEM who suffer 8 -14 MHDs per month (with <15 headache days in a 30-day period) • Pooled analysis of people with HFEM and chronic migraine, to allow review of patients in whom chronic migraine is defined as ≥8 MHDs per month	The base case analysis has been presented separately for patients with chronic and episodic migraine in patients who have a history of ≥3 prior preventive treatment failures. The company consider the subgroup of patients experiencing ≥8 MHDs per month (i.e. chronic and HFEM) to be a clinically meaningful subgroup.	The ERG understands the rationale for combining chronic and HFEM patients, however this is inconsistent with previous migraine appraisals.

Special considerations including issues related to equity or equality	None	None	NA	NA

Abbreviations: BSC, best supportive care; EQ-5D-5L : 5 level EuroQol 5 dimensions 5 level; HFEM: high-frequency episodic migraine; MHD, migraine headache days; MSQ-v2.1, Migraine-Specific Quality of Life Questionnaire Version 2.1; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS: Personal Social Services.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The CS included a systematic review (SR) of GMB and relevant comparators. Overall, there were no concerns with searches. However, the ERG noted limitations with the inclusion criteria. Trials that did not report separate data for patients who had failed previous preventive medications were excluded. This limited the comprehensiveness of the analyses conducted by the company on an 'all-comers' population (i.e. data from patients included in analyses regardless of how many previous failed preventive treatments). In addition, evidence synthesis methods sometimes lacked consistency and comprehensiveness in application. For example, in some analyses only data from CONQUER were used when similar data were available from other company trials (see section 3.1.4 for further details).

3.1.1 Searches

Table 8 summarises the ERG's comments on the company's search strategy for clinical effectiveness literature.

Table 8 ERG appraisal of evidence identification for the effectiveness review

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	Yes	1. Originally there was no PRISMA flow chart. This was submitted after the Points for Clarification stage 2. The original submission referred to SR1/SR2/SR3/SR4. After Points for Clarification it was clear that this was one SR updated on 3 occasions
Were appropriate sources searched?	Yes	The search used: 1. bibliographic databases (MEDLINE, Embase, Cochrane CDSR, Cochrane CENTRAL) 2. Trial Registers (ClinicalTrials.gov) 3. Conference Proceedings (as listed) 4. HTA repositories (as listed)
Was the timespan of the searches appropriate?	Yes	1. The original search was conducted in 2017 and covered from database inception to December 2017.

		2. Three subsequent updates covered Dec 2017 -Oct 2018/Oct 2018 - Aug 2019/Aug 2019 - Oct 2019
Were appropriate parts of the PICOS included in the search strategies?	Yes	The search strategies combine terms for migraine (P) with terms for Galcanezumab and comparators (I) and terms for RCTs (S)
Were appropriate search terms used?	Yes	1. The full search strategies are provided for each of the databases. 2. In line with best practice, these combine thesaurus terms with free text terms and drug registry numbers
Were any search restrictions applied appropriate?	NA	
Were any search filters used validated and referenced?	Yes	1. RCT search filters are applied in both the MEDLINE and Embase searches 2. The filter used in the MEDLINE search is the Cochrane Highly Sensitive Search filter 3. The filter used in the Embase search is referred to as being the Cochrane RCT filter. 4. The Cochrane RCT filter was only published in 2019 and is not the same as the one being used here

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE (NA)
ERG, evidence review group; RCT, randomised controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HTA, health technology assessment.

3.1.2 Inclusion criteria

Full details of inclusion criteria are provided in Table 8, Appendix D of the CS. Phase II, III, and IV randomised controlled trials (RCTs) examining the safety and effectiveness of either GMB or botulinum toxin A were eligible for inclusion in the systematic review. These criteria were appropriate and reflected the decision problem.

Trials that did not include separate data for patients who had failed previous preventive medications were excluded. These criteria limit the comprehensiveness of the 'all comers' (includes all patients regardless of how many previous failed medications) ITC analyses (see CS section B.2.8.2.1.1). The ERG identified a Cochrane review that included a number of additional potentially relevant studies to inform the 'all comers' ITC (see points for clarification [PFC] question A15 for further details). The company responded that the 'all comers' analyses were not central to the submission and therefore they chose not to include these studies. However, the ERG notes that results from the ITC on the 'all-comers' population are presented in the CS and they have been used to inform parameters in the ERG's economic model and ERG base case (see section 1.1.1.2).

3.1.3 Quality assessment

Included studies were critically appraised using the Cochrane risk of bias tool (v1). The judgements from these assessments were summarised in Appendix D of the CS: Table 12 (for trials included in the ITC), Table 13 (trials in EM patients), Table 14 (trials in CM patients), Table 15 (trials in mixed EM and CM patient populations), Table 16 (trials in unspecified migraine populations). The key trials that informed the submission were mainly judged to be at low risk of bias. The company's REGAIN trial was judged low risk of bias for all components of the risk of bias tool. Appendix D originally judged the company's CONQUER trial to be at an unclear risk of bias. But in response to PFC question A9, the company clarified these judgements were based on publicly available material. When taking into account data reported in the company submission, they judged the trial to be at low risk of bias. Risk of bias assessments were not reported for EVOLVE-1 or EVOLVE-2.

The two included trials on botulinum toxin A (PREEMPT-1 and PREEMPT-2) were judged to be at low risk of bias or most categories, but judged to be at high risk of outcome reporting bias, since limited baseline characteristics were available for patients with ≥ 3 previous failed preventive treatments. This judgement was based on a report by the Canadian Agency for Drugs and Technologies in Health (CADTH)[7] that conducted subgroup analyses in this population.

However, since these subgroup analyses were conducted by a national technology assessment centre, the ERG considered it unlikely the lack of available data was due to outcome reporting bias. However, the ERG agrees that the lack of information on baseline characteristics for this subgroup is an important source of uncertainty (see section 1.1.1.1 for further discussion).

3.1.4 Evidence synthesis

The CS focused on a subgroup of patients with ≥ 3 prior preventive medications included in the company trials: CONQUER, REGAIN, EVOLVE-1 and EVOLVE-2. However, the CS also summarised data not specific to patients who had failed ≥ 3 prior preventive medications from

CONQUER on the effectiveness of GMB compared with placebo. These data were reported in combined CM and EM populations; as well as separately for CM, HFEM, and EM patients. These trial data are summarised in more detail in section 3.2.

The company pooled baseline monthly MHDs for CM patients using both arms of the CONQUER study (GMB and Placebo) to inform the economic model (see Sections 1.1.1.3 and 1.1.1.1). However, the company did not use similar available data from REGAIN which would likely have increased precision of these estimates.

Data on patient counts from REGAIN and CONQUER were naively pooled to inform the 50% response rate (i.e. ≥ 50% reduction in baseline monthly MHDs) for patients who had failed ≥ 3 prior preventive medications in the economic model (see section 1.1.1.2). This was done by adding the number of responders and the number of included patients in the trial arms and calculating proportions. However, these data could have been formally meta-analysed on an appropriate scale (e.g. log-odds) resulting in more valid estimates with a more appropriate characterisation of the underlying uncertainty.

The baseline monthly MHD for EM was pooled from both arms of the CONQUER study (GMB and Placebo) to inform the economic model (see section 4.2.3). However, data from EVOLVE-1 and EVOLVE-2 were available but were not pooled with the baseline data from CONQUER which would have increased precision of the estimate.

Indirect treatment comparison analyses were also conducted comparing the effectiveness of GMB with botulinum toxin A. These analyses are discussed in more detail in sections 3.3 and 3.4.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The following sections summarise and critique the company trial data. The main concerns identified by the ERG were the limited available data on all outcomes for the key DTT-3 population (i.e. patients with ≥ 3 prior preventive treatment failures), and generalisability of the trial data to the NHS. For example, [redacted] of DTT-3 patients in CONQUER had failed on treatments not routinely used in the UK. The European Medicines Agency (EMA) identified some uncertainties in the safety of GMB for pregnant women and patients with cardiovascular risks which should be taken into account.

3.2.1 Relevant trials – CONQUER, REGAIN, EVOLVE-1, EVOLVE-2, CGAJ

The key clinical evidence in the CS is based on subgroup analyses of patients with ≥ 3 prior preventive treatment failures in four randomized controlled trials (RCTs). All subgroup analyses were unplanned, with the exception of data from CONQUER. Trials are summarized in Table 9.

The CS presented data from CONQUER showing that GMB was more effective than placebo in the joint (CM and EM) population. Subgroup analyses that considered CM and EM patients separately found that GMB was more effective than placebo in both populations.

Table 9 Summary of efficacy and safety trials CONQUER, REGAIN, EVOLVE-1, EVOLVE-2 (based on CS, Table 5)

Study	CONQUER	REGAIN	EVOLVE-1	EVOLVE-2	CGAJ
Study design	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 3 months + 3 months open-label treatment	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 3 months + 9 months open-label treatment + 4 months post-treatment follow up	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 6 months + 4 months post-treatment follow up	Phase III, randomised, multicentre, double blind, placebo-controlled. double blinded treatment + 6 months + 4 months post-treatment follow up	Phase III, multicentre, randomised open-label study 12 months open-label treatments and 4 months post-treatment follow-up
Population	ICHD-3 criteria for a diagnosis of migraine with or without aura or chronic migraine, and **who have previously failed 2 to 4 standard-of-care treatments** (categories) for migraine prevention	ICHD-3 beta criteria for chronic migraine	Episodic migraine, ICHD-3 criteria 1.1 or 1.2	Episodic migraine, ICHD-3 criteria 1.1 or 1.2	Episodic or chronic migraine ICHD-3 criteria (1.1, 1.2, or 1.3)
Intervention(s)	Galcanezumab (120 mg/month) with Galcanezumab 240 mg loading dose	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month	Galcanezumab (120 mg/ month) with Galcanezumab 240 mg loading dose Galcanezumab 240 mg/month
Comparator(s)	Placebo for 3 months	Placebo for 3 months	Placebo for 6 months	Placebo for 6 months	-

Study	CONQUER	REGAIN	EVOLVE-1	EVOLVE-2	CGAJ
Outcomes assessed in trial and relevant to decision problem	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline Proportion of patients with chronic migraine with ≥30% reduction in mean monthly MHDs from baseline	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** NA	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline	**Primary outcome:** Overall mean change from baseline in monthly MHDs **Other outcomes informing cost-effectiveness model:** Proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline	Outcomes do not inform the economic model

MHD=migraine headache days, ICHD=International Classification of Headache Disorders, NA=not applicable

ERG comments on design and generalisability

The ERG noted that subgroups of patients who had failed ≥ 3 prior preventive medications were the appropriate population to address questions on the efficacy of GMB, given the company's positioning. The outcomes were also judged to be relevant and appropriate. Unfortunately, the length of the placebo-controlled period in all trials was limited to either three (CONQUER, REGAIN) or six (EVOLVE-1 and EVOLVE-2) months. Therefore, it is challenging to judge the long-term effectiveness of GMB compared with placebo or best supportive care, as the company assumes patients will experience these benefits over a 25-year period (CS section B.3.3.2.4). Similar uncertainties in long-term effectiveness have been raised for similar treatments in earlier appraisals (see section 4.2.2 for further discussion)[1]

The ERG identified a few factors that may impact on generalisability of the GMB trial populations to the NHS context. First, for some patients, the prior preventive medication failures were for treatments not routinely used in the UK. This was particularly the case for patients with ≥ 3 prior preventive medication failures. In this subgroup of the CONQUER trial, [redacted] in the placebo group and [redacted] in the GMB group had failed on medication not used in the UK (see Table 8, company response to ERG PFC letter). Information about the most common preventive medications in the CONQUER trial not routinely used in the UK was only provided for the combined EM and CM study populations. The company's response to question A4 of the ERG's PFC letter indicated that, in the CONQUER trial, the most common medication failures not available in the UK were for valproate ([redacted]), flunarizine ([redacted]) and medications locally approved ([redacted]

[redacted]). Similar data were not provided for other trials conducted by the company.

Second, patients could have received botulinum toxin A prior to galcanezumab as one of their earlier treatment failures ([redacted] in the CONQUER trial, company response to question A4 of the PFC), which does not reflect the company's positioning of GMB and may also not reflect standard clinical practice in the UK should GMB be approved.

Primary and key secondary outcomes

Table 10 summarises clinical effectiveness for the subgroup of patients with 3-4 preventive medication failures from CONQUER, REGAIN, EVOLVE-1, and EVOLVE-2 considered by the company to be the most clinically relevant population to inform clinical and cost-effectiveness of GMB.

Table 10 Clinical effectiveness of galcanezumab versus placebo for key outcomes in patients with ≥ 3 prior preventive medication failures (based on CS Tables 27, 28, 30, 31, 33, 34 and 35)

Study	Outcome	CM: Effect (95% CI)	EM: Effect (95% CI)	HFEM: Effect (95% CI)
CONQUER	**Change from baseline in mean migraine headache days**	[redacted]	[redacted]	[redacted]
	Change from baseline in mean headache days	[redacted]	[redacted]	[redacted]
	≥ 50% reduction from baseline in migraine headache days	[redacted]	[redacted]	[redacted]
	≥ 30% reduction from baseline in migraine headache days	[redacted]	-	[redacted]
REGAIN	**Change from baseline mean migraine headache days**	[redacted]	-	-
	Change from baseline mean headache days	-	-	-
	≥ 50% reduction from baseline in migraine headache days	[redacted]	-	-
	≥ 30% reduction from baseline in	-	-	-

Study	Outcome	CM: Effect (95% CI)	EM: Effect (95% CI)	HFEM: Effect (95% CI)
	migraine headache days			
EVOLVE 1 and 2 pooled	**Change from baseline mean migraine headache days**	-	-	-
	Change from baseline mean headache days	-	-	-
	≥ 50% reduction from baseline in migraine headache days	-	[redacted]	-
	≥ 30% reduction from baseline in migraine headache days	-	-	-

GMB 120mg was associated with a greater mean change in monthly MHD compared with placebo for all patient subgroups. Chronic migraine patients experienced approximately [redacted] extra migraine free days compared with placebo (CONQUER: [redacted]; REGAIN: [redacted]) than for episodic migraine (CONQUER: [redacted]) or high frequency episodic migraine patients (CONQUER: [redacted]).

A similar pattern was found with mean headache days (HDs). There was a reduction in monthly HDs for all patient groups compared with placebo and [redacted].

In the CONQUER trial, the proportion of GMB patients with ≥ 50% reduction from baseline in MHDs days (CS, Table 28) were similar for CM ([redacted]), EM ([redacted]), and HFEM ([redacted]) patients. REGAIN, which included only CM patients, found lower response rates for GMB ([redacted]) than in CONQUER. Differences with placebo were [redacted] for CM (CONQUER: [redacted]) than EM (CONQUER: [redacted]) and HFEM (CONQUER: [redacted]) patients largely due to the [redacted] placebo response rates in the latter subgroups.

The proportion of GMB patients with ≥ 30% reduction from baseline in MHDs was available only for CM patients in CONQUER. As above, GMB patients ([redacted]) were [redacted] likely to respond than placebo ([redacted]) ([redacted]).

Excluding prior botulinum toxin A failures

As noted above, NHS patients would be unlikely to receive botulinum toxin A as one of their ≥ 3 prior preventive medication failures at the point of eligibility for GMB. Table 6 of the Company's response to PFC reported data that excluded these patients from the analyses. However, these data are limited because the Company did not report separate estimates for CM, EM and HFEM patients.

The difference in mean change in monthly MHDs was slightly [redacted] when excluding patients with prior botulinum toxin A failure ([redacted]) compared with all patients with ≥ 3 prior preventive medication failure ([redacted]). The odds ratios for achieving 30% and 50% response (ie reduction from baseline in monthly MHDs at month 3) were [redacted] when excluding patients with prior botulinum toxin A failure (OR=[redacted] and OR=[redacted], respectively) compared with all patients with ≥ 3 prior preventive medication failure ([redacted] and [redacted]).

Quality of life

Table 11 shows all patient subgroups receiving GMB experienced improvements in quality of life compared with placebo. All differences were [redacted], except for Migraine Specific Quality of Life Questionnaire (MSQ) role restrictive subscale in HFEM patients. Mean differences with placebo met criteria for minimally important differences[8] (3.2 points on role-restrictive function and 7.5 points on emotional function for group differences) in all patient groups and therefore were likely to be clinically meaningful.

For EM and HFEM patients, CIs for differences in quality of life measures were wide, with lower bounds close to zero. Estimates for CM patients were more precise with lower and upper CIs suggesting a clinically meaningful effect.

Table 11 Mean difference in health related quality of life mean change from baseline difference: GMB versus placebo in patients with ≥ 3 prior preventive medication failures (based on CS Tables 29, 32, 34)

Study	Outcome	Chronic migraine	Episodic Migraine	High frequency episodic migraine
CONQUER	MSQ total	[redacted]	[redacted]	[redacted]
	MSQ role function-restrictive	[redacted]	[redacted]	[redacted]
	MSQ role function-emotional	[redacted]	[redacted]	-
REGAIN	MSQ total	-	-	-
	MSQ role function-restrictive	[redacted]	-	-

	MSQ role function-emotional	-	-	-

CI: confidence interval; MSQ: Migraine Specific Quality of Life Questionnaire

Discontinuation

Discontinuation was low in all the company conducted trials. For example, in the 3-month double blind phase of CONQUER, [redacted] of patients discontinued for any reason in the GMB group and [redacted] in the placebo group (CS, Figure 4). Only [redacted] discontinued due to adverse events in the GBM group and [redacted] discontinued in the placebo group (CS, Figure 4).

Longer term evidence of discontinuation for GMB is provided in CGAJ (12 month open label study), the open-label phase of CONQUER (data up to 6 months), and the open-label phase of REGAIN (data up to 12 months). Discontinuation due to adverse events was [redacted] in REGAIN [redacted] clinical study report [CSR] CGAI section 12.2.1.2), followed by CONQUER ([redacted] CS section B.3.2.2.6.3) and CGAJ ([redacted] CS section B.3.2.2.6.3).

Four month washout periods were used to assess the impact of discontinuation from GMB in four trials (REGAIN, CGAJ, EVOLVE-1, EVOLVE-2).

For CM patients, the REGAIN trial found that at month 16 of the post-treatment (washout) period, patients had experienced a waning in reduction from baseline of [redacted] monthly MHD compared with month 12 after treatment discontinuation [redacted] compared to [redacted], Table 52, Company response to PFCs and Figure 2 below); that is, patients' improvement reduced by [redacted] over the four month period.

The ERG notes that the company's extrapolation of these waning treatment effects in the economic model is highly uncertain. The company extrapolated from this four-month post-treatment (washout) period to assume monthly change in MHDs for patients who had responded to GMB would continue to wane at the same rate back to baseline frequency of monthly MHDs over a period of [redacted] months after discontinuation of treatment (see section 4.2.6 for further details). However, Figure 2 does not support the assumption of a linear waning effect even within the four-month post-treatment (washout) period. It is possible that the waning effect has a complex, unknown, form beyond the observation period and that larger reductions in effectiveness may have occurred after the 4-month washout period of REGAIN. The implications of these assumptions to the economic model are discussed in more detail in section 4.2.6.

Although study CGAJ also included CM patients, the ERG were unable to find similar data reported for this study. Appropriate pooling of wash out data from REGAIN and CGAJ, taking into account

the non-linear nature of the waning effect after discontinuation, may have provided more plausible estimates. It would have also enabled an assessment of heterogeneity of waning effects across trials.

Figure 2 Washout data – REGAIN (reproduced from CS, Figure 17)

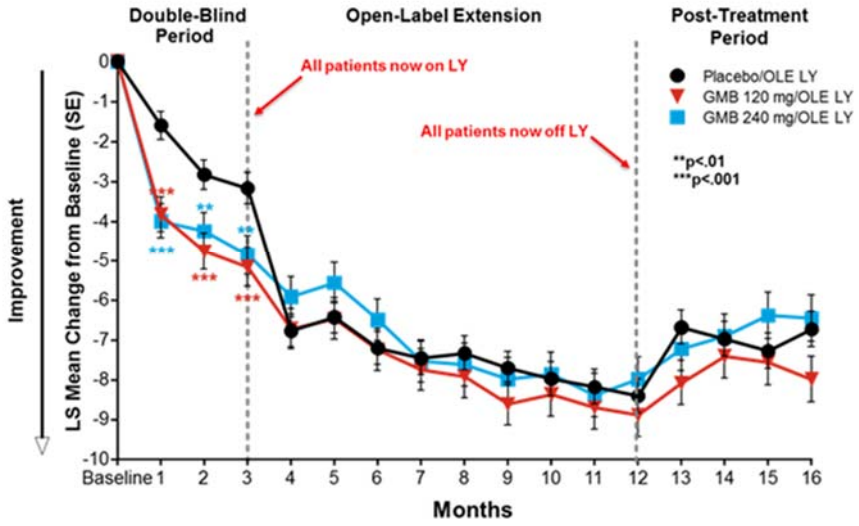
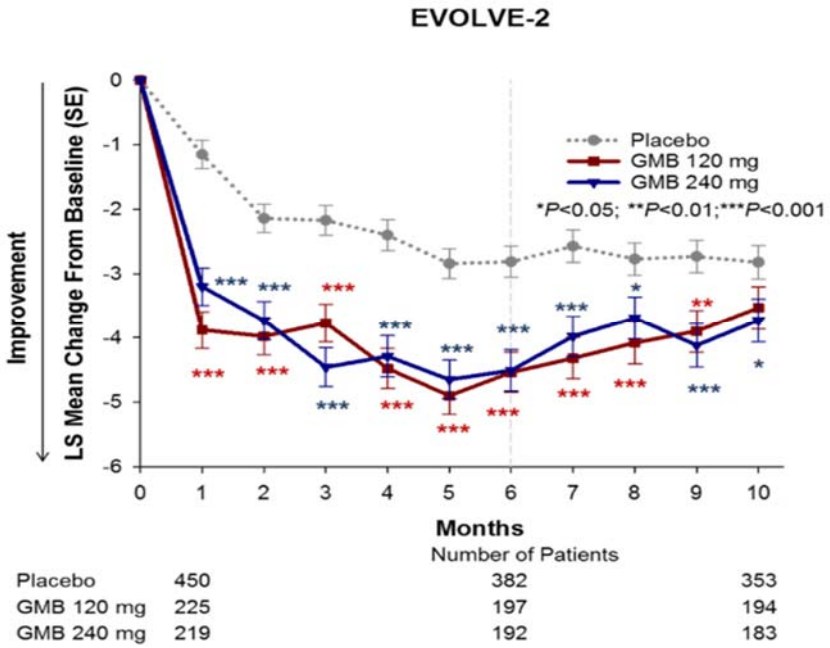


Figure 3 illustrates the quadratic function fitted to the waning data from EVOLVE-2 for MHDs in EM patients. This is a more sophisticated approach than used for CM patients, and is likely to better account for the non-linear nature of the waning effects observed. The company extrapolated from this four-month period assuming that monthly change in MHDs would continue to wane at the same rate back to baseline frequency of monthly MHDs. Based on these data, the company assumed the treatment effect would wane back to baseline monthly MHDs over a period of [redacted] months after discontinuation of treatment. The ERG were unable to find similar data for EVOLVE-1. The CS reported that when data from EVOLVE-1 and EVOLVE-2 were pooled this led to implausible predictions. It is unclear from the CS the extent to which waning effects differed between trials of EM patients. For a more detailed discussion of the implications for the economic model see section 4.2.6.

Figure 3 Washout period EVOLVE-2 (reproduced from CS, Figure 16)



Safety

The CS reported no deaths and relatively few serious adverse events (SAEs) (see CS section B.2.9 for further details). There do not appear to be any additional safety issues identified for GMB in comparison with other currently recommended treatments for patients with ≥ 3 prior preventive medication failures.

In the CONQUER study, two patients in the GMB group and two in the placebo group experienced SAEs. The most frequently reported adverse effects across all GMB trials were injection site pain ([redacted] injection site reaction ([redacted]), vertigo ([redacted]), constipation ([redacted]) and pruritus ([redacted]).

The EMA identified some uncertainties about the safety of GMB. First, there is very limited data on safety in pregnancy as pregnant women were excluded from clinical trials of GMB. This is an important uncertainty as the majority of migraine patients are females of child bearing age.[9]

Second, in common with other CGRP antagonists, GMB could theoretically aggravate ischemic events such as stroke, transient ischaemic attack and myocardial infarction. This is because CGRP is thought to have a protective effect on cardiovascular health. Clinical trials have not found meaningful differences between GMB and placebo groups on cardiovascular (CV) related outcomes. However, as noted by the EMA, higher risk (i.e. with recent acute CV events and/or serious CV risk) and older age (> 65 years) patients were excluded from clinical trials. Therefore, potential CV risks cannot be ruled out at this stage.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1 EM population

No indirect comparisons were carried out for EM as BSC is the comparator of interest for which the Placebo arm of GMB trials was taken as a proxy.

3.3.2 CM population

Due to the lack of direct RCT evidence comparing GMB to botulinum toxin A in CM patients, the company conducted ITCs to compare the two treatments. Two studies of botulinum toxin A with data available for the population of patients who have failed at least 3 previous therapies were identified and included: PREEMPT-1 and PREEMPT-2 (data for this subgroup were available in a report by CADTH[7]). However, no data on the proportion of responders were available for botulinum toxin A in the target patient population, so ITC in the 'all-comers' CM population were conducted to supplement the results. However, the ERG notes that whilst the SR was appropriate for studies reporting outcomes for CM patients who failed ≥ 3 preventive treatments, it was not sufficiently inclusive for the 'all-comers' CM population (see Section 3.1.2). Therefore, the 'all-comers' population results should be interpreted with caution as they may only include a subset of the relevant studies.

1.1.1.1 Assessment of ITC assumptions

The key assumption for ITC is that patient populations are comparable across all included studies (i.e. the consistency, or transitivity, assumption) which implies that the studies included in the indirect comparison do not differ with respect to the distribution of known treatment effect modifiers. Results of the ITC will still hold when study characteristics differ if they are not treatment effect modifiers.

Baseline patient characteristics

Baseline patient characteristics of CM patients who have previously been unsuccessfully treated with at least 3 prior preventive migraine treatments were similar in the REGAIN and CONQUER trials (CS, Table 38). For further discussion, see section 3.2.1.

Full baseline characteristics for CM patients who have previously been unsuccessfully treated with at least 3 prior preventive migraine treatments were not reported for the botulinum toxin A trials (PREEMPT-1 and -2).[7] Although these values have been considered in a previous NICE TA,[10] they are redacted and were not made available to the ERG. Only baseline MHD data for this subgroup of patients in the PREEMPT-1 and -2 studies were available[7] and are presented in Table 12 along with comparable values for CONQUER and REGAIN. The populations appear to be comparable across the trials on this characteristic, although it is not possible to draw conclusions about the comparability

between the galcanezumab subgroups of REGAIN and CONQUER and the PREEMPT subgroups on other potential effect modifying characteristics.

Table 12 Baseline mean migraine headache days in CM patients with ≥ 3 prior preventive medication failures

	BSC/Placebo			Galcanezumab			Botulinum toxin A		
Study	**N**	**Mean**	**SD**	**N**	**mean**	**SD**	**N**	**mean**	**SD**
CONQUER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
REGAIN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
PREEMPT-1[a]	109	19.7	4.05	-	-	-	107	19.5	4.03
PREEMPT-2[a]	139	19.2	4.30	-	-	-	124	19.3	3.8

[a] monthly values based on 28 day month; BSC, best supportive care; CM, chronic migraine; N, number of patients included; SD, standard deviation.

Detailed baseline characteristics for CM patients in the 'all-comers' population were available for REGAIN (GMB vs placebo, see CSR for REGAIN[11] for further details) and PREEMPT-1 and -2 (botulinum toxin A vs placebo)[7] (see also CS, Table 38). Populations appeared comparable across these studies on baseline characteristics, including on potential effect modifiers such as baseline MHD, age and gender (see Table 13) and values are similar to those in the DTT-3 population (Table 12). The only substantial difference between trials was the proportion of DTT-3 patients in the analyses (REGAIN range [redacted] PREEMPT-1 31-32%; PREEMPT-2 36-39%). The proportion of DTT-3 patients could be an effect modifier as differences between GMB and placebo in pre-planned subgroup analyses were highest in patients with ≥ 2 failed preventive treatments, followed by patients with ≥ 1 failed preventive treatments, and then on the all-comers population.[9] If the proportion of included DTT-3 patients is an effect modifier, this can present problems for the consistency assumption in the 'all-comers' population ITC. Although this would likely result in conservative estimates of the relative treatment effect of GMB compared to botulinum toxin A, i.e. favouring botulinum toxin A.

Table 13 Baseline characteristics in CM patients for 'all-comers' population (based on CS table 38, CSR REGAIN[11], and CADTH Report[7])

Study	Age: Years (SD)	Gender: % females	Proportion of DTT-3 patients at baseline	Baseline MHDs: mean (SD)	Baseline HDs: mean (SD)
REGAIN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PREMPT-1[a]	**Botulinum toxin A:** 41.2 (10.49) **Placebo:** 42.1 (10.46)	**Botulinum toxin A:** 89.1% **Placebo:** 85.8%	**Botulinum toxin A:** 31.38% (107/341) **Placebo:** 32.25% (109/338)	**Botulinum toxin A:** 19.10 (4.04), n=341 **Placebo:** 19.10 (4.05), n=338	**Botulinum toxin A:** 20.0 (3.73), n=341 **Placebo:** 19.8 (3.71), n=338
PREMPT-2[a]	**Botulinum toxin A:** 41.0 (10.39) **Placebo:** 40.9 (10.82)	**Botulinum toxin A:** 86.2% **Placebo:** 84.6%	**Botulinum toxin A:** 35.73% (124/347) **Placebo:** 38.82% (139/358)	**Botulinum toxin A:** 19.2 (3.94), n=347 **Placebo:** 19.8 (3.71), n=358	**Botulinum toxin A:** 19.9 (3.63), n=341 **Placebo:** 19.7 (3.65), n=358

[a] monthly values based on 28 day month; CM, chronic migraine; DTT-3, difficult to treat population failed on 3 previous therapies; GMB, galcanezumab; MHD, migraine headache days; HD, headache days; n, number of patients included; SD, standard deviation.

Study characteristics

In addition, the studies of GMB and botulinum toxin A differed in the following characteristics, which may affect the estimated relative effects:

- definition of headache/migraine headache – galcanezumab: ≥30 minutes duration; botulinum toxin A: ≥ 4 continuous hours;
- statistical methods for calculating treatment effects – galcanezumab: mixed model repeated measures; botulinum toxin A: analysis of covariance;
- double blind treatment periods - galcanezumab trials: 3 months; botulinum toxin A: 24 weeks;
- the placebo is different in GMB (REGAIN two injections at each dosing visit, CONQUER two injections at visit 3 and one injection thereafter) and botulinum toxin A studies (31-39 injections sites).

As noted by the company, the placebo response in the all-comers population in the PREEMPT trials is higher than that in REGAIN or CONQUER, which may be partly explained by the perception of stronger efficacy related to a more invasive treatment.[12, 13] However, it is unclear whether this is an effect modifier and how much this will impact the reliability of the ITC in patients with ≥ 3 prior preventive medication failures. Nevertheless, using different types of placebo interventions as the common link for an ITC can lead to a violation of the consistency assumption required for ITC.[14]

For the PREEMPT trials, limited evidence was available for outcomes at week 12 and all ITC used data at 24 weeks. The low number of included studies is another limitation with at most two studies per direct comparison and four studies per network. The sample size of the individual study groups, for the treatment resistant patient population was also small and this is reflected in the uncertainty of the estimates and the width of the 95%CIs.

ERG comment

Given the limitations outlined above, it is unclear whether the included trials are sufficiently homogeneous to satisfy the consistency assumption and the results of the ITCs must be interpreted with caution.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The methods used for ITC are adequate: the Bucher method was used to compare GMB to botulinum toxin A via the placebo common comparator. Fixed and random effects meta-analyses were used to pool REGAIN and CONQUER studies to obtain effects for GMB vs Placebo and PREEMPT-1 and -2 to obtain results of botulinum toxin A vs placebo prior to applying the Bucher method for ITC. However, there is not enough information to estimate between-study heterogeneity (only 2 studies per comparison) hence results of fixed and random effects meta-analyses are very similar. The fixed effect model results were chosen to perform the ITC, which the ERG considers appropriate.

Although CM patients with ≥ 3 prior preventive medication failures were the population of interest for comparison between GMB and botulinum toxin A, ITC were also carried out in the 'all-comers' population, defined as including patients regardless of how many previous treatment failures they had experienced (see Table 14). Evidence for this population is obtained from REGAIN and the botulinum toxin A studies (PREEMPT-1 and -2), but not from the CONQUER study which only included patients with 2-4 prior treatment failures (see Table 9).

No data were available from the PREEMPT studies on the proportion of patients with 30% or greater reduction in MHD, which is of most relevance for the CM population so this outcome could not be considered in an ITC. There were also no data on adverse events (AE), so no ITC were conducted.

Table 14 Outcomes for which indirect treatment comparisons were carried out (from CS Table 37)

Outcomes	All-comers population	Treatment-resistant population
50% or greater reduction in monthly Migraine Headache Days	X	NA
CFB in monthly Migraine Headache Days	X	X
CFB in monthly Headache Days	X	X
CFB in MSQ-RFR	X	X
CFB in MSQ-RFP	X	X
CFB in MSQ-EF	X	X

Abbreviations: CFB – change from baseline; MSQ-RFR - Migraine Specific Quality of life instrument Role Function-Restrictive; MSQ RFP- Migraine Specific Quality of life instrument Role Function-Preventive; MSQ -EF- Migraine Specific Quality of life instrument Emotional Function; NA – not available

3.4.1 CM patients with ≥ 3 prior preventive medication failures

ITCs to compare GMB to botulinum toxin A for CM patients with ≥ 3 prior preventive medication failures were carried out for the following outcomes: mean change from baseline (CFB) in the number of monthly MHD and HD, and three domains of the Migraine-Specific Quality of Life Questionnaire (Role Function-Restrictive, Role Function-Preventive and Emotional Function). Results are summarised in the CS (Table 41) and show that [redacted]. Results of the ITC for this outcome were used in both the company's and ERG's economic models, and are therefore presented in detail below along with the ERG's comments.

Change from baseline in mean MHD

Data for the subgroup of patients with ≥ 3 prior preventive medication failures (DTT-3 population) from the CONQUER, REGAIN and PREEMPT-1 and -2 trials were used to derive an indirect comparison of GMB vs botulinum toxin A, using the placebo arm as the common comparator. Table 15 shows the data sources and ITC results. The ITC indicates that GMB [redacted] mean MHD from baseline by [redacted] days compared to botulinum toxin A (Table 15) and the result [redacted].

Table 15 Mean difference in change from baseline in mean MHD for CM DTT-3 population: data sources and ITC results

	GMB vs Placebo				Botulinum toxin A vs Placebo			
Source	**N Placebo**	**N active**	**mean difference**	**95% CI**	**N Placebo**	**N active**	**mean difference**	**95% CI**
CONQUER*	42	42	[redacted]	[redacted]				
REGAIN*	[redacted]	36	[redacted]	[redacted]				
Pooled	[redacted]	[redacted]	[redacted]	[redacted]				
PREEMPT 1					109	107	-2.1	-3.89 to -0.31
PREEMPT 2					139	124	-3.5	-5.04 to -1.96
Pooled					248	231	-2.9	-4.07 to -1.74
ITC GMB vs Botulinum toxin A (fixed effect model)			[redacted]	[redacted]				

* CI for mean change from baseline across months 1- 3 for GMB and Placebo used in the ITC is wider than in company's main analyses (presented in Tables 27 and 33 of the company submission) as it does not account for the repeated nature of the measurements.

CI, confidence interval; GMB, galcanezumab; ITC, indirect treatment comparison; MHD, migraine headache days; N, number of patients included.

ERG comment

Precision in this ITC could have been increased if the variance of the mean difference in the changes from baseline in MHD calculated accounting for repeated measures over time for the CONQUER and REGAIN studies had been used (as reported in Tables 27 and 33 of the CS). Instead, the variance for the mean difference between GMB and placebo calculated for the purposes of the ITC did not account

for the repeated nature of the measurements, leading to slightly wider CIs in Table 15 and consequently less precision in the ITC results. However, this is unlikely to have a meaningful impact on model results.

3.4.2 CM patients 'all-comers' population

ITCs to compare GMB to botulinum toxin A for the general population of CM patients regardless of prior treatment failures ('all-comers') were carried out for the following outcomes: proportion of patients with at least 50% reduction in monthly MHD, mean change from baseline in the number of monthly MHD and HD, and three domains of the Migraine-Specific Quality of Life Questionnaire (Role Function-Restrictive, Role Function-Preventive and Emotional Function). Results are summarised in CS Tables 39 and 40 and show that [redacted].

The ERG notes that the SR was not sufficiently inclusive for the 'all-comers' CM population (see Section 3.1.2 and 3.3). Therefore, results should be interpreted with caution as they may only include a subset of the relevant studies.

None of these ITCs were used by the company in their economic model. However, the ERG used the ITC of GMB with botulinum toxin A for the proportion of patients with at least 50% improvement in MHD in scenario analysis and the in the ERG's base-case see Section 6.1. Therefore, data sources and results for this ITC are presented in detail below along with the ERG's comments.

Proportion of patients with at least 50% reduction in monthly MHD (Responders - 50%)

Data for the 'all-comers' population from the REGAIN and PREEMPT-1 and -2 trials were used to derive an indirect comparison of GMB vs botulinum toxin A, using the placebo arm as the common comparator. Table 16 shows the data sources and ITC results.

The ITC indicates that the odds of patients achieving a 50% or greater reduction in monthly MHD are [redacted] in patients receiving GMB compared to botulinum toxin A (Table 16) [redacted].

Table 16 Percentage of patients with at least 50% reduction in monthly MHD from baseline in the CM 'all-comers' population: data sources and ITC results

	GMB vs Placebo				Botulinum toxin A vs Placebo			
Source	**n/N (proportion) Placebo**	**n/N (proportion) active**	**Odds ratio**	**95% CI**	**n/N (proportion) Placebo**	**n/N (proportion) active**	**Odds ratio**	**95% CI**
REGAIN*	[redacted]	[redacted]	[redacted]	[redacted]				
Pooled	[redacted]	[redacted]	[redacted]	[redacted]				

PREEMPT 1					98/261 (0.375)	104/294 (0.354)	1.38	0.97 to 1.96
PREEMPT 2					104/294 (0.354)	142/279 (0.509)	1.89	1.35 to 2.65
Pooled					260/539	202/555	1.63	1.28 to 2.07
ITC GMB vs Botulinum toxin A (fixed effect model)			[redacted]	[redacted]				

* odds ratio calculated from simple proportion for ITC, CI is wider than if using categorical, pseudo-likelihood-based repeated measures analysis in company's main analyses presented in page 25 of the company submission (odds ratio 2.09 95%CI 1.56 to 2.80).

CI, confidence interval; GMB, galcanezumab; ITC, indirect treatment comparison; MHD, migraine headache days; n, number of responders; N, number of patients included.

ERG comment

Precision in the ITC could have been increased if the odds ratio which accounted for the repeated measures over time in the REGAIN study had been used (as reported in page 25 of the CS). Instead, an odds ratio between GMB and placebo based on simple proportions was calculated for the purposes of the ITC, leading to slightly wider CIs for the comparisons of GMB to Placebo Table 16 and consequently less precision in the ITC results. However, this is unlikely to have a meaningful impact on model results. The fact that other relevant studies may not have been included is likely to have a greater impact on the uncertainty in these analyses (Section 3.3).

The REGAIN and PREEMPT studies included both treatment naïve and previously treated patients. The CONQUER study included patients with 2-4 previous treatment failures which is a subset of the types of patients included in REGAIN and PREEMPT. An argument could be made to also include results from the full CONQUER population in the ITC for 'all-comers'. However, the company's choice to exclude this study is also defensible and is a more conservative option (i.e. will lead to less precise results and ensures the populations are, in principle, more homogeneous across GMB and botulinum toxin A studies).

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG verified the company's ITC methods and code and were able to reproduce all the results. No additional analyses were carried out.

3.6 Conclusions of the clinical effectiveness section

The CS included a systematic review of GMB and relevant comparators. Overall, there were no concerns with the searches. However, the ERG noted inconsistencies in how the resulting data were synthesised. For example, estimates used in the economic model were not always based on all available relevant data (see Sections 4.2.3, 1.1.1.5 and 4.2.7 for more details).

The CS rightly focused on the DTT-3 population (i.e. patients with ≥ 3 prior preventive treatment failures) as the most relevant data to inform the decision problem. However, there were limited available data for all outcomes in this population. In addition, there were concerns about the generalisability of included participants since most DTT-3 patients in CONQUER had failed on a treatment not used in the UK.

Differences in effectiveness between GMB and botulinum toxin A were informed by ITCs using placebo as the common comparator. The company acknowledged a number of limitations with these analyses. First, there were a small number of participants included in only four relevant trials. Second, there were differences in trial methods including definition of headache/migraine headache, statistical methods for calculating treatment effects, and double-blind treatment periods. Third, substantially higher placebo response rates were observed in PREEMPT-1 and PREEMPT-2 compared with placebo response rates in REGAIN and CONQUER (although it is unclear whether placebo response rates are an effect modifier). In addition, the ERG notes that the SR may not have been sufficiently inclusive for the 'all-comers' CM population (see Sections 3.1.2 and 3.3). These limitations make the conclusions from the indirect comparisons highly uncertain.

4 COST EFFECTIVENESS

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the economic model.

4.1 ERG comment on company's review of cost-effectiveness evidence

The company performed a targeted literature review (TLR) to identify cost-effectiveness evaluations of prophylactic interventions used to treat people with migraine. The inclusion and exclusion criteria are provided in Table 22 in Appendix G of the CS. In brief, studies were included in the review if they assessed the cost-effectiveness of any preventative treatments for migraine. A broad range of studies were considered for inclusion. These included cost-effectiveness, cost-utility, and cost-minimisation, cost studies and utility studies.

In total, sixteen studies were considered to meet the eligibility criteria for the review. These studies are summarised in Appendix G of the CS. No published cost-effectiveness studies of galcanezumab were identified.

The CS outlines that the structure of the economic model presented in the CS was based on the approach described in the NICE TAs of erenumab and fremanezumab,[15, 16] as well as four of the sixteen studies identified in the TLR: three studies assessing erenumab in episodic and chronic migraine[17-19] and one study assessing fremanezumab in episodic and chronic migraine.[20]

The ERG notes the potential importance of one study in the TLR, which was not considered when developing the company's model structure. This was a US study published by the Institute for Clinical and Economic Review[21] which reported on the cost effectiveness of erenumab and fremanezumab compared to no treatment for episodic migraine, and to botulinum toxin A for chronic migraine. Importantly, unlike the company's model, this model considered not only frequency of migraine, but also severity, with severity of headache/migraine categorised as either mild, moderate or severe. The company provided a short summary and critique of the Institute for Clinical and Economic Review study in Appendix G, Section G.1.3.2 and highlighted the incorporation of severity as a strength of the study.

In response to clarification questions the company outlined a number of reasons for the exclusion of severity from the economic model including: considerable increase in the model complexity; a lack of data to inform the granularity that would be required to incorporate severity within the current health

states of the model; the difficulty in capturing severity given its subjectivity; and the lack of severity included in previous NICE TAs.[2, 6, 22]

Despite this, the ERG considers the approach of incorporating migraine severity to be relevant. A brief summary of the Institute for Clinical and Economic Review study is reported in Appendix G, Section G.1.3.2. Further details of the relevance of incorporating migraine severity in the economic model are provided in Section 4.2.2 and Section 4.2.7.

The ERG is otherwise satisfied with the company's review of the cost-effectiveness literature.

4.2 ERG's summary and critique of company's submitted economic evaluation

The company presented a *de novo* analysis based on a Markov model. The ERG notes that the model structure appears similar to the structures used in the economic evaluations identified in the cost-effectiveness review (Section 4.1)

4.2.1 NICE reference case checklist

A summary of the company's *de* novo economic evaluation is presented in Table 17 with comment on the similarity of the analysis to the NICE reference case.

Table 17 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The model considered QALY benefits to treated individuals.
Perspective on costs	NHS and PSS	Costs considered were NHS and PSS.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Fully incremental cost–utility analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The economic model used a time horizon of 25 years – sufficient to capture important differences.
Synthesis of evidence on health effects	Based on systematic review	Systematic review was conducted for evidence of health effects. Indirect treatment comparison was conducted to combine relevant clinical trial data. This is potentially appropriate but there is inconsistency between the use of results from an individual trial and

		all of the available data for relevant populations.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were presented in QALYs. Measured directly from patients in the trials. Utility data was mapped from MSQ to EQ-5D-3L. Disutility associated with number of monthly migraine headache days.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utilities were populated using Migraine-Specific Quality of Life Questionnaire (MSQ) data collected by patients in the CONQUER trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	UK population valuation set used within mapping, described in Gillard, 2012. [23]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No special weighting undertaken.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs considered were NHS and PSS. Resource use was taken from a US survey but priced using prices relevant to the NHS and PSS.

NHS, national health service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

4.2.2 Model structure

The company developed a *de novo* cost-effectiveness model in Microsoft Excel to evaluate the cost-effectiveness of galcanezumab versus relevant comparators in two parallel analyses, separating episodic migraine (including a separate subgroup of HFEM) from chronic migraine. Both analyses were conducted with a dedicated set of input parameters. For both episodic and chronic migraine patients, galcanezumab was compared to BSC; an additional analysis comparing galcanezumab to botulinum toxin A was conducted for chronic migraine.

Within the model, the impact of migraine is captured by 30 health states representing the frequency of migraine headache per 30-day model cycle. This is used to drive differences in HRQoL and costs in the model, with quality adjusted life-years (QALYs) and costs generated for each state and then combined as a weighted average according to the proportion of patients in each state. Within each separate state, and for each model cycle, the distribution of patients across the range of monthly MHD

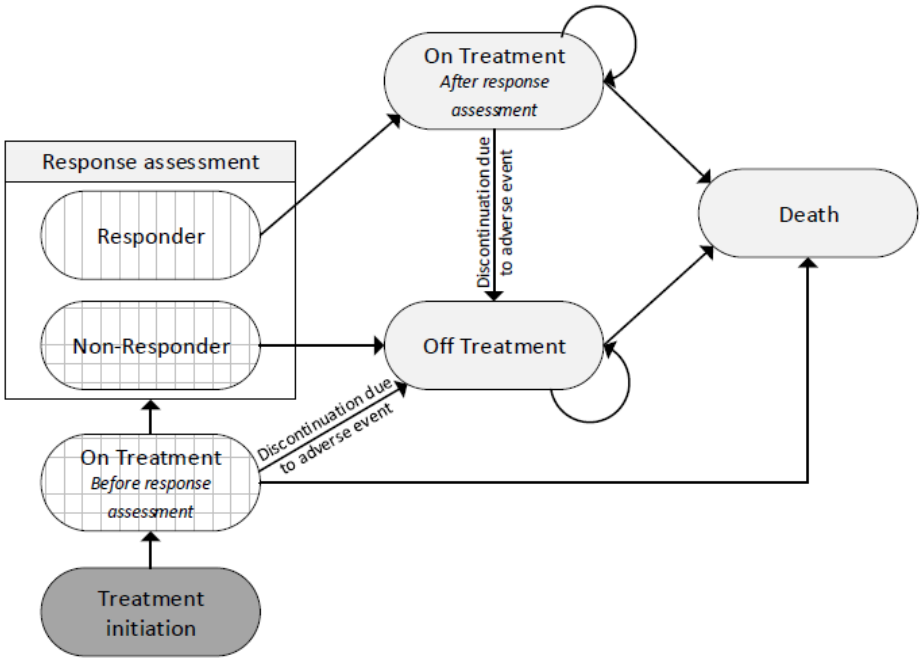
(ranging from 0 to 30 per cycle/month) is estimated by fitting a parametric distribution to trial data on the frequency of MHD. The choice of distribution was based on goodness of fit analyses. For the EM population, a negative binomial distribution was fitted to data from the all-comers population from the EVOLVE-1 and EVOLVE-2 trials. For the CM population a beta binomial distribution was fitted to data for the all-comers population of the REGAIN trial (see CS, Appendix S, pg. 122).

To account for the impact of treatment, the model shifts these distributions through changes in mean monthly MHD for different groups of patients, with differing mean monthly MHDs assumed according to the treatment received and whether patients are classified as responders, non-responders or have discontinued due to AEs. The treatment effect in the model therefore has two dimensions: i) the distribution of patients across different categories i.e. how many patients are classified as responders, non-responders and discontinuers and ii) the assumed mean monthly MHD within categories i.e. being classified as responder on galcanezumab implies a different mean monthly MHD to being classified as responder on BSC.

Response in the model is assessed following three model cycles (90 days). Following assessment of response, non-responders are assumed to discontinue treatment. The response threshold applied was a reduction of 50% in monthly MHDs in the EM population and 30% reduction in monthly MHDs in the CM populations respectively. Patients may also discontinue treatment at any time, with separate discontinuation rates applied in the period prior to and post assessment of response. Patients discontinuing treatment, either due to non-response or adverse events are assumed to rebound to baseline monthly MHDs over varying time horizons.

A schematic of the model structure can be seen in Figure 4.

Figure 4 Model structure (from CS, Figure 11, pg. 107)



Costs and utilities per monthly MHD are identical for galcanezumab and comparators in both episodic and chronic migraine (see Sections 4.2.7 and 4.2.8 for more information). Differences in total costs and utilities across the modelled galcanezumab and comparator arms are therefore driven by the difference in mean MHD (and the corresponding distribution of population monthly MHD).

ERG comment

The ERG considers the Markov model submitted by the company to be restrictive in its simplicity, as it does not account for several important aspects of migraine. These include a focus on migraine frequency to the exclusion of other indicators of migraine severity and the omission of the natural history of migraine. Despite this, the ERG does acknowledge the similarity of the model structure to the models used in the NICE technology appraisals of erenumab[15] and fremanezumab[16]; that is, they are driven by response rate and the mean change in MHDs. The ERG, however, also notes important differences in the company's approach to modelling the distribution of monthly MHDs. A more detailed exposition of these issues is presented below.

Durability of the treatment effect

An implicit assumption of the economic analysis is that effects of treatment as observed at 90 days are extrapolated throughout the time horizon of the model. The company justifies this assumption on the basis of long-term data from the REGAIN and CGAJ studies. The company also notes that this is consistent with assumptions made in the appraisal of erenumab and fremanezumab. The ERG, however notes that these studies provide only limited follow up (maximum 1 year) and that neither

study provides comparative evidence. As such these studies provide only limited evidence to support the assumption of a durable treatment effect. Further, the ERG highlights concerns raised in the previous appraisals regarding the plausibility of extrapolating the short-term comparative evidence over long periods of time and that this has been identified as a significant source of uncertainty.

The ERG, concurs with these previous assessments and considers the assumption of an ongoing durable treatment effect to represent a significant source of uncertainty. However, the ERG also highlights that this uncertainty may be mitigated if patients are regularly monitored with a view to discontinuing treatment where it is no longer beneficial.

Omission of migraine severity and headache frequency

A limitation of the economic model structure is that it focuses on frequency of migraine and does not account for other dimensions of the condition which may impact on both HRQoL and costs. Specifically, the model does not account for changes in either migraine severity or the frequency of headache that is not classified as a migraine. Clinical advice received by the ERG highlighted that both migraine severity and headache frequency are aspects that are important in determining the overall burden of the disease. Further comments from the ERG's clinical advisor suggest that an effective treatment (such as galcanezumab) would likely impact upon both these aspects as well as migraine frequency.

With regards to severity of migraine, the ERG notes the US economic evaluation highlighted in Section 4.1, where both migraine frequency and severity were included in the model structure using a tripartite classification of mild, moderate and severe migraine. In response to the ERG's clarification questions, the company outlined several reasons why this structure was not adopted in its *de novo* model. These included the lack of appropriate data to inform the granularity that would be required to incorporate severity in the model. The ERG accepts that some assumptions may have been made to incorporate severity into the model but considers that these may have been appropriate in the context of providing a richer economic analysis better able to reflect the benefits of treatment. In this regard, the ERG also notes that scenario analyses presented assuming differential utilities between treatment arms may allow the model to capture these other dimensions of migraine – see Section 4.2.7 for further discussion.

Omission of natural history

The CS acknowledges that a limitation of the presented model is the exclusion of natural history. The company justifies this exclusion in their clarification response and outlined that this was due to lack of data on the long-term effects of migraine and in particular how this might impact upon active treatments.

The ERG considers this an important omission and notes that one important consequence of this exclusion is that mean monthly MHDs remain constant for all patients through the entire 25-year time horizon. The only exception to this being the initial treatment effect and waning of this effect assumed after discontinuing active treatment. This assumption of near constant monthly MHDs lacks face validity and is counter to the available evidence on natural history. For example, a 30-year prospective Swiss study[5] identified by the ERG found that the frequency of migraine fluctuated significantly within individual patients, with a substantial proportion of patients showing complete remission of symptoms by the end of the 30 year follow up period. Other studies also offer similar findings and suggest a pattern of decreasing frequency and remission of headache and migraine symptoms with increased age. [24-26] In this regard it has been observed that symptoms in female patients will tend towards resolution post menopause (women comprise about 75% of migraine patients[27]).

This reduction in the severity of migraine over time is likely to have important consequences for the cost-effectiveness of any active treatment, particularly when considered in the context of the assumption of continued lifetime treatment. This is because natural history will tend to erode the benefits of treatment, rending continued treatment increasingly less cost-effective. Given this effect, the ERG emphasises the importance of clinicians complying with the summary of product characteristics (SmPC) recommendation that patients be regularly reviewed to assess the need for continued treatment.[28] This will ensure that patients only continue to receive treatment where it is both beneficial and cost-effective.

The ERG also notes scenario analyses presented in the appraisal of erenumab[15] and fremanezumab[16] which attempt to model positive discontinuation (discontinuation as a result of treatment success). Such scenarios align better with the SmPCs issued for the CGRP treatments in that they attempt to account for the need to continually assess the ongoing need for treatment. However, interpretation of such scenarios is problematic due to the lack of long-term evidence on the duration of treatment and durability of any continued benefits post discontinuation. Further, where such scenarios omit the role of natural history, they are likely to overestimate the benefits of treatment as they attribute remission of symptoms solely to receipt of an active therapy. The potential impact of this natural decline in severity of migraine in older patients is explored in scenario analysis in Section 6.

While the tendency for patient symptoms to resolve in older adulthood is well established, there is also evidence to suggest that patients with episodic migraine will often progress to develop chronic migraine. This phenomenon was highlighted in the company's clarification response when asked to comment on the impact of natural history. In their response, the company highlighted that the omission of natural history and the tendency for some patients to migrate from episodic to chronic migraine was likely to lead to the company model underestimating the cost-effectiveness of galcanezumab in the EM population. The ERG, however, disagrees with this assertion as it assumes

that CM patients do not have access to active therapies; both fremanezumab and botulinum toxin A are approved in the CM population.

Distribution of migraine headache days – ineligible patients

The ERG is concerned with the company's approach to modelling the distribution of MHDs. The model makes predictions about the distribution of monthly MHDs that are inconsistent with the licence and described modelled populations. This is particular apparent at baseline where the model predicts that a proportion of patients will start with < 4 MHDs per month despite this being inconsistent with the licenced indication and company positioning. Furthermore, when the EM population is modelled, it predicts that a proportion of patients will start with > 15 MHDs per month, which would be classified as CM. Similarly, when the CM population is modelled it predicts that a proportion of patients will start with < 8 MHDs per month. The extent of these inconsistencies is described in Table 18.

Table 18 Proportion of patient's ineligible for galcanezumab at baseline

	Mean MHDs at baseline	Proportion with < 4 MHDs according to company fitted distribution at baseline	Proportion < 8 MHDs at baseline	Proportion > 15 MHDs at baseline	Total proportion ineligible for treatment at baseline
Chronic (vs BSC)	[redacted]	[redacted]	[redacted]	N/A	[redacted]
Chronic (vs botulinum toxin A)	[redacted]	[redacted]	[redacted]	N/A	[redacted]
Episodic (vs BSC)	[redacted]	[redacted]	N/A	[redacted]	[redacted]
HFEM (vs BSC)	[redacted]	[redacted]	N/A	[redacted]	[redacted]

BSC, best supportive care; HFEM, high frequency episodic migraine; MHDs, migraine headache days.

Considering the impact of this issue on model predictions, the ERG expects that this will lead to some inaccuracy in the predicted distribution of monthly MHDs throughout the time horizon of the model, but that this will not impact significantly on model results because model outputs (costs and QALYs) are largely a linear function of monthly MHDs; the distribution of MHD is only important when model outputs are non-linearly related to monthly MHDs. This, however, remains a source of uncertainty in the model and the ERG considers that it may have been more appropriate to have modelled truncated distributions. This would have ensured model predictions retained face validity and would have improved model accuracy.

Distribution of migraine headache days – responder/non-responder distributions

The ERG notes a point of difference between the company's approach to modelling the distribution of monthly MHDs and the NICE TAs of fremanezumab[16] and erenumab.[15] In the previous appraisals the distribution of monthly MHDs was modelled separately for responders and non-responders i.e.

different distribution were fitted to each. In contrast, the company's model fits a single pooled distribution to all patients. While both are potentially valid approaches, the former has the advantage that it allows for differences in the distribution of monthly MHDs between responders and non-responders to be reflected in the model and may therefore more accurately reflect the overall distribution of monthly MHDs.

In the response to clarification questions, the company stated this approach was undertaken because at the time of model finalisation, the CONQUER trial was still ongoing and there were concerns regarding the appropriateness of the distributions, given low patient numbers. Following a request from the ERG, the company assessed the estimated distributions to responders and non-responders, and visually compared the estimated pooled distributions to the fitted responder/non-responder distributions, concluding that both approaches produced similar predicted distributions of monthly MHDs.

The ERG expects that this simplification will likely lead to some inaccuracies in the predicted distribution of monthly MHDs. As with the previous issue, the ERG, however, does not expect this to impact significantly on model results because model outputs (costs and QALYs) are largely a linear function of monthly MHDs.

Inability to conduct incremental analysis

While the broad structure of the economic analysis is common across both EM and CM populations, the company utilises different inputs to model the monthly change in MHDs for galcanezumab depending upon whether the comparator is BSC or botulinum toxin A. This is implemented because data on the change in MHD stratified by response is not available for botulinum toxin A. The consequence of this inconsistency is that a fully incremental analysis, in which the cost-effectiveness of BSC, galcanezumab and botulinum toxin A are compared together, cannot be conducted. The ERG considers this a significant limitation of the model and, while the limitations in the available data are recognised, does not consider this a reasonable approach. See Section 1.1.1.3 for a full exploration of this issue.

4.2.3 Population

Galcanezumab is licensed for the prophylaxis of migraine in adults who have at least 4 migraine days per month. The economic analysis presented in the CS covers the narrower subpopulation of patients who both have at least 4 migraine days per month and have failed ≥ 3 prior prophylactic treatments.

Within the economic analysis, this population is divided into three sub populations; episodic migraine, high frequency episodic migraine (a subgroup of episodic migraine) and chronic migraine. Episodic migraine is defined as patients with fewer than 15 headache days per month, with at least 4 being

migraine days. High frequency episodic migraine is defined as patients with fewer than 15 headache days per month and 8 to 14 migraine days. Chronic migraine is defined as patients who experience 15 or more headache days per month of which at least 8 or more are migraine days. This division of the population was implemented to reflect the provision of botulinum toxin A which is restricted to patients with chronic migraine. In line with the marketing authorisation all scenarios excluded patients with fewer than 4 migraine days per month.

The modelled baseline characteristics were age, sex and mean MHD, which were drawn from the relevant subgroups of the CONQUER trial. These are summarised in Table 19.

Table 19 Baseline patient characteristics (adapted from Table 51 CS pg. 117)

	Age (years)	Gender (% Female)	Mean MHD
Episodic	[redacted]	[redacted]	[redacted]
High frequency episodic migraine	[redacted]	[redacted]	[redacted]
Chronic - Failed at least 3 preventive treatments	[redacted]	[redacted]	[redacted]

MHD, migraine headache days

ERG comment

The ERG considers the modelled populations to be broadly reflective of those treated in practice but notes that the clinical data used in the model are drawn from the sub-population of patients who have received 3 or more previous prophylactic therapies including patients who have previously failed botulinum toxin A (Section 3.2.1). This is inconsistent with provision of botulinum toxin A in the NHS and the expected positioning of galcanezumab. The episodic and HFEM populations are currently ineligible for botulinum toxin A on the NHS and therefore are unlikely to have previously failed botulinum toxin A. In the CM population, galcanezumab is likely to displace botulinum toxin A as the preferred treatment for patients who have failed ≥ 3 prior prophylactic treatments and therefore the incident population will be naïve to botulinum toxin A. The ERG requested at the PFC stage that the company present revised analyses limiting the population to patients who had not previously received botulinum toxin A. To consider the current population of patients who have already failed botulinum toxin A, the ERG further requested that the company consider the relevance of this population in relation to the positioning of galcanezumab. In response, the company stated that galcanezumab would only be considered at a 5th line position after patients have cycled through 3 oral preventatives and botulinum toxin A.. The company's response also included additional results excluding patients who had failed botulinum toxin A and showed that galcanezumab was similarly effective compared with placebo, though point estimates for several key outcomes were slightly

smaller. The company, however, did not provide scenario analyses in the botulinum toxin A failure population. .

The ERG notes that the company based the baseline characteristics used in the model on the CONQUER trial, while clinical data used to model treatment effects was drawn from all four trials (CONQUER, REGAIN, EVOLVE-1 and -2). This represents an inconsistency in the economic analysis. Exploratory analyses carried out by the ERG, however, demonstrated that this has very limited impact on cost-effectiveness (results not reported). Moreover, the ERG notes that the modelled population is likely to be a more reasonable reflection of the prevalent population who would be eligible for galcanezumab. The modelled population may, however, be less reflective of the incident population, who are likely to be younger with a mean age under 40.[29, 30] This may impact on the appropriateness of the modelled time horizon of 25 years. It may also have further consequences when considering the potential impact of natural history as patients' age will be a significant factor in determining the rate at which patients experience any age-related decline in the severity and frequency of migraine.[5, 30] This is explored in scenario analysis in Section 6.

4.2.4 Interventions and comparators

Galcanezumab was modelled as a self-administered subcutaneous injection using a pre-filled pen, with an initial loading dose of 240mg followed by a single monthly injection at a dose of 120mg. Patients receiving galcanezumab were assumed to use acute headache or migraine medication and healthcare resources associated with migraine in line with the mean MHD frequency, see Section 4.2.8.

The EMA authorisation of galcanezumab recommends that treatment benefit should be assessed within three months after initiation of treatment, and evaluation of the need to continue treatment is recommended regularly thereafter.[28] In the economic analysis, initial response to treatment was therefore assessed at the end of cycle 3 (day 90). This initial assessment aligned with the effectiveness evidence available from the CONQUER trial. In line with the model structure presented in Section 4.2.2, patients who did not meet the response criteria in the 90-day assessment period were assumed to discontinue treatment. Discontinuation was applied for the proportion failing to reduce mean MHDs by ≥ 50% versus baseline in the episodic migraine analysis; and ≥ 30% mean MHDs in the chronic migraine analysis. Responders to treatment were assumed to remain on treatment for the lifetime of the model, with a "negative" discontinuation rate applied to account for discontinuation resulting from AEs, see 1.1.1.4 for further discussion.

Comparators assessed in the economic evaluation were dependent upon the population under consideration. In the episodic migraine population, galcanezumab was compared with BSC. Best supportive care was assumed to consist of acute management of migraine using simple analgesics (i.e.

ibuprofen, aspirin or paracetamol), a triptan with or without paracetamol or a non-steroidal anti-inflammatory drug (NSAID). Like the prophylactic strategies, BSC was also modelled in terms of response and non-response. However, response to BSC was assumed to be temporary, such that responders returned to baseline MHD after a period of 12 months.

In the CM population galcanezumab was compared with BSC, as well as botulinum toxin A. Dosing of botulinum toxin A, was 200mg every 12 weeks or 84 days. Response for botulinum toxin A was assessed after 3 months in line with the assessment period for galcanezumab and BSC. Note this differs from the length of the assessment period used in the appraisal of botulinum toxin A which used a period of 24 weeks, but is likely a reasonable reflection of actual pracctice.[10] Scenario analysis was presented assuming an assessment period of 6 cycles (180 days), which is approximately equivalent to an assessment period of 24 weeks. The results of this scenario analysis show this assumption has no material impact on the ICER.

The two other CGRP therapies, erenumab[15] and fremanezumab,[16] were not included in the company's base-case, nor were they included as comparators explored in any scenario analysis. The company also did not present a comparison versus other preventative treatments topiramate, propranolol, amitriptyline or gabapentin, which is in line with their recommendation as earlier options in the treatment pathway.

ERG comment

Omission of other CGRPs as comparators

The ERG considers that the model comparators are consistent with the NICE scope, but is concerned about the omission of erenumab and fremanezumab. As of the date of the CS neither erenumab nor fremanezumab had received a NICE recommendation and both were subject to ongoing appraisals. Fremanezumab has, however, since received a recommendation for use in patients with chronic migraine who have failed ≥ 3 prior preventative treatment failures. The appraisal of erenumab is ongoing. The approval of fremanezumab means it is likely to rapidly become standard of care in the relevant chronic migraine population and therefore represents a relevant comparator for galcanezumab.

Reflecting the ERG's concerns about the omission of erenumab and fremanezumab as comparators the ERG requested, at the PFC stage, that the company consider the impact of erenumab and fremanezumab becoming relevant comparators in the near future. The company's response noted recent approval in patients with chronic migraine, and agreed that fremanezumab would represent a potential comparator in this population. The company's response, however, highlighted that neither erenumab nor fremanezumab had received a NICE recommendation when the company received its

invitation to participate in the NICE appraisal process and that fremanezumab was not standard of care at the time of the company's submission.

The ERG recognises that at the time of the CS neither erenumab nor fremanezumab represented standard care and that any comparison of erenumab or fremanezumab with galcanezumab may have been speculative at the time of the production of the CS. The ERG, however, emphasises the importance of considering the relative cost-effectiveness of all CGRPs to ensure that the most cost-effective CGRP treatment is used in the NHS and to ensure continued efficient use of scarce NHS resources.

Sequential therapy

The company's economic model does not consider the potential for sequential treatment with active therapies i.e. the possibility that botulinum toxin A and galcanezumab may be used in sequence either as botulinum toxin A followed by galcanezumab or galcanezumab followed by botulinum toxin A. In a full economic analysis, it is appropriate not only to consider active therapies as direct comparators, but also to consider the comparative cost-effectiveness of alternative treatment sequences. This allows the optimum positioning of active treatments to be established. For example, it may be more cost-effective to use galcanezumab as a 5th line treatment following use of the cheaper botulinum toxin A, than to use it as 4th line treatment. Partial precedent for the evaluation of treatment sequences rather than simple comparisons of active treatments can be observed in many of the recent appraisals of biologics for the treatment of psoriasis,[31-33] where it is typically assumed that patients will cycle through 3 or more active treatments.

Regarding the plausibility of sequential treatment, the ERG notes the successful appeal in the appraisal of erenumab[34] which upheld that the committee should have considered eremumab as a 5th line therapy for patients who had failed botulinum toxin A. Clinical advice received by the ERG concurs that 5th line positioning of CGRPs is a plausible treatment sequence and noted that this would be the effective treatment sequence for the large prevalent population of patients who have failed of botulinum toxin A. Our clinical advisor, however, caveated this by noting that due to the limited availability of botulinum toxin A and the more burdensome administration associated with it, the preferred position for galcanezumab and other CGRPs in the incident population would be as a 4th treatment, with botulinum toxin A positioned as a 5th line treatment. In this regard the ERG notes that there is nothing in the NICE recommendation for botulinum toxin A that precludes prior use of CGRPs. The ERG does not present analysis including these additional comparators due to the significant resource required to conduct these analyses, but considers this an important issue that should be addressed.

Life-time treatment

The ERG questions the plausibility of the assumption that patients responding to galcanezumab remain on therapy for the lifetime of the model. The ERG notes that the SmPC for galcanezumab[28] states that evaluation of the need to continue treatment is recommended regularly following initial assessment of response. Advice from the ERG's clinical advisor suggests that continued lifetime treatment with galcanezumab is unlikely and that in practice it is likely that patients would periodical discontinue treatment. The clinical advisor to the ERG, however, also highlighted that such discontinuation of treatment may be temporary and that the majority of patients who discontinue treatment are likely to subsequently resume treatment.

The ERG further highlights that the assumption of continued treatment is very important when considering the relative cost-effectiveness of active therapies, including galcanezumab, to BSC because natural history data suggest that migraine severity and prevalence decline with age. This implies that the benefits of continuous treatment with an active therapy may diminish over time, with important consequences for cost-effectiveness. See Section 4.2.2 for a detailed exploration of this issue.

4.2.5 Perspective, time horizon and discounting

The analyses assumed the perspective of the NHS and Personal Social Services (PSS), and future costs and benefits were discounted at 3.5% per annum.

The time horizon of the base case analyses was 25 years and was considered to represent a lifetime time horizon. Two scenario analyses considering time horizons of 10 and 45 years were also presented. The company justified the choice of a 25-year time horizon noting committee preferences in the appraisal of eremumab and fremanezumab for a lifetime time horizon. The company describes that a 25-year time horizon is sufficiently long for all benefits and costs to be accounted for and that the uncertainty from short-term clinical trial data would inherently make any long-term estimates unreliable. The company also noted that the prevalence of migraine reduces significantly with age and particularly after the menopause.[35]

The ERG considers the company's choice of a 25-year time horizon reasonable in the context of the modelled cohort with an average age of 46. As noted in Section 4.2.3 a longer time horizon may, however be more appropriate if considering an incident population with a younger mix of patients. The ERG, further notes that the absence of long-term data on the effectiveness of galcanezumab and comparator therapies means that projections over such long-time horizons are subject to significant uncertainty. A long time horizon also exacerbates the problems associated with not modelling natural history and in the view of the ERG this represents a significant weakness in the presented model with

potentially important implications for the estimated cost-effectiveness of galcanezumab. See Section 4.2.2 for further discussion.

4.2.6 Treatment effectiveness

As described in Section 4.2.2, migraine frequency is captured using probability distributions which describe the proportion of patients across the 30 migraine health states. The treatment effect in the model operates by shifting these distributions through mean monthly MHD, with separate distributions modelled for responders, non-responders, and those who discontinue treatment. The effectiveness of a specific treatment is determined by the proportion of patients classified as a responder, non-responder or "discontinuer" as well as the mean monthly MHDs for each of these groups. The following sections describe the data and assumptions made by the company to populate the proportion of patients classified as responders, non-responders, and discontinuers, as well as what being in each of these groups means in terms of migraine frequency (monthly MHDs).

1.1.1.2 Response rate

The response rate is assessed at 3 months (90 days) for all treatments. Response was defined as the proportion of patients achieving a ≥ 50% or ≥ 30% reduction in mean monthly MHDs for episodic or chronic migraine, respectively.

In the episodic migraine setting, the response rate was estimated using data from the DTT-3 subpopulation of EVOLVE-1 and -2, and CONQUER. In the HFEM subgroup analysis the response rate was obtained from the DTT-3 population of the CONQUER trial.

For the chronic migraine population, response rates were drawn from the DTT-3 population of the CONQUER trial with the response rate for botulinum toxin A assumed to be equivalent to galcanezumab. This assumption of equivalent response rates was justified on the basis of the ITC for 'all-comers' and 50% response rate, which found no evidence of statistically significant difference in response rates. The modelled response rates and their respective sources are shown in Table 20.

Table 20 Proportion of responders at the 3-month assessment

Analysis	Galcanezumab	Comparator	Source
Episodic (vs. BSC) – 50%	[redacted]	[redacted]	Naïve pooled response rate from the DTT-3 population from EVOLVE-1, -2 and CONQUER
Chronic (vs. BSC) – 30%	[redacted]	[redacted]	CONQUER, DDT-3
Chronic (vs. botulinum toxin type A) – 30%	[redacted]	[redacted]	CONQUER, DTT-3

High Frequency Episodic Migraine (vs. BSC) – 50%	[redacted]	[redacted]	CONQUER, DTT-3

BSC, best supportive care; DTT-3, difficult to treat population who have failed on ≥ 3 previous therapies.

ERG comment

Source of response data

The company appears to take a selective approach to modelling the proportion of responders. In the episodic migraine population data is drawn from a naïve pooling of all relevant studies, while in the chronic migraine population the company selects only the CONQUER trial when relevant data are also available from REGAIN. Because response data at the 30% threshold in the DTT-3 population is not reported for REGAIN in the CS, the ERG is unclear of the impact of this omission.

Assumption of equal response rates for galcanezumab and botulinum toxin

The company cites the reason for rejecting the ITC results and assuming equal response rates for galcanezumab and botulinum toxin A, to be the lack of a statistically significant difference in response rates based on the ITC of the 50% response rate in the 'all-comers' population. The ERG does not agree that this is a valid reason to exclude the results of the ITC, a non-statistically significant finding only suggests uncertainty regarding the magnitude of the difference and a properly specified model should account for this uncertainty. The ERG however, does consider there to be a degree of validity to the assumption of equal response rates given the data available. Data on response for botulinum toxin A patients is limited to the 50% criteria (and not available for the more relevant 30% cut-off) and is only available for the 'all-comers' population. Modelling of treatment effect on response therefore would require assumptions to be made regarding the generalisability of the results of the ITC to both a different population and outcome measure. There are also a number of other issues identified with the ITC regarding the comparability of the patient populations, completeness of data, as well as notable differences in the proportion of placebo responders which may further justify rejecting the estimates obtained from the ITC (see Section 3.4.2). Regarding this specific assumption the ERG, however, notes that similar assumptions were accepted in the appraisal of fremanezumab.[16]

The ERG also notes that we are asked to accept the results of a similar ITC for the outcome change from baseline in monthly MHDs. While this analysis is subject to fewer limitations than the ITC for response, due to data being available for the same outcome and in the DTT-3 population, other limitations of the ITC remain. This is a potential inconsistency and if we are to accept the results of the ITC of MHDs then arguably we should do this so for all outcomes. In Section 6 alternative assumptions are explored by the ERG regarding how to incorporate the results of the ITCs.

1.1.1.3 Change in monthly migraine headache days: Responders and non-responders

Following the assessment of response in the model, responders and non-responders experience a change in mean monthly MHDs. The magnitude of the change is dependent upon the population under consideration, the treatment received and in the case of chronic migraine the comparison being made.

For all comparisons between galcanezumab and BSC (EM, HFEM and CM populations) the magnitude of the change in monthly MHDs was based on the relevant DTT-3 subpopulation of the CONQUER trial.

In the comparison between galcanezumab and botulinum toxin A (CM population only) evidence on the respective size of the change in monthly MHDs for botulinum toxin A responders is not available. The company therefore approximates the change in MHDs using data from an ITC of MHDs implemented in the DTT-3 population. Importantly, this ITC does not distinguish between responders and non-responders and is for the whole DTT-3 population i.e. responders and non-responders combined. The company therefore makes a number of assumptions about the change in monthly MHDs for responders and non-responders. For galcanezumab responders, the change in monthly MHDs is estimated based on a pooled analysis of the REGAIN and CONQUER trials, using data on change in monthly MHDs for the whole population i.e. responders and non-responders combined. For botulinum toxin A responders, the change is estimated relative to galcanezumab using the results of the ITC on change in MHDs, which reports a reduction of [redacted] MHDs per month. For both galcanezumab and botulinum toxin non-responders, the change in MHDs is derived by pooling the placebo arms of REGAIN and CONQUER. A summary of the change in MHDs for each population and comparison is present in Table 21.

Table 21 Change from baseline in mean MHDs for responders and non-responders

Analysis	Galcanezumab	Comparator	Source
Episodic (vs. BSC)			
Responders	[redacted]	[redacted]	CONQUER DTT-3 population
Non-responders	[redacted]	[redacted]	CONQUER DTT-3 population-
Chronic (vs. BSC)			
Responders	[redacted]	[redacted]	CONQUER DTT-3 population
Non-responders	[redacted]	[redacted]	CONQUER DTT-3 population
Chronic (vs. botulinum toxin type A)			
Responders	[redacted]	[redacted]	GMB values from GMB arms of REGAIN and CONQUER (DTT-3), botulinum toxin A

			calculated relative to GMB based on ITC
Non-responders	[redacted]	[redacted]	Pooled Placebo arms of REGAIN and CONQUER (DTT-3)
High Frequency Episodic Migraine (vs. BSC)			
Responders	[redacted]	[redacted]	CONQUER DTT-3 population
Non-responders	[redacted]	[redacted]	CONQUER DTT-3 population

BSC, best supportive care; DTT-3, difficult to treat population who have failed on ≥ 3 pervious therapies; GMB, galcanezumab; MHD, migraine headache days.

Responders to active therapies are assumed to retain their change in monthly MHDs for the duration of the model time horizon. Responders to BSC are assumed to wane back to baseline monthly MHDs over a period of 12 cycles. Non-responders are assumed to discontinue treatment following response assessment, at which point they wane back to baseline MHDs over time. The duration of this waning varies according to the treatment received and the population considered. See Section 1.1.1.5, Table 23 for a summary of the respective waning assumptions.

ERG Comment

The ERG has concerns with the sources used to generate the CFB in MHDs, the assumption of waning in responders to BSC, the approach used to generate values in the botulinum toxin A comparison, and the use of the ITC for the botulinum toxin A comparison. These are discussed below.

Sources of data used

As with the response data used in the model, the company appears to have taken a selective approach regarding which data sources to use in the model.

In the episodic population the company have omitted to use relevant data from EVOLVE-1 and -2, despite the fact that data on response are taken from a pooled analysis of the EVOLVE trials (1 and 2) and CONQUER. In the chronic migraine BSC comparison, the CONQUER trial is used, omitting data available from REGAIN. This is consistent with the response data used but stands in contrast to the botulinum toxin A comparison where values are sourced from both the CONQUER and REGAIN trials.

The reasons for this inconsistent approach are not clear. In general an approach based on using all available data would be more rational and would act to reduce uncertainty. Similar to the response outcome, the impact of the company's selective approach is unknow because relevant values were not reported as part of the CS.

Waning of response in BSC patients

The company's base-case assumes that any response to BSC is not durable and that patients wane back to baseline MHDs over a period of 12 months. Underlying this assumption is the fact that response to BSC is based on the placebo arm of the relevant trial evidence and therefore does not reflect the benefit of therapy but rather the combination of factors that constitute the placebo effect.

The contention that placebo effects are not durable is, however, a debatable issue and unknown given the lack of longer-term comparative evidence. Placebo effects may plausibly reflect several factors that would lead to persistent response. These could include the effects of regression to the mean, natural history and response to 4th line preventive treatments that would comprise BSC. The assumption that these effects wane is therefore subject to uncertainty.

Further, even if one accepts the underlying assumption that the placebo effect is not durable, the ERG questions whether unilateral application of waning is appropriate. This is because the effects of galcanezumab as observed in the supporting trial evidence will also include a placebo effects (this is one reason why relative treatment effects are measured relative to placebo and not to baseline). The waning of the placebo effects would therefore act on both treatment arms equally, such that a proportion of responders to galcanezumab will also wane back to baseline.

Given these uncertainties regarding the persistence of placebo effects, the ERG considers a series of scenarios in Section 6 exploring alternative assumptions regarding the response to BSC and the persistence of the placebo effect.

Inconsistent approach to modelling of botulinum toxin A comparison

The ERG accepts that the lack of stratified data on change in monthly MHDs for botulinum toxin A by responder status, means that some assumptions must be made but finds the logic of the company's approach difficult to comprehend. The company's approach appears to be centred on the assumption that the relative difference in MHDs for the whole population is indicative of the relative difference in monthly MHDs for responders. This assumption, however, cannot hold when the change in MHDs for non-responders and the response rate are assumed to be the same across both treatment groups, and necessarily implies that the model will make predictions that do not align with the results of the ITC. See Appendix 1 for a simple mathematical proof of this assertion. Indeed, where the response rate is < 100% this approach will imply that the model will predict a difference in MHDs that is lower than that estimated by the ITC. Even if we accept this assumption on the grounds that this is an approximation, it is unclear why the company took an approach in which the values used for galcanezumab contradict those used in the BSC – relative effects could have been applied to the values used in the BSC comparison. This means that the model makes predictions that contradict the

supporting trial evidence and importantly means that an incremental analysis in which the cost-effectiveness of galcanezumab, BSC and botulinum toxin A is assessed cannot be conducted.

Validity of ITC

As noted in Section 3.3, there are several concerns regarding the comparability of the trials included in the ITC and concerns as to whether the included trials are sufficiently homogeneous to satisfy the consistency assumption. Specifically, differences were noted in the definition of migraine headache; the statistical methods for calculating treatment effects; the assessment periods and the placebo used.

The impact of the differences between included studies is unknown, but it means that the results of the ITC are subject to uncertainty beyond that captured in the confidence intervals and by extension in the probabilistic economic analysis. Further, because the magnitude and direction of any bias resulting from these differences is unknown, it is unclear whether the estimated benefits of galcanezumab are either in whole or in part, a reflection of these potential biases. As such, the results of the economic analysis for the comparison between galcanezumab and botulinum toxin A should be interpreted with caution.

1.1.1.4 Discontinuation rate

The per cycle discontinuation probabilities applied differed in the assessment and post assessment periods. The values used in the assessment period were common across subpopulations with values for BSC and galcanezumab drawn from the CONQUER trial. The corresponding values for botulinum toxin A were drawn from the PREEMPT trials. In the post assessment period, the per cycle discontinuation probability for galcanezumab was drawn from the open label CGAJ study. This study assessed the safety and tolerability of galcanezumab over a period of 12 months. The modelled rate of discontinuation was based only on those patients classified as discontinuing due to AEs; patients discontinuing for other reasons were therefore excluded from this calculation. The modelled per cycle discontinuation probability for botulinum toxin A was based on data from the COMPEL study.[36] This study was a prospective open label trial which followed up patients receiving botulinum toxin A for a period of 108 weeks. Table 22 summarises the per cycle discontinuation probabilities applied in the model.

Table 22 Probability of discontinuation (adapted from Table 58 & Table 59 CS pg. 124 & 125)

	Probability of discontinuation	Reference
Assessment period		
Galcanezumab	[redacted]	CONQUER CSR[37]
Botox*	[redacted]	Diener et al. 2014[38]
BSC	[redacted]	CONQUER CSR[37]
Post assessment period		

Galcanezumab	[redacted]	Study CGAJ[39]
Botulinum toxin A*	[redacted]	COMPEL trial[36]
BSC	[redacted]	Study CGAJ[39]

* only applicable for chronic migraine patients with a history of at least 3 prior treatment failures

ERG comment

The ERG considers the sources used by the company to model to be generally reasonable, but has some concerns about the validity of using these values in a comparative context and the plausibility of the rates of discontinuation implied. Specifically, the ERG notes that these studies are in quite different populations. The COMPEL study is only in chronic migraine patients while the CGAJ study is combination of both episodic and chronic patients. As such the COMPEL study considers a population with much greater frequency of migraine headache (11.4 vs 22 MHD per month). The predicted rates of discontinuation are also very different with the rate applied to galcanezumab being four times that applied to the botulinum toxin A arm of the model. This difference in the discontinuation rate seems very large and does not fully align with the data from these studies which actually suggests that a smaller proportion of galcanezumab patients experienced serious AE than on botulinum toxin A patients (4.8% vs 10.5%). This higher rate of discontinuation also stands in contrast with the rates of discontinuation observed in the trial evidence which suggest that the short-term rate of discontinuation is actually higher for botulinum toxin A.

This model difference in the discontinuation rate is important in the context of the company's base-case and acts to favour of galcanezumab. This is due to the fact that patients discontinuing galcanezumab are assumed to benefit from a further reduction in MHDs over and above those enjoyed by responders to treatment. Increasing the discontinuation rate for galcanezumab therefore leads to the ICER decreasing. However, under more plausible assumptions, where discontinuers do not receive a premium, this differential rate of discontinuation acts in the favour of botulinum toxin A.

Given the lack of comparative evidence on the rate of discontinuation and the potential for this parameter to distort the results of the economic analysis, the ERG considers that a more reasonable assumption would be to assume equal rates of discontinuation across both active treatments. Section 6 therefore present scenario analysis considering alternative assumptions regarding the rate of discontinuation in the post assessment period.

1.1.1.5 Change in monthly migraine headache days for "discontinuers"

Patients classified as discontinuers comprise of two subgroups – those who discontinue prior to assessment of response and those who discontinue in the post assessment period. In both groups, patients are assumed to wane back to baseline monthly MHDs. The position from which they wane

from however, differs. Patients discontinuing in the assessment period are assumed to be non-responders and therefore wane back from the mean monthly MHDs for this group. Patients discontinuing in the post assessment period wane back from the corresponding mean monthly MHDs for responders.

The period over which patients wane back to baseline MHDs is assumed to be common across both these subgroups of discontinuers, but differed according to the population modelled and treatment under consideration. For galcanezumab patients, the waning period was estimated by extrapolating data from the pivotal trials, several of which included a washout period in which patients were observed following discontinuation of treatment. For the EM and HFEM populations, the EVOLVE-2 trial was used to model the waning period. In the chronic population, the REGAIN trial was used to model the waning period. A linear extrapolation was assumed in both populations. The waning period for BSC and botulinum toxin A were based on assumptions. The waning periods for each treatment and population are summarised in in Table 23.

Table 23 Modelled discontinuation parameters

Analysis	Galcanezumab	Comparator	Source
Episodic (vs. BSC)			
Waning period (months)	[redacted]	[redacted]	EVOLVE-2, 'all-comers' population
Chronic (vs. BSC)			
Waning period (months)	[redacted]	[redacted]	REGAIN, 'all-comers' population
Chronic (vs. botulinum toxin type A)			
Waning period (months)	[redacted]	[redacted]	REGAIN, 'all-comers' population
High Frequency Episodic Migraine (vs. BSC)			
Waning period (months)	[redacted]	[redacted]	EVOLVE-2, 'all-comers' population

BSC, best supportive care.

ERG Comment

The ERG is satisfied with the company's underlying assumption that patients discontinuing treatment wane back to baseline monthly MHDs but has several substantial concerns regarding the period over which they are assumed to wane.

The concerns centre around the quality of the data used to generate the predicted waning periods and concerns regarding the clinical and face validity of the estimates produced.

With regard to the quality of the data used, the ERG notes that the estimated waning periods are based on very short term follow up data of just 4 months. This limited follow up is of concern in the context of the length of the projected waning periods which range from [redacted] months. The ratio of extrapolated to observed data is therefore very high. The extrapolation of this limited data also relies on the assumption that waning is linear; an assumption that does not appear to be supported by the REGAIN wash out data (Section 3.2.1). Further, it is not clear that the washout data are generalisable to a population discontinuing due to adverse events rather than as part of a protocol driven washout period.

The waning periods applied in the model for the chronic population are very long, and imply a waning period that is significantly longer (24x) than that assumed for botulinum toxin A. The ERG considers this unreasonable without some evidence to justify a different waning period across these two active therapies. The ERG also considers the difference in waning period between chronic and episodic migraine patients difficult to justify clinically with chronic migraine patients assumed to wane back over a period that is 4 times longer than episodic patients ([redacted] months). Further, the ERG fails to comprehend why different waning periods are used for galcanezumab depending on the treatment it is being compared to. This is inconsistent and serves to undermine the potential for an incremental cost-effectiveness analysis. Because of the way it is implemented, this assumption also means that patients discontinuing treatment experience an initial decline in MHDs i.e. discontinuing leads to an improvement in symptoms.

Given these concerns regarding the predicted waning period, the ERG presents several scenarios in Section 6, in which alternative assumptions are made regarding the duration of the waning period.

4.2.7 Health related quality of life

To model the impact of migraine on HRQoL, utility values were assigned to each of the 30 health states. Utility values were derived by mapping MSQ v2.1 values collected in the CONQUER trial (whole population) to EQ-5D-3L using a published mapping algorithm.[23] The same utility set was used for patients with episodic and chronic migraine. This broad approach is consistent with that adopted in the previous appraisals of erenumab and fremanezumab.[15, 16]

The company noted in their submission that EQ-5D data were collected as part of the CONQUER trial. The company, however, considered the mapped MSQ v2.1 values a preferable source of HRQoL data. This was justified on the basis that the EQ-5D data collected, required patients to evaluate their HRQoL on the day of the clinical visit. The company outlined that this may lead to elicited values underestimating the impact of migraine on HRQoL, due to more severe patients not attending clinical visits. Consistent with this argument, a comparison of mapped and directly generated utility values

shows that mapped values predict a substantially larger impact of migraine frequency on HRQoL, see CS Figure 18.

To evaluate the most appropriate approach to modelling utilities, the company consider several alternative assumptions. The assumptions considered were:

- Whether separate utility sets should be used for episodic and chronic migraine patients;
- The functional form of the relationship between utility values and migraine frequency;
- Whether a treatment effect should be included to reflect differences in HRQoL over and above those reflected in migraine frequency.

Regarding whether separate utility data sets should be used for episodic and chronic migraine patients, a comparison of HRQoL values for the two found that the predicted values were generally consistent across the two groups, with only limited evidence of divergence in patients experiencing > 14 monthly MHDs. On this basis, the company concluded that it was reasonable to use a common utility set across both groups.

With regards to the appropriate functional form, the company found that linear and quadratic models both fitted the data well, with the quadratic relationship observed to have a moderately better fit based on AIC and BIC criteria. The company, however, selected the linear model on the grounds that this is a more parsimonious model. The ERG notes also that this is consistent with the previous appraisals of erenumab and fremanezumab.

In exploring the possibility of a treatment related difference in utility values, the company noted that the utility values for galcanezumab were higher across all mean MHD values compared with placebo. Further, regression analysis demonstrated a strong, statistically significant, benefit of galcanezumab relative to placebo. To align with previous committee preferences for a common utility set across treatment arms, the company, however, chose to ignore this evidence and opted not to use treatment specific utility values in the base-case analysis. Scenario analysis presented by the company exploring the use of treatment specific utilities showed it had a modest impact on ICER values.

Table 24 illustrates the utility values applied in the economic model for each MHD health state. In line with the assumptions outlined above, the utility values used in the model were common to both the EM and CM populations, as well as to all treatments and comparators modelled. Based on the modelled utilities, the utility for patients ranges from [redacted] for patients experiencing 30 migraine days a month to [redacted] in patients experiencing no migraine days per month.

Table 24: Utility values for each MHD health state (from Table 61, CS)

MHD	On treatment (pooled)

0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
13	[redacted]
14	[redacted]
15	[redacted]
16	[redacted]
17	[redacted]
18	[redacted]
19	[redacted]
20	[redacted]
21	[redacted]
22	[redacted]
23	[redacted]
24	[redacted]
25	[redacted]
26	[redacted]
27	[redacted]
28	[redacted]
29	[redacted]
30	[redacted]

Abbreviations: MHD, migraine headache day.

ERG comment

Appropriateness of the CONQUER trial as source of utility values

The ERG notes two related issues regarding the source of the MSQ data used to generate the utility values used in the model. Firstly, that the utility values were based on the whole population of the CONQUER trial and not just on the relevant subgroup of patients who have failed ≥ 3 previous

preventative therapies. Secondly, that the utility values are based on data from the CONQUER trial alone, even though relevant HRQoL data were collected in both EVOLVE trials, as well as in the REGAIN trial.

In response to queries raised by the ERG at the PFC stage, the company justified the decision to use the CONQUER trial alone by noting that the EVOLVE and REGAIN trials included treatment naïve patients. As such the company considered that the CONQUER trial, which restricted recruitment to patients who had failed 2 to 4 preventive medication categories (not treatments), was most representative of the modelled population. The ERG agrees with the company's logic, but notes that the whole CONQUER trial population represents a broader population of patients than would be eligible for treatment with galcanezumab. As such, the predicted utility gains may not reflect those realised in the more restrictive population of patients who have failed ≥ 3 previous preventative therapies. Further, the ERG notes that because of the availability of relevant HRQoL from the EVOLVE and REGAIN trials in patients who have failed ≥ 3 previous preventative therapies, there is no need to utilise this broader population to generate utility values. The ERG also notes that scenario analysis presented by the company using the relevant subpopulation of patients who have failed ≥ 3 previous preventative therapies from all four trials results in a substantial increase in the ICER.

Appropriateness of treatment related utilities

Despite the company's conservative assumption to use a single set of utility values for both galcanezumab and BSC patients, compelling clinical evidence was presented to support the use of differential utilities. While no clinical explanation for these differences is presented by the company, the ERG considers that there is scope for such differential utilities between treatments as a result of uncaptured benefits. Specifically, the ERG notes that the company model does not capture either severity of migraine or frequency of headache. Both of these factors have the potential to drive HRQoL over and above a reduction in MHD and may explain the observed differences between treatment arms. Further, the ERG highlights supporting clinical evidence provided in Section 3.4 of the CS which reports a reduction in HDs that exceeds the reduction in MHDs. With regard to the previous appraisals, the ERG notes the lack of compelling empirical or clinical evidence presented to justify the use of differential utility values.

External validity of predicted utilities

In the general population of individuals aged 46 (the average age of the modelled cohort) mean utility is estimated to be 0.847 based on values reported in Ara and Brazer (2011).[40] This is notably higher than the utility value computed for patients experience zero MHD's which range from [redacted] to [redacted] depending on the source population. This apparent inconsistency, however, may be explained by limitations in the model structure which makes no account of severity, and by extension, headache frequency. Clinical advice received by the ERG suggested it is common that migraine patients will

continue to experience frequent headaches even when migraine days are significantly reduced. Further, our clinical experts commented that it is common for migraine patients to have co-morbidities which may also act to impact upon quality-of-life, further depressing reported utility values.

Generalisability of utility values over the time horizon

A limitation of the approach to modelling HRQoL is the assumption that utility values remain constant throughout the time horizon of the model and therefore make no account of the fact that quality of life may evolve over time. The impact of this omission may be considerable given the long-time horizon of 25 years, as there is significant scope for natural history to impact on the underlying severity of headache and migraine, as well as for the effects of aging to impact upon quality-of-life. The impact of natural history on quality-of-life is unknown, but it is reasonable to expect that the severity of headache and migraine declines in line with frequency and therefore that the disutility associated with migraine days will diminish over time. The impacts of aging may also act to assuage the benefits of reducing migraine days due to the accumulation of co-morbidities and increased frailty associated with aging. In this regard the ERG notes it is common when considering long-time horizons for utilities to be adjusted to account for the impact of aging and that this practice has been accepted on multiple occasions in previous technology appraisals considering extended time horizons.

4.2.8 Resources and costs

The company's model included galcanezumab acquisition costs, administration costs along with health state costs that were associated with the management of acute migraine.

Galcanezumab acquisition costs were sourced from MIMS and estimated per cycle based on a dose of 120 mg every 30 days. In line with the SmPC, the model allows for a loading dose of 240 mg in the first cycle. Administration costs for galcanezumab were included in the first cycle and account for the training of patients to self-administer. No further administration costs were included thereafter – implying all patients can successfully self-administer galcanezumab.

The botulinum toxin type A treatment cost comprised an acquisition cost and a regular administration cost based on an 84 day (12-week dosing) schedule. Drug acquisition costs for botulinum toxin type A were based on the British National Formulary (BNF) and estimated per cycle as per galcanezumab. A confidential CMU discount is available for botulinum toxin A. All analyses presented by the company is exclusive of this discount. Administration costs were based on NHS tariffs, follow-up attendance for single professional (code 400).[41]

Additional costs associated with acute medication received were assumed to vary in line with MHD and were included as part of health state costs. Table 25 summarises the drug and acquisition costs applied in the model per cycle.

Table 25: Unit costs of the elements of prophylactic treatment

	Pack cost	Cost per 30 day cycle	Initial administration costs	Administration costs – ongoing per cycle	Total cost per cycle
Galcanezumab 120mg	List price: £386.50 PAS Price: [redacted]	List price: £386.50 PAS Price: [redacted]	£39.68	£0.00	[redacted] in the first cycle [redacted] thereafter.
Botulinum toxin type A 200 mg	£276.40	£98.74	£0.00	£41.43	£140.17

PAS, patient access scheme.

ERG comment

The ERG notes the omission of any administration costs for galcanezumab beyond the first cycle and the implicit assumption that all patients will be able self-administer. Consultation with clinical advisors to the ERG suggests that this is not a reasonable assumption and that it is likely that a proportion of patients will not be able to self-administer. This may be for a range of reasons. For example, people with physical or mental disabilities, the elderly or those who have a phobia of needles may not be able to self-administer. The ERG further notes that in the appraisal of fremanezumab the committee concluded it was unlikely that everyone having fremanezumab would be capable of self-administering treatment for the reasons outlined above.[16] In that appraisal it was agreed that applying an administration costs for 10% of people was reasonable, though this proportion was subject to uncertainty and had little effect on the model results. For parity with the previous appraisal of fremanezumab, the ERG implements a scenario in Section 6 applying an administration cost for 10% of galcanezumab patients.

The SmPC states that in patients receiving galcanezumab the need to continue to treatment should be evaluated regularly.[28] The company's economic model, however, does not include any monitoring costs to account for the routine review that patients would undergo. The ERG considers this a potential omission from the model, as advice received from clinical advisors to the ERG suggests that patients would normally be reviewed every 6 to 12 months to evaluate the need to continue therapy. The ERG, however, also highlights that the economic model does not permit "positive" discontinuation (i.e. discontinuation in successfully treated patients). This may mitigate the need to

include such costs, as to include them would be inconsistent with the underlying assumption of continuous treatment. See Section 4.2.4 for a full discussion of positive discontinuation.

1.1.1.6 Disease management

Other included healthcare resources identified by the company as supportive of the condition were: GP visits, emergency department visits, hospitalisations, nurse practitioner consultations and neurologist consultations. Unit costs were obtained from the most recent NHS reference cost schedule [42] and the Personal Social Services Research Unit (PSSRU) handbook.[43] The rates of consumption of these resources were sourced from Munakata et al,[44] a US specific survey of migraine patients. In line with values reported in Munakata et al[44] resource use varied with monthly migraine frequency, with a greater frequency of migraines associated with greater healthcare costs. Unit costs associated with the management of migraine are reported in Table 64 of the CS and model cycle consumption rates are presented in Table 65 of the CS, along with the total per cycle cost of disease management by MHD health state.

In addition to the healthcare resources described, the economic analysis also captures acute medication use, which similarly varied by monthly MHD. Acute medication costs included those associated with triptans, acetaminophen (paracetamol and containing products) and NSAIDs. Resource costs per MHD were estimated based on resource data collected as part of the CONQUER trial, full details of which are reported in Appendix V of the CS.

Unit costs used in the economic model are presented in Table 64 of the CS and model cycle consumption rates are presented in Table 65, along with the total per cycle cost of disease management by MHD health state.

ERG comment

The costs attributable to each of the 30 health states have an important role in the economic analysis, with an associated impact on cost-effectiveness. For example, in the EM sub-population the costs associated with the management and acute care of migraine account for 54% of total costs in the galcanezumab arm and 100% in the BSC. Within the company's economic analysis, about three quarters of the health state costs are associated with the supportive management of migraine, with the remainder attributed to acute medications used. Increasing the costs associated with either the management or acute treatment of migraine will tend to favour more effective therapies as it increases the costs associated with managing migraine.

In considering the values used by the company to populate these costs the ERG is relatively satisfied with the company's approach to the modelling of acute treatment costs, which are drawn principally from the available trial evidence, an approach consistent with the previous appraisals of erenumab and

fremanezumab. The ERG, however, has some concerns about the company's approach to modelling the healthcare and management costs associated with migraine and in particular those used to estimate the consumption rates of healthcare resources.

In the erenumab and fremanezumab appraisals the use of healthcare resources was based on the National Health and Wellness Survey (NHWS) 2016.[45] This study aimed to characterise the incremental migraine burden from the European patients' perspective according to frequency of migraine. The study included patients from five European countries (France, Germany, Italy, Spain and the UK). The NHWS study collected cross section data from respondents based on headache days with healthcare consumption evaluated based on four categories of headache days per month < 4, 4 to 7, 8-14, > 14. In this appraisal the company did not use the NHWS study, but instead opted to use a US survey Munakata et al,[44] which presented data on average healthcare resource in migraine population along with the average migraine days per month. Unlike the NHWS study, the Munakata et al[44] study did not explore the impact of migraine or headache days on healthcare consumption. To model the relationship between the MHDs and healthcare consumption the company therefore assumed a simple linear relationship between MHD and resource use by dividing average resource use by the average number of migraine days to generate figures per MHD.

In considering the appropriateness of these two approaches the ERG notes the company's comment in their submission that the resource rates are similar to those used in previous appraisals and that the method employed allows for a more complete relationship between MHD and resource consumption. The ERG, however, contests this statement and notes that resource consumption rates tend to be higher using the company's approach than using the data available from the NHWS. See Table 26 for a side by side comparison. Furthermore, the ERG considers that there are several factors that favour the use of the NHWS. Firstly, the NHWS study is more likely to be representative of resource consumption in the NHS given the population recruited is based on European patients, including UK patients. Secondly, the NHWS includes information on how resource use relates to frequency of headache. This avoids the need to make strong assumptions about the relationship between migraine frequency and healthcare utilisation. The ERG notes that the assumption of a linear relationship between MHD and healthcare utilisation is entirely arbitrary and is not supported by the available data from the NHWS. Thirdly, the ERG considers that there is a case for using the NHWS on the grounds that this is consistent with the previous appraisals and allows for a greater degree of parity in the evaluation of the cost-effectiveness of the alternative CGRPs. In this regard it is important to note that use of the Munakata et al[44] study offers an advantage to galcanezumab as predicted care costs are greater using the Munakata et al[44] study compared with the NHWS.[45]

Table 26 Side by side comparison of health state consumption rates (derived from CS Table 65)

MHD	Hospitalisations		A&E Visits		GP Visits		Nurse Practitioner Visits		Neurologist Visits	
	Munakata	NHWS	Munakata	NHWS	Munakata	NHWS	Munakata	NHWS	Munakata	NHWS
0	0	0.023	0	0.030	0	0.202	0	0.063	0	0.003
1	0.0039	0.042	0.0088	0.067	0.0379	0.288	0.0379	0.102	0.0116	0.015
2	0.0078	0.042	0.0176	0.067	0.0758	0.288	0.0758	0.102	0.0232	0.015
3	0.0117	0.042	0.0264	0.067	0.1137	0.288	0.1137	0.102	0.0348	0.015
4	0.0156	0.040	0.0352	0.058	0.1516	0.413	0.1516	0.175	0.0464	0.013
5	0.0195	0.040	0.0440	0.058	0.1895	0.413	0.1895	0.175	0.0580	0.013
6	0.0234	0.040	0.0528	0.058	0.2274	0.413	0.2274	0.175	0.0696	0.013
7	0.0273	0.040	0.0616	0.058	0.2653	0.413	0.2653	0.175	0.0812	0.013
8	0.0312	0.040	0.0704	0.092	0.3032	0.553	0.3032	0.048	0.0928	0.038
9	0.0351	0.052	0.0792	0.092	0.3411	0.553	0.3411	0.048	0.1044	0.038
10	0.0390	0.052	0.0880	0.092	0.3790	0.553	0.3790	0.048	0.1160	0.038
11	0.0429	0.052	0.0968	0.092	0.4169	0.553	0.4169	0.048	0.1276	0.038
12	0.0468	0.052	0.1056	0.092	0.4548	0.553	0.4548	0.048	0.1392	0.038
13	0.0507	0.052	0.1144	0.092	0.4927	0.553	0.4927	0.048	0.1508	0.038
14	0.0546	0.052	0.1232	0.092	0.5306	0.553	0.5306	0.048	0.1624	0.038
15	0.0585	0.052	0.132	0.117	0.5685	0.585	0.5685	0.127	0.1740	0.073
16	0.0624	0.052	0.1408	0.117	0.6064	0.585	0.6064	0.127	0.1856	0.073
17	0.0663	0.052	0.1496	0.117	0.6443	0.585	0.6443	0.127	0.1972	0.073
18	0.0702	0.052	0.1584	0.117	0.6822	0.585	0.6822	0.127	0.2088	0.073
19	0.0741	0.052	0.1672	0.117	0.7201	0.585	0.7201	0.127	0.2204	0.073
20	0.0780	0.052	0.1760	0.117	0.7580	0.585	0.7580	0.127	0.2320	0.073
21	0.0819	0.052	0.1848	0.117	0.7959	0.585	0.7959	0.127	0.2436	0.073
22	0.0858	0.052	0.1936	0.117	0.8338	0.585	0.8338	0.127	0.2552	0.073
23	0.0897	0.052	0.2024	0.117	0.8717	0.585	0.8717	0.127	0.2668	0.073
24	0.0936	0.052	0.2112	0.117	0.9096	0.585	0.9096	0.127	0.2784	0.073
25	0.0975	0.052	0.2200	0.117	0.9475	0.585	0.9475	0.127	0.2900	0.073
26	0.1014	0.052	0.2288	0.117	0.9854	0.585	0.9854	0.127	0.3016	0.073

27	0.1053	0.052	0.2376	0.117	1.0233	0.585	1.0233	0.127	0.3132	0.073
28	0.1092	0.052	0.2464	0.117	1.0612	0.585	1.0612	0.127	0.3248	0.073
29	0.1131	NA	0.2552	NA	1.0991	NA	1.0991	NA	0.3364	NA
30	0.1170	NA	0.2640	NA	1.1370	NA	1.1370	NA	0.3480	NA

NHWS, National Health and Wellness Survey

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Galcanezumab has a confidential PAS, comprising a simple discounted price of [redacted] per 120mg dose. This is a discount of approximately [redacted] on the list price.

The cost effectiveness results outlined in this section are provided from a corrected and updated company analysis following the ERG's clarification questions and subsequent model corrections. The results presented below include the simple PAS discount for galcanezumab. Note that the company do not present a combined analysis for all migraine patients in which the outcomes of EM and CM are combined.

5.1.1 Base case results

Table 27 presents the base-case deterministic analysis of galcanezumab for the EM population. It shows that galcanezumab was associated with increased costs (cost difference of [redacted]) and was more effective (gain of [redacted] QALYs), compared with BSC. The company's base-case ICER was £29,230 per QALY.

Table 27 Updated company base case results: Episodic migraine, vs BSC (Table 53, PFC response)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,230

For the CM population comparisons were presented with both BSC and botulinum toxin A. Incremental results cannot be generated using the company's base-case model because of the alternative modelling approaches used in these two comparisons. As noted in Section 4.2.2 and Section 1.1.1.3 this is a fundamental weakness in the company's approach to modelling the comparison between galcanezumab and botulinum toxin A. As a consequence of this limitation results of the company's economic analysis for the CM population are presented separately for each comparator, see Table 28 and Table 29.

In the comparison with BSC, galcanezumab was associated with increased costs (cost difference of [redacted]) and was more effective (gain of [redacted] QALYs), compared with BSC. The company's base-case ICER was £8,080 per QALY.

In the comparison with botulinum toxin A, galcanezumab was associated with increased costs (cost difference of [redacted]) and was more effective (gain of [redacted] QALYs), compared with botulinum toxin. The company's base-case ICER was £2,560 per QALY.

Table 28 Updated company base case results: Chronic migraine, vs BSC (Table 54, PFC response)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,080

Table 29 Updated company base case results: Chronic migraine, vs botulinum toxin (Table 55, PFC response)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Botulinum toxin	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,560

5.1.2 Probabilistic sensitivity analysis

The ERG performed a probabilistic sensitivity analysis (PSA), on behalf of the company using the updated model running 5,000 iterations of the economic model.

In the episodic population the mean probabilistic ICER of galcanezumab compared with BSC was £29,034 per QALY. The cost-effectiveness plane showing the results of the PSA can be seen in **Error! Reference source not found.**. As can be seen from **Error! Reference source not found.**, the cost-effectiveness of galcanezumab is subject to considerable uncertainty and there is a substantial risk that the ICER in this population is greater than the typical thresholds of £20 to £30k per QALY gained.

[redacted]

The mean probabilistic ICER of galcanezumab compared with BSC in the chronic population was £7,987 per QALY. The cost-effectiveness plane showing the results of the PSA can be seen in **Error! Reference source not found.**. As with the Episodic population the mean cost-effectiveness of galcanezumab is subject to considerable uncertainty, however, unlike the EM population this uncertainty is contained well within typical willingness to pay thresholds and as such the probability of the ICER being greater that of £20 to £30k per QALY gained is very low.

[redacted]

The probabilistic ICER in the comparison with botulinum toxin was £1,531 per QALY. Similar to the comparison with BSC the cost-effectiveness plane shows a very low probability that the ICER exceeds the typical thresholds of £20 to £30k per QALY gained, see **Error! Reference source not found.**.

[redacted]

5.1.3 Subgroup analysis of high frequency episodic migraine (HFEM)

This analysis used efficacy data from the CONQUER clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have the baseline characteristics of the overall EM population. Responders had baseline mean MHDs of [redacted] compared to [redacted] for non-responders. The galcanezumab treatment effect compared to BSC was [redacted] MHDs in responders and [redacted] MHDs in non-responders. At least a 50% reduction in MHDs was seen in [redacted] of galcanezumab patients and [redacted] of BSC patients.

Table 30 presents the result of the subgroup analysis. The results of this analysis show that incremental costs and QALYs are consistent with the main analyses of EM and CM, with the ICER for galcanezumab versus BSC lying marginally below that in the whole EM population.

Table 30 Updated company base case results: High frequency episodic migraine, vs BSC

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]		
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,346

5.2 Company's sensitivity analyses

The company presented a series of deterministic sensitivity analyses (DSA) in the form of univariate sensitivity analyses to assess the impact of varying key model input parameters upon the ICER. The DSA inputs can be seen in the company's economic model. A series of tornado diagrams summarising the most influential parameters for each population EM and CM are presented in **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.**. The results indicate that varying the rate of response for either galcanezumab, botulinum toxin A, or BSC has a significant impact on the estimated ICER. The reduction in monthly migraine days experienced by responders to treatment was also found to be significant driver of cost-effectiveness

[redacted]

[redacted]

[redacted]

5.3 Additional scenario analysis requested by the ERG and PFC

Several additional scenarios were requested by the ERG and were provided by the company at the clarification questions stage. The scenarios related to the utility values used in the model, the source of treatment effectiveness data used in the model, the methods used in the galcanezumab vs botulinum toxin A comparison, assumptions made regarding the duration of the placebo response, and assumptions made regarding waning following discontinuation of botulinum toxin A. A brief exposition of the issues and results from these analyses is presented below.

HRQoL scenarios

The ERG noted that the company generated the utility values used in the economic analysis from the whole population of the CONQUER trial (i.e. not just patients who failed ≥ 3 preventive treatments). The company therefore supplied an additional analysis where utility values used in the economic model are generated for the subpopulation who failed ≥ 3 prior preventative treatments. The results of this analysis are presented in Table 31.

Table 31 Utility values from CONQUER in the failed ≥ 3 prior preventative treatment subpopulation

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC)	Table 23	[redacted]	[redacted]	£26,847
CM (vs BSC)	Table 24	[redacted]	[redacted]	£7,421
CM (vs Botox)	Table 25	[redacted]	[redacted]	£2,352

In addition to the above, the ERG also highlighted to the company that MSQ data from which utilities were mapped was also available in the REGAIN and EVOLVE studies. As part of the response the company provided an additional scenario analysis in which all four trials were used as a source of utility values. In line with the modelled population, utility values were only drawn from the population of patients who had failed ≥ 3 preventive treatments. Results of this additional analysis are presented in Table 32.

Table 32 Scenario analysis using CONQUER pooled with REGAIN and EVOLVE failed ≥3 prior preventative treatment subpopulation

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC)	Table 32	[redacted]	[redacted]	£37,149
CM (vs BSC)	Table 33	[redacted]	[redacted]	£10,269
CM (vs Botox)	Table 34	[redacted]	[redacted]	£3,254

Source of treatment effectiveness data

At the PFC stage, the ERG noted that the company uses different studies to populate treatment effect parameters within the model, with some based on CONQUER alone, while others combine data from CONQUER and REGAIN. In the company's response they therefore decide to present a series of scenario analyses in which all results were based on the CONQUER trial alone, see Table 33. Unfortunately, no results were presented where all inputs were based on both the CONQUER and REGAIN studies.

Table 33 Scenario analysis using CONQUER inputs only

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC)	Table 42	[redacted]	[redacted]	£29,412
CM (vs BSC)	Table 43	[redacted]	[redacted]	£8,080
CM (vs Botox), fixed effects ITC	Table 44	[redacted]	[redacted]	£2,965
CM (vs Botox), Random effects ITC	Table 45	[redacted]	[redacted]	£2,828

Methods used in the comparison between galcanezumab and botulinum toxin A

At the PFC stage the ERG requested that the company present a scenario analysis using the same modelling approach adopted for the comparison of galcanezumab with BSC (so as to allow for a full incremental analysis). In response, the company provided an analysis in which the mean change from baseline in monthly MHDs for responders was approximated by making assumptions about the mean change from baseline in monthly MHDs for non-responders (assumed equal to BSC). Scenario analyses using this approach are presented in Table 34.

Table 34 Scenario analysis, approximated responder and non-responder MHDs for botulinum toxin A

Population	Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
CM (vs Botox)	Table 47	[redacted]	[redacted]	Galcanezumab Dominates

Post placebo response duration

At the PFC stage the ERG noted that in the company's base-case it is assumed that patients who respond to BSC wane back to baseline after a period of 12 months. As no data are available to support this assumption, the company were requested to justify this assumption and why they did not consider that the placebo effect would impact on both galcanezumab and BSC arms equally. In the company's response, they presented two scenarios considering alternative assumptions regarding the duration of the placebo effect. In the first they assumed that placebo responders maintained their response for the

life-time of the model. In the second, it was assumed that the placebo effect waned after a period of 60 months. The results of this analysis are presented in Table 35.

Table 35 Scenario analysis, dissipation of the placebo effect

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
EM (vs BSC) no dissipation of placebo effect	Table 48	[redacted]	[redacted]	£50,282
CM (vs BSC) no dissipation of placebo effect	Table 49	[redacted]	[redacted]	£18,578
EM (vs BSC) dissipation of placebo effect over 60 months	Table 50	[redacted]	[redacted]	£36,918
CM (vs BSC) dissipation of placebo effect over 60 months	Table 51	[redacted]	[redacted]	£10,239

Waning of treatment effect following discontinuation

As part the clarification process the ERG highlighted that there is a significant difference in the assumed waning period for patients receiving galcanezumab and botulinum toxin A ([redacted] vs 3 months) and that there was no evidence presented by the company to justify this difference. As part of their response, the company provided an additional scenario analysis in which the waning period for both galcanezumab and botulinum toxin A was assumed to be [redacted] cycles based on data from the REGAIN trial. The result of this analysis is presented in Table 36.

Table 36 Scenario analysis where patients who discontinue galcanezumab and botulinum toxin A return to baseline MHDs over 72 cycles

Population	Points for Clarification response Table	Incremental Costs	Incremental QALYs	ICER (£/QALY)
CM (vs Botox)	Table 53	[redacted]	[redacted]	£10,903

5.4 Model validation and face validity check

Validation undertaken by the company

The company stated that the internal validity of the model processes was assessed by an independent third party who undertook a technical validation of the model. This included an assessment of the scope of the model, its ease of use, model inputs, accuracy, sensitivity analyses, VBA coding, and results. The company stated that the model was deemed suitable with only minor discrepancies identified, which were subsequently rectified. The predictions of the economic analysis were compared with the results of the trial to assess their face validity.

Validation undertaken by the ERG

As part of the ERG assessment of the economic analysis the ERG checked the internal validity of the model and considered the face validity of the model's predictions. This included a series of model calculation checks, including pressure tests and formula auditing. The ERG felt that the executable model was in general well presented, but contained a degree of redundancy, in that it contained calculations that did not contribute to model function. Several minor model errors were identified as part of the ERG's validation checks. These errors concerned the timing of when post-response discontinuation was applied; the duration over which waning occurred post discontinuation and the functionality of the probabilistic analysis. A number of inconsistencies were also identified in the values to model the rate of discontinuation. These errors were corrected by the ERG, and a revised model supplied to the company with altered cells highlighted to aid verification. These corrections did not impact substantively on the model's predictions. Revised results are presented in Section 6.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory analyses undertaken by the ERG

The ERG conducted the following exploratory analyses for patients with episodic migraine and chronic migraine.

1) Including galcanezumab administration cost for 10% of patients

As discussed in Section 4.2.8, the ERG considers the company's omission of administration costs beyond the first model cycle to be unrealistic. It is likely that a proportion of the population would not be capable of self-administering galcanezumab. For parity with the appraisal of fremanezumab, the ERG assumes an administration cost for 10% of the population. This has been costed as a 30-minute appointment with a Band 5 hospital-based nurse at an hourly rate of £38.00.[43]

2) Alternative resource consumption rates

In Section 1.1.1.6, the ERG discussed concerns regarding the resource use consumption values used to calculate disease management costs. The ERG used alternative values generated by the NHWS[45] and presented in Table 26. The ERG considered these values more appropriate than those presented in the US study Munakata et al[44] (see Section 1.1.1.6). Furthermore, using NHWS resource use results is consistent with the previous appraisals of erenumab and fremanezumab.

3) Alternative source used to generate HRQoL

In Section 4.2.7, the ERG discussed concerns regarding the source of the MSQ data used to generate the utility values used in the model. The original utility values were based on the whole of the CONQUER trial, not only on those patients who have failed ≥ 3 previous preventative therapies. In addition, the modelled values excluded MSQ data captured in relevant populations in the EVOLVE and REGAIN trials. In response to clarification questions the company presented a scenario analysis restricting the CONQUER study to the relevant population and a further scenario in which utility values are based on data from CONQUER, EVOLVE and REGAIN (in the DTT-3 population).

4) Differential utilities to include treatment effect

As described in Section 4.2.7, the ERG considered the company's assumption of using the same utility values for both galcanezumab and comparator to be too conservative given compelling evidence presented to support differential utilities. The ERG therefore presents a scenario in which the model allows a treatment effect on HRQoL. This was done using functionality already contained within the company model.

5) Age-related disutility

The ERG considers the assumption that HRQoL remains constant over time for a given number of MHDs to be strong, given the 25-year time horizon of the economic model. To account for age-related disutility, the ERG considers a scenario analysis in which the utilities used in the model are weighted according to literature derived age-decrements for the UK general population.[40] These utilities are presented in Table 37.

Table 37 General population age decrements

Age (5-year intervals)	Baseline Utility	Weight
45-50	0.8639	1.000
50-55	0.8344	0.966
55-60	0.8222	0.952
60-65	0.8072	0.934
65-70	0.8041	0.931
70-75	0.779	0.902
75-80	0.7533	0.872
80-85	0.6985	0.809
85<	0.6497	0.752

6) Consistent waning period between episodic and chronic migraine populations

As described in Section 1.1.1.3, the ERG considers the waning periods used for patients discontinuing galcanezumab to be inconsistent and unrealistic. The company's base case model assumes waning periods of [redacted] months, [redacted] months for episodic, chronic (vs. BSC) and chronic (vs. Botulinum toxin type A), respectively (see Table 23).

To explore the impact of the length of the modelled waning period on the company's base case ICER, the ERG considers a waning period of [redacted] months for patients discontinuing galcanezumab in all three cases. In these scenarios, the company's assumptions of a 1-month waning period for BSC and 3 months for botulinum toxin type A are retained.

7) Consistent waning period between galcanezumab and botulinum toxin A

In Section 1.1.1.5, the ERG highlighted that the waning periods applied to galcanezumab and botulinum toxin A are very different. There is, however, no evidence to justify this difference. As part the clarification response, the company presented the cost-effectiveness results of assuming a [redacted] month waning period for both galcanezumab and botulinum toxin A. Given the ERG's concerns

regarding a waning period of [redacted] months, the ERG also presents a further scenario in which the waning period for both galcanezumab and botulinum toxin A is assumed to be [redacted] months.

8) Removal of treatment waning

To explore the impact of the modelled waning period on the base case ICERs in all populations, an illustrative and exploratory scenario is presented to illustrate the removal or treatment waning. This assumption is consistent with the previous appraisals of erenumab[46] and fremanezumab.[22] This analysis is achieved by setting the waning period to 1 month for patients discontinuing due to AEs (discontinuers) and patients discontinuing due to lack of response (non-responders). This is applied to all treatments.

9) Dissipation of placebo effect

In Section 1.1.1.3, the ERG described the inconsistency in the company's approach to modelling the dissipation of the placebo (BSC) effect. The company base case assumes a unilateral application of the placebo dissipation by applying it only to placebo responders and not to galcanezumab responders. This is despite the fact that effects of galcanezumab as observed in the supporting trial evidence likely also include a placebo effect.

As detailed in Section 5.3, in response to clarification questions, the company presented two analyses. One in which the dissipation of the placebo effect was removed, and one in which the placebo effect dissipates after 60 months. The scenario analysis presented below utilises the company scenario in which placebo dissipation was removed. This scenario is selected over the 60-month placebo dissipation scenario due to the previously highlighted issue of unilateral application of this dissipation effect in the latter scenario. The ERG notes, however that the preference would have been to match both galcanezumab and placebo i.e. for the placebo effect to dissipate in both arms. This is due to the strength of the assumption required to remove placebo dissipation in the placebo arm i.e. placebo effect is assumed to be experienced for 25 years.

10) Patients discontinuing treatment assumed to wane back from responder MHDs

As described in Section 1.1.1.5, the ERG considers the modelled change from baseline in MHDs for galcanezumab patients (vs. botulinum toxin type A) to lack face validity. One consequence of this approach is that the model predicts patients who discontinue galcanezumab will initially receive a further reduction in MHDs before waning back to baseline. The ERG therefore presents a scenario in which this further reduction in MHDs on discontinuation is removed so that patients wane back from the MHD applied to responders. Note that, due to the way in which the model is structured, the

removal of this effect also leads to a reduction in the waning period from approximately [redacted] months to [redacted] months.

11) Exploration of alternative methods of incorporating indirect evidence on the effectiveness of galcanezumab compared with botulinum toxin A

As is described throughout Section 4.2.6, the ERG has concerns regarding the company's approach to generate the modelled treatment effects for galcanezumab and botulinum toxin. In particular, it is noted that the use of a different model structure for this comparison means that a full incremental analysis cannot be implemented.

The ERG therefore considers several alternative treatment effect scenarios using the response-based model structure used in the comparison between galcanezumab and BSC. In all these scenarios the ERG assumes that the effectiveness parameters for galcanezumab are the same as those used in the company's base analysis for the BSC comparison. This ensures an incremental analysis can be conducted. The parameters changed across the individual scenarios are therefore those used in the botulinum toxin A arm of the model and focus on the effectiveness parameters: response rate and change in MHDs for responders. Change in MHDs for non-responders is assumed common across galcanezumab and botulinum toxin A in all scenarios. In total, four scenarios are implemented as follows:

- ERG Scenario 11a: Assume equal effectiveness across all parameters for galcanezumab and botulinum toxin A
- ERG Scenario 11b: Response rate differs between galcanezumab and botulinum toxin A – relative effect based on ITC of responders (50%; whole population: 'all-comers').
- ERG Scenario 11c: Change from baseline in MHD for responders allowed to differ between galcanezumab and botulinum toxin A – value estimated using the ITC of change from baseline in MHD (DTT-3 population)
- ERG Scenario 11d: Scenario 11b and Scenario 11c combined

The modelled parameters for each of these scenarios can be seen in Table 38. Where the response rate is allowed to differ between galcanezumab and botulinum toxin, the odds ratio from the ITC of response (50%, whole population) is applied to the response rate for galcanezumab (30%). Where the change in MHDs for responders can differ, the treatment effect is drawn from the ITC of change in MHD (DTT-3 population) and applied using the formula presented in Appendix T of the CS. This allows an estimate of the change in MHD for responders in the botulinum toxin A arm to be calculated. Note that in all these scenarios the rate of discontinuation in the post-assessment period is

assumed to be common to both active treatments, where this is not done, this analysis will produce non-sensical results.

Table 38 Alternative treatment effectiveness parameters (response-based model structure)

Scenario	CFB MHD botulinum toxin A responders	CFB MHD botulinum toxin A non-responders	Response rate botulinum toxin A	CFB MHD GMB responders	CFB MHD GMB non-responders	Response rate GMB
11a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11b	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11c	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11d	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CFB, change from baseline; GMB, galcanezumab; MHD, migraine headache days

In considering the most appropriate set of assumptions to model the treatment effect, the ERG considers that a valid argument can be made for all four of these scenarios, as each has its own advantages and disadvantages. For the purpose of producing the ERG base case, the ERG prefers Scenario 11d, as this best aligns with the previous committee decision in fremanezumab to accept the results of the ITC as valid (despite the noted issues). Exploratory analyses are, however, also run on the ERG base-case considering the alternative treatment effect scenarios.

12) Incorporation of natural history

A significant limitation of the company's model is the exclusion of the natural history of migraine due to a lack of data on the long-term effects of migraine. The ERG considers this an important omission likely to impact considerably on the cost-effectiveness of any active treatment. The ERG therefore implements an exploratory scenario in which migraine symptoms improve in all patients over time. This scenario assumes all patients gradually revert to complete remission (0 MHDs) by the end of the modelled time horizon (25 years). This analyses therefore assumes by 70 years old, patients no longer suffer from migraine. This a strong assumption, and is implemented only to illustrate the potential effects of natural history rather than to represent a definitive analysis suitable for decision making.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

A summary of the ERG exploratory analyses for patients with episodic migraine are presented in

Table 39. For chronic migraine patients, a summary of the pairwise analyses are presented in Table 40 and a summary of the fully incremental analyses are presented in Table 41. ERG base case results for chronic migraine patients are presented in Table 42 (for full results of the incremental analyses see Appendix 3). These results are presented inclusive of the PAS available for galcanezumab, but exclude the CMU discount for botulinum toxin A. Results including the CMU discount are presented in a confidential Appendix.

All results are presented deterministically. The ERG's preference would have been to present results probabilistically, however due to time constraints the ERG was unable to implement this in the ERG base case.

6.2.1 Interpreting the results for episodic migraine

The deterministic ICER for episodic migraine is £34,370 in the ERG base case (

Table 39). Three ERG analyses resulted in a considerable increase in the company base case ICER: using the NHWS resource use increased the ICER by £6,820; using the combined data from CONQUER, REGAIN, EVOLVE-1 and EVOLVE-2 to generate utilities increased the ICER by £7,919; and the removal of the dissipation of placebo effect increased the ICER by £7,689. The incorporation of differential utilities to reflect a treatment effect resulted in a decrease the ICER by £15,998. The incorporation of natural history as an exploratory analysis increased the ICER to over £30,000 per QALY.

6.2.2 Interpreting the results for chronic migraine

The assumption around which treatment effectiveness values to use is a driver of cost-effectiveness. Assuming equal effectiveness of galcanezumab and botulinum toxin A (Scenario 11a) results in an ICER of £64,281 and assuming equal response rates and differential CFB in MHDs (Scenario 11c) results in an ICER of £8,454. The ERG's preferred assumption of differential response rates and CFB in MHD produces an ICER of £11,734.

The deterministic ICER for chronic migraine is £22,830 in the ERG preferred base case which uses treatment effectiveness Scenario 11d (Table 42). Three alternative ERG base cases are presented which use the alternative treatment effectiveness estimates from the ITC of galcanezumab compared to botulinum toxin A. The alternative ICERs are: £190,641 (ERG base case including Scenario 11a); £45,840 (ERG base case including Scenario 11b); and £24,539 (ERG base case including Scenario 11c).

Scenario 11 and the ERG base cases include a key assumption: equal long-term discontinuation rates between galcanezumab and botulinum toxin A. This is despite the CS presenting differential long-

term discontinuation rates for galcanezumab (0.44%) and botulinum toxin A (0.1%). The ERG assumes the long-term discontinuation rate is 0.44% for both treatments, due to issues around the validity of using these results due to the sources used to generate them (see Section 1.1.1.4 for more details) and the considerable influence these differential rates have on the cost-effectiveness results. Analyses undertaken by the ERG show that maintaining the differential discontinuation rates, results in galcanezumab being dominated by botulinum toxin A in numerous scenarios.

The incorporation of natural history as an exploratory analysis increased the ERG preferred base case ICER by almost £35,000.

Table 39 Exploratory ERG analyses (episodic migraine)

Analysis	Discounted costs		Discounted QALYs		ICER	Change from company base case ICER
	Galcanezumab	BSC	Galcanezumab	BSC		
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	**£29,230**	-
ERG correction of model errors	[redacted]	[redacted]	[redacted]	[redacted]	£29,313	£83
1) Galcanezumab administration cost for 10% of patients	[redacted]	[redacted]	[redacted]	[redacted]	£29,563	£334
2) Alternative resource consumption rates	[redacted]	[redacted]	[redacted]	[redacted]	£36,049	£6,820
3) Alternative source used to generate HRQoL	[redacted]	[redacted]	[redacted]	[redacted]	£37,149	£7,919
4) Differential utilities for galcanezumab and comparator	[redacted]	[redacted]	[redacted]	[redacted]	£13,232	-£15,998
5) Age-related disutility	[redacted]	[redacted]	[redacted]	[redacted]	£30,247	£1,017
8) Removal of treatment waning	[redacted]	[redacted]	[redacted]	[redacted]	£36,918	£7,689
9) Dissipation of placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	£36,918	£7,689
ERG base case (1, 2, 3, 4, 5, 9)	[redacted]	[redacted]	[redacted]	[redacted]	**£34,370**	**£5,140**
Base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	£37,633	£8,403

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; QALY, quality-adjusted life year
Note: All results correspond to deterministic analyses, scenario 12: natural history is for illustrative purposes only.

Table 40 Exploratory ERG analyses - Chronic migraine pairwise analyses (separate models for comparison to BSC and botulinum toxin)

Analysis	Comparator	Discounted Costs	Discounted QALYs	Pairwise

		Galcanezumab	Comparator	Galcanezumab	Comparator	ICER	Change from company base case
Company base case	**BSC**	[redacted]	[redacted]	[redacted]	[redacted]	**£8,080**	-
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	**£2,560**	-
ERG correction of model errors	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,053	-£27
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£4,203	£1,643
1) Galcanezumab administration cost for 10% of patients	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,243	£163
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,255	£694
2) Alternative resource consumption rates	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,892	£6,813
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£9,534	£6,974
3) Alternative source used to generate HRQoL	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,269	£2,189
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£3,254	£694
4) Differential utilities for galcanezumab and comparator	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£4,456	-£3,624
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	n/a
5) Age-related disutility	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£8,347	£268
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£2,622	£61
6) Consistent waning period between episodic and chronic migraine populations	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£9,602	£1,522
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£25,168	£22,608
7) Consistent waning period between galcanezumab and botulinum toxin A	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£5,464	£2,904
8) Removal of treatment waning	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,068	£1,988
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£42,566	£40,006
9) Dissipation of placebo effect	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£22,344	£14,264
	Botulinum toxin A	n/a	n/a	n/a	n/a	n/a	n/a
	BSC	n/a	n/a	n/a	n/a	n/a	n/a

10a) Patients discontinuing treatment assumed to wane back from responder MHDs	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£26,645	£24,085
10b) Equivalent long-term discontinuation rate for galcanezumab and botulinum toxin (0.44%)	BSC	n/a	n/a	n/a	n/a	n/a	n/a
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£11,742	£9,181

BSC, best supportive care; ERG, evidence review group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness analysis; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

Table 41 Exploratory ERG analysis - Scenario 11 (chronic migraine)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
11a) Equal effectiveness (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,281
11b) Response rate differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,167
11c) CFB in MHD differs (ITC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,454
11d) 11b and 11c combined	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,734

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses

Table 42 ERG base case and exploratory analysis (chronic migraine)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab	
ERG base case 4 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11d)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,830**
ERG exploratory analysis							
ERG base case 1 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11a)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£190,641
ERG base case 2 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,840
ERG base case 3 (1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11c)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,539
ERG preferred base case + Incorporation of natural history (12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,721

BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness analysis; ITC, indirect treatment comparison; MHDs, migraine headache days; QALY, quality-adjusted life year

Note: All results correspond to deterministic analyses, scenario 12: natural history is for illustrative purposes only.

6.3 Conclusions of the cost effectiveness section

The company performed a targeted literature review to identify cost-effectiveness evaluations of preventative treatments for people with migraine. No prior economic evaluations of galcanezumab were identified in the review, but several relevant studies were identified for other preventative treatments including other CGRPs. The identified studies included economic evaluations carried out as part of the NICE appraisal of erenumab and fremanezumab, as well as the Institute for Clinical and Economic Review report which considered the cost effectiveness of erenumab and fremanezumab.

The company developed a *de novo* economic analysis to appraise the cost and benefits of galcanezumab treatment in patients with episodic and chronic migraine. These groups were evaluated separately. For both episodic and chronic migraine populations, galcanezumab was compared to BSC; an additional analysis comparing galcanezumab to botulinum toxin A was conducted for chronic migraine patients.

The model structure developed was similar to that used in previous NICE appraisals of CGRPs and is driven by frequency of migraine modelled in terms of average monthly MHDs. For comparisons with BSC, the mean reduction in monthly MHD change is linked to response, with treatment effectiveness data sourced from four pivotal trials EVOVLE-1 and -2, REGAIN and CONQUER. For comparisons with botulinum toxin A, data from an ITC of change from baseline in MHDs was used to populate the model. The model structure used in the botulinum toxin A comparison was different to that used in the BSC comparison due to lack of data on change in MHDs for botulinum toxin A by response status. Consequently, a full incremental analysis of galcanezumab, BSC and botulinum toxin A cannot be conducted using the company's model.

ICERs for galcanezumab as compared to BSC in the company's base case were £29,230 for EM and £8,080 for CM. In CM, the ICER for galcanezumab as compared to botulinum toxin was £2,560. Presented PSAs suggested a high likelihood of acceptability at thresholds of £20,000 and £30,000 in the chronic migraine population.

The ERG's critique identified substantive structural uncertainties associated with the company's approach that potentially limit the reliability of company's analysis. Specifically, the ERG noted the focus on migraine frequency to the exclusion of other trial outcomes. This represents a limitation of the present economic analysis as other aspects of migraine including severity and frequency of non-migraine headache may impact on the burden of the condition. The economic analysis also makes strong assumptions about the durability of the treatment effect extrapolating short term effects observed over a period of 3 months to a 25-year time horizon, this together with the omission of the modelling of the effects of natural history means there is substantial uncertainty regarding the long-term benefits of galcanezumab.

While high quality trial evidence is available to support the comparisons to BSC, the comparison of galcanezumab with botulinum toxin A is considered weak because it is drawn from an ITC which is subject to several uncertainties and concerns regarding its validity. These include concerns regarding the comparability of the respective trial populations, notable differences in the observed placebo response rate, as well as differences in the definition of headache/migraine headache across studies. Given these limitations, the results of the economic analysis for this comparison should be interpreted with caution and are subject to additional uncertainty, not expressed in the probabilistic analysis.

The economic analysis presented by the company also has the significant limitation of only evaluating the cost-effectiveness of specific treatments rather than evaluating alternative treatment sequences. This is an important omission, as the positioning of galcanezumab within the treatment pathway may have important implications for its cost-effectiveness. It is also inconsistent with clinical practice where it is anticipated that galcanezumab would be used as part of a treatment sequence, being positioned either prior to or post botulinum toxin A treatment.

In addition to the largely structural issues described above, the ERG also identified many issues relating to the inputs and assumptions used in the model. These related to:

- The most appropriate sources of effectiveness data;
- The most appropriate way to incorporate the limited data on the relative effectiveness for the galcanezumab versus botulinum toxin comparison;
- Assumptions made regarding the duration of waning effects post discontinuation of treatment;
- The durability of responses to BSC;
- The sources of HRQoL data used in the model;
- The appropriateness of modelling different HRQoL for specific treatments;
- The omission of administration costs for galcanezumab beyond the first cycle of the model;
- Concerns regarding the source of data used to model resource use consumption rates.

To address these concerns the ERG implemented extensive further scenario analyses and proposed an alternative base-case analysis to address several of the key uncertainties identified. The main changes implemented by the ERG included:

- The revision of the model structure used in the botulinum toxin A comparison so that a consistent model structure was used across all comparisons allowing for a full incremental analysis to be implemented;
- Revision of assumptions so that a common value of [redacted] months is used to represent the waning period across all populations and treatments being evaluated;

- Revision of the source of utility data to include all trials reporting HRQoL data in the relevant failed > 3 preventative treatments population;
- The incorporation of treatment specific utilities;
- Revision of the resource consumption rates in line with previous appraisals of CGRPs.

All of these scenarios were found to have a substantive impact on the ICER (> £3,000 change in the ICER).

The results of the ERG's revised base-case imply an ICER of £34,370 in the EM population and an ICER of £22,830 of in the CM population. An exploratory analysis incorporating natural history highlights the potential for continuous treatment with galcanezumab to substantially increase the ICER and the importance of adhering to SMPC guidance which outlines the need to regularly evaluate patients to assess the continuing need for treatment.

7 REFERENCES

1. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine.* . London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/html-content-2

2. National Institute for Health and Care Excellence. *Erenumab for preventing migraine*. London: NICE; 2018.

3. Bolay H, Ozge A, Saginc P, Orekici G, Uluduz D, Yalin O, et al. Gender influences headache characteristics with increasing age in migraine patients. *Cephalalgia* 2015;**35**:792-800. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25424708

4. Houle TT, Turner DP, Smitherman TA, Penzien DB, Lipton RB. Influence of random measurement error on estimated rates of headache chronification and remission. *Headache* 2013;**53**:920-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23721239

5. Merikangas KR, Cui L, Richardson AK, Isler H, Khoromi S, Nakamura E, et al. Magnitude, impact, and stability of primary headache subtypes: 30 year prospective Swiss cohort study. *BMJ* 2011;**343**:d5076.

6. National Institute For Health And Care Excellence. *Erenumab for preventing migraine*. London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/html-content-2

7. Canadian Agency for Drugs and Technologies in Health (CADTH). *onabotulinumtoxinA for injection (Botox). Common Drug Review. Clinical Review Report*: CADTH; 2015.

8. Cole JC, Lin P, Rupnow MF. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. *Cephalalgia* 2009;**29**:1180-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19830883

9. European Medicines Agency. *Emgality. International non-proprietary name: galcanezumab. Procedure no. EMEA/H/C/004648/0000*. EMA; 2018. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/emgality [accessed 17th April 2020].

10. National Institute for Health and Care Excellence. *Botulinum toxin type A for the prevention of headaches in adults with chronic migraine*. London: NICE; 2012. Available from: https://www.nice.org.uk/guidance/ta260

11. Eli Lilly and Company. *A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study: Final Results from the Double-Blind Treatment Phase and Interim Results from the Open-Label Treatment Phase Galcanezumab (LY2951742) Migraine Prevention*. Washington, USA; 2017.

12. Diener HC, Schorn CF, Bingel U, Dodick DW. The importance of placebo in headache research. *Cephalalgia* 2008;**28**:1003-11. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18727647

13. Diederich NJ, Goetz CG. The placebo treatments in neurosciences New insights from clinical and neuroimaging studies. *Neurology* 2008;**71**:677-84.

14. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009;**62**:857-64. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19157778

15. National Institute for Health and Care Excellence. *Single Technology Appraisal. Erenumab for preventing migraine*. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10302/documents

16. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine [ID1368]. Single Technology Appraisal*. London: NICE. Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/committee-papers

17. Lipton RB, Brennan A, Palmer S, Hatswell AJ, Porter JK, Sapra S, et al. Estimating the clinical effectiveness and value-based price range of erenumab for the prevention of migraine in patients with prior treatment failures: a US societal perspective. *J Med Econ* 2018;**21**:666-75. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29571276

18. Sussman M, Benner J, Neumann P, Menzin J. Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: Results from the US societal and payer perspectives. *Cephalalgia* 2018;**38**:1644-57.

19. Porter JK, Di Tanna GL, Villa G, Brennan A, Palmer S, Lipton RB, et al. Parametric Modelling of Migraine Day Frequency In Migraine Prevention: A Case Study Of Erenumab Clinical Trial Data. *Value Health* 2017;**20**:A733. Available from: https://doi.org/10.1016/j.jval.2017.08.2004

20. Smolen L, Gandhi SK, Klein T, Iyer R, Thompson S, Cohen JM, et al. PND21 10-YEAR COST-EFFECTIVENESS ANALYSES OF FREMANEZUMAB AS PREVENTIVE TREATMENT IN CHRONIC AND EPISODIC MIGRAINE. *Value Health* 2019;**22**:S273. Available from: https://doi.org/10.1016/j.jval.2019.04.1294

21. Institute for Clinical and Economic Review. *Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value. Final Evidence Report*. ICER; 2018. Available from: https://icer-review.org/wp-content/uploads/2017/11/ICER_Migraine_Final_Evidence_Report_070318.pdf [accessed 20th April 2020].

22. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine. Final appraisal document [ID1368]*. NICE; 2020. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10339/documents [accessed 17th April 2020].

23. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. *Value Health* 2012;**15**:485-94. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22583459

24. Hagen K, Kristoffersen E, Winsvold B, Stovner L, Zwart J. Remission of chronic headache: An 11-year follow-up study. Data from the Nord-Trøndelag Health Surveys 1995–1997 and 2006–2008. *Cephalagia* 2018;**38**:2026-34.

25. Bigal M, Lipton R. The prognosis of migraine. *Curr Opin Neurol* 2008;**21**:301-8.

26. Lyngberg A, Rasmussen B, Jørgensen T, Jensen R. Prognosis of migraine and tension-type headache: a population-based follow-up study. *Neurology* 2005;**65**:580-5.

27. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalagia* 2007;**27**:193-210.

28. European Medicines Agency. *EMGALITY (galcanezumab). United Kingdom. Summary of Product Characteristics*. 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/emgality-epar-product-information_en.pdf [accessed 16th March 2020].

29. Bigal M, Liberman J, Lipton R. Age-dependent prevalence and clinical features of migraine. *Neurology* 2006;**67**:246-51.

30. Victor T, Hu X, Campbell J, Buse D, Lipton R. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia* 2010;**30**:1065-72.

31. National Institute for Health and Care Excellence. *Brodalumab for treating moderate to severe plaque psoriasis [TA511]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta511 [accessed 20th April 2020].

32. National Institute for Health and Care Excellence. *Certolizumab pegol for treating moderate to severe plaque psoriasis [ta574]*. NICE; Available from: https://www.nice.org.uk/guidance/ta574/resources/certolizumab-pegol-for-treating-moderate-to-severe-plaque-psoriasis-pdf-82607142805189 [accessed 20th April 2020].

33. National Institute for Health and Care Excellence. *Tildrakizumab for treating moderate to severe plaque psoriasis [TA575]*. NICE; 2019. Available from: https://www.nice.org.uk/guidance/ta575 [accessed 20TH aPRIL 2020].

34. National Institute for Health and Care Excellence. *Single Technology Appraisal. Appeal Hearing. Advice on erenumab for preventing migraine [ID1188]* NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/appeal-decision [accessed 20th April 2020].

35. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1789-858.

36. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of Onabotulinum toxin A for the prevention of chronic migraine: COMPEL study. *J Headache Pain* 2018;**19**:13. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29404713

37. Data on File. *Eli Lilly and Co.: I5Q-MC-CGAW Clinical Study Report*; 2019.

38. Diener H-C, Charles A, Goadsby PJ, Holle D. New therapeutic approaches for the prevention and treatment of migraine. *The Lancet Neurology* 2015;**14**:1010-22.

39. Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, et al. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. *BMC Neurol* 2018;**18**:188. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30413151

40. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health* 2011;**14**:539-45.

41. NHS England, NHS Improvement. *2017/18 and 2018/19 National Tariff Payment System*. London. Available from: https://improvement.nhs.uk/documents/1044/2017-18_and_2018-19_National_Tariff_Payment_System.pdf

42. NHS Improvement. *National schedule of NHS costs -Year 2018-2019*. Available from: https://improvement.nhs.uk/resources/national-cost-collection/ [accessed 20th April 2020].

43. Curtis L, Burns A. *Unit Costs of Health and Social Care 2019*. Canterbury, Kent: Personal Social Services Research Unit, University of Kent 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/

44. Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, Tierce J, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2009;**49**:498-508. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19245386

45. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain* 2018;**19**:82. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30203163

46. National Institute for Health and Care Excellence. *Erenumab for preventing migraine. Final appraisal document*. London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/html-content-2

APPENDIX 1

Proof that the difference in monthly MHDs for the whole population cannot equal the difference in monthly MHDs for responders unless response is 100% or there is no treatment difference.

Where:

$Rsp_{galc/bot}$ = Response rate for galcanezumab/botulinum toxin A

$R\_MHD_{galc/bot}$= change in monthly MHDs for responders to galcanezumab/botulinum toxin A

$NR\_MHD_{galc/bot}$= change in monthly MHDs for non-responders to galcanezumab/botulinum toxin A

The difference in month MHDs for the whole population can be written as:

$$\left(Rsp_{galc} * R\_MHD_{glac} - \left(1 - Rsp_{galc}\right) * NR\_MHD_{galc}\right) - \left(Rsp_{bot} * R\_MHD_{bot} - (1 - Rsp_{bot}) * NR\_MHD_{bot}\right) \quad (1)$$

And the difference in monthly MHDs for responders can be written as:

$$R\_MHD_{galc} - R\_MHD_{bot} \quad (2)$$

Setting equations (1) and (2) equal to one another as implied by the company's analysis

$$\left(Rsp_{galc} * R_{MHD_{glac}} - \left(1 - Rsp_{galc}\right) * NR_{MHD_{galc}}\right) - \left(Rsp * R_{MHD_{bot}} - (1 - Rsp_{bot}) * NR_{MHD_{bot}}\right) = R\_MHD_{galc} - R\_MHD_{bot} \quad (3)$$

If $Rsp_{galc} = Rsp_{bot}$ and $NR\_MHD_{galc} = NR\_MHD_{bot}$ then equation (3) collapses to

$$Rsp * R\_MHD_{galc} - Rsp * R\_MHD_{bot} = R\_MHD_{galc} - R\_MHD_{bot} \quad (4)$$

This can be rearranged to:

$$Rsp * (R\_MHD_{galc} - R\_MHD_{bot}) = R\_MHD_{galc} - R\_MHD_{bot} \quad (5)$$

Equation (5) can only be true when either the response rate equals 100% or the difference in month MHDs for responders is zero. In the latter case this also implies that the difference in monthly MHDs for the whole population is zero i.e. that the treatments are equally effective. Where the response rate is < 100% and the difference in monthly MHDs for responders is non-zero, equation (5) also implies that the difference in the MHDs between treatments will always be smaller than the difference for responders.

APPENDIX 2

Table 43 Quality assessment of included CEA study using Drummond et al. checklist completed by the ERG

	CEA quality assessment questions	Answer (Yes/No/Unclear)	Notes/Explanation for No or Unclear
1	Was the research question stated?	Yes	-
2	Was the economic importance of the research question stated?	Yes	-
3	Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	-
4	Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	-
5	Were the alternatives being compared clearly described?	Yes	-
6	Was the form of economic evaluation stated?	Yes	-
7	Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	-
8	Was/were the source(s) of effectiveness estimates used stated?	Partly	Effectiveness estimates from the ITC were stated but the details of the analysis used to generate the parameters were not initially available.
9	Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	-
10	Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	Full details to reproduce the ITCs (such as all data sources used; calculations to transform extracted data to useable data; justification for random or fixed effects and R script) were not initially provided.
11	Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	-
12	Were the methods used to value health states and other benefits stated?	Yes	-

13	Were the details of the subjects from whom valuations were obtained given?	Partly	The trial sources were provided but no detail was given on whether utilities were restricted to patients who have failed ≥3 prior therapies.
14	Were productivity changes (if included) reported separately?	Yes	-
15	Was the relevance of productivity changes to the study question discussed?	Yes	-
16	Were quantities of resources reported separately from their unit cost?	Yes	-
17	Were the methods for the estimation of quantities and unit costs described?	Yes	-
18	Were currency and price data recorded?	Yes	-
19	Were details of price adjustments for inflation or currency conversion given?	N/A	-
20	Were details of any model used given?	Yes	-
21	Was there a justification for the choice of model used and the key parameters on which it was based?	Partly	The company provided justification for using the model structure selected (e.g. precedent for previous CGRP-i appraisals). However, the company did highlight a previous model in which severity was captured yet severity was not included.
22	Was the time horizon of cost and benefits stated?	Yes	-
23	Was the discount rate stated?	Yes	-
24	Was the choice of rate justified?	Yes	-
25	Was an explanation given if cost or benefits were not discounted?	N/A	-
26	Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	-
27	Was the approach to sensitivity analysis described?	Yes	-

28	Was the choice of variables for sensitivity analysis justified?	Yes	-
29	Were the ranges over which the parameters were varied stated?	Yes	-
30	Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Partly	Company did not consider sequential treatment of active interventions i.e. botulinum toxin A following galcanezumab etc. This approach of sequential treatments has been common in appraisals of interventions compared to active comparators in other therapeutic indications.
31	Was an incremental analysis reported?	Partly	Correct pairwise incremental analysis was reported for episodic in which there was only one comparator. However, for the chronic migraine population, pairwise analyses were presented rather than a fully incremental analysis despite there being two comparators.
32	Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	-
33	Was the answer to the study question given?	Yes	-
34	Did conclusions follow from the data reported?	Yes	-
35	Were conclusions accompanied by the appropriate caveats?	No	-
36	Were generalisability issues addressed?	Partly	Incident population (which could be considerably lower than the modelled population) was not addressed.

APPENDIX 3

Table 44 ERG Scenario 11a) Equal effectiveness (ITC)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£1,189
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£64,281

Table 45 ERG Scenario 11b) Response rate differs (ITC)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£1,295
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£34,167

Table 46 ERG Scenario 11c) CFB in MHD differs (ITC)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£7,825
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£8,454

Table 47 ERG Scenario 11d) 11b and 11c combined

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£5,641
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£11,734

Table 48 ERG base case 1 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11a)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£9,416
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£190,641

Table 49 ERG base case 2 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11b)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£10,341
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£45,840

Table 50 ERG base case 3 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11c)

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£14,592
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,539

Table 51 ERG base case 4 (Scenarios 1, 2, 3, 4, 5, 6, 7, 10a, 10b, 11d) – preferred

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£14,344
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£22,830

Table 52 ERG preferred base case + 12) Incorporation of natural history

Intervention	Costs	QALYs	Incremental costs	Incremental QALYs	ICER
BSC	[redacted]	[redacted]	-	-	-
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	£467
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	£57,721

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Galcanezumab for preventing migraine [ID1372]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 12 June** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 ERG correction of inconsistencies after discontinuation (Galcanezumab vs botulinum toxin A analysis)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 93 states "As described in Section 4.2.6.4, the ERG considers the modelled change from baseline in MHDs for galcanezumab patients (vs. botulinum toxin type A) to lack face validity. One consequence of this approach is that the model predicts patients who discontinue galcanezumab will initially receive a further reduction in MHDs before waning back to baseline. The ERG therefore presents a scenario in which this further reduction in MHDs on discontinuation is removed so that patients wane back from the MHD applied to responders."	Please amend ERG analysis to also apply the correction to the botulinum toxin A arm under 'Calc-Tx 2' tab	Lilly advises for accurate results, the correction implemented by the ERG under scenario 10a is also corrected for the botulinum toxin A arm, and the ERG analyses be subsequently updated.	Thank you for highlighting this. We concur that this scenario should be applied to both model arms. We have updated the model and results accordingly.

Issue 2 HFEM subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10 states "Combining chronic migraine (CM) and HFEM groups in some analyses: the ERG noted that in some analyses data from both	Please amend as follows: "Combining chronic migraine (CM) and HFEM groups in some analyses: the ERG noted that in some analyses data from both groups were combined. This is inconsistent with the	Lilly suggest amending the wording to make it clear that we believe HFEM is not clinically distinct from CM but rather the burden of disease is similar to CM.	Text deleted as suggested.

groups were combined. This is inconsistent with the decision problem which argues these groups are distinct (see section 2.3). However, the ERG is aware that there is significant debate in the literature regarding the distinctiveness of HFEM in comparison with CM and episodic migraine (EM) (see section 2.2.1 for further detail)"	decision problem ~~**which argues these groups are distinct**~~ (see section 2.3). However, the ERG is aware that there is significant debate in the literature regarding the distinctiveness of HFEM in comparison with CM and episodic migraine (EM) (see section 2.2.1 for further detail).	The Company submission states, "that patients with HFEM have a burden of disease similar to CM and as a result, experts in the field have proposed revising the definition of chronic migraine to include patients with 8-14 MHDs per month." (section B.1.1, page 9).	

Issue 3 Unplanned subgroup analyses in the summary of the key issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10 states "Only limited available data are available for all outcomes on the DTT-3 population: most company trial data for this population was based on small samples sizes and unplanned subgroup analyses (see section 3.2)."	Please amend as follows "Only limited available data are available for all outcomes on the DTT-3 population: most company trial data for this population was based on small samples sizes and unplanned subgroup analyses, **except for CONQUER** (see section 3.2)."	The statement is misleading, and Lilly advise amending the wording to make it clear that most outcome analyses were actually pre-planned in the CONQUER study. This has been tabulated in the Company submission (Company submission; Table 11, page 46)	Not a factual inaccuracy. It is stated that "most" data are from unplanned analyses, not all.

Issue 4 Exploration of natural history in the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10 states	Please amend as follows	Lilly advise amending this wording. The natural history of migraine is discussed in different sections of	For accuracy this was changed to

"The natural history of the condition is not discussed"	"The natural history of the condition **~~is not discussed~~ was not included in the economic model due to lack of evidence**"	the Company submission (page 19, 20, 112, 155) including the chronification and the reduction of migraine prevalence in post-menopausal women. The wording in its current form may imply that this was an oversight or deliberate omission on the part of Lilly, when in fact the Company submission acknowledges that natural history was not considered in the model due to a lack of robust evidence.	"The natural history of the condition **is not ~~discussed~~ included in the economic evaluation.**"

Issue 5 Generalisability of the CONQUER trial results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10 states "A majority of the participants included in the CONQUER trial had failed on a treatment not used in the UK"	Please amend as follows "**Approximately [redacted] of the participants included in the CONQUER trial had failed at least one treatment not used in UK clinical practice**"	In the Company clarification questions response A4, Lilly has noted that using a modified definition of medication categories which included only medications used in UK clinical practice and excluded those not used in UK clinical practice, [redacted] in the placebo group and [redacted] patients in the GMB group had at least one treatment not used in UK clinical practice (Table 9, page 13)	For accuracy this was changed to "**approximately [redacted] of the participants included in the CONQUER trial had failed at least one treatment not used in the UK…**" (on page 11)

Issue 6 Consideration of severity and HDs outcomes in the Company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25, table 7 states "The ERG notes that the severity of MHDs and HDs is not captured in the submission"	Please amend as follows "The ERG notes that the severity of MHDs and HDs is not ~~**captured in the submission**~~ **considered in the economic model**"	Data on severity and HDs is presented in the Company submission as Change from baseline in PGI-S scores. Please see Table 16, page 55 Table 18, page 58 Table 21, page 64 Table 25, page 68 Table 28, page 72 Table 31, page 76	Changed to "The ERG notes that the severity of MHDs and HDs is not **captured in the** ~~**submission**~~ **economic model**"

Issue 7 Estimates used in the economic model from the comparison to botulinum toxin A in chronic migraine

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11 states "While high quality trial evidence is available to support the comparisons to best supportive care (BSC), the comparison of galcanezumab with botulinum toxin A are therefore drawn from an ITC, with significant concerns regarding the validity of the predicted effect estimates"	Please amend as follows "While high quality trial evidence is available to support the comparisons to best supportive care (BSC), the comparison of galcanezumab with botulinum toxin A are therefore drawn from an ITC, with significant concerns regarding the validity of **these synthesised data** ~~**predicted effect estimates**~~"	The statement is misleading as it implies the base case uses the predicted responder/non-responder estimates (using the formula in Appendix T) and not the synthesised ITC estimates. Lilly suggests amending the wording to make this clear. Predicted estimates for responder/non-responder MHDs were only explored in a scenario analysis (Company submission; page 120).	For clarity removed the word 'predicted' and clarified the meaning of the sentence as follows: "While high quality trial evidence is available to support the comparisons to best supportive care (BSC), the comparison of galcanezumab with botulinum toxin A ~~**are therefore**~~ **is** drawn from an ITC, with significant concerns regarding the validity

			of **the resulting ~~predicted~~ effect estimates**"
Page 13 states "Due to limited data on change in monthly MHDs in a responder population, the company adopts a different model structure for the comparison with BSC. This approached, referred to as the combined population approach, uses data from the ITC of MHDs (DTT-3 population) to approximate the difference in MHDs in responders to galcanezumab and botulinum toxin A."	Please amend as follows "Due to limited data on change in monthly MHDs in a responder population, the company adopts a different model structure **~~for~~ from** the comparison with BSC. This approach**~~ed~~**, referred to as the combined population approach, uses data from the ITC of MHDs (DTT-3 population) **applied to the combined responder and non-responder populations ~~to approximate the difference in MHDs in responders to galcanezumab and botulinum toxin A~~**."		Not a factual inaccuracy. We have corrected the typos, as suggested.

Issue 8 Exclusion of additional studies for botulinum toxin A in the all-comers indirect comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 31 states "The ERG identified a Cochrane review that included a number of additional potentially relevant studies to inform the all comers ITC (see points for clarification [PFC] question A15 for further details). The company responded that the 'all comers' analyses were not central to the submission and therefore they	Please amend as follows "The ERG identified a Cochrane review that included a number of additional potentially relevant studies to inform the all comers ITC (see points for clarification [PFC] question A15 for further details). The company responded that the **target population relevant to the decision problem were patients with a history of ≥3 prior preventative failures (DDT-3). Apart from PREEMPT-1 and 2, no additional Botox trials were included in the all-comers analyses to ensure consistency**	The statement is incomplete and does not provide the reader with the full justification for excluding other botulinum toxin A studies from the all-comers ITC. Lilly advise amending the wording to make this clear (Company clarification responder; A15c, page 31)	Not a factual inaccuracy. The ERG has summarised the company's position and cross-referenced to the points for clarification question where the company's full reasoning is detailed.

chose not to include these studies"	**as this was only a supportive analysis to strengthen the confidence in the DTT-3 ITC to botulinum toxin A ~~'all comers' analyses were not central to the submission and.~~ Therefore, they chose not to include these studies"**		

Issue 9 Pooling of response rate data from REGAIN and CONQUER

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32 states "Data from REGAIN and CONQUER were naively pooled to inform the 50% response rate (i.e. ≥ 50% reduction in baseline monthly MHDs) for patients who had failed ≥ 3 prior preventive medications in the economic model (see section 4.2.6.1). This was done by adding the number of responders and the number of included patients in the trial arms and calculating proportions. However, these data could have been formally meta-analysed on an appropriate scale (e.g. log-odds) resulting in more valid estimates with a more appropriate characterisation of the underlying uncertainty.	Please amend as follows "Data on **patient counts** from REGAIN and CONQUER were naively pooled to inform the 50% response rate (i.e. ≥ 50% reduction in baseline monthly MHDs) for patients who had failed ≥ 3 prior preventive medications in the economic model (see section 4.2.6.1). This was done by adding the number of responders and the number of included patients in the trial arms and calculating proportions. However, these data could have been formally meta-analysed on an appropriate scale (e.g. log-odds) resulting in more valid estimates with a more appropriate characterisation of the underlying uncertainty.	Lilly suggest amending the wording to accurately reflect which data was used in the meta-analysis for the 50% response rate.	Text added as suggested, for clarity.

Issue 10 Mean change in monthly MHDs, excluding prior botulinum toxin A

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 37 states "Typos in response rates for Table 25 of the CS make it difficult to compare with analyses excluding patients with prior botulinum toxin A. Two rows in Table 25 are labelled "Proportion of patients with 50% reduction from baseline in monthly MHDs" but have different data. It is likely these rows were meant to reflect 50% and 30% reduction from baseline in monthly MHDs but it is unclear."	Please amend as follows "**The mean percentage of patients who achieved ≥30% and ≥50% reduction of migraine headache days from baseline at month 3 was [redacted]** ~~**Typos in response rates for Table 25 of the CS make it difficult to compare with analyses excluding patients with prior botulinum toxin A. Two rows in Table 25 are labelled "Proportion of patients with 50% reduction from baseline in monthly MHDs" but have different data. It is likely these rows were meant to reflect 50% and 30% reduction from baseline in monthly MHDs but it is unclear."**~~	Lilly can confirm the last row in Table 25 of the Company submission should state "Proportion of patients with **≥30%** reduction from baseline in monthly MHDs in ITT population over 3 months"	Not a factual inaccuracy at the time of writing the ERG report. The ERG thanks the company for clarifying the heading in Table 25 of their submission. We have amended this paragraph as follows: "The difference in mean change in monthly MHDs was slightly [redacted] when excluding patients with prior botulinum toxin A failure [redacted]) compared with all patients with ≥ 3 prior preventive medication failure [redacted]). The odds ratios for achieving 30% and 50% response (ie reduction from baseline in monthly MHDs at month 3) were [redacted] when excluding patients with prior botulinum toxin A failure (OR=[redacted] and OR=[redacted], respectively) compared with all patients with ≥ 3 prior preventive medication failure ([redacted])."

Issue 11 REGAIN analyses informing the ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39 states "The proportion of DTT-3 patients could be an effect modifier as differences between GMB and placebo in unplanned subgroup analyses where highest in patients with ≥ 2 failed preventive treatments, followed by patients with ≥ 1 failed preventive treatments, and then on the all-comers population"	Please amend as follows "The proportion of DTT-3 patients could be an effect modifier as differences between GMB and placebo in **~~unplanned~~ pre-planned** subgroup analyses were **~~where~~** highest in patients with ≥ 2 failed preventive treatments, followed by patients with ≥ 1 failed preventive treatments, and then on the all-comers population".	Lilly suggests amending the statement to make it clear which analyses were planned and unplanned in REGAIN. Treatment resistant status (failed ≥1 or ≥ 2 prior preventatives, or not) was pre-specified in REGAIN and the corresponding treatment by subgroup interaction was statistically significant (Section 11.4.1.8 from the REAGIN CSR). The DTT-3 (failed ≥ 3 prior preventatives) analyses were unplanned.	Text corrected as suggested (page 42).

Issue 12 Results and methodology undertaken for the ITCs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 42, table 15 legend states "*simple mean difference at 3 months used for ITC, CI is wider if using least square standard error as in company's main analyses presented in Tables 27 and 33 of the company submission."	Please amend as follows "***~~simple~~ mean change from baseline across month1-3 for galcanezumab and placebo used for ITC**, CI is wider **than in ~~if using least square standard error as in~~** company's main analyses presented in Tables 27 and 33 of the company submission."	Lilly advises amending the statements to make it clear that the mean differences from CONQUER and REGAIN (as displayed in table 15) were computed accounting for repeated measures over time. These are the same estimates computed which are displayed in tables 27 and 33 of the Company submission. The estimates for CONQUER and REGAIN in table	Text changed as follows (page 45): "CI for mean change from baseline across months 1- 3 for GMB and Placebo used in the ITC is wider than in company's main analyses (presented in Tables 27 and 33 of the company submission) as it does not

		15 are therefore not simple mean differences at 3 months.	account for the repeated nature of the measurements."
Page 43 states "Precision in this ITC could have been increased if the mean difference in the changes from baseline in MHD calculated accounting for repeated measures over time for the CONQUER and REGAIN studies had been used (as reported in Tables 27 and 33 of the CS). Instead, a simple mean difference between GMB and placebo was calculated for the purposes of the ITC, leading to slightly wider CIs in Table 15 and consequently less precision in the ITC results. However, this is unlikely to have a meaningful impact on model results."	Please amend the ERG comments regarding the ITC for CM patients with ≥ 3 prior preventive medication failures (section 3.4.1) to reflect the methodology in the justifications.	However, the CI of the mean difference between galcanezumab and placebo for this ITC were computed with the default method (Hedges method) from the meta package from R. This leads to wider CIs (than in tables 27 and 33 of the Company submission) and consequently less precision in the ITC results. The ITC results are therefore conservative.	Text changed as follows (page 45-46): "Precision in this ITC could have been increased if the variance of the mean difference in the changes from baseline in MHD calculated accounting for repeated measures over time for the CONQUER and REGAIN studies had been used (as reported in Tables 27 and 33 of the CS). Instead, the variance for the mean difference between GMB and placebo calculated for the purposes of the ITC did not account for the repeated nature of the measurements, leading to slightly wider CIs in **Error! Reference source not found.** and consequently less precision in the ITC results."

Issue 13 ERG request for botulinum toxin A failures analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 58 states "To consider the current population of patients who have already failed botulinum toxin A, the ERG further requested that the company present scenario analysis for a population of patients who have failed ≥ 4 prior prophylactic treatments one of which was botulinum toxin A, where galcanezumab would be fifth line therapy. The company's response included additional results excluding patients who had failed botulinum toxin A and showed that Galcanezumab was similarly effective compared with placebo, though point estimates for several key outcomes were slightly smaller. The company, however, did not provide appropriate scenario analyses of the botulinum toxin A failure population citing time restrictions as the reason this could not be done	Please amend as follows "To consider the current population of patients who have already failed botulinum toxin A, the ERG further requested that the company **consider the relevance of this population in relation to a 3rd or 4th line position. In response, the company stated that botulinum toxin A would only be considered at a 5th line position after patients have cycled through 3 oral preventatives and botulinum toxin A** ~~**present scenario analysis for a population of patients who have failed ≥ 4 prior prophylactic treatments one of which was botulinum toxin A, where galcanezumab would be fifth line therapy**~~. The company's response included additional results excluding patients who had failed botulinum toxin A and showed that Galcanezumab was similarly effective compared with placebo, though point estimates for several key outcomes were slightly smaller. The company did not provide ~~**appropriate**~~ scenario analyses of the botulinum toxin A failure population ~~**citing time restrictions as the reason this could not be done"**~~	The wording relating to the additional analyses requested by the ERG during clarification is inaccurate. Clarification question B26, which the report seems to be referring to, only request an additional scenario analysis where the impact of excluding botulinum toxin A failures is modelled (analysis requested in clarification question A4). Lilly were not asked to provide an analysis with respect to a 5th line population, post botulinum toxin A (clarification question B25). Lilly advise the wording is updated to reflect this.	We have revised the text as follows "To consider the current population of patients who have already failed botulinum toxin A, the ERG further requested that the company **consider the relevance of this population in relation to the positioning of galcanezumab. In response, the company stated that galcanezumab would only be considered at a 5th line position after patients have cycled through 3 oral preventatives and botulinum toxin A** ~~**present scenario analysis for a population of patients who have failed ≥ 4 prior prophylactic treatments one of which was botulinum toxin A, where galcanezumab would be fifth line therapy**~~. The company's response also included additional results excluding patients who had failed botulinum toxin A and showed that galcanezumab was similarly effective

			compared with placebo, though point estimates for several key outcomes were slightly smaller. The company did not provide ~~**appropriate**~~ scenario analyses **in** the botulinum toxin A failure population ~~**citing time restrictions as the reason this could not be done Scenario analysis exploring this population are therefore presented in Section**~~ ~~Error! Reference source not found.~~ ~~**of this report."**~~

Issue 14 Relevance of erenumab and fremanezumab as comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 60 states "The company's response noted recent approval in patients with chronic migraine, and agreed that fremanezumab would represent a potential comparator in this population. The company's response, however, highlighted that neither erenumab nor fremanezumab had received a NICE recommendation when the company received its invitation to participate in the NICE appraisal process and that fremanezumab	Please amend as follows "The company's response noted recent approval in patients with chronic migraine and agreed that fremanezumab would represent a potential comparator in this population. The company's response, however, highlighted that neither erenumab nor fremanezumab had received a NICE recommendation when the company received its invitation to participate in the NICE appraisal process and that fremanezumab was not standard of care at the time of the company's submission. **Additionally, the company noted that an indirect comparison to fremanezumab was**	The justification described for Lilly's exclusion of fremanezumab is incomplete. Lilly advise updating the wording to accurately reflect the response to clarification questions B21, where it states that an indirect comparison to fremanezumab was not feasible due to a lack of data in the target population of patients that failed ≥3 prior preventative treatment failures.	Not a factual inaccuracy.

was not standard of care at the time of the company's submission.	**not feasible due to a lack of data in the target population of patients that failed ≥3 prior preventative treatment failures from the fremanezumab trials**"		

Issue 15 Total costs for galcanezumab in the first cycle

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 76, table 25 states the first cycle costs as "[redacted]"	Please amend as follow "[redacted]"	The first cycle costs also include the cost of loading dose for galcanezumab which includes an additional dose.	Amended as suggested.

Issue 16 ICER, ERG scenario 11c)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 100, table 41 "11c) CFB in MHD differs (ITC) – Incremental ICER £8,454"	Please amend as follows "11c) CFB in MHD differs (ITC) – Incremental ICER **£8,637**"	Incremental ICER as reported in ERG amended cost effectiveness model when 'Scenario 11' is set to 3 and 'Scenario 10b', cell H56 is set to New under the 'ERG scenarios' tab	We are satisfied with the ICER we have presented. As explained in our report the rate of discontinuation was assumed common across treatments for all these scenarios.

Issue 17 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 70 states "In the chronic population, the CONQUER trial was used to model the waning period"	Please amend as follows "In the chronic population, the ~~**CONQUER**~~ **REGAIN** trial was used to model the waning period"	Typo	Corrected.
Page 77 states "In the erenumab and fremanezumab appraisals the use of healthcare resources was based on the National Health and Wellness Survey (NHWS) 2017"	Please amend as follow **"**In the erenumab and fremanezumab appraisals the use of healthcare resources was based on the National Health and Wellness Survey (NHWS) ~~**2017**~~ **2016**"	Typo. The paper by Vo et al. which was used in the fremanezumab appraisal was based on the NHWS conducted in 2016	Corrected (page 78).
Page 36 states "The proportion of GMB patients with ≥ 30% reduction from baseline in MHDs was available only for CM patients in CONQUER. As above, GMB patients ([redacted]) were [redacted] likely to respond than placebo ([redacted])."	Please amend as follows The proportion of GMB patients with ≥ 30% reduction from baseline in MHDs was available only for CM patients in CONQUER. As above, GMB patients ([redacted] were [redacted] likely to respond than placebo ([redacted]).	Typo - Correction suggested as per Table 28, page 72 of Company Submission	Corrected.
Page 38 states "For CM patients, the REGAIN trial found that at month 16 of the post-treatment (washout) period, patients had experienced a waning in reduction from baseline	Please amend as follows For CM patients, the REGAIN trial found that at month 16 of the post-treatment (washout) period, patients had experienced a waning in reduction from baseline of [redacted]**monthly** MHD compared with month 12 after treatment	Typo - Please add the word the 'monthly' to make it clear to the reader the period in which reduction in MHD occur in the washout period in REGAIN	Word added.

of [redacted] MHD compared with month 12 after treatment discontinuation [redacted] compared to [redacted], Table 52, Company response to PFCs and **Error! Reference source not found.** below); that is, patients' improvement reduced by [redacted] over the four month period"	discontinuation [redacted] compared to [redacted], Table 52, Company response to PFCs and **Error! Reference source not found.** below); that is, patients' improvement reduced by [redacted] over the four month period"		
Page 63, table 20 has incorrect value for comparator Chronic (vs botulinum toxin type A – 30%): [redacted]	Please replace with [redacted]**%**	Typo - Correction suggested as per Table 57, page 123 of Company Submission	Corrected.

Issue 18 ACIC marking errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 77 states "This analysis used efficacy data from the CONQUER clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have the baseline characteristics of the overall EM population. Responders had baseline mean MHDs of [redacted] compared to [redacted] for non-responders. The galcanezumab treatment effect compared to BSC was	Please amend as follow **"**This analysis used efficacy data from the CONQUER clinical trial in patients with 8-14 monthly headache days. This patient group was assumed to have the baseline characteristics of the overall EM population. Responders had baseline mean MHDs of [redacted] compared to [redacted] for non-responders. The galcanezumab treatment effect compared to BSC was [redacted] MHDs in responders and [redacted] MHDs in non-responders. At least a 50% reduction in MHDs was seen in [redacted] of	Please redact unpublished AIC information in the report	Marking updated as noted (text is on page 84, not page 77).

[redacted] MHDs in responders [redacted] MHDs in non-responders. At least a 50% reduction in MHDs was seen in [redacted] of galcanezumab patients and [redacted] of BSC patients	galcanezumab patients and [redacted] of BSC patients"		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Galcanezumab for preventing migraine

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background

- Headache disorder with recurring attacks usually lasting 4-72 hours
- Often accompanied by nausea, vomiting, sensitivity to light/sound
- Factors triggering attacks can include stress, change in sleep pattern, overtiredness, menstruation, caffeine/alcohol consumption
- Prevalence 5-25% in women; 2-10% in men
- Negative impact on personal, work and social life
- The severity of the condition can vary over time
- Chronic migraine (CM) is defined as 15 or more headache days a month with at least 8 of those having features of migraine
- Episodic migraine (EM) is defined as less than 15 headache days a month; the burden on quality of life can be similar to that of chronic migraine

1.2 Treatment pathway

For the prophylactic treatment of migraine, NICE clinical guideline 150 recommends offering topiramate or propranolol and to consider amitriptyline. After the failure of at least 3 prior preventative therapies best supportive care (BSC) is offered which includes acute treatments such as triptans, analgesics and antiemetics. NICE technology appraisal guidance 260 recommends botulinum toxin type A for the prophylaxis of headaches in adults with chronic migraine that has not responded to at least 3 prior pharmacological therapies and whose condition is appropriately managed for medication overuse. NICE technology appraisal guidance 631 recommends fremanezumab for preventing chronic migraine in adults if at least 3 preventive drug treatments have failed. However, fremanezumab is unlikely to be established practice at this time.

The company's evidence submission positioned galcanezumab as a treatment option after 3 or more failed preventative therapies. At this position it considered BSC and botulinum toxin type A (CM only) as the relevant comparators.

1.3 The technology

Galcanezumab (Emgality, Eli Lilly) is a humanised IgG4 monoclonal antibody that binds calcitonin gene-related peptide (CGRP) thus preventing its biological activity. Elevated blood concentrations of CGRP have been associated with migraine attacks. It has a marketing authorisation in the UK and is indicated for the prophylaxis of migraine in adults who have at least 4 MHDs per month. The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly via autoinjector, with a 240 mg loading dose as the initial dose. Treatment benefit should be assessed within 3 months after initiation of treatment. Any further decision to continue treatment should be taken on an individual patient basis. Evaluation of the need to continue treatment is recommended regularly thereafter. The list price of galcanezumab is £386.50 per 120mg dose.

1.4 Clinical evidence

The company's systematic literature review identified 4 randomised, multicentre, double-blind, placebo-controlled trials in people with migraine:

- CONQUER (episodic and chronic migraine)
- REGAIN (chronic migraine)
- EVOLVE-1 (episodic migraine)
- EVOLVE-2 (episodic migraine)

Galcanezumab was given at a 120mg dose each month following an initial 240mg loading dose. The length of the placebo-controlled period in all trials was either 3 (CONQUER, REGAIN) or 6 (EVOLVE-1 and EVOLVE-2) months. The primary outcome assessed in all trials was overall mean change from baseline in monthly MHDs. Other outcomes included the proportion of patients with episodic migraine with ≥50% reduction in mean monthly MHDs from baseline and the proportion of patients with chronic migraine with ≥30% reduction in mean monthly MHDs from baseline. The subgroup population under consideration in the company submission was patients who had failed ≥3 prior preventive medications. Baseline data was taken from the CONQUER trial which included a population who had failed 2-4

previous treatments. Unplanned analyses were conducted on the other 3 trials to model treatment effects for the subgroup of people with ≥3 previous failed treatments.

1.5 Key trial results

Trial efficacy outcomes at 3 (CONQUER, REGAIN) and 6 (EVOLVE-1 and EVOLVE-2) months in people with ≥3 prior preventive medication failures.

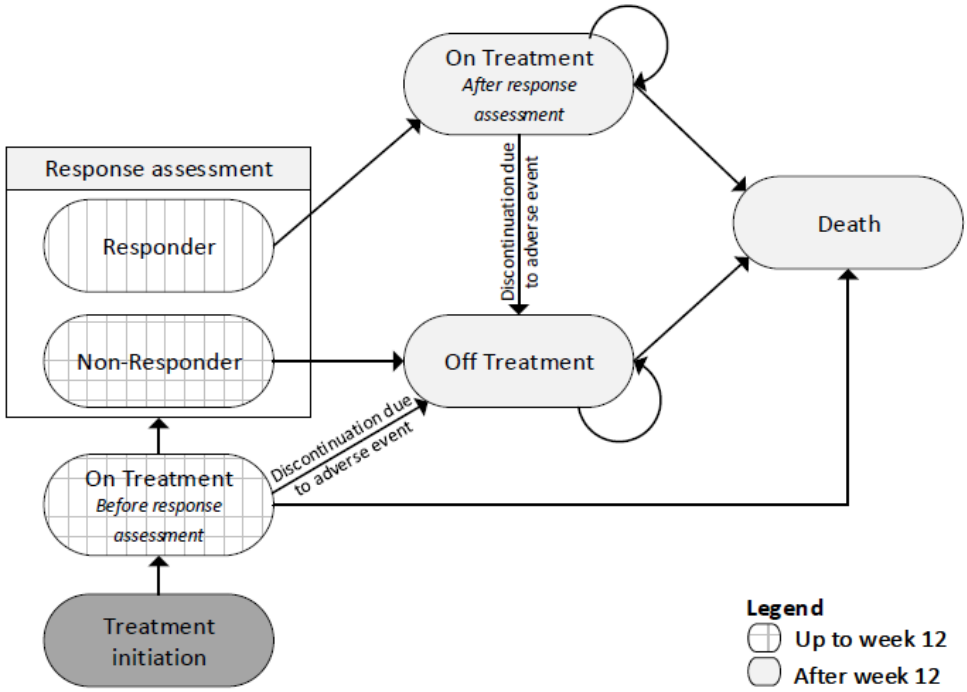
Study	Outcome	CM: Effect (95% CI)	EM: Effect (95% CI)	HFEM: Effect (95% CI)
CONQUER	Change from baseline in mean migraine headache days	[redacted]	[redacted]	[redacted]
	Change from baseline in mean headache days	[redacted]	[redacted]	[redacted]
	≥ 50% reduction from baseline in migraine headache days	[redacted]	[redacted]	[redacted]
	≥ 30% reduction from baseline in migraine headache days	[redacted]	-	[redacted]
REGAIN	Change from baseline mean migraine headache days	[redacted]	-	-
	≥ 50% reduction from baseline in migraine headache days	[redacted]	-	-
EVOLVE 1 and 2 pooled	≥ 50% reduction from baseline in migraine headache days	-	[redacted]	-

CM: chronic migraine, EM: episodic migraine, HFEM: high frequency episodic migraine, CI: confidence interval, OR: odds ratio

Source: based on company submission tables 27, 28, 30, 31, 33, 34 and 35

1.6 Model structure

The company presented a semi-Markov model structure comprised of four health states; on-treatment, off-treatment due to non-response, off-treatment due to adverse events and death. The model had an assessment period (month 1 – 3) and post-assessment period (month 4 onwards). Each of the health states is associated with a mean monthly MHD frequency, and the response assessment period allows differentiation between responders and non-responders.



Source: company submission figure 11

1.7 Key model assumptions

The company made a number of assumptions in the design of its economic model. Key model assumptions are listed below:

- Cycle length is 30 days
- Clinical meaningful response criteria of 30% or greater reduction in MHD for CM and 50% or greater reduction in MHD for EM and HFEM patients
- Responder and non-responder efficacy results combined as observed in CONQUER for galcanezumab when compared to botulinum toxin A

- Treatment responders remain on treatment and are assumed to maintain responder, or combined mean change MHDs, until the end of the time horizon
- Patients who discontinue active treatment due to non-response or adverse events (AEs) switch to BSC treatment only and revert to baseline monthly MHDs for the remainder of the time horizon
- Patient who discontinue active treatment are assumed to wane back to baseline monthly MHDs at different rates based on available data for the respective modelled treatments
- Responders in the BSC arm in the model wane back to baseline MHDs over 12 months, non-responders wane back immediately in the next cycle
- No excess mortality in the model
- No positive discontinuation rule was applied in the model, discontinuation is purely captured through the assessment of response and due to AEs
- Assessment of response for botulinum toxin A is assumed to take place at 90-days
- Placebo arms from the trial assumed as a proxy for BSC in the model
- 25-year lifetime horizon in base case
- Pooled utility values were chosen based on recent NICE committee preferences from a similar NICE technology appraisal for migraine

1.8 Overview of how quality-adjusted life years accrue in the model

In the company's model, the impact of migraine is captured by 30 health states representing the frequency of migraine headache per 30-day model cycle. Each health state is associated with a utility value that determines the accumulation of QALYs in the model. Quality-adjusted life years are generated for each state and combined with costs based on the proportion of patients in each state.

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 A lifetime model time horizon (45 years) is preferred to 25 years

Issue 2 High frequency episodic migraine is not considered clinically distinct from episodic or chronic migraine

Issue 3 Galcanezumab should be considered in treatment sequences before and after botulinum toxin A

Issue 4 Results from the ITC should be used for the different response rates between galcanezumab and botulinum toxin A, and the change from baseline in MHD for responders

Issue 5 It is appropriate to assume consistent discontinuation rates and waning periods for galcanezumab and botulinum toxin A. It is also preferable to assume consistent waning periods between episodic and chronic migraine populations

Issue 6 Alternative source should be used to generate HRQoL, differential utilities to be used to reflect a treatment effect, and assume that natural history will impact on the severity of migraine over time

Issue 7 Administration costs should be applied for 10% of people receiving galcanezumab, and alternative utility values generated by National Health and Wellness Survey.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The trials are not designed to assess the position of galcanezumab in the company's proposed use
- The systematic review is not comprehensive enough to include a full population irrespective of number of previous treatment failures
- Long term evidence for treatments is not available
- Data on response rates is not available for all treatments
- There is uncertainty in the rates of treatment discontinuation
- There is uncertainty in the distribution of migraine headache days

2.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for galcanezumab but do not include the confidential commercial medicine unit discount for botulinum toxin A.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) for galcanezumab between £20k and £30k per QALY gained compared with BSC in episodic migraine (see table 1a), under £20k per QALY gained compared with BSC in chronic migraine (see table 1b) and between £20k and £30k per QALY gained compared with botulinum toxin A in chronic migraine (see table 1c). However, there are uncertainties associated with the ICERs that should be considered (see sections 3 and 4). These estimates do not include the commercial arrangements for botulinum toxin A, because these are confidential and cannot be reported here. Estimates that included these commercial arrangements would be higher than those reported above.

2.5 The technology is unlikely to be considered innovative (see table 3).

2.6 No equalities issues were identified (see table 3).

3. Key issues for consideration

Issue 1 – Time horizon

Questions for engagement	1. Will all the costs and benefits of galcanezumab be captured over 25 years? 2. Is a lifetime time horizon more appropriate than 25 years?
Background/description of issue	**The company** used a 25-year time horizon in its economic model as this was considered an appropriate duration over which to fully capture the lifetime costs and benefits of galcanezumab. The company defined lifetime as 25 years in its base case and noted that previous appraisals for erenumab and fremanezumab used 10 years which the committee did not consider to be sufficiently long enough. The company also noted that the uncertainty from short-term clinical trial data would inherently make any long-term estimates unreliable for longer time horizons. Scenario analyses were provided which included 10 and 45-year time horizons. **The ERG** considered the 25-year time horizon in the company's economic model to be sufficient to capture important differences. However, the ERG noted that the incident population are likely to have a mean age under 40 and the company's modelled population may not reflect this. This could impact on the appropriateness of a 25-year time horizon. The ERG agrees that the lack of long-term effectiveness data for galcanezumab and comparator therapies could result in significant uncertainties with a longer time horizon. There are also problems with the company's approach of not modelling the natural history of migraine and how these could be exacerbated by a longer time horizon. It is possible that quality of life may change over time but the company assumed that utility values would remain constant over the time horizon. This could have a significant impact when using a longer time horizon such as 25 years.
Why this issue is important	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Technical team preliminary judgement and rationale	It is possible that a 25-year time horizon is sufficient and that extending this could introduce further uncertainty into the model because the natural history of migraine is not captured.

	However, in the previous migraine appraisals of erenumab and fremanezumab, the committee preferred a lifetime time horizon, in line with the NICE reference case. The technical team consider that the time horizon should be extended to lifetime to ensure that all costs and benefits are adequately captured.

Issue 2 – High frequency episodic migraine

Questions for engagement	3. Is high frequency episodic migraine a clinically distinct subgroup? 4. If yes, what definition of "high-frequency" is used in clinical practice?
Background/description of issue	**The company** submission included a subgroup of patients within the episodic migraine group which they categorised as 'high frequency episodic migraine' (HFEM). This subgroup was defined as patients with 8-14 monthly MHDs who suffer <15 headache days per month. The company noted that HFEM has a burden of disease similar to that of chronic migraine and that experts suggested that HFEM should be recognised as a separate clinical group. As people with HFEM whose condition does not respond to 3 or more treatments do not currently have access to specialist treatment options, the company presented data to address this unmet need. **The ERG** highlighted that there is debate in the clinical community about the company's claim that HFEM represents a distinct subgroup of patients. The ERG sought advice from 2 Consultant Neurologists specialising in migraine treatment who suggested these patients were a neglected and important clinical subgroup. However, there was uncertainty in the advice as the 2 clinical advisers disagreed whether HFEM was a clinically distinct subgroup. The ERG also noted that previous appraisals on erenumab and fremanezumab have judged that HFEM was not a clinically meaningful category.
Why this issue is important	Recommendations would only be made for subgroups that are recognised as clinically relevant and distinct. Unless HFEM is a clinically recognised subgroup, it should not be considered separately.
Technical team preliminary judgement and rationale	There is no clear definition of HFEM as a subgroup and there is no consensus on whether it is clinically distinct from either episodic or chronic migraine. Therefore, HFEM should not be

	considered separately in the model or analysis. The data for HFEM should be considered within the episodic migraine group.

Issue 3 – Position of galcanezumab in the treatment pathway

Questions for engagement	5. Would galcanezumab be considered as an option once botulinumtoxin toxin A has failed, is not considered to be appropriate or has not been tolerated? 6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?
Background/description of issue	**The company** submission positioned galcanezumab as a 4th line treatment option for people whose migraine has failed 3 or more preventative treatments. This would position galcanezumab to allow comparison with best standard care (BSC) for episodic migraine and botulinum toxin A and BSC for chronic migraine. The CONQUER trial was the primary source of evidence in the company submission as it specifically assessed the efficacy of galcanezumab in people with 2-4 prior treatment failures. This trial included international study locations where potentially botulinum toxin A was one of the 3 prior failed treatments. **The ERG** considered the positioning of galcanezumab to be generally appropriate. However, they note that there is a potentially large prevalent population of chronic migraine patients who have already received botulinum toxin A as a failed preventive treatment. Therefore, galcanezumab would represent a fifth-line option for these patients. The ERG considered it important to explore different sequences of treatment where galcanezumab was given before or after botulinum toxin A. The ERG noted that the appeal in the erenumab appraisal upheld that the committee should have considered the use of erenumab as 5th line following failed treatment with botulinum toxin A. This sequence has not been explored in the company's submission or as part of the ERG's analysis.
Why this issue is important	There is potentially a substantial population of people whose chronic migraine has failed 3 or more treatments that include botulinum toxin A so it is worth considering galcanezumab at different points in the treatment pathway.
Technical team preliminary judgement and rationale	The company have not provided clinical or cost-effectiveness evidence for galcanezumab when used in a sequence either before or after botulinum toxin A. It is therefore unclear whether it is reasonable to consider galcanezumab in this position. A scenario should be provided that considers galcanezumab in the treatment pathway before use of botulinum toxin A and a scenario where galcanezumab is used after as 5th line.

Issue 4 – Indirect treatment comparison for chronic migraine

Questions for engagement	7. Is galcanezumab more effective at preventing migraines than botulinum toxin A? 8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?
Background/description of issue	Direct evidence comparing galcanezumab to BSC was available for episodic migraine so an indirect treatment comparison (ITC) in this population was not required. As no direct evidence comparing galcanezumab to botulinum toxin A was available for chronic migraine, the company conducted an ITC. A systematic literature review identified the PREEMPT-1 and PREEMPT-2 trials for botulinum toxin A where patients had failed 3 or more prior preventative treatments. The galcanezumab trials used in the comparison were the REGAIN and CONQUER studies in people with chronic migraine. The company noted some limitations with the botulinum toxin A data when considering the target population of people with a history of 3 or more failed prior preventative treatments: • A key outcome, response rate, was missing • Missing baseline characteristics • Small sample size To account for these limitations, the company conducted additional analyses which included a population with <3 prior failed preventative treatments, termed 'all-comers'. However, the ≥50% response rate was not included in the ITC as data from the botulinum toxin A trials was not available for a population with 3 or more prior treatment failures. The company noted that baseline characteristics were generally comparable across the PREEMPT and REGAIN trials for the all-comers population. The company also noted the following considerations with the data used in their base case analysis: • Treatment effects assessed at 3 months for galcanezumab and at 24 weeks for botulinum toxin A • Monthly estimates based on 28 days for botulinum toxin A and 30 days for galcanezumab • The definitions for continuous measurements of outcomes vary across studies The results of the ITC showed [redacted] comparing galcanezumab with botulinum toxin A in either all-comer or ≥3 failed treatment populations. The company did not use the results from the ITC for the responder rates due to the lack of statistically significant results and

	instead opted to assume equal response rates for galcanezumab and botulinum toxin A. [redacted] The results from this outcome were used in the company's economic model. In addition to the limitations identified by the company, **the ERG** noted that the studies of galcanezumab and botulinum toxin A differed in the following characteristics. These may affect the estimated relative effects: • substantially higher placebo response rates were observed in PREEMPT-1 and PREEMPT-2 compared with placebo response rates in REGAIN and CONQUER • definition of headache/migraine headache – galcanezumab: ≥30 minutes duration; botulinum toxin A: ≥4 continuous hours • statistical methods for calculating treatment effects – galcanezumab: mixed model repeated measures; botulinum toxin A: analysis of covariance • double blind treatment periods - galcanezumab trials: 3 months; botulinum toxin A: 24 weeks • the placebo is different in galcanezumab (REGAIN two injections at each dosing visit, CONQUER two injections at visit 3 and one injection thereafter) and botulinum toxin A studies (31-39 injections sites). The ERG has concerns regarding the company's approach to generate the modelled treatment effects for galcanezumab and botulinum toxin. In particular, it is noted that the use of a different model structure for this comparison means that a full incremental analysis cannot be implemented. The ERG therefore considers several alternative treatment effect scenarios using the response-based model structure used in the comparison between galcanezumab and BSC:

	• Scenario 11a: Assume equal effectiveness across all parameters for galcanezumab and botulinum toxin A • Scenario 11b: Response rate differs between galcanezumab and botulinum toxin A – relative effect based on ITC of responders (50%; whole population: 'all-comers'). • Scenario 11c: Change from baseline in MHD for responders allowed to differ between galcanezumab and botulinum toxin A – value estimated using the ITC of change from baseline in MHD (DTT-3 population) • Scenario 11d: Scenario 11b and Scenario 11c combined In considering the most appropriate set of assumptions to model the treatment effect, the ERG considered that a valid argument can be made for all four of these scenarios, as each has its own advantages and disadvantages. For the purpose of producing the ERG base case, the ERG prefers Scenario 11d. **The ERG** noted that the ITC should be interpreted with some caution as the systematic review was not sufficiently inclusive for the 'all-comers' CM population which creates some uncertainty as this group has been used to inform parameters in the ERG's economic analysis.
Why this issue is important	A lack of direct comparative evidence means the comparison of effectiveness between galcanezumab and botulinum toxin A for people with chronic migraine has to be estimated. Limitations with the ITC means that the results have to be interpreted with some caution. This uncertainty is carried through the model and into the cost-effectiveness estimates.
Technical team preliminary judgement and rationale	There are justifications to consider the scenario put forward by the company for equal response rates as well as scenarios based on the ITC response rates as suggested by the ERG. It may be appropriate to consider a scenario where the response rates differ between treatments (relative effect based on ITC of responders) and the change in MHDs for responders also differ (value estimated from ITC). The technical team's preference is therefore to incorporate scenario 11d from the ERG's base case.

Issue 5 – Long-term treatment effectiveness and discontinuation

Questions for engagement	9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds? 10. What proportion of people are expected to restart treatment after it was stopped for any reason? 11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)? 12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A? 13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?
Background/description of issue	The length of the placebo-controlled period in all trials was limited to either three (CONQUER, REGAIN) or six (EVOLVE-1 and EVOLVE-2) months. An implicit assumption of the economic analysis is that effects of treatment as observed at 90 days are extrapolated throughout the time horizon of the model. The company justifies this assumption on the basis of long-term data from the REGAIN and CGAJ studies. In the company's model, responders to galcanezumab at 90 days would continue on treatment for the lifetime of the model. People whose migraine did not respond at 90 days or those who experienced adverse events were assumed to discontinue treatment (negative discontinuation). The company's model assumes people discontinuing treatment will wane back to baseline MHDs. The company used the REGAIN trial to model the galcanezumab waning period for chronic migraine, the EVOLVE-2 trial for episodic migraine, and used assumptions for BSC and botulinum toxin A. These produced estimates of treatment effect waning ranging from [redacted] months across the treatments with galcanezumab showing a longer period than botulinum toxin A and differences between episodic and chronic migraine. The company has also provided an additional scenario analysis where the waning period is assumed equal for galcanezumab and botulinum toxin A. The company used different trials to obtain discontinuation rates for galcanezumab, botulinum toxin A and BSC. From these values, the probability of discontinuing treatment was applied in the assessment and post-assessment periods. Using these values, a higher rate of discontinuation was applied to galcanezumab than that applied to botulinum toxin A.

	The ERG is satisfied with the company's underlying assumption that patients discontinuing treatment wane back to baseline monthly MHDs but has several substantial concerns regarding the period over which they are assumed to wane. The ERG noted concern that the estimates of long-term treatment effect were based on short term follow-up data. The ERG also considered the differences in waning between treatments and between episodic and chronic migraine to be unreasonable without evidence to justify the differences. Different scenarios were provided by the ERG to explore the effects of alternative durations of treatment effect waning. The ERG's preferred approach used in its base case for chronic migraine (vs botulinum toxin A) assumes that people discontinuing treatment would wane back from responder MHDs. The ERG was also concerned with the discontinuation rate values applied in the model. It considered the values applied to galcanezumab to be very large and not in line with the data from trials which would suggest a lower rate compared to botulinum toxin A. The ERG suggested that the higher discontinuation rate for galcanezumab reduces the ICER as patients experience an initial further decline in MHDs when discontinuing treatment. The ERG, therefore, prefers to assume that the rates of discontinuation are consistent across treatments.
Why this issue is important	The addition of any duration of treatment effect waning is likely to accrue QALYs and costs in the model and impact the ICER.
Technical team preliminary judgement and rationale	The short-term follow-up data means there is uncertainty in the long-term treatment effects of galcanezumab. It is also unclear what the duration of waning would be following treatment discontinuation. The preference is to assume consistent discontinuation rates and waning periods for galcanezumab and botulinum toxin A. It is also preferable to assume consistent waning periods between episodic and chronic migraine populations. Scenarios should be considered which explore different assumptions of waning durations. ICERs should also be provided for a scenario where treatment is restarted following discontinuation for any reason.

Issue 6 – Health related quality of life

Questions for engagement	15. Should relevant utility data from the EVOLVE and REGAIN trials be included?

	16. Should the same utility values be used for both galcanezumab and comparators? 17. Should age-related disutilities be applied? 18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?
Background/description of issue	**The company** noted in their submission that EQ-5D-5L data were collected as part of the CONQUER trial and mapped to EQ-5D-3L. The migraine-specific quality of life questionnaire (MSQ) data was collected in the EVOLVE-1, EVOLVE-2, REGAIN and CONQUER trials. MSQ data from only the CONQUER trial were mapped to EQ-5D-3L using a published mapping algorithm. Data from the EVOLVE-1, EVOLVE-2 and REGAIN trials were not used in the model. The company considered that utility values as mapped from MSQ to EQ-5D-3L to be a preferable source of HRQoL data and considered them more reliable citing that this was also preferred in previous migraine appraisals. A broad approach was taken to use the same utility set across episodic and chronic migraine. The company also used a single set of utility values for both galcanezumab and BSC patients. **The ERG** noted two related issues regarding the source of the MSQ data used to generate the utility values used in the model. Firstly, that the utility values were based on the whole population of the CONQUER trial and not just on the relevant subgroup of patients who have failed ≥3 previous preventative therapies. Secondly, that the utility values are based on data from the CONQUER trial alone, even though relevant HRQoL data were collected in both EVOLVE trials, as well as in the REGAIN trial. The ERG also noted that scenario analysis presented by the company using the relevant subpopulation of patients who have failed ≥3 previous preventative therapies from all four trials results in a substantial increase in the ICER. A further limitation of the company's approach to modelling HRQoL is the assumption that utility values remain constant throughout the time horizon of the model and therefore make no account of the fact that quality of life may evolve over time. It also does not account for other dimensions of the condition which may impact on both HRQoL and costs. Specifically, the model does not account for changes in either migraine severity or the frequency of headache that is not classified as a migraine. Clinical advice received by the ERG highlighted that both migraine severity and headache frequency are aspects that are important in determining the overall burden of the disease. Further comments

	from the ERG's clinical adviser suggested that an effective treatment (such as galcanezumab) would likely impact upon both these aspects as well as migraine frequency. The ERG considered that the observed differences between treatment arms could potentially be explained by changes in either migraine severity or the frequency of headache. As such, there is evidence to support the use of differential utilities between treatments rather than the single set of utility values as used by the company.
Why this issue is important	Utility values will directly impact the cost-effectiveness estimates.
Technical team preliminary judgement and rationale	The relevant subpopulation with ≥3 failed previous preventative therapies from the included trials should be used to generate utility values. The severity and natural history of migraine should be accounted for in the utility values which should be adjusted to increase over time. Further, a differential utility should be applied that reflects treatments effects.

Issue 7 – Resource costs

Questions for engagement	19. What proportion of people would not be able to self-administer galcanezumab? 20. Should an additional cost for people who cannot self-administer be included in the model? 21. Should additional monitoring costs from the 6 to 12 month patient reviews be included in the model? 22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?
Background/description of issue	**The company's** model included drug acquisition costs, administration costs along with resource use costs that were associated with each MHD. This approach to resource use by MHD was identified from a literature review by Lipton et al. which utilised resource use data from the Munakata et al. survey of US migraine patients. Adverse reaction costs were not included in the economic model. **The ERG** highlighted that administration costs for galcanezumab were included but only for the first cycle and the company assumed that patients would self-administer thereafter. The ERG did not consider this to be reasonable because some patients would not be able to self-administer. This was also identified in the fremanezumab appraisal where the committee concluded that an administration cost should be applied to 10% of patients.

	The ERG also noted that monitoring costs were not included as clinical advice suggested that galcanezumab patients would be reviewed every 6 to 12 months. In this appraisal the company opted to use a US survey (Munakata et al) which presented data on average healthcare resource in migraine population along with the average migraine days per month and did not explore the impact of migraine or headache days on healthcare consumption. The ERG suggests that a more robust estimate of healthcare resource costs could be derived from the National Health and Wellness Survey (NHWS) 2016 which included patients from the UK and explored the impact of migraine or headache days on healthcare consumption.
Why this issue is important	Estimates of resource use and costs feed into the economic model and would impact the cost-effectiveness analyses. Misrepresenting costs in the economic model will affect the ICER.
Technical team preliminary judgement and rationale	It is reasonable to assume that not all patients would be able to self-administer galcanezumab. Therefore, it is appropriate to assume that a proportion of people having galcanezumab will have their treatment administered by a healthcare professional It is also reasonable to consider alternative healthcare resource costs generated by NHWS.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1a: Technical team preferred assumptions and impact on the cost-effectiveness estimate (deterministic: episodic migraine – galcanezumab vs BSC)

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**£29,230**	**–**
ERG corrections	The ERG corrections to the model are acceptable	£29,313	+£83
Time horizon	Issue 1: Company sensitivity analyses 45 years	£28,929	-£301
Alternative source used to generate HRQoL	Issue 6: data based on failed ≥3 previous preventative treatments population	£37,149	+£7,919
Differential utilities for galcanezumab and comparator	Issue 6: incorporation of differential utilities to reflect a treatment effect	£13,232	-£15,998
Age-related disutility	Issue 6: natural history will impact on the severity of migraine over time	£30,247	+£1,017
Galcanezumab administration cost for 10% of patients	Issue 7: not all patients could self-administer	£29,563	+£334
Alternative resource consumption rates	Issue 7: alternative values generated by NHWS	£36,049	+£6,820
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£26,313**	**-£2,917**

Table 1b: Technical team preferred assumptions and impact on the cost-effectiveness estimate (deterministic: chronic migraine – galcanezumab vs BSC)

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**£8,080**	
ERG corrections	The ERG corrections to the model are acceptable	£8,053	-£27
Time horizon	Issue 1: Company sensitivity analyses 45 years	£7,920	-£160
Consistent waning period between episodic and chronic migraine populations	Issue 5: no difference in treatment waning across migraine population	£9,602	+£1,522
Alternative source used to generate HRQoL	Issue 6: data based on failed ≥3 previous preventative treatments population	£10,269	+£2,189
Differential utilities for galcanezumab and comparator	Issue 6: incorporation of differential utilities to reflect a treatment effect	£4,456	-£3,624
Age-related disutility	Issue 6: natural history will impact on the severity of migraine over time	£8,347	+£268
Galcanezumab administration cost for 10% of patients	Issue 7: not all patients could self-administer	£8,243	+£163
Alternative resource consumption rates	Issue 7: alternative values generated by NHWS	£14,892	+£6,813
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£10,486**	**+£2,406**

Table 1c: Technical team preferred assumptions and impact on the cost-effectiveness estimate (deterministic: chronic migraine – galcanezumab vs botulinum toxin A)

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**£2,560**	
ERG corrections	The ERG corrections to the model are acceptable	£4,203	+£1,643
Time horizon	Issue 1: Company sensitivity analyses 45 years	Galcanezumab dominates	N/A
Response rate differs (ITC) and Change from baseline in MHD differs (ITC)	Issue 4: scenario 11d from ERG	£11,734	+£9,174
Consistent waning period between episodic and chronic migraine populations	Issue 5: no difference in treatment waning across migraine populations	£25,168	+£22,608
Consistent waning period between galcanezumab and botulinum toxin A	Issue 5: no difference in treatment waning between treatments	£5,464	+£2,904
Discontinuers wane back from responder MHDs	Issue 5: removal of further reduction in MHDs	£26,645	+£24,085
Equal discontinuation rate	Issue 5: Equivalent discontinuation rates across treatments	£11,742	+£9,181
Alternative source used to generate HRQoL	Issue 6: data based on failed ≥3 previous preventative treatments population	£3,254	+£694
Differential utilities for galcanezumab and comparator	Issue 6: incorporation of differential utilities to reflect a treatment effect	Dominated	N/A
Age-related disutility	Issue 6: natural history will impact on the severity of migraine over time	£2,622	+£61
Galcanezumab administration cost for 10% of patients	Issue 7: not all patients could self-administer	£3,255	+£694
Alternative resource consumption rates	Issue 7: alternative values generated by NHWS	£9,534	+£6,974

Alteration	Technical team rationale	ICER	Change from base case
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£22,859**	**+£20,299**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Generalisability of trial results	The ERG noted limitations of the included trials. Some of the prior preventive medication failures were for treatments not routinely used in the UK. Although the company submission focused on a subgroup of patients with ≥3 prior preventive medications, some data was summarised which was not specific to this population. These data were reported in combined CM and EM populations; as well as separately for CM, HFEM, and EM patients. Also, the company pooled baseline monthly MHDs for CM patients using both arms of the CONQUER study (galcanezumab and placebo) to inform the economic model. However, the company did not use similar available data from REGAIN which would likely have increased precision of these estimates.	As the trials are not designed to assess the position of galcanezumab in the company's proposed use, it is unclear how generalisable the results are. There is some uncertainty which will have to be considered when determining the cost-effectiveness of galcanezumab.
Systematic review	The ERG noted limitations with the inclusion criteria. Trials that did not report separate data for patients who had failed previous preventive medications were excluded. This limited the comprehensiveness of the analyses conducted by the company on an 'all-comers' population (i.e. data from patients included in analyses regardless of how many previous failed preventive treatments). In addition, evidence synthesis	Unknown impact on ICER.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	methods sometimes lacked consistency and comprehensiveness in application. For example, in some analyses only data from CONQUER were used when similar data were available from other company trials.	
Extrapolation of data	Data from the included studies was available up to a 90-day assessment period. There is no long-term clinical effectiveness data, therefore relative effectiveness estimates have to be extrapolated beyond what was observed in the trials at 90 days. The extrapolation of long-term effectiveness is uncertain because there is no data which can be used for external validation.	The uncertainty with extrapolation may lead to an underestimation of the ICERs.
Response rate	Data on patient counts from REGAIN and CONQUER were pooled to inform the 50% response rate (i.e. ≥50% reduction in baseline monthly MHDs) for patients who had failed ≥3 prior preventive medications in the economic model. The ERG considers that more valid estimates could have been attained through meta-analysis by using log-odds. The baseline monthly MHD for EM could have used data from the EVOLVE studies as well as CONQUER to increase precision of the estimate. Also, the results of the ITC should not have been rejected and should be used for response rates.	Unknown impact on ICER.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Discontinuation rate	The predicted rates of discontinuation are different with the rate applied to galcanezumab being four times that applied to the botulinum toxin A arm of the model. This difference in the discontinuation rate does not fully align with the data from the studies. The ERG considers that a more reasonable assumption would be to assume equal rates of discontinuation across both active treatments.	This model difference in the discontinuation rate is important in the context of the company's base-case and acts in favour of galcanezumab. Increasing the discontinuation rate for galcanezumab leads to the ICER decreasing.
Distribution of migraine headache days	Ineligible patients: The ERG is concerned with the company's approach to modelling the distribution of MHDs. The model makes predictions about the distribution of monthly MHDs that are inconsistent with the licence and described modelled populations. Responder/non-responder distributions: The ERG notes a point of difference between the company's approach to modelling the distribution of monthly MHDs and the NICE TAs of fremanezumab and erenumab. In the previous appraisals the distribution of monthly MHDs was modelled separately for responders and non-responders. In contrast, the company's model fits a single pooled distribution to all patients.	This remains a source of uncertainty in the model and the ERG considers that it may have been more appropriate to have modelled truncated distributions. This would have ensured model predictions retained face validity and would have improved model accuracy. The ERG expects that this simplification will likely lead to some inaccuracies in the predicted distribution of monthly MHDs. As with the previous issue, the ERG, however, does not expect this to impact significantly on model results because model outputs (costs and QALYs) are largely a linear function of monthly MHDs.

Table 3: Other issues for information

Issue	Comments
Implementation of company model	Several minor model errors were identified as part of the ERG's validation checks. These errors were corrected by the ERG, and a revised model supplied to the company with altered cells highlighted to aid verification. These corrections did not impact substantively on the model's predictions.
Safety	The EMA identified some uncertainties about the safety of galcanezumab. First, there is very limited data on safety in pregnancy as pregnant women were excluded from clinical trials of galcanezumab. Second, in common with other CGRP antagonists, galcanezumab could theoretically aggravate ischemic events such as stroke, transient ischaemic attack and myocardial infarction. Adverse reaction costs were not included in the economic model.
Response criteria	Assessed by reduction in mean MHDs by ≥50% versus baseline in the episodic migraine analysis; and ≥30% mean MHDs in the chronic migraine analysis.
Innovation	The technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts. It has been noted in previous appraisals in this area that migraine prevalence is higher in women than men, meaning a restriction of access will be a greater disadvantage to women. The technical team considered that this was not an equality issue which could be addressed in its recommendations.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Galcanezumab for preventing migraine [ID1372]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Thursday 30 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Hamish Lunagaria**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Eli Lilly & Company**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	Lilly believes that a 25-year time horizon is sufficiently long to capture all material benefits and costs in the cost effectiveness analysis between treatments. Longer-time horizons would introduce greater uncertainty for decision-making since the analysis extrapolates from short-term clinical data of less than 1 year. There is also a lack of data concerning the impact of the natural history of disease on health-related quality of life (HRQoL) of patients with migraine over-time. The Technical team's preliminary judgment and rationale states that '*extending the time horizon could introduce further uncertainty into the model because the natural history of migraine is not captured'.* However, applying both a longer time-horizon and unfounded assumptions regarding the natural history of disease on HRQoL, given the lack of insufficient evidence, would greatly exacerbates the uncertainty than applying a longer-time horizon alone. However, to ensure consistent decision-making to previous NICE technology appraisals of erenumab and fremanezumab (1, 2), Lilly accepts the application of a lifetime (45-year) time horizon without the application of natural history assumptions for galcanezumab.
2. Is a lifetime time horizon more appropriate than 25 years?	
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	Lilly believes that high frequency episodic migraine (HFEM, i.e. between 8 and 14 migraine headache days per month, and less than 15 headache days per month) should be defined as a clinically distinct subgroup within episodic migraine. However, it is not yet classified as a clinically distinct subgroup by NICE or the third edition of the International Classification of Headache Disorders (3, 4). Experts in the field acknowledge that the burden of disease for patients with HFEM is similar to that of chronic migraine and have proposed that the definition of chronic migraine be

	revised to recognise HFEM as a separate clinical group (5-7). HFEM is specifically mentioned and defined by the British Association for the Study of Headache within their comments in the draft remit and scope for the technology appraisals of fremanezumab and galcanezumab (8, 9). The proposal to classify HFEM as a clinically distinct group was also supported by UK neurologists in an advisory board sponsored by Eli Lilly in June 2020 (10). There was consensus that in clinical practice, patients would be treated according to the degree of disability and quality of life, rather than solely by headache frequency (5-7, 11). However, while HFEM patients have a burden similar to chronic migraine patients, they did not qualify for botulinum toxin A or fremanezumab therapy based on NICE guidance (2, 12).
4. If yes, what definition of “high-frequency” is used in clinical practice?	Lilly believes that HFEM is defined as the occurrence of 8-14 migraine headache days (MHDs) per month. However, there is no consensus definition of HFEM in the field of migraine research and different studies have defined HFEM as 8-14 migraine headache days (MHDs) per month (5-7, 11, 13), 9-14 monthly MHDs (14, 15) or 10-14 monthly MHDs (5, 16). Based on the most recent studies demonstrating comparable burden of illness of HFEM with chronic migraine (5-7, 11), Lilly considers a definition of 8-14 monthly MHDs to be the most appropriate definition, which aligns with the definitions used in the clinical trials for galcanezumab.
Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinum toxin A has failed, is not considered to be appropriate or has not been tolerated?	Lilly believes that galcanezumab would be an option for patients once botulinum toxin A has failed, is not considered to be appropriate or has not been tolerated, as well as a desirable alternative to botulinum toxin A, in the treatment pathway. Clinical trial data supports galcanezumab as an option for prevention of migraine in patients who have previously failed botulinum toxin A preventive therapy. In post-hoc analyses of the three pivotal trials for galcanezumab (REGAIN, EVOLVE-1 and EVOLVE-2) which included a pooled analyses of 129 patients who failed botulinum toxin A, significant decreases from baseline in the number of monthly MHDs were observed for 120 mg (-3.91) galcanezumab overall versus placebo (-0.88) across 3-month time points for patients who

	failed botulinum toxin A. Corresponding data for patients with chronic migraine showed significant decreases: 120 mg (-3.18) galcanezumab versus placebo (0.16) (17). Professional and patient organisations have also expressed a desire to position CGRPs such as galcanezumab for patients with chronic migraine with a history of ≥3 failed prior preventative treatments, which would include patients that have previously failed botulinum toxin A at fourth line. Feedback from the British Association for the Study of Headache (BASH) during the appraisal of fremanezumab reveals that treatment options are needed for patients with chronic migraine in England that had failed botulinum toxin A (18), and who would also benefit from fifth line treatment with galcanezumab as well as at fourth line. While there are no data published describing the patient numbers of such non-responders to botulinum toxin A, a snap poll conducted by the Migraine Trust reveals that 15.7% of patients receiving botulinum toxin A (representing 8.4% of chronic migraine patients overall) failed to respond to treatment, therefore presenting a sizeable population of patients that may be eligible for treatment with galcanezumab (19).
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	Additional data on the clinical and cost effectiveness of galcanezumab in this population of patients with chronic migraine are described in Appendix A and B respectively. Note that results are described only for patients in CONQUER with a history of ≥3 failed prior preventatives among patients with prior botulinum toxin A failure (i.e. fourth line galcanezumab). With regards to the population of patients who failed fourth line botulinum toxin A and were treated with fifth line galcanezumab, the patient numbers are too small ([redacted]) to provide any robust, meaningful or clinically significant results. Hence, the clinical outcomes in this subpopulation has not been described. Therefore, the clinical and cost effectiveness results for patients with a history of ≥3 failed prior preventatives among patients who failed prior botulinum toxin A serves as a proxy for the fifth line prior botulinum toxin A failed patients.
Issue 4: Indirect treatment comparison for chronic migraine	

7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	Due to the lack of head-to-head trial data with botulinum toxin A, it was necessary to carry out an indirect comparison. The results of the indirect comparisons are the best available evidence which shows a consistent trend towards a benefit of galcanezumab over botulinum toxin A in all the endpoints included in the analysis for the 'DTT-3' (history of ≥3 failed prior preventatives) population, although only the result on the change in MHDs was statistically significant. Lilly acknowledges that there are limitations to the indirect comparison, as highlighted in the Company submission and ERG report. The impact on results are unknown and hence, the results should be interpreted with caution. However, Lilly believes the results presented in the submission to be generally conservative. Some of the differences between the REGAIN and CONQUER trials for galcanezumab and PREEMPT trials for botulinum toxin A, were explored in sensitivity analyses. Considering a consistent 12-week timepoint for the 'all-comers' indirect comparison for the change from baseline in MHDs endpoint (Sensitivity 2) shows a greater mean difference than the base case estimates ([redacted]), implying that the base case estimates used to inform the economic analysis for the 'DTT-3' population and which used inconsistent time points (3-months for galcanezumab and 24-weeks for botulinum toxin A) could have underestimated the treatment effect for galcanezumab and the ICERs, particularly since the economic analysis assumed a 90-day assessment period for botulinum toxin A rather than 24-weeks.

Figure 1 Forest Plot: Indirect comparisons summary for the Change from baseline in monthly Migraine Headache Days (MHD) and monthly Headache Days (HD) for Galcanezumab 120mg versus Botox via Placebo

Furthermore, the committee for the previous technology appraisal for fremanezumab had accepted that on balance fremanezumab could plausibly have a benefit over botulinum toxin A given the same level of uncertainty over the indirect comparison to botulinum toxin A as is present for galcanezumab (2). A recent CGRP Patient Experience Survey conducted by The Migraine Trust highlighted that 80% agreed or strongly agreed that using a CGRP drug improved their quality of life by varying reasons, such as reduced frequency of migraine attacks or reduced severity of attacks. Given these determinations it is plausible that the benefit of galcanezumab is favourable over botulinum toxin A.

Lilly would also like to take this opportunity to address concerns regarding outstanding uncertainties about the generalisability of results of the CONQUER trial. As part of the clarification response Lilly attempted to alleviate concerns regarding the number of patients included in the analyses that had failed prior botulinum toxin A within the DTT-3 population. Presented below is an analysis whereby the treatment effect from the trial is adjusted using baseline patient data from InovPain, a real-world registry of patients from France with migraine (20).

	In this analysis, patient-level data from CONQUER were weighted to match aggregated registry data for patients with migraine with a history of ≥2 failed prior preventatives, following which the weighted CONQUER patient data were reanalysed using a priori defined CONQUER methodology. Results of the weighted analyses confirmed that galcanezumab was superior to placebo for overall mean change from baseline in the number of monthly MHDs during the 3-month double-blind treatment phase in patients with chronic migraine (LSM difference [95% CI] from placebo in primary analysis: -3.12 (-3.92,-2.32), p<0.0001; LSM difference [95% CI] from placebo in weighted analysis: -3.13 (-4.02,-2.24), p<0.0001) (20). Sensitivity analyses were conducted and led to the same conclusions. Although not directly related to the UK population of patients of interest, these data lead us to accept that the treatment effects observed in CONQUER are generalisable to a real-world cohort of patients with similar history of failed prior preventatives. Lilly also notes an error in the descriptions of the trial data used to inform the submission and cost effectiveness analysis for galcanezumab in the technical report. The report states that the *'The trials are not designed to assess the position of galcanezumab in the company's proposed use'.* However, the main body of evidence is from the CONQUER study which was specifically designed to assess the safety and efficacy of galcanezumab in a difficult-to-treat patient population, that is, patient that have history of between 2 to 4 failed prior preventative medication categories due to lack of efficacy or safety and tolerability. This evidence base speaks directly to the target population of patients that will be eligible for galcanezumab in clinical practice and can truly be considered difficult-to-treat since the definition of failures did not include any other reasons such as failure due to contraindications. Analyses for this subgroup were pre-specified in the CONQUER study (21). Lilly however acknowledges that post-hoc data was presented for this target population from the pivotal trials (22).
8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?	Based on Lilly's response to question 7, it is highly plausible that a difference in response rate would be seen for galcanezumab compared to botulinum toxin A. Lilly's original position to assume equal response rates for a 30% reduction in monthly MHDs from baseline (response rate) was due to the lack of publicly available data for this endpoint from the assessed botulinum toxin A trials. However, the treatment effect estimated from the odds ratio for the 'all-comers' population for the 50% response rate endpoint could plausibly be used as a proxy for a 30% response rate in the DTT-3

	population. A similar approach was used to discern a treatment effect for 30% response rate in the technology appraisal for fremanezumab (2). Therefore, for decision-making to stay consistent across appraisals, Lilly accepts the Technical team's preferred scenario to apply a treatment effect to the 30% response rate outcome as estimated from the indirect comparison to botulinum toxin A from the all-comers population.
Issue 5: Long-term treatment effectiveness and discontinuation	
9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	Lilly agrees with the ERGs assessment to assume that treatment with galcanezumab would not be continued indefinitely for a patient's lifetime and that treatment continuation was contingent on a periodic assessment by a clinician (likely, on an annual basis), in line with the Summary of Product Characteristics for galcanezumab (23). However, there is no data available from the galcanezumab trials or from practice for the average treatment duration for patients that are continuing to derive benefit for galcanezumab. In previous appraisals for migraine prevention, it has been proposed that people with chronic migraine would stop treatment when the migraine frequency had reduced to 10 migraine days a month for at least 3 months (2). There is no consensus for a stopping rule in episodic migraine. Currently, there is limited data to support the long-term effectiveness of galcanezumab beyond 5 months after stopping treatment. It has been suggested to assume that the minimum duration of time that a patient would be off treatment would be between 5 months (corresponding to the wash out period (24, 25)) to 8 months (allowing an additional 3 months to qualify as chronic migraine as per ICHD definition (3)). A lower threshold has been suggested for restarting treatment, as it may be unreasonable to allow patients to experience a worsening of migraine to the same level experienced prior to initiation of galcanezumab. Lilly is in agreement with comments from the ERG that the cost effectiveness of galcanezumab may be underestimated if in reality a positive discontinuation rule is implemented in practice for patients deriving continuous benefit from galcanezumab treatment, but there is no empirical data to inform

	such a scenario. Therefore, Lilly considers that it is not appropriate to present a positive discontinuation scenario (2).
10. What proportion of people are expected to restart treatment after it was stopped for any reason?	In the recent technology appraisal for fremanezumab, it was assumed that 20% of migraine patients who initially responded to treatment would discontinue every 64 weeks (2). It may be reasonable to assume that a similar proportion would restart galcanezumab within a year of discontinuing treatment as their migraine frequency may have returned to baseline levels. However, no data is currently available from clinical trials or real-world studies on the proportion of patients expected to restart treatment after stopping for any reason, and there is a lack of long-term washout data to determine at what point patients would return to pre-treatment baseline levels to restart treatment. Therefore, Lilly considers it is not appropriate to present a positive discontinuation scenario.
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	Lilly agrees that the trajectory and functional form of the waning period back to baseline for patients that discontinue treatment with galcanezumab is complex and likely non-linear in nature (as depicted in Fig 2, washout data for chronic patients from REGAIN; Fig 3 and Fig 4, washout data for episodic patients from EVOLVE-1 and EVOLVE-2,respectively). The washout data presented in the Company submission shows that the change in MHDs after patients stop treatment with galcanezumab slowly creeps back towards baseline levels. However, at 5 months post-treatment discontinuation, patients are still deriving significant clinical benefit compared to placebo, when washout data collection ended.

Figure 2 Washout data from REGAIN

Abbreviations: GM, galcanezumab (treatment arm); LSMean, least-squares mean; LY, galcanezumab (drug); OLE, open-label extension; SE, standard error

Fig 3 Washout data from EVOLVE-1

Abbreviations: GM, galcanezumab (treatment arm); LSMean, least-squares mean; LY, galcanezumab (drug);; SE, standard error

	Fig 4 Washout data from EVOLVE-2  **Abbreviations**: GM, galcanezumab (treatment arm); LSMean, least-squares mean; LY, galcanezumab (drug);; SE, standard error Therefore, the duration of this continued benefit off-treatment is uncertain beyond 5-months but is very likely much longer than that observed in the washout period for the trials. As no further long-term data exists for galcanezumab off-treatment beyond 5-months, Lilly accepts the Technical team's preference to assume a consistent waning period for the episodic and chronic models to return to baseline MHDs approximately 1-year once patients discontinue treatment due to adverse events or loss of response.
12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	Lilly accepts the Technical team's preference to assume a consistent waning period back to baseline MHDs post-discontinuation for galcanezumab and botulinum toxin A. However, to Lilly's knowledge,

	no data is currently available describing a sustained effect of botulinum toxin A off-treatment for patients who discontinue due to loss of response or other causes.
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	Based on feedback from the Association of British Neurologists (ABN) and BASH,(18, 26) it is assumed that all eligible patients would be treated with galcanezumab for at least 3 months in UK clinical practice before being assessed for a therapeutic response, at which point one of two stopping rules would be applied in practice, based on a predetermined therapeutic response. • a negative stopping rule – people with a lack of therapeutic response at 3 months would no longer be treated with galcanezumab • a positive stopping rule – people with evidence of therapeutic response at 3 months would continue treatment for 6-12 months, following which treatment would be withdrawn for as long as they were able to maintain the desired level of response. This is supported by studies on migraine prevention in topiramate, where it was demonstrated that the likelihood of maintained benefit following treatment cessation would be greater if the patients were treated for 6-12 months before stopping treatment.(27) The assumptions proposed by BASH seem reasonable and Lilly agree that galcanezumab treatment will not be maintained indefinitely in practice for patients continuing to derive a response after a certain period of time. However, there are no data currently available on the treatment effect following cessation of galcanezumab and subsequent restart. In past technology appraisals the clinical experts indicated it would be difficult to implement a positive rule in practice and furthermore the committee concluded it was not appropriate to include a positive discontinuation rule for the base case analyses for erenumab and fremanezumab (1, 2). Therefore, Lilly considers it is not appropriate to include a positive discontinuation scenario for galcanezumab.

Issue 6: Health related quality of life	
15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	Lilly agrees with the Technical team's preference to apply utility values estimated for the specific population of patients with a history of ≥3 failed prior preventatives, pooled for patients across all studies (that is, CONQUER, EVOLVE-1, EVOLVE-2 and REGAIN pooled).
16. Should the same utility values be used for both galcanezumab and comparators?	Lilly believes it is most appropriate to apply differential utilities values for the analysis of galcanezumab compared to best supportive care (BSC), taking account of the observed treatment effect in the clinical trials. Doing so, could account for additional aspects of migraine which may impact HRQoL not captured solely through the change in the frequency of MHDs. In Lilly's base case analysis, pooled utilities values were estimated and applied to both treatment arms in the economic model (i.e. for galcanezumab and BSC arm) to keep assumptions consistent with the past determination made in the technology appraisal for fremanezumab (5). However, compelling evidence was presented of a [redacted]) treatment effect for galcanezumab compared to placebo (BSC).

Figure 5 Scatterplot of the observed and predicted MSQ utilities by number of migraine headache days (CONQUER ITT)

Abbreviations: GMB, galcanezumab; MHD, migraine headache day; MSQ, migraine-specific quality of life questionnaire

When the covariate 'study treatment' was included in the regression analysis it showed that the utility values for patients receiving galcanezumab are higher than those for patients receiving placebo for the same number of migraine headache days (depicted in Figure 5). This may indicate that the treatment effect may have a benefit beyond reducing the number of monthly migraine headache days. The magnitude of the coefficient for the treatment effect is greatest for the pooled study estimates for patients with a history of ≥3 failed prior preventatives preferred by the Technical team. The treatment effect is [redacted] across all datasets (Table 1).

Table 1 Regression parameters of the mixed model considering month 1 to 3

	CONQUER ITT	CONQUER ITT Pr(>|t|)	CONQUER Failed ≥3 prior preventatives	CONQUER Failed ≥3 prior preventatives Pr(>|t|)	CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2 – Failed ≥3 prior preventatives	CONQUER, REGAIN, EVOLVE 1 and EVOLVE 2 – Failed ≥3 prior preventatives Pr(>|t|)
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MHD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MHD, migraine headache day

Additional supportive clinical information is provided in the response to question 18 on the impact of migraine symptoms on HRQoL and the application of differential utilities.

17. Should age-related disutilities be applied?

Lilly accepts the technical team's preference to apply age-related disutilities considering there is conflicting evidence regarding migraine-specific mortality and the application of a lifetime time horizon.

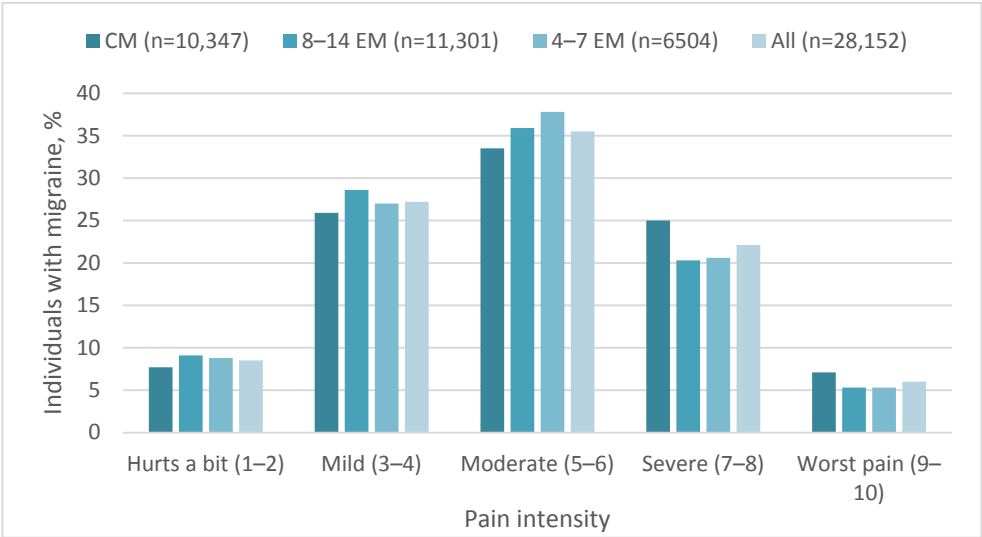
Lilly also believes it is not appropriate to assume all patients with migraine will improve overtime to account for the natural history of disease. Natural history of disease is likely more heterogeneous and its impact on the costs and benefits for preventative treatments such as galcanezumab is unknown. There is evidence to support the decline in prevalence after the onset of menopause for female patients, however, the same assumptions cannot be applied to male patients or to a proportion of patients that experience chornification, or to patients who have a history of hysterectomy (42). Therefore, as highlighted by ERG, applying the natural history scenario for all patient to improve back to 0 MHDs overtime is an extremely strong assumption. Due to the lack of data concerning the impact of the natural history of migraine, particularly on HRQoL of patients with

	migraine overtime, it is not appropriate to apply a natural history scenario to determine the cost effectiveness of preventative treatments.
18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	Migraine is a complex neurological condition and its impact on patient's HRQoL is multifaceted. Health-state utility values (HSUVs) were estimated using the migraine-specific quality of life questionnaire (MSQ) collected within the trials, with estimates predicted on data for reductions in MHDs. The original base case assumption of pooling health-state utility values (HSUVs) across treatment arms, without taking account of the treatment effect, implies that all aspects of HRQoL are captured solely through changing monthly frequencies of MHDs. However, the interplay between the complex nature of the 'ictal' burden (that is, the experience of the migraine attack itself) and 'interictal burden (that is, the experience in between migraine attacks) on HRQoL is unlikely captured through reduction in MHDs alone. Thereby underestimating the impact preventative treatments such as galcanezumab have on HRQoL and also its cost effectiveness compared to best supportive care treatments. The application of a treatment effect to HSUVs may capture the additional HRQoL benefit of preventative treatment such as reductions in the intensity/severity of pain associated with migraine attacks, disability caused by migraine attacks and the interictal burden between attacks. Several studies have been performed to qualitatively and quantitatively capture the complex nature of symptoms that impact patient's HRQoL. **General impact of migraine** Migraine causes negative effects on various areas of patients' lives. A cross-sectional study in adults with episodic migraine (EM) or chronic migraine (CM) in Germany, Italy, and the USA who completed an online survey reported important limitations resulting from migraine in private, professional, and social aspects of life, mainly the disruption of daily routines, significant strain in personal relationships, difficulty caring for children, and missed days of work, deadline, or social events (28). In addition, anxiety and frustration were frequently cited as the emotional consequences of migraine in private/social life and professional life (29). A number of studies have also highlighted the substantial impact of migraine on patients' physical health. Patients have remarked on the intensity of pain and the discomfort caused by light and noise during attacks, and how this has made sleep difficult, and had various other effects, including bodily pain, tiredness, sweating, and loss of memory (30). Poor sleep quality, in particular, has been shown to be associated with poor health, significant functional and cognitive impairment, and psychiatric comorbidity (31).

	The different psychosocial difficulties related to migraine were investigated in a systematic review of 51 papers reporting clinical trials and observational studies (32). A total of 34 psychosocial difficulties were identified. The most frequently studied were related to eight areas: emotional problems, decreased vitality and fatigue, pain, difficulties at work, decreased physical health, decreased mental health, poor social functioning, and increased global disability. The review found that there were two major determinants of improvements in psychosocial difficulties: (1) decreased frequency of headaches; and (2) migraine treatments. Symptomatic medications in the included studies were triptans, which showed evidence for improving emotional problems and work efficiency. However, the most important determinants of improvements in psychosocial difficulties were preventatives medications, which showed evidence for improving emotional problems, work efficiency, global disability, physical health, and mental health (32). In regard to the economic relationship, research has reported predictive factors for higher total costs among patients treated for migraine, which included lower health index utility score per the SF-6D (Short Form 6 Dimension) and lower physical functioning per the PCS (physical composite summary) of the SF-12 (Short-Form Health Survey) (29). Notably, comorbidities were not statistically significant predictors of being in the highest cost category. Measures associated with the frequency of migraine, including preventive eligibility per current or past use of migraine preventives and preventive eligibility per acute medication overuse, were also significant predictors in the model. This research further demonstrated the importance of variables that capture the ictal and interictal disease burden when evaluating economic outcomes. **Pain** Patients report that pain is the most intense and disabling symptom during a migraine attack. In a US cross-sectional, real-world analysis, pulsating/throbbing pain and unilateral pain were the most bothersome symptoms associated with migraine (i.e. impacted lifestyle or work), being reported as such in >50% of patients, both EM and CM (33). This was despite patients taking acute and/or preventatives treatment. Pain was also the most commonly self-reported symptom of migraine in 91.7% of users in an analysis of data from the Migraine Buddy© smartphone application (34). Overall, 63.6% of all migraine records from the application (n=28,152 attacks recorded in 3900 individuals) reported a pain intensity of ≥5 (on a scale of 1–10, where 10 = worst pain), which corresponded to an

inability of individuals to perform some of even any activities (34). Pain intensity was similar regardless of migraine frequency. (Figure 6).

Figure 6 Pain intensity reported in migraine records captured by the Migraine Buddy© smartphone application across 17 European countries (34)



Abbreviations: CM, chronic migraine; EM, episodic migraine

Other migraine symptoms

In addition to pain, several other symptoms that are characteristic of migraine attacks have been described by patients. The importance of non-pain symptoms has been highlighted by regulatory agencies. Both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) emphasize the value of measuring symptoms from the patient perspective and recommend the assessment of migraine-associated symptoms (N/V, photophobia, phonophobia) when evaluating migraine treatment efficacy (35).

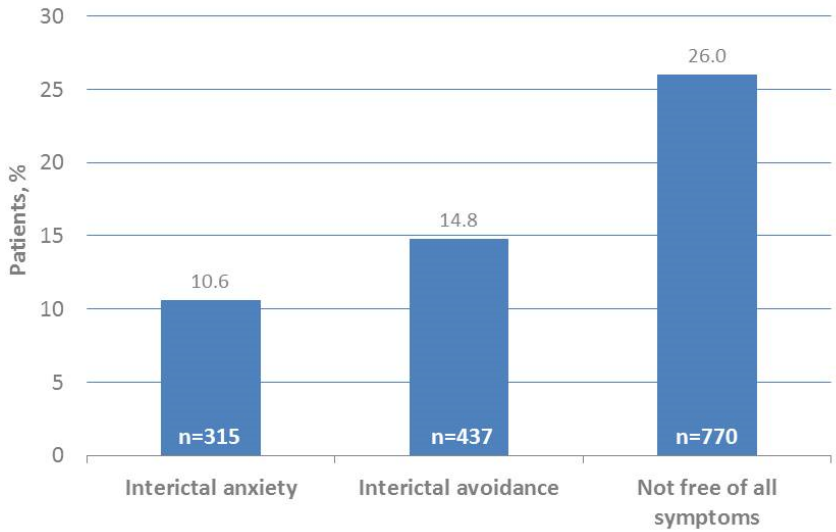
In the Swedish population-based survey of 423 patients with self-considered migraine (45% diagnosed by a physician), symptoms of migraine attacks included photo-/phonophobia (96% of patients), throbbing/aggravation (87%), prodrome (81%), nausea and vomiting (N/V; 79%), unilateral

	pain (77%), and aura (44%).(36) Aura was more frequently reported by patients with a physician's diagnosis of migraine versus those with self-considered migraine (61% vs 29%). The most troublesome symptoms during migraine attacks were photophobia (in 6% of patients), phonophobia (3%), and nausea (5%). As described above, 86% of patients described pain as the most troubling symptom. Migraine symptoms related to mood and cognition were commonly reported in an analysis of data captured by the Migraine Buddy© smartphone application across 17 European countries (n=28,152 attacks in 3900 self-diagnosed individuals). Symptoms that included nausea, anxiety, confusion, blurred vision, moodiness, or giddiness were reported in 87.3% of individuals. Symptoms related to environment such as tinnitus, and sensitivity to light, noise, or smell were reported in 85.5% of individuals (34). A relatively high rate of anxiety and/or depression during a migraine attack (as a symptom or trigger) was also reported in 44.8% of individuals with CM, 40.9% with EM and 8–14 migraine days/month, and 34.7% with EM and 4–7 migraine days/month (34). **Health-related quality of life between migraine attacks** Migraine not only adversely affects patient's HRQoL during an attack, but also has an impact between attacks (37). Interictal burden has been defined as 'any loss of health or well-being attributable to a headache disorder reportedly experienced while 'headache-free' (38). There are numerous reasons why patients with migraine continue to experience the negative impact of their disease between attacks; for example, in those experiencing frequent attacks, excessive worry, and fear about when the next attack will strike may occur (38). Avoidance behaviours might also occur, with patients trying to limit triggers through lifestyle compromises that may ultimately diminish pleasure in life. The importance of interictal burden lies in the fact that this period is typically present for more days in the month than the ictal period, especially in those with EM (38). The extent of interictal burden in 6455 patients with headache (2959 of which had migraine, 45.8%) was determined in a European cross-sectional survey using modified cluster sampling from the adult population (18–65 years of age) in nine countries (the EuroLight Project) (38, 39) . EuroLight involved the administration of a questionnaire that included questions with 'yes/no' answers regarding elements of headache burden likely to be experienced interictally, as follows: ▪ Q1. Were you anxious or worried about your next headache episode? ▪ Q2. Was there anything you could not do or did not do because you wanted to avoid getting a headache?

- Q3. Did you feel completely free from all headache symptoms?

>70% of patients with migraine gave an 'adverse response' to one of the three questions (i.e. yes to Q1 and Q2, and 'no' to Q3), indicating the considerable degree of interictal burden experienced (39). Figure 7 presents in detail the results to response of each question.

Figure 7 Participants with migraine in the EuroLight Project reporting interictal burden (38)



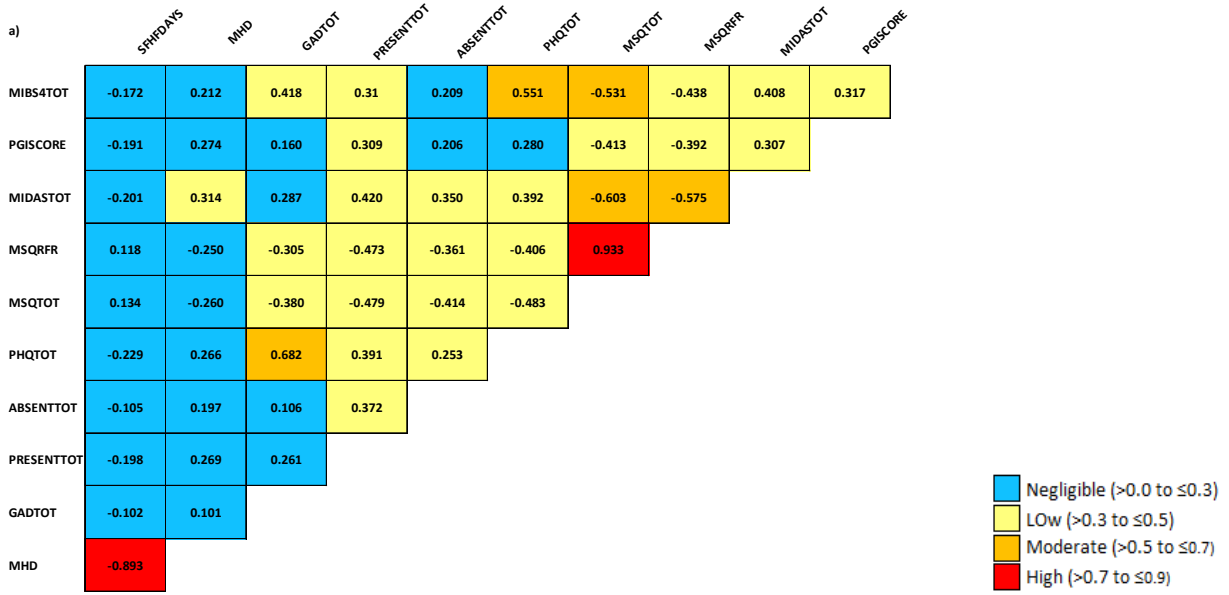
Lilly has conducted an analysis to determine if treatment with galcanezumab can reduce interictal burden, i.e. migraine-related impairment between attacks. A correlation analysis was subsequently conducted on patient-reported outcomes (PROs) collected in the CONQUER study (Table 2) to assess whether the interictal burden was adequately captured in other measures included in the study (40).

Table 2 Outcomes included in the correlation analysis

Patient-Reported Outcomes		**Outcome Measurement**
MIBS-4	**Migraine Interictal Burden Scale**	**Disruptions to life on days <u>without</u> headache**
MIDAS	Migraine Disability Assessment	Disability due to migraine headache
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire	Functioning in various aspects of life
PGI-S	Patient Global Impression of Severity	Severity of overall migraine illness
GAD-7	Generalized Anxiety Disorder	Anxiety symptoms
PHQ-9	Patient Health Questionnaire	Depression symptoms
WPAI	Work Productivity and Activity Impairment	Impact of migraine on ability to do work and regular activities
Additional Outcomes		**Outcome Measurement**
Monthly migraine headache days		Days per month with migraine headache
Symptom-free headache-free days		Days per month with no headache or other migraine symptoms

Patients treated with galcanezumab experienced statistically significant greater reductions in interictal burden (LS mean change, -1.8-point reduction on the MIBS-4 scale) compared to placebo (LS mean change, -0.8 point reduction on the MIBS-4 scale). The Spearman's Rank Correlation Coefficients (Rho) were determined for MIBS-4 correlation to other PRO outcome measures. The correlation analysis of the MIBS-4 and monthly migraine headache days was negligible to low at 0.21 - 0.33, indicating that 'ictal' measures, such as migraine headache days, do not fully capture the interictal burden in migraine. MIBS-4 most strongly correlated with PHQ-9 and MSQ Total but was highest for MSQ Total post-treatment (Figure 8). Since the MSQ was designed to measure both ictal and interictal burden of migraine (recall period of 4 weeks), this correlation would be expected (40).

Figure 8 Heat maps show correlations between outcomes examined at Months 0 (a), Months 3 (b) and Months 6 (c), CONQUER ITT



b)

	SFHFDAYS	MHD	GADTOT	PRESENTTOT	ABSENTTOT	PHQTOT	MSQTOT	MSQRFR	MIDASTOT	PGISCORE
MIBS4TOT	-0.304	0.333	0.458	0.41	0.253	0.534	-0.676	-0.614	0.507	0.426
PGISCORE	-0.354	0.388	0.261	0.396	0.212	0.366	-0.550	-0.551	0.498	
MIDASTOT	-0.380	0.468	0.383	0.480	0.324	0.489	-0.682	-0.688		
MSQRFR	0.453	-0.530	-0.448	-0.590	-0.403	-0.589	0.972			
MSQTOT	0.446	-0.520	-0.497	-0.600	-0.403	-0.624				
PHQTOT	-0.392	0.416	0.745	0.474	0.245					
ABSENTTOT	-0.138	0.202	0.172	0.417						
PRESENTTOT	-0.426	0.493	0.330							
GADTOT	-0.280	0.298								
MHD	-0.854									

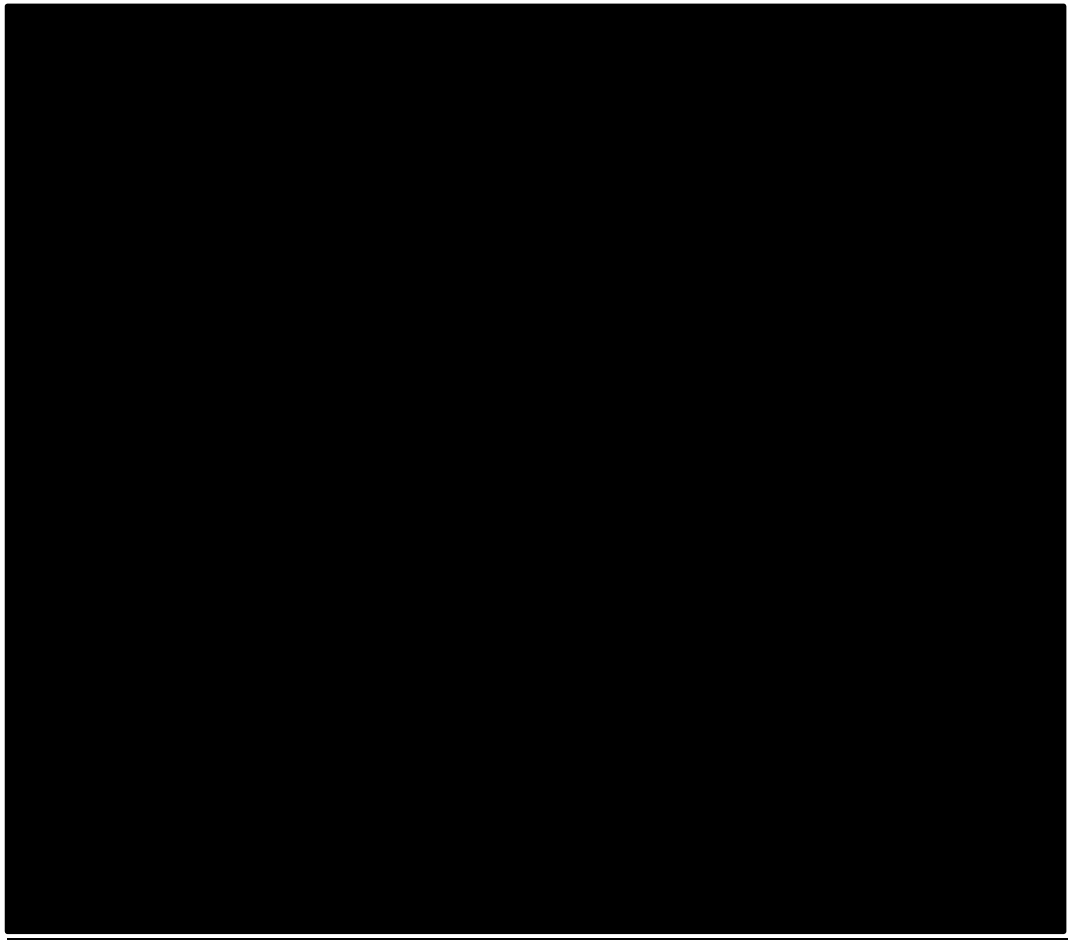
Negligible (>0.0 to ≤0.3)
LOw (>0.3 to ≤0.5)
Moderate (>0.5 to ≤0.7)
High (>0.7 to ≤0.9)

The analysis concluded that multiple outcomes should be measured when evaluating the efficacy of preventatives treatments for migraine to more fully understand the implications to patients.

Correlation of monthly MHDs with other measures of health status for migraine

Similar to the correlation analysis undertaken for the MIBS-4 for the entire CONQUER ITT population, another analysis was undertaken for PRO measures by migraine subtype using CONQUER trial data. The results of this analysis are presented in Fig 9 for chronic patients and Fig 10 for episodic patients (41).

Figure 9 Heat maps show correlations between outcomes examined at Months 0 (a), Months 3 (b) and Months 6 (c), Chronic Migraine CONQUER ITT

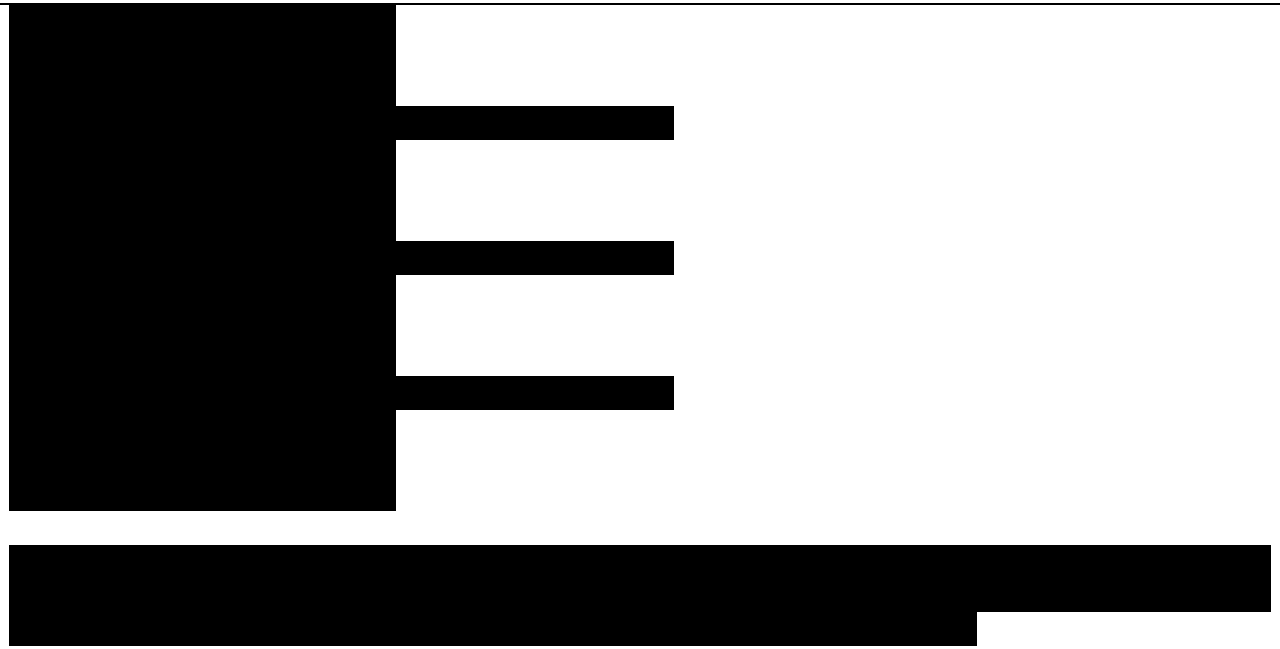


[redacted]The moderate and high correlations suggest that MHDs alone do not capture the entire impact of migraine on health-related quality of life for patients.


[redacted]

Figure 10 Heat maps show correlations between outcomes examined and Months 0 (a), Months 3 (b) and Months 6 (c), Episodic Migraine CONQUER ITT

. In line with the findings from the chronic migraine population, this indicates that MHD alone does not capture the entire impact on health-related quality of life for patients.



Application of a treatment effect for health-state utility values

The review of HRQoL data above presents a qualitative and quantitatively review of the 'ictal' and interictal burden of migraine that impacts patient's HRQoL. Not all can be attributed to a change in monthly frequencies of MHDs. Symptoms associated with the intensity and severity of pain of a migraine attack, disability caused by migraine attacks, or impact of HRQoL between attacks is unlikely to be explained through a change MHD frequency alone. However, these could be explained by the administration of preventative medication which has been shown as one of the most important determinants of improvements in psychosocial difficulties, which evidence showed for improved emotional problems, work efficiency, global disability, physical health, and mental health (32).

Correlation analyses have shown that MHDs alone is poorly correlated with other specific measures of health status used to capture the impact of migraine on HRQoL, thus implying important aspects of HRQoL are not captured in the economic analysis which may underestimate galcanezumab's cost

effectiveness compared to BSC. Empirical clinical trial data show consistent [redacted] treatment effects compared to placebo (BSC) on symptomatic measures other than frequency of MHDs such as severity (PGI-S), physical and emotional impact of disruption of normal functioning (MSQ), disability (MIDAS) and psychological measures (PHQ-9), presented in Table 3 below for the ITT population in CONQUER, that is patient that have failed ≥2 prior preventatives (21).

Table 3 Summary of PROs in CONQUER ITT Population (21)

	Placebo	Galcanezumab 120 mg
Patient Global Impression of Severity Rating LOCF Endpoint		
Number of patients	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]
LSMean Change (SE)	[redacted]	[redacted]
p-value vs placebo	[redacted]	[redacted]
Migraine Specific Quality of Life Questionnaire		
MSQ Total Score at Month 3		
Number of patients	[redacted]	[redacted]
Baseline (SD)[a]	[redacted]	[redacted]
LSMean Change (SE)	[redacted]	[redacted]
Diff vs placebo (SE)	[redacted]	[redacted]
p-value vs placebo	[redacted]	[redacted]
MSQ, Role function restrictive at Month 3		
Number of patients	[redacted]	[redacted]
Baseline (SD)[a]	[redacted]	[redacted]
LSMean Change (SE)	[redacted]	[redacted]
Diff vs placebo (SE)	[redacted]	[redacted]
p-value vs placebo	[redacted]	[redacted]
MIDAS total score (Mean change from baseline to LOCF endpoint)		
Number of patients	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]
LSMean Change (SE)	[redacted]	[redacted]
p-value vs placebo	[redacted]	[redacted]
Patient Health Questionnaire-9 Overall Score (Mean change from baseline to LOCF endpoint)		

	Number of patients [redacted] [redacted] Baseline (SD) [redacted] [redacted] LSMean Change (SE) [redacted] [redacted] p-value vs placebo [redacted] [redacted] **Generalized Anxiety Disorder Scale Total Score (Mean change from baseline to LOCF endpoint)** Number of patients [redacted] [redacted] Baseline (SD) [redacted] [redacted] LSMean Change (SE) [redacted] [redacted] p-value vs placebo [redacted] [redacted] [a] Baseline values are for the entire ITT population (Placebo [redacted], GMB 120 mg [redacted]) **Abbreviations**: LOCF, last observation carried forward; LSMean, least-squares mean; MIDAS, migraine disability assessment; MSQ, migraine-specific quality of life questionnaire; SD, standard deviation; SE, standard error Therefore, Lilly agrees with the Technical team's judgement and rationale to include differential HSUVs for galcanezumab compared to BSC. Including the treatment effect may effectively capture the impact that preventative treatments have on other migraine symptoms, beyond those associated with a reduction of MHDs alone.
Issue 7: Resource costs	
19. What proportion of people would not be able to self-administer galcanezumab? 20. Should an additional cost for people who cannot self-administer be included in the model?	Lilly believes the assumptions applied in the past technology appraisal of fremanezumab to assume 10% of patients will not be able to self-administer is also reasonable to consider for galcanezumab (5). The cost applied by the ERG in its base case economic analysis is also reasonable.
21. Should additional monitoring costs from the 6 to 12 month patient reviews be included in the model?	Lilly believes no additional monitoring costs should be applied in the economic model. If a positive discontinuation period is not applicable then it is not appropriate to consider these costs, as highlighted in the ERG report. Including an additional assessment cost otherwise may double-count the costs estimated applied under resource use in the economic model. Furthermore, if a cost for annual review is included for galcanezumab then it should be included for comparator treatments, including BSC. It is unreasonable to assume a regular assessment for patients on botulinum toxin A or patients receiving BSC would not occur in practice, particularly if patients are experiencing MHD frequency defined as ≥HFEM (≥8 monthly MHDs).

22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	Lilly agrees with the Technical team's preference to apply resource use estimated from the National Health and Wellness Survey (2016) to remain consistent with past technology appraisal for fremanezumab (5).

References

1. National Institute for Health and Care Excellence. Erenumab for preventing migraine: Final Appraisal Document [ID1188] 2019 [Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/html-content-2.
2. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine [ID1368]: Final Appraisal Document 2020 [Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/final-appraisal-determination-document.
3. The International Headache Society. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia : an international journal of headache. 2018;38(1):1-211.
4. National Institute for Health and Care Excellence. Headaches in over 12s: diagnosis and management (CG150). 2015.
5. Pozo-Rosich P, Quintana M, Torres M, Fernandez-Morales J, Alvarez-Sabin J. EHMTI-0288. A clinical comparison demonstratessimilarities between chronic and high frequencyepisodic migraine. 4th European Headache and Migraine Trust International Congress; Copenhagen, Denmark2014. p. E28.
6. Guglielmetti M, Raggi A, Ornello R, Sacco S, D'Amico D, Leonardi M, et al. The clinical and public health implications and risks of widening the definition of chronic migraine. Cephalalgia : an international journal of headache. 2019:333102419895777.
7. Adams AM, Reed ML, Fanning KM, Buse DC, Goadsby PJ, Olesen J, et al. Exploring the Boundaries Between Episodic and Chronic Migraine: Results from the CaMEO Study (502). Neurology. 2020;94.
8. National Institute for Health and Care Excellence. Fremanezumab for preventing migraine: response to consultee and commentator comments on the draft remit and draft scope (pre-referral) 2018 [Available from: https://www.nice.org.uk/guidanca/ta631/documents/scope-consultation-comments-and-responses.
9. National institute for Health and Care Excellence. Galcanezumab for preventing migraine ID1372: Response to consultee and commentator comments on the draft remit and draft scope (pre-referral) 2019 [Available from: https://www.nice.org.uk/guidance/gid-ta10454/documents/scope-consultation-comments-and-responses.
10. Data on File. Eli Lilly and Co.: Migraine Definition Controversies Advisory Board Meeting: Executive Summary. 2020.
11. Chalmer MA, Hansen TF, Lebedeva ER, Dodick DW, Lipton RB, Olesen J. Proposed new diagnostic criteria for chronic migraine. Cephalalgia : an international journal of headache. 2019:333102419877171.
12. National Institute for Health and Care Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. Technology Appraisal Guidance [TA260]. 2012.
13. Krymchantowski AV, Da Cunha Jevoux C, Bigal ME. Topiramate plus nortriptyline in the preventive treatment of migraine: A controlled study for nonresponders. Journal of Headache and Pain. 2012;13(1):53-9.

14. Katsarava Z, Manack A, Yoon MS, Obermann M, Becker H, Dommes P, et al. Chronic migraine: classification and comparisons. Cephalalgia : an international journal of headache. 2011;31(5):520-9.
15. Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, et al. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia : an international journal of headache. 2011;31(1):18-30.
16. Torres-Ferrus M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich P. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. Cephalalgia : an international journal of headache. 2017;37(2):104-13.
17. Ailani J, Pearlman E, Zhang Q, Nagy AJ, Schuh K, Aurora SK. Positive response to galcanezumab following treatment failure to onabotulinumtoxinA in patients with migraine: post hoc analyses of three randomized double-blind studies. Eur J Neurol. 2020;27(3):542-9.
18. National Institute for Health and Care Excellence (NICE). Fremanezumab for preventing migraine [ID1368] Appraisal Consultation Document 2019 [cited 2019 April]. Available from: https://www.nice.org.uk/guidance/gid-ta10339/documents/129-2.
19. National Institute for Health and Care Excellence. Galcanezumab for preventing migraine [ID1372]: Technical engagement papers. 2020.
20. Paget M-A, Tockhorn-Heidenreich1 A, Belger M, Chartier F, Lanteri-Minet M. EPO3109: Generalisability of the CONQUER trial results to routine clinical practice: galcanezumab versus placebo in patients with inadequately controlled migraine. European Journal of Neurology. 2020;27 1018–228.
21. Data on File. Eli Lilly and Co.: I5Q-MC-CGAW Clinical Study Report. 2019.
22. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Sexson M, Govindan S, Pearlman EM, et al. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure. Cephalalgia : an international journal of headache. 2019;39(8):931-44.
23. Eli Lilly and Company. EMGALITY Summary of Product Characteristics 2019 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/emgality.
24. Stauffer VL, Wang S, Voulgaropoulos M, Skljarevski V, Kovacik A, Aurora SK. Effect of Galcanezumab Following Treatment Cessation in Patients With Migraine: Results From 2 Randomized Phase 3 Trials. Headache. 2019;59(6):834-47.
25. Data on File. Eli Lilly and Co.: I5Q-MC-CGAJ Clinical Study Report 2017.
26. National Institute for Health and Care Excellence. Erenumab for preventing migraine: Committee Papers. 2019.
27. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2007;6(12):1054-62.
28. Ruiz de la Torre E, Martelletti P, Craven A, Walsh D, Evans S, Dumas P, et al. Real-world patient perspective on the burden and impact of migraine. J Headache Pain. 2017;18:111.
29. Ford JH, Ye W, Nichols RM, Foster SA, Nelson DR. Treatment patterns and predictors of costs among patients with migraine: evidence from the United States medical expenditure panel survey. J Med Econ. 2019;22(9):849-58.
30. Ruiz de Velasco I, Gonzalez N, Etxeberria Y, Garcia-Monco JC. Quality of life in migraine patients: a qualitative study. Cephalalgia : an international journal of headache. 2003;23(9):892-900.

31. Walters AB, Hamer JD, Smitherman TA. Sleep disturbance and affective comorbidity among episodic migraineurs. Headache. 2014;54(1):116-24.
32. Raggi A, Giovannetti AM, Quintas R, D'Amico D, Cieza A, Sabariego C, et al. A systematic review of the psychosocial difficulties relevant to patients with migraine. J Headache Pain. 2012;13(8):595-606.
33. Ford JH, Jackson J, Milligan G, Cotton S, Ahl J, Aurora SK. A Real-World Analysis of Migraine: A Cross-Sectional Study of Disease Burden and Treatment Patterns. Headache. 2017;57(10):1532-44.
34. Vo P, Paris N, Bilitou A, Valena T, Fang J, Naujoks C, et al. Burden of Migraine in Europe Using Self-Reported Digital Diary Data from the Migraine Buddy(c) Application. Neurol Ther. 2018;7(2):321-32.
35. Burgess SM, Gauthier M, Cala ML. Comparison of Patient-Reported Outcomes Requirements in Medical Guidelines for Pain, Migraine, Rheumatoid Arthritis, and Systemic Lupus Erythematosus: Europe Vs. United States. Value in Health. 2015;18(7):A743.
36. Linde M, Dahlof C. Attitudes and burden of disease among self-considered migraineurs--a nation-wide population-based survey in Sweden. Cephalalgia : an international journal of headache. 2004;24(6):455-65.
37. Chaushev N, Milanov I. Impact of migraine and migraine treatment on patient's capacity to work and quality of life. J Clin Med. 2009;2:26-31.
38. Lampl C, Thomas H, Stovner LJ, Tassorelli C, Katsarava Z, Lainez JM, et al. Interictal burden attributable to episodic headache: findings from the Eurolight project. J Headache Pain. 2016;17:9.
39. Steiner TJ, Stovner LJ, Katsarava Z, Lainez JM, Lampl C, Lanteri-Minet M, et al. The impact of headache in Europe: principal results of the Eurolight project. J Headache Pain. 2014;15:31.
40. Lipton RB, Buse DC, Sandoe CH, Ford JH, Hand AL, Jedynak JP, et al. Interictal burden of migraine: correlations with other measures of migraine burden and effects of galcanezumab migraine-preventive treatment. 14th European Headache Federation Virtual 20202020.
41. Data on File. Eli Lilly and Co.: Overall Correlation Spearman by Migraine Category. 2020.
42 Wang SJ, Fuh JL, Lu, SR et al. Migraine prevalence during menopausal transistion. Headache. 2003;43:470-478

NICE National Institute for Health and Care Excellence

Technical engagement response form

Galcanezumab for preventing migraine [ID1372]

Appendices

Appendix A. Clinical effectiveness of galcanezumab in the CONQUER trial: intent-to-treat patients with chronic migraine with ≥3 prior preventatives medication category failures, including botulinum toxin A

Baseline characteristics for patients from the CONQUER trial with a history of ≥3 prior preventatives treatment failures were described in Appendix L of the Company submission for the full population (DTT-3; Appendix L.1) as well as for subgroup of patients with chronic migraine (DTT-3-CM; Appendix L.2). We describe in this document an additional subgroup, namely patients with chronic migraine with a history of ≥3 prior preventatives treatment failures, including botulinum toxin A (DTT-3-CM-BOT).

Baseline demographics for the DTT-3-CM-BOT group are presented in Table 1. Overall, patients within DTT-3-CM-BOT are similar to those in DTT-3-CM subgroup. Patients in both populations are mostly female ( ) with similar mean ages ( ) and a similar mean duration of migraine illness ( ). Consistent with the use of botulinum toxin A after 3 oral preventatives (1), the DTT-3-CM-BOT subgroup included a smaller proportion of patients with a history of ≥3 prior treatment failures ( ) and a higher proportion of those with a history of ≥4 prior treatment failures compared to the DTT-3-CM subgroup.

At baseline, the frequency and severity of migraines was marginally higher in DTT-3-CM-BOT vs DTT-3-CM group: mean monthly MHDs = days; mean PGI-S = . The two groups also showed differences in the quality of life measures: MIDAS mean total score = and mean MSQ-role function restrictive domain = .

Table 1 Baseline demographics and disease characteristics in CONQUER trial: patients with chronic migraine with ≥3 prior preventatives medication category failures, including botulinum toxin A

Characteristic	Placebo (N=13)	GMB 120 mg (N=17)	Total (N=30)
Demographic characteristics			
Age (years)			
Mean (±SD)			
Sex, n (%)			
Male			
Female			
Race, n (%)			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			

White	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Body Mass Index (kg/m2)			
Mean (±SD)	[redacted]	[redacted]	[redacted]
Region, n (%)			
North America	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]
Disease characteristics			
Qualifying preventatives medication failures in past 10 years[a], n (%)			
2 medication failures	[redacted]	[redacted]	[redacted]
3 medication failures	[redacted]	[redacted]	[redacted]
4 medication failures	[redacted]	[redacted]	[redacted]
Total number of failed individual preventatives meds lifetime, mean (±SD)	[redacted]	[redacted]	[redacted]
Total number of failed individual preventatives meds past 10 years, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of monthly headache days, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of monthly MHDs, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of monthly migraine attacks, mean (±SD)	[redacted]	[redacted]	[redacted]
MSQ Role Function-Restrictive domain, mean (±SD)	[redacted]	[redacted]	[redacted]

MIDAS total score, mean (±SD)	[redacted]	[redacted]	[redacted]
Duration of migraine illness, years, mean (±SD)	[redacted]	[redacted]	[redacted]
Number of comorbidities, mean (±SD)	[redacted]	[redacted]	[redacted]
PGI-S, mean (±SD)	[redacted]	[redacted]	[redacted]

Abbreviations: ITT, intent-to-treat; N, number of ITT patients; n, number of patients within each specific category; SD, standard deviation. PGI-S, Patient Global Impression – Severity; meds, medications; MHDs, migraine headache days; MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality of Life Questionnaire; SD, standard deviation; yrs, years.
a. Based on any medications taken for migraine prevention in the patient's lifetime; not limited to standard-of-care treatments from inclusion criterion. Failure defined as discontinuation due to no response/inadequate response, or medical history event (safety/tolerability). Contraindications did not count as treatment failures.

In the CONQUER trial, the reduction in the frequency of monthly MHDs was [redacted] in the DTT-3-CM-BOT subgroup during the double-blind treatment phase. As shown in Table 2, overall mean change from baseline was [redacted] days for galcanezumab compared with [redacted] days for placebo (mean change difference from placebo = [redacted]). The results are improved but comparable to the overall DTT-3-CM subgroup (mean change difference from placebo: [redacted]).

The overall response rate was also [redacted] in the DTT-3-CM-BOT subgroup during the double-blind treatment phase. As shown in Table 3, the proportion of patients with ≥30% reduction from baseline in monthly MHDs over 3 months was [redacted] for galcanezumab compared with [redacted] for placebo ([redacted]). The results are improved but comparable to the overall DTT-3-CM subgroup ([redacted] for galcanezumab vs [redacted] for placebo; [redacted]).

Table 2 Change from baseline in the number of monthly migraine headache days in CONQUER trial: patients with chronic migraine with ≥3 prior preventatives medication category failures among patients who failed botulinum toxin A in the last 10 years

	Placebo (N=13)	GMB 120 mg (N=16)
Baseline (SD)[a]	[redacted]	[redacted]
Overall LS Mean (SE)	[redacted]	[redacted]
Difference vs. placebo (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: CI, confidence interval; diff, difference; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; N, number of subjects in the analysis population with nonmissing

baseline value and at least one nonmissing postbaseline value; SD, standard deviation; SE, standard error; vs, versus.

[a]Baseline mean values are for the entire CM subpopulation with ≥3 prior preventatives medication failures among patients who failed botulinum toxin A in the last 10 years ([redacted])

Table 3 ≥30% reduction from baseline in monthly MHDs in CONQUER trial: patients with ≥3 prior preventatives medication category failures among patients who failed botulinum toxin A in the last 10 years

Proportion of patients with ≥30% reduction from baseline in monthly MHDs over 3 months		
	Placebo (N=13)	**GMB 120 mg (N=16)**
Overall responders, %[a]	[redacted]	[redacted]
Odds Ratio (95% CI)	[redacted]	[redacted]
***P*-value vs. placebo**	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ITT, intent-to-treat; N, number of subjects in the analysis population with nonmissing baseline value and at least one nonmissing postbaseline value; vs, versus.

Table 4 lists the prior preventative medications received by each patient included in the analysis for patients with chronic migraine with a history of ≥3 prior preventatives medication category failures within the last 10 years (with MHD data), among patients who have failed prior botulinum toxin A. The list broadly reflects use of preventative medications used in UK clinical practice among patients that have failed prior botulinum toxin A. The most commonly failed oral medications include amitriptyline, propranolol and topiramate.

Table 4 Listing of prior preventatives medication failures in CONQUER trial: population of patients with chronic migraine with a history of ≥3 prior preventatives medication category failures within the last 10 years (with MHD data), among patients who have failed prior botulinum toxin A

Treatment group	ID No	Listing of failed preventatives treatments
Placebo ([redacted])	[redacted]	
Galcanezumab 120 Mg ([redacted])	[redacted]	

Appendix B. Cost effectiveness of galcanezumab in the CONQUER trial: patients with chronic migraine with ≥3 prior preventatives medication category failures, including botulinum toxin A

B.1 Clinical variables and parameters

Table 5 Change from baseline in monthly MHDs for responders and non-responders at month 3 (30% response rate)

Population and intervention	Responders		Non-responders		Source
	N	Mean CFB in MHD	N	Mean CFB in MHD	
Chronic migraine – patients who have experienced ≥4 prior failures					
Galcanezumab	[redacted]	[redacted]	[redacted]	[redacted]	Analysis is based on CGAW only, patients at least 3 prior preventatives medication category failures among patients who have failed botulinum toxin A in the past 10 years
BSC	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BSC, best supportive care; CFB, change from baseline; MHD, migraine headache days

Table 6 Probability of 30% response rate across month 1 to 3

Population and intervention	30% response rate	Source
Chronic migraine – patients who have experienced ≥4 prior failures		
Galcanezumab	[redacted]	Analysis is based on CGAW only, patients at least 3 prior preventatives medication category failures among patients who have failed botulinum toxin A in the past 10 years;
BSC	[redacted]	

Abbreviations: BSC, best supportive care

B.2 Cost-effectiveness results

Company new base assumptions align with the Technical team's preferred assumptions. The analysis takes into account the PAS for galcanezumab but not the CMU discount for Botox, which remains confidential to the Lilly.

Company New base case assumptions
ERG corrections
Time horizon
Consistent waning period between episodic and chronic migraine populations
Alternative source used to generate HRQoL
Differential utilities for galcanezumab and comparator

Age-related disutility
Galcanezumab administration cost for 10% of patients
Alternative resource consumption rates

B.3 ICERs

Treatment	Total cost	Total life years	Total QALYs	Inc. Cost	Inc. QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,389
BSC	[redacted]	[redacted]	[redacted]			

References

1. National Institute for Health and Care Excellence (NICE). Headaches - NICE Pathway 2017 [cited 2019 April]. Available from: https://pathways.nice.org.uk/pathways/headaches].

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Technical engagement response form

Galcanezumab for preventing migraine [ID1372]

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Deadline for comments **5pm** on **Thursday 30 July 2020**

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Notes on completing this form

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**The Migraine Trust**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	
2. Is a lifetime time horizon more appropriate than 25 years?	It makes sense to use a lifetime time horizon if this has been the preferred time horizon for erenumab and fremanezumab as the treatments are comparable.
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	Although people meeting the definition of high frequency episodic migraine are underserved by treatment and support there is a debate from clinicians as to whether it is a clinically distinct subgroup. Where there is no consensus it makes sense to follow the decision taken in the appraisals for erenumab and fremanezumab, unless there is evidence to support high frequency episodic migraine as a clinically distinct subgroup.
4. If yes, what definition of “high-frequency” is used in clinical practice?	
Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinumtoxin toxin A has failed, is not considered to be appropriate or has not been tolerated?	There are people with chronic migraine for whom botulinumtoxin A is not an effective treatment. At this point in time there are limited options available to this patient group in terms of treatment. Galcanezumab could be considered an option for these people. Although it’s important galcanezumab is considered in the same way as other CGRP mAbs and not necessarily just as the option that follows a failure of effect with botulinumtoxin A but as an option after a few preventives (of any treatment class) have failed and people continue to be debilitated by migraine.

	There are also issues with availability and access to Botox which may make it an unsuitable option for some people, these may be less of an issue for galcanezumab. Botulinumtoxin A needs to be administered in clinic and waiting times are long, over a year in some cases. This may be exacerbated by current covid-19 delays and limitations imposed on access to hospital treatment. In many cases galcanezumab will be self-administered at home enabling quicker access to treatment and the possibility of virtual clinical reviews and monitoring.
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	Galcanezumab should be considered at the same stage of treatment as other CGRP mAbs.
Issue 4: Indirect treatment comparison for chronic migraine	
7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	As far as we know the direct comparison between galcanezumab and botulinum toxin A has not been studied. There is recent (2020) real world evidence that suggests a CGRP compound is beneficial in patients who did not respond to botulinum toxin A and had failed several preventives (Lanbru et al, A prospective real-world analysis of erenumab in refractory chronic migraine, The Journal of Headache & Pain, 2020)
8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?	
Issue 5: Long-term treatment effectiveness and discontinuation	

9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	
10. What proportion of people are expected to restart treatment after it was stopped for any reason?	
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	
12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	
Issue 6: Health related quality of life	
15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	
16. Should the same utility values be used for both galcanezumab and comparators?	
17. Should age-related disutilities be applied?	
18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	Other factors that may impact include the severity of migraine and any co-morbidities the person has (as these may limit treatments that can be offered safely).

Issue 7: Resource costs	
19. What proportion of people would not be able to self-administer galcanezumab?	Not all patients will be able to self-administer galcanezumab, the 10% identified in the fremanezumab appraisal seems a reasonable assumption.
20. Should an additional cost for people who cannot self-administer be included in the model?	If additional costs for people who cannot self-administer have been included in other CGRP mAbs (fremanezumab) appraisals it would make sense to apply for galcanezumab due to the similarities in administration.
21. Should additional monitoring costs from the 6 to 12 month patient reviews be included in the model?	
22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	

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Galcanezumab for preventing migraine [ID1372]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Association of British Neurologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil

Questions for engagement

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	Migraine is a lifelong condition but the greatest impact is in midlife, the incidence decreases after the menopause in women, therefore most costs and benefits will be captured over 25 years
2. Is a lifetime time horizon more appropriate than 25 years?	A lifetime horizon would be difficult given the dynamic course of migraine, even 25 years' time horizon is subject to assumptions due to lack of any long term data of the drug and its comparators.
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	Migraine frequency lies on a spectrum from low frequency episodic migraine (LFEM), through high frequency (HFEM) to chronic migraine (CM). Although IHS classification (ICHD-3) does not identify HFEM migraine as a distinct group, patients with HFEM tend to behave more like CM, in particular they have higher levels of disability compared to low frequency episodic and more comparable to those with CM. In prospective data on botulinum toxin A for CM using a modified positive stopping rule, a high risk of relapse was noted if the treatment was stopped in those with more than 10 days a month for three consecutive months. (Khalil *et al*, TJHP 2014(15);54:1-9). We consider that HFEM has been the most ignored group as patients cannot access treatments licensed for CM despite having high levels of disability. We feel this should either be considered as a distinct group, or with CM, rather than with LFEM.

4. If yes, what definition of “high-frequency” is used in clinical practice?	Some clinicians use an average of 10-14, others use 8-14, migraine days per month for at least 3 months
Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinumtoxin toxin A has failed, is not considered to be appropriate or has not been tolerated?	Yes CGRP mabs seem to be the most appropriate choice following failure of botulinum toxin A for CM. Recent approval of an alternative CGRP monoclonal antibody for CM, fremanezumab, (TA631) after failure of 3 treatments would make galcanezumab look inferior if this was to be approved only for botulinum toxin A failures. As there is no head to head comparison between galcanezumab and fremanezumab, we propose that galcanezumab should be recommended following failure of 3 preventive treatments in CM.
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	Yes Pooled post hoc analyses from 3 double-blind, placebo-controlled, phase 3 migraine studies (episodic EVOLVE-1 and -2; chronic REGAIN); of 129 patients who failed botulinum toxin A showed: Significant decreases from baseline in the number of monthly headache days (MHDs) for 120 mg (3.91) and 240 mg (5.27) galcanezumab v. placebo (0.88). For patients with CM there were similar significant decreases in MHDs: 120 mg (3.18) and 240 mg (4.26) galcanezumab v. placebo (0.16). Significant decreases in the number of MHDs per month ***with acute medication*** for 120 mg (4.35) and 240 mg (4.55) galcanezumab v. placebo (0.83). Estimates of ≥50% response were 41.3% (120 mg) and 47.5% for (240 mg) galcanezumab v. 9.4% placebo i.e. maximum therapeutic gain of 38.1%. (Ailani *et al* European Journal of Neurology 2020;27:542-49)

Issue 4: Indirect treatment comparison for chronic migraine	
7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	Unknown as no head to head comparison. A cohort sub-analysis of a 1yr extension study on the use of fremanezumab for CM (Cowan *et al* IHC-PO-404, 2019 abstract) showed that of n28 who previously had been treated with botulinum toxin A, 23 preferred fremanezumab, with over 70% reporting reduced attack frequency and intensity.
8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?	No head to head comparison: when looking at the study data below it must be kept in mind that in the galcanezumab trials the measure were monthly ***migraine*** days (MMDs) rather than monthly ***headache*** days as in the botulinum toxin A trials (pooled PREEMPT data Dodick *et al*, Headache 2010). CONQUER Study (Mulleners *et a*l, Neurology, 2020): (both episodic and CM who had failed 2-4 treatments) showed -4.1 galcanezumab v -1 day placebo reduction in MMDs (a gain of 3.1 days) at 12 weeks. PREEMPT study (CM only, around two third of patients had either tried one or no prophylactic treatment) showed -8.4 botulinum toxin A v -6.6 placebo MHDs (a gain of 1.8 days) at 24 weeks. REGAIN study: patients with CM showed a ***50% responder rate*** 27.5% galcanezumab v 15% placebo ie 12.5% 'therapeutic gain', compared to data from PREEMPT of 50% responder rate of 47% botulinum toxin A v 35% placebo ie 12% 'therapeutic gain'

	The post hoc analyses of galacanezumab in those who were post-botulinum toxin A failures reported a 50% responder rate to be 41.3- 47.5% (dose dependent) v 9.4% placebo i.e. maximum therapeutic gain of 38.1%.
Issue 5: Long-term treatment effectiveness and discontinuation	
9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	Current usual practice for migraine preventative treatment is to continue treatment until migraine has been controlled for 6-12 months before a trial without medication. Only a small percentage (10-20%) will continue preventive therapy for longer and sometimes indefinitely. There is no reason why the outcome would be any different with galcanezumab, although there is no long term data available and assumptions are only made with 6 months (EVOLVE-1 and -2) and 3 months (REGAIN and CONQUER) studies. Outcomes for botulinum toxin A from Hull Headache clinic shows that: at 2 years around 60% of patients (228/300) who had a positive response were able to stop treatment of which 112 (29.7%) showed a sustained response and remained episodic. (Ahmed et al, IHC-PO-418). at 5 years 86% of patients (160/186) who had a positive response were able to stop treatment of which 105 (56.4%) showed a sustained response and remained episodic. (Ahmed et al, IHC-PO-419) In light of these data, we can extrapolate that around a third of patients would be able to come off galcanezumab at 2 years, and half would be able to stop by year 5.

10. What proportion of people are expected to restart treatment after it was stopped for any reason?	There is no long term data available for galcanezumab. If botulinum toxin A is used as comparison, data from the Hull Headache clinic shows that 26.7% (61/228) of patients who had successfully stopped treatment relapse and restart treatment. (Ahmed et al, IHC-PO-419)
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	Galcanezumab is required monthly, so it is likely that the waning period would be one month. For botulinum toxin A, 3 monthly treatment means a longer waning period.
12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	Yes. Botulinum toxin A waning period is 3 months whereas for galcanezumab it is 1 month
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	The standard clinical practice for preventive therapies is to wean off treatment after 6-12 months but those who worsen may require another 6-12 months. Only a small percentage (10-20%) will continue indefinitely. NICE recommends to stop treatment with botulinum toxin A following successful conversion to episodic migraine, although some centres continue treatment until the MHDs reduce to less than 10 days per month for three months (Khalil *et a*l, TJHP 2014). The data from Hull Headache clinic on botulinum toxin A indicates that 30% of the initial cohort at 2 years and 50% at 5 years will be able to maintain positive discontinuation (Ahmed *et a*l, IHC-PO-418,419)
Issue 6: Health related quality of life	

15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	Yes: Migraine specific quality of life questionnaire (MSQ) is used in all trials (EVOLVE-1, EVOLVE-2, REGAIN and CONQUER). These can be mapped to EQ5-D-3L to provide more reliable health related quality of life data that is previously used for other migraine appraisals.
16. Should the same utility values be used for both galcanezumab and comparators?	Yes: Utility value for both should be done on the same population i.e. number of failures on previous preventive therapy
17. Should age-related disutilities be applied?	The natural history of migraine is to improve with age. Most women show improvement after menopause. The major disability is during productive age and this should be taken in to consideration.
18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	Some clinicians consider 'Headache Load' (a measure of frequency and severity of headache) as a measure of headache related disability. Visits to the General Practitioner and attendance at A & E are other parameters used in evaluating quality of life measures.
Issue 7: Resource costs	
19. What proportion of people would not be able to self-administer galcanezumab?	Most people are able to easily self-inject. We feel only a very small number of patients (<5%) that are needle-phobic would require assistance
20. Should an additional cost for people who cannot self-administer be included in the model?	Unlikely to be a significant impact
21. Should additional monitoring costs from the 6 to 12 month patient reviews be included in the model?	Costs of monitoring need to be built into the model. Initial 3 month follow up to assess response may be done as a virtual visit depending on local resources. For those continuing treatment, then 6 monthly monitoring costs should be included: these could be done by virtual visits

22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	The data from Munakata et al was based on patients in the US healthcare system. A UK based data will be more robust. The National Health and Wellness Survey (NHWS) did include patients from the UK and could possibly provide better information.

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Deadline for comments **5pm** on **Thursday 30 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Association for the Study of Headache**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	**Migraine is more common in patients between ages 15-45, predominantly females. Migraine has a natural history, and prevalence data indicates a significant fall off in numbers after this age. The time horizon of 25 years is therefore likely to capture lifetime cost and benefits of galcanezumab, though lack of long-term data both for galcanezumab and comparators may increase the degree of uncertainty associated with any assumptions.**
2. Is a lifetime time horizon more appropriate than 25 years?	**This horizon would be subject to more uncertainty.**
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	**Although IHS classification (ICHD-3) does not identify high frequency episodic migraine (HFEM) as a distinct group, patients with HFEM tend to behave more like chronic migraine (CM). Khalil et al in their prospective data on Botox in CM used a modified positive stopping rule where treatment was only stopped if the number of headaches were less than 10 for three consecutive months (and not 14 days as recommended by NICE). They noticed high risk of relapse if the treatment was stopped in those with more than 10 days a month. (Khalil et al, TJHP 2014(15);54:1-9). In our opinion, this group being considered with infrequent episodic migraine has been the most ignored one as they cannot get access treatments licensed for CM while show disability similar to CM. We feel this should either be considered as a distinct group or with CM rather than infrequent episodic migraines.**
4. If yes, what definition of "high-frequency" is used in clinical practice?	**Some clinicians use 10-14 days and others 8-14 days. There is lack of consensus.**

Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinumtoxin toxin A has failed, is not considered to be appropriate or has not been tolerated?	**CGRP mAbs are appropriate choices following failure of onabotulinumtoxinA in CM. Given the recent approval of fremanezumab (TA631) for CM under the same criteria as onabotulinumtoxinA, and as the data for galcanezumab and fremanezumab are comparable, and there is no head-to-head comparison available, we propose that galcanezumab should also be recommended following failure of three preventive treatments in CM.**
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	**Pooled data from three double-blind placebo-controlled phase 3 studies (EVOLVE 1 and 2 on episodic and REGAIN on chronic) include 129 patients (CM) who failed onabotulinumtoxinA. The 50% responder rates were 41.3% for 120 mg galcanezumab and 47.5% for 240 mg galcanezumab compared to 9.4% for placebo (Therapeutic Gain of 31.9% – 38.1%) Ailani et al *European Journal of Neurology* 2020;27:542-49**
Issue 4: Indirect treatment comparison for chronic migraine	
7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	**1. There is no head to head comparison between galcanezumab and onabotulinumtoxinA.** **2. The evidence from Trial 295 (Phase 2b) on CM for erenumab have shown the 50% responder rate for erenumab as 38.5% (140 mg) and 34.8% (70 mg) compared to placebo 15.3% (A therapeutic gain of 19.5% - 23.2%). [Tepper et al *Lancet Neurology* 2017; 16(6):425-34]. This was significantly greater than onabotulinumtoxinA i.e., 47% compared to placebo 35% (A therapeutic gain of 12%) [Dodick et al *Headache* 2010].** **3. In evaluating patients' preference for a treatment Cowan et al (IHC-PO-404, 2019 abstract) reported 23 of the 28 patients preferred fremanezumab than onabotulinumtoxinA for CM.**
8. In chronic migraine, are the response rates for	**1. The REGAIN Phase 3 study for galcanezumab in CM [Detke et al *Neurology* 2018] showed a**

galcanezumab equivalent to botulinum toxin A?	**50% responder rate for mean monthly migraines of 27.5% versus 15% for placebo (Therapeutic gain of 12.5%) compared to 12% for onabotulinumtoxinA in the PREEMPT study (Dodick et al, *Headache*, 2010).** **2. In the CONQUER study (Mulleners et al *Neurology*, 2020) patients with both episodic and CM who had failed 2-4 treatments showed reduction of 4.1 monthly migraine days from baseline of 13.4 compared to only one reduction of 1 day from baseline of 13 in placebo at three months. The PREEMPT study showed -8.4 vs -6.6 days in favour of onabotulinumtoxinA (a gain of 1.8 days) at 24 weeks. Around two third of patients had either tried one or no prophylactic treatment in PREEMPT compared to 2-4 failures in CONQUER, although the latter had some patients with episodic migraine.**
Issue 5: Long-term treatment effectiveness and discontinuation	
9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	**1. In real-life clinical practice, preventive treatment, if effective is continued for an initial period of 6-12 months following which attempt to withdrawal is made. If unsuccessful the treatment is continued for another 6-12 months. Only a very small percentage (10-20%) will continue preventive therapy for a longer period. There is no reason why the outcome would be any different with galcanezumab, although there is no long term data available other than from 6 month (EVOLVE 1 and 2) and three month (REGAIN and CONQUER) studies.** **2. A two-year outcome for onabotulinumtoxinA from a UK centre shows that at 2 year around 60% of patients (228/300) who had a positive response were able to stop treatment of which**

	112 (29.7%) showed a sustained response and remained episodic. (Ahmed et al, IHC-PO-418). **3. A five year outcome for onabotulinumtoxinA from a UK centre shows that at 5 year 86% of patients 160/186 who had a positive response were able to stop treatment of which 105 (56.4%) showed a sustained response and remained episodic. (Ahmed et al, IHC-PO-419)** **In light of these data, we can assume that at least one-third of patients would be able to come off the treatment at 2 years and 50% would be able to stop the treatment by year 5.**
10. What proportion of people are expected to restart treatment after it was stopped for any reason?	**There is no long term data available for galcanezumab. OnabotulinumtoxinA is used as comparison, The data from Hull Headache clinic shows that 26.7% (61/228) of patients who had successfully stopped the treatment relapse and restart the treatment. (Ahmed et al, IHC-PO-419)**
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	**The half-life of galcanezumab is 25-30, so it is likely that the waning period would be of the order of 2-3 half-lives (i.e. 2-3 months). For onabotulinumtoxinA, the waning period usually starts after 2-3 months, but can be more prolonged.**
12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	**Yes**
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine	**1. The current clinical practice for all oral preventive therapies is to wean off the treatment after 6-12 months and those who worsen may require another 6-12 months. Only a very small**

frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	**percentage (10-20%) will continue indefinitely.** **2. NICE recommends stopping treatment with onabotulinumtoxinA following successful conversion to episodic migraine although some centres continue treatment until the monthly headache days reduce to less than 10 days per month for three months (Khalil et al, TJHP 2014).** **3. The data from Hull Headache clinic on onabotulinumtoxinA indicates that 30% of the initial cohort at two years and 50% at 5 years will be able to maintain positive discontinuation (Ahmed et al, IHC-PO-418,419)**
Issue 6: Health related quality of life	
15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	**Migraine specific quality of life questionnaire (MSQ) is used in all trials (EVOLVE-1, EVOLVE-2, REGAIN and CONQUER). These are to be mapped to EQ5-D-3L as this will provide more reliable health related quality of life data that is previously used for other migraine appraisals.**
16. Should the same utility values be used for both galcanezumab and comparators?	**Utility value for both should be done on the same population i.e., number of failures on previous preventive therapy.**
17. Should age-related disutilities be applied?	**The natural history of migraine is to improve with age. Most women show improvement after menopause. The major disability is during productive age and this should be taken in to consideration.**

18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	**Some clinicians consider Headache Load as a measure of headache related disability. This includes frequency and severity of headache. Visits to the General Practitioner and attendance at A&E are other parameters used in evaluating quality of life measures.**
Issue 7: Resource costs	
19. What proportion of people would not be able to self-administer galcanezumab?	**Most patients would be able to self-administer. Either a face to face training at the first injection or provision of demonstration video would be adequate. We feel only a very small number of patients (<5%) that are needle-phobic would require assistance.**
20. Should an additional cost for people who cannot self-administer be included in the model?	**As the number requiring assistance is so small, it will have no impact on the overall cost of treatment.**
21. Should additional monitoring costs from the 6 to 12 month patient reviews be included in the model?	**Patients will be seen at the start of the treatment to capture headache related data and quality of life measures, followed by three month virtual visit for assessment of response. Further follow up at 6 months and a year can all be virtual visits.**
22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	**The data from Munakata et al includes US patients where the healthcare system is different from the UK. A UK based data will be more robust. The National Health and Wellness Survey (NHWS) did include patients from the UK and could possibly provide better information.**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Galcanezumab for preventing migraine [ID1372]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	AbbVie
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	▪ Although the time horizon of the model is sufficient enough to capture all the associated costs and benefits of galcanezumab, the absence of long-term data on its effectiveness means that projections over such long-time horizons are subject to significant uncertainty.
2. Is a lifetime time horizon more appropriate than 25 years?	▪ In a lifetime model there is significant uncertainty in terms of the durability of the treatment effect, compliance to the treatment and discontinuation and the corresponding impact on clinical effectiveness of galcanezumab therapy. As a result, any long-term estimates on the cost-effectiveness of galcanezumab therapy may become unreliable.
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	▪ Currently the international classification of headache does not recognise HFEM, however Chalmer et al. 2019 identified that the current chronic migraine (CM) diagnosis has some limitations and the migraine community is suggesting classifying CM as ≥8 migraine days per month (proposed CM), disregarding the need for ≥15 headache days per month. ▪ The European headache federation do not have a definition of HFEM but in a recent consensus paper they have suggested definitions for resistant and refractory migraine: Resistant migraine is defined by having failed at least 3 classes of migraine preventatives and suffer from at least 8 debilitating headache days per month for at least 3 consecutive months without improvement; definition can be based on review of medical charts. Refractory migraine is defined by having failed all of the available preventatives and suffer from at least 8 debilitating headache days per month for at least 6 consecutive months. Drug failure may include lack of efficacy or lack of tolerability. Debilitating headache is defined as headache causing serious impairment to conduct activities of daily living despite the use of pain-relief drugs

	with established efficacy at the recommended dose and taken early during the attack; failure of at least two different triptans is required.
4. If yes, what definition of "high-frequency" is used in clinical practice?	▪ AbbVie believes that given the growing evidence on the burden of HFEM and difficult-to-treat migraines, as described in the recent consensus paper by the European headache federation, the UK clinical practice will evolve by classifying CM as ≥8 migraine days per month.
Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinumtoxin toxin A has failed, is not considered to be appropriate or has not been tolerated?	▪ In the context of i) limited experience with CGRPs in "real-life" and ii) long-term clinical experience with onabotulinumtoxinA, it may plausible that clinicians will initiate treatment with onabotulinumtoxinA first before they offer CGRPs in patients who do not respond to onabotulinumtoxinA after two treatment cycles. AbbVie would like to highlight the REPOSE and PREDICT studies which reported a high level of patient and physician satisfaction with onabotulinumtoxinA treatment. ▪ Regarding galcanezumab's positioning in patients who do not tolerate onabotulinumtoxinA treatment, AbbVie wants to highlight the wealth of long-term evidence, beyond the registration studies PREEMPT 1 and 2, which demonstrates that onabotulinumtoxinA is a well-tolerated and safe therapy in CM. ▪ RCT: Two-year outcomes from the REPOSE study - over 600 patients in seven European countries, including 94 from the UK - demonstrated that the long-term use of onabotulinumtoxinA is effective and well tolerated, with sustained reductions in headache-day frequency and significant improvement in quality of life. ▪ RCT: The long-term safety and tolerability of onabotulinumtoxinA was demonstrated over 108 weeks and nine cycles of treatment in phase IV COMPEL study and no new safety concerns were identified. An additional analysis of the COMPEL study results demonstrated that the incidence of overall AEs and the most common AEs decreased with repeated administration of onabotulinumtoxinA. ▪ RWD: HULL Migraine Clinic provide the largest consolidated source of UK real-world evidence for the effect of onabotulinumtoxinA in CM prophylaxis, and results extend for up to seven years of treatment. In this dataset, all patients had failed at least three prior preventive treatments (except for 14 patients who initiated treatment before the

	NICE guidance came into effect in 2012). This makes the evidence from HULL Migraine Clinic particularly relevant to the decision problem in this appraisal. ▪ 2-year data: HULL Migraine Clinic reported 294 patients with an initial response to onabotulinumtoxinA of which 87.4% (n=257) experienced a successful treatment response over two years of follow up: patients were either still on treatment or had successfully withdrawn treatment without relapse to CM. ▪ 5-year data: HULL Migraine Clinic reported that over five years of follow up, 80.2% (n=101) of initial responders (n=126) experienced a successful treatment response, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to CM. ▪ 7-year data: HULL Migraine Clinic reported 56.4% responders (388 out of 687) based on Hull Criteria with a good safety profile. ▪ RWD: A multicentre, retrospective chart review of 211 patients from 7 private neurology practices in Australia demonstrated that onabotulinumtoxinA is an effective, safe and well-tolerated therapy at 2 treatment cycles and beyond in adults with inadequately controlled CM. ▪ RWD: PREDICT - a Canadian, multicentre, prospective, observational study in adult 196 patients with CM demonstrates that onabotulinumtoxinA treatment for up to 2 years (7 treatment cycles) improved health-related quality of life and reduced headache days.
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	▪ Although AbbVie advocates for the availability of treatment options in patients with CM who may not respond to onabotulinumtoxinA treatment, the manufacturer did not provide clinical or cost-effectiveness evidence for galcanezumab after onabotulinumtoxinA treatment. ▪ AbbVie would like to challenge the clinical adviser's opinion that "CGRPs in the incident population would be as a 4th treatment, with onabotulinumtoxinA positioned as a 5th line treatment": ▪ Positioning onabotulinumtoxinA after CGRPs is not supported either by existing NICE technology appraisal guidance or in relevant clinical guidelines such as those issued by BASH in 2019 (or any head-to-head RCT). OnabotulinumtoxinA has been found to be cost-effective as a 4th line treatment - for patients who have not responded to at least three prior

pharmacological prophylaxis therapies (TA260). The NICE review of fremanezumab (TA631) gave no reason to suppose that it is more cost-effective than onabotulinumtoxinA for CM, thereby justifying an earlier position in the patient pathway.

- The manufacturer in this appraisal didn't present any modelling of potential sequential treatment scenarios that could inform recommendations on positioning.
- OnabotulinumtoxinA is a "tried and tested" treatment for CM and physicians have long-term clinical experience with it. Little is known about the long-term clinical outcomes of CGRPs in particular safety and tolerability, two endpoints of importance for a chronic condition like migraine. In contrast, a wealth of long-term evidence, beyond the registration studies PREEMPT 1 and 2, is available which demonstrates the durability of effect, safety and tolerability of onabotulinumtoxinA treatment for the prevention of CM (question 5 for full list of studies).
- Evidence previously seen and heard by NICE from patients and patient organisations in earlier CGRP appraisals, suggests that they value the availability of different treatment options in a condition where clinical responses can vary significantly from one patient to another. It would be inimical to this objective, as well as not supported by clinical or cost-effectiveness evidence, for NICE to position onabotulinumtoxinA as a fifth line option.
- AbbVie does not agree with the statement that access to onabotulinumtoxinA is restricted since onabotulinumtoxinA treatment is available across numerous centres in the UK

  [redacted]

  AbbVie is committed to work with the NHS to facilitate access to onabotulinumtoxinA treatment including initiatives such as the implementation of a nurse–led migraine onabotulinumtoxinA service (Jones et al. PO-01-064). Clinical experts have noted that administration by nurses is now used by the majority of UK centres treating NHS patients with onabotulinumtoxinA for CM. Administration of onabotulinumtoxinA by a specialist nurse rather than a neurology consultant represents a more efficient use of NHS resources as demonstrated by an updated cost-effectiveness analysis of onabotulinumtoxinA treatment where the ICER reduced by £2,474 per QALY (from £16,306 to £13,832 per QALY). The ERG should consider a scenario analysis where onabotulinumtoxinA is offered by a specialist nurse instead of a neurology consultant since the former better represents UK clinical practice.
- AbbVie would also like to highlight the RWD from Andreou, Hull, REPOSE and COMPEL which report long-term outcomes with onabotulinumtoxinA in patients who normally are excluded from clinical trials including those with chronic

	persistent headache, refractory migraine of headache, prior acute headache medications, and medication overuse. Clinical experience with CGRPs in these patients is limited.
Issue 4: Indirect treatment comparison for chronic migraine	
7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	▪ AbbVie believes that the ITC comparing galcanezumab with onabotulinumtoxinA should be interpreted with caution for the following reasons: i) The ITC includes a low number of studies and sample size in the network making the results of the economic analysis subject to high level of uncertainty; ii) The efficacy of galcanezumab reported in the ITC is informed by a small number of participants: 78 patients for galcanezumab vs. 231 patients for onabotulinumtoxinA (3x more patients with onabotulinumtoxinA vs. galcanezumab); iii) The evidence to support the tolerability of galcanezumab treatment beyond the duration of the RCT is limited. Given the chronic nature of the condition, tolerability of treatment is a key outcome in migraine as patients have to be on treatment for a long period of time. ▪ In this context of high uncertainty as to the efficacy, safety and tolerability of galcanezumab, AbbVie would like to highlight the available evidence for onabotulinumtoxinA treatment from various clinical settings and sources which provides certainty about its long-term effectiveness, safety and tolerability (question 5 for full list of studies). ▪ OnabotulinumtoxinA treatment also results in clinically meaningful improvements in quality of life (QoL) and disability as seen by evidence from the RCT and RWD across different clinical settings: ▪ In PREEMPT 1 and 2, onabotulinumtoxinA significantly reduced headache severity (as measured by improved HIT-6 scores at all time points) compared with placebo. ▪ In the REPOSE study, MSQ scores showed significant reductions from baseline in Role Function-Restrictive domain at each follow-up session. ▪ Following treatment with onabotulinumtoxinA, PREDICT participants reported significantly higher MSQ scores, exceeding MIDs for all three domains: role restrictive, role preventive, and emotional function. Consistent with previous

	clinical and observational studies, onabotulinumtoxinA treatment significantly improved quality of life in individuals with CM (as determined by MSQ). ▪ In Santoro et al. 2017 (Italy) onabotulinumtoxinA effectively reduced headache-related disability and improved patients' quality of life. ▪ In the Sant Andrea Hospital study, onabotulinumtoxinA reduced the mean HIT-6 score during all the treatment period up to 2 years. ▪ In the Australian RWD study, reductions in the adverse impact of headaches, reflected in significant mean (SD) changes in HIT-6 scores of –11.7 (9.8) after 2 treatment cycles (n=80; p<0.001) and –11.8 (12.2) at final follow-up (n=68; p<0.001), respectively, represent a clinically meaningful reduction in HIT-6 scores. ▪ In a retrospective study of 94 patients in Taiwan onabotulinumtoxinA significantly improved MIDAS score from 60 at baseline to 30 at 12 weeks. ▪ OnabotulinumtoxinA treatment for CM reduced symptoms of comorbid conditions such as depression and anxiety: ▪ Results from the COMPEL study show that approximately 80% of patients treated with onabotulinumtoxinA experience a clinically meaningful improvement in comorbid depression and anxiety. ▪ OnabotulinumtoxinA treatment for CM is associated with reductions in the impact of headache on daily activities and work productivity: ▪ Analysis of secondary endpoints in the FORWARD study showed mean baseline scores on the WPAI-SHP were 4.8 in the onabotulinumtoxinA group and 5.1 in the topiramate group. At Week 12, the scores had improved to 3.3 and 4.4 respectively, and at Week 36, to 3.5 and 4.4, respectively, a significant and clinically meaningful difference.
8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?	▪ The efficacy of galcanezumab reported in the ITC is subject to high level of uncertainty since it is informed by just 78 patients compared to 231 patients for onabotulinumtoxinA (3x more patients for onabotulinumtoxinA vs. galcanezumab). This uncertainty is reflected in the width of CIs. ▪ The response rates provided for galcanezumab are not only informed by limited number of patients but also from limited duration trials beyond at which point there is limited evidence about its effectiveness, safety and tolerability. In contrast, RWD from the UK clinical practice (HULL Migraine Clinic) shows that over five years of follow up, 80.2% (n=101) of

	initial responders to onabotulinumtoxinA treatment (n=126) experienced a successful treatment response, i.e., were either still on treatment or had successfully withdrawn treatment without relapse to cm. Over 7 years of follow-up, 56% (n=388) responded to onabotulinumtoxinA treatment, based on Hull Criteria, and reported related quality of life (HULL Migraine Clinic).
Issue 5: Long-term treatment effectiveness and discontinuation	
9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	▪ AbbVie advocates for treatment continuation in patients who respond to therapies in migraine similar to other conditions such as lipid lower therapies where treatment is not discontinued as a result of a response to the therapy. RWD from the UK shows that just 4 months after treatment discontinuation, as a result of the positive stopping rule, a high number of patients relapsed to a chronic pattern hence required their treatment to be resumed (Andreou et al).
10. What proportion of people are expected to restart treatment after it was stopped for any reason?	▪ AbbVie agrees with the clinical advisor that the majority of patients who discontinue treatment are likely to subsequently resume treatment. RWD from the UK (Andreou et al) confirms that patients who stopped treatment as a result of the positive stopping rule resumed therapy when their condition relapsed to a chronic pattern.
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	▪ It is unrealistic to assume a 24x longer waning period with galcanezumab compared to onabotulinumtoxinA especially since there is no evidence to justify such an assumption. ▪ The estimated waning periods for galcanezumab are based on just 4 months follow-up data and is not from the relevant population of patients discontinuing from adverse events. There is also an uncertainty around the duration of the waning of the treatment effect when the waning periods observed in a 4-month study for galcanezumab were extrapolated to up to 71 months and assumed to be higher than for onabotulinumtoxinA (without any evidence to justify this assumption). ▪ The waning period has been shown to have a considerable impact on the final ICER. When the treatment effect (reduction in MHDs) in patients who discontinue is removed for both galcanezumab and onabotulinumtoxinA this leads to a significant increase in the ICER: from £2,560 (Lilly's base case) to £42,566.

12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	▪ There is no evidence to justify a longer waning period for galcanezumab over onabotulinumtoxinA. ▪ There is available long-term RWD for onabotulinumtoxinA which demonstrates the maintenance of treatment effect in responders who have discontinued treatment: HULL Migraine Clinic reported that 58% of initial responders who have stopped treatment remained episodic after 5 years. Similar evidence is not available for galcanezumab.
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	▪ AbbVie advocates for treatment continuation in patients who respond to therapies in migraine similar to other conditions such as lipid lower therapies where treatment is not discontinued as a result of a response to therapy. RWD from the UK shows that just 4 months after treatment discontinuation, as a result of the positive stopping rule, a high number of patients relapsed to a chronic pattern hence required their treatment to be resumed (Andreou et al). ▪ Recently published TA631 recommended fremanezumab in patients with CM without the application of the positive stopping rule. We note that this would lead to the continuing treatment with fremanezumab of patients whose migraine has become episodic, even though NICE has separately concluded in TA631 that fremanezumab is not cost-effective in the treatment of episodic migraine. ▪ Updated cost-effectiveness analysis of onabotulinumtoxinA suggest that the application of the positive stopping rule may not be necessary to ensure cost-effectiveness.
Issue 6: Health related quality of life	
15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	▪ Utility values should be aligned with the subpopulation of interest in this appraisal. AbbVie agrees with the ERG that the relevant subpopulation with ≥3 failed previous preventative therapies from the included trials should be used to generate utility values. This scenario analysis - using the subpopulation of patients who have failed ≥3 previous preventative therapies from all four trials - results in a substantially higher ICER for galcanezumab.

16. Should the same utility values be used for both galcanezumab and comparators?	▪ The scope of having differential utilities is due to the differences in efficacy seen in the ITC between galcanezumab and onabotulinumtoxinA. However, the ITC included a low number of studies in the network and small sample sizes therefore the results are subject to high level of uncertainty. Specifically, the reported efficacy for galcanezumab in the ITC is informed by just 78 patients compared to 231 patients for onabotulinumtoxinA (3x more patients for onabotulinumtoxinA vs. galcanezumab). ▪ AbbVie would also like to highlight available RWD from UK centre showing a positive utility associated with onabotulinumtoxinA treatment over 5 and 7 years of treatment: ▪ Five year follow-up data from the population of interest taking onabotulinumtoxinA in HULL Migraine Clinic showed that over 80% of the initial responders were still on treatment after 5 years or had successfully withdrawn and maintained the treatment effect. ▪ Seven-year follow-up data from the same centre showed that 56% of patients (n=388) responded based on Hull Criteria and reported improved health related quality of life outcome.
17. Should age-related disutilities be applied?	▪ AbbVie concurs with ERG comment that the impact of aging may also act to assuage the benefits of reducing migraine days due to the accumulation of co-morbidities and increased frailty associated with aging. Considering the long-term duration of the model, this might have a material impact on the total HRQoL
18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	▪ Factors impacting HRQoL: severity of migraine, frequency of headache; AEs, treatment adherence, regular evaluation of monthly galcanezumab treatment ▪ Factors impacting costs: proportion of patients self-administering galcanezumab, monitoring of regular galcanezumab treatment, drop-out rates. Administration of onabotulinumtoxinA by a specialist nurse rather than a neurology consultant represents a more efficient use of NHS resources as demonstrated by a recently published updated cost-effectiveness analysis of onabotulinumtoxinA treatment where the ICER reduced by £2,474 per QALY (from £16,306 to £13,832 per QALY). AbbVie believes that the ERG should consider a scenario analysis where onabotulinumtoxinA is offered by a specialist nurse instead of a neurology consultant since the former better represents UK clinical practice.
Issue 7: Resource costs	

19. What proportion of people would not be able to self-administer galcanezumab?	▪ The assumption that after the first treatment cycle all patients (100%) will self-administer galcanezumab is optimistic. AbbVie believes that it is reasonable to expect that some patients would not be able to self-administer (therefore treatment administered by a healthcare professional) including those with physical or mental disabilities and/or those who have a phobia of needles (or a preference for oral tablets). It is also reasonable to account for frequent monitoring visits and costs in order to ensure compliance with monthly galcanezumab as well as to evaluate treatment response. ▪ EHF guidelines recommend an evaluation of response to onabotulinumtoxinA treatment after each treatment cycle. The manufacturer's economic model should also account for similar hospital visits to evaluate the response to monthly galcanezumab (at similar intervals recommended by EHF for onabotulinumtoxinA). ▪ In summary, the manufacturer's assumption of a zero-cost administration post-first treatment cycle - as applied in the economic model - is not reasonable and does not reflect the actual healthcare resources needed in "real-life" to administer galcanezumab as well as to monitor compliance and treatment response for all eligible patients.
20. Should an additional cost for people who cannot self-administer be included in the model?	▪ Previous appraisal of fremanezumab applied an administration cost for 10% of fremanezumab patients. This figure (10%) is arbitrary as there is no evidence from clinical practice to inform this assumption. It is likely that this figure is conservative if someone takes into account patient surveys in other chronic conditions such as rheumatoid arthritis (RA) where 20% of RA sufferers reported that they would not consider a treatment that required self-injection.
21. Should additional monitoring costs from the 6 to 12-month patient reviews be included in the model?	▪ EHF guidelines recommend an evaluation of response to onabotulinumtoxinA treatment after each treatment cycle. The manufacturer's economic model should also account for similar hospital visits to evaluate the response to monthly galcanezumab at similar intervals recommended by EHF for onabotulinumtoxinA.

22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	▪ AbbVie agrees with ERG that the NHWS study is more likely to be representative of resource consumption in the NHS since it has recruited patients from Europe and the UK. ▪ The use of NHWS study it will be consistent with previous appraisals of erenumab and fremanezumab.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Galcanezumab for preventing migraine [ID1372]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm** on **Thursday 30 July 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	Please see our comment on time horizon below.
2. Is a lifetime time horizon more appropriate than 25 years?	The Final Appraisal Document (FAD) for the appraisal of erenumab (pg 13) concluded that a lifetime time horizon was appropriate for the modelling of erenumab in this indication. This was because the Committee felt that a lifetime time horizon would fully capture the costs and benefits associated with treatment. Similarly, the FAD for the appraisal of fremanezumab (pg 14) concludes that "a lifetime time horizon is necessary to capture all relevant costs and benefits associated with fremanezumab". In the fremanezumab FAD it was noted that although the modelled population had an average age of over 40 years (as is the case for the galcanezumab appraisal, where the population age at baseline is modelled as ~45 years), people much younger than this would receive treatment in clinical practice and this should be reflected in the time horizon. Therefore, for consistency with prior, recent appraisals in this indication, and to ensure all relevant costs and benefits are captured, a lifetime time horizon is more appropriate than a 25-year time horizon.
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	In the appraisals of erenumab (FAD, pg 8) and fremanezumab (FAD, pg 6), the Committee concluded that "high-frequency episodic migraine is not a distinct subgroup". The high-frequency episodic migraine subgroup should be approached consistently between appraisals and therefore should not be considered as a clinically distinct subgroup for the galcanezumab appraisal.
4. If yes, what definition of "high-frequency" is used in clinical practice?	N/A – see above

Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinumtoxin toxin A has failed, is not considered to be appropriate or has not been tolerated?	Any assessment of galcanezumab in this population should be based on clinical evidence and cost-effectiveness analysis in this specific subgroup of patients who have previously failed or been found to be intolerant to treatment with botulinum toxin A, or for whom treatment with botulinum toxin A is not appropriate. Although not referenced in the specific question here, we note that the technical engagement report describes Issue 3 as "Galcanezumab should be considered in treatment sequences before and after botulinum toxin". We are not aware that any decision problem has been addressed for the use of galcanezumab at an earlier line of therapy than botulinum toxin A (i.e. *before*). The cost-effectiveness evidence submitted by the manufacturer is for patients with a history of ≥3 prior preventive treatment failures; this represents the same line of therapy at which botulinum toxin is recommended by NICE, and therefore does not provide evidence in support of a positioning *before* botulinum toxin A.
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	Any assessment of galcanezumab in this population should be based on clinical evidence and cost-effectiveness analysis in this specific subgroup of patients who have previously failed or been found to be intolerant to treatment with botulinum toxin A, or for whom treatment with botulinum toxin A is not appropriate.
Issue 4: Indirect treatment comparison for chronic migraine	
7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	There are considerable uncertainties associated with the indirect treatment comparison (ITC) performed, as was the case for the appraisals of erenumab and fremanezumab. In both the erenumab and fremanezumab appraisals, the ITCs demonstrate results for erenumab/fremanezumab versus botulinum toxin A in the subgroup of patients with ≥3 prior treatment failures that were numerically favourable but not statistically significant; in both appraisals the Committee concluded that it is uncertain whether erenumab/fremanezumab is more clinically effective than botulinum toxin A. The results of the ITC for galcanezumab versus botulinum toxin A with regards to response rates similarly find numerically favourable, but not statistically significant, results for galcanezumab versus botulinum toxin A – therefore, the conclusion should similarly be that it is uncertain whether galcanezumab is more clinically effective than botulinum toxin A.

	The Technical Engagement report suggests that the ERG and the NICE Technical Team favour scenario 11d for the cost-effectiveness analysis. Scenario 11d combines scenario 11b and 11c and therefore models differing response rates between galcanezumab and botulinum toxin A on the basis of the ITC result for the 'all-comers' population (11b) and also models a different profile (change from baseline) of MHDs for galcanezumab compared to botulinum toxin A. We have a number of concerns with this preference for scenario 11d: 1. In both the erenumab (FAD, pg 13/14) and fremanezumab (FAD, pg 12) appraisals, the uncertainties arising from the ITC results led the Committee to conclude that they should consider both analyses incorporating the relative effect estimates from the ITC but <u>also analyses in which the same effectiveness (e.g. odds ratio of 1) is assumed</u>. For consistency, scenario 11d should not solely be considered, but considered alongside scenario 11a. 2. It appears that for scenario 11b, ITC results from the 'all-comers' population are favoured; this is presumably on the basis that an ITC for the outcome of 50% response rate was not conducted for the ≥3 prior treatment failure population, on the basis that 'data from the botulinum toxin A trials was not available for a population with 3 or more prior treatment failures' (galcanezumab Technical engagement report, pg 13). Novartis do not believe that this is accurate: in both the erenumab appraisal and fremanezumab appraisal, an ITC was performed versus botulinum toxin A in the subpopulation of patients with ≥3 prior treatment failures for the outcome of 50% response rate. The Scottish Medicines Consortium Detailed Advice Document (DAD)[1] for botulinum toxin in chronic migraine reports a responder rate for the subgroup of patients who received at least 3 prior prophylactic medications (Table 3 of the DAD), where responder rate is noted as being defined as "decrease from baseline of at least 50%", therefore corresponding to a 50% responder rate. Given the availability of this data, we believe an ITC in the subgroup of interest should be possible and should constitute the basis for decision-making. 3. In both the erenumab and fremanezumab appraisals, the monthly migraine day (MMD) distribution (profile) of patients who respond to treatment was assumed to be the same for erenumab/fremanezumab and botulinum toxin. We acknowledge that for the galcanezumab appraisal, the cost-effectiveness model approaches the modelling of MMD/MHD profile for responders and non-responders in a different manner based on

	mean change in MHD values, and that a dedicated ITC was conducted to inform this. Nevertheless, as the results of the ITC informing this are associated with considerable uncertainty, and given that the MMD/MHD profile of responders to erenumab and fremanezumab was not assumed to differ to that of responders to botulinum toxin in their respective appraisals, we believe that scenario 11a – in which the MHD profile of galcanezumab and botulinum toxin is assumed to be the same – should also be considered by the Committee. [1] SMC DAD available at: https://www.scottishmedicines.org.uk/medicines-advice/botulinum-toxin-a-botox-resubmission-69211/ [Last accessed 30/07/20]
8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?	Please see above response
Issue 5: Long-term treatment effectiveness and discontinuation	
9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	No comment.
10. What proportion of people are expected to restart treatment after it was stopped for any reason?	Treatment restart was not considered in the erenumab or fremanezumab appraisals. Consistency should be applied unless there is clinical evidence for retreatment with galcanezumab that allows such a scenario to be reliably modelled.
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	Our understanding is that in the NICE appraisal of fremanezumab (FAD, pg 15/16), the Committee-preferred assumption was that patients who negatively discontinued fremanezumab reverted to baseline MMDs immediately. In the erenumab appraisal, patients who negatively discontinued erenumab were assumed to revert to non-responder Week 12 MMDs, but again this was assumed to occur immediately. If a more gradual decline of treatment effect in negative discontinuers is to be applied in the galcanezumab model, this should be predicated on relevant evidence to support this. Separately, we note that the assumption in the galcanezumab model is that patients who respond to best supportive care (BSC) wane back to baseline MHDs over the course of 1 year. We note that this is inconsistent with the erenumab appraisal, in which responders to BSC were assumed to maintain their MMD distribution for the lifetime time horizon of the model.

12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	Any modelled difference in waning periods after treatment discontinuation should be based on clinical evidence of differences in waning periods between galcanezumab and botulinum toxin A.
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	In both the erenumab (FAD, pg 17) and fremanezumab (FAD, pg 16/17) appraisals, the Committee concluded that positive stopping rules were not appropriate to consider. Consistency should be applied unless there is clinical evidence for positive discontinuation and retreatment with galcanezumab that allows such a scenario to be reliably modelled.
Issue 6: Health related quality of life	
15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	In the NICE appraisal of erenumab, quality of life data from all pivotal studies that collected the relevant quality of life outcome (Study 295, ARISE, STRIVE) were mapped to EQ-5D to inform the economic analysis. In the NICE appraisal of fremanezumab, only quality of life data from the FOCUS trial were used in the mapping algorithm; however, this was because the HALO trails did not recruit patients relevant to the decision problem (≥3 prior treatment failures). Consideration should be given to the use of quality of life data from all studies of galcanezumab that include patients relevant to the decision problem.
16. Should the same utility values be used for both galcanezumab and comparators?	In the NICE appraisal of fremanezumab (FAD, pg 18/19), the incorporation of an effect of treatment on utilities beyond that associated with the impact of treatment on the frequency of migraine days was not considered appropriate. In the NICE appraisal of erenumab (FAD, pg 19/20), the topic of treatment-related differences in utility between erenumab and botulinum toxin was considered via a scenario analysis which aimed to reflect the impact on utility of differences in the mode and frequency of administration of the two treatments; however, the Committee did not judge this scenario to be clinically plausible, and hence no treatment-related differences in utility were considered in the erenumab appraisal. Therefore, for consistency, the same utility values should be used for both galcanezumab and comparators unless there is clear evidence in support of the application of differential utilities that was not present in the appraisals of fremanezumab and erenumab.
17. Should age-related disutilities be applied?	No comment.
18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	No comment.
Issue 7: Resource costs	

19. What proportion of people would not be able to self-administer galcanezumab?	No comment.
20. Should an additional cost for people who cannot self-administer be included in the model?	No comment.
21. Should additional monitoring costs from the 6 to 12 month patient reviews be included in the model?	No comment.
22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	No comment.

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Technical engagement response form

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Teva UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	Given the assumptions taken by the company within the modelling, it is clear that a 25-year horizon will not capture all the costs and benefits of galcanezumab. The company model assumes that treatment with galcanezumab continues indefinitely (except for discontinuations associated with adverse events). Therefore, due to the low rate of discontinuations, it must be assumed that a portion of the modelled population remain on treatment after 25 years and so any costs and benefits accumulated after this time period (where they remain on treatment) would not be incorporated into an analysis with a 25-year horizon. A lifetime horizon is therefore the most appropriate time horizon to capture all coats and benefits of galcanezumab. This should be applied to the economic model in this appraisal, alongside the other modifications detailed below.
2. Is a lifetime time horizon more appropriate than 25 years?	Teva agrees that a lifetime horizon is the most appropriate time horizon, in line with the previous preferences expressed by the committee during the appraisals of fremanezumab and erenumab. The final Technology Appraisal Guidance on fremanezumab concluded that, "*The committee understood that extending the time horizon could increase the uncertainty. But it noted that arbitrarily capping the time horizon could also increase uncertainty because long-term costs and benefits were not captured…. The committee concluded that it preferred a lifetime time horizon to ensure that all relevant costs and benefits associated with fremanezumab were captured.*" A similar decision was also included within the Final Appraisal Document for erenumab.
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	No additional evidence was presented by the company that had not been previously considered by the NICE committee in regard to high-frequency episodic migraine as a clinically distinct subgroup.

	Clinical opinion previously sought by Teva (and as expressed in previous committee meetings) is that patients at the highest migraine frequencies of episodic migraine have a high need for treatment. However, as agreed by the committee in the previous appraisals, there is only limited literature examining this subgroup and none (that Teva is aware of) that has tried to define the clinical identifying features of high-frequency episodic migraine. Furthermore, the International Headache Society whom has published the ICHD-3 diagnostic criteria for migraine (the internationally recognised criteria), do not provide any definition or include HFEM as a clinically distinct subgroup. The NICE committee has twice recently assessed this subgroup in detail during the appraisals of erenumab and fremanezumab. In both cases (within the Final Appraisal Document for erenumab and the final Technology Appraisal Guidance for fremanezumab) the committee has concluded that "*High-frequency episodic migraine is not a clinically distinct subgroup.*"
4. If yes, what definition of "high-frequency" is used in clinical practice?	There is no clear and accepted definition of high-frequency episodic migraine. Teva has never found a consistent definition of high-frequency episodic migraine used either within the literature or by UK based clinical experts. Definitions that Teva has encountered vary between 8-14 and 10-14 monthly headache days, with various additional restrictions on monthly headache days.
Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinum toxin A has failed, is not considered to be appropriate or has not been tolerated?	Predicated on discussions with clinical experts, anti-CGRP therapies have a potential role after botulinum toxin A has failed, is not considered to be appropriate or has not been tolerated. galcanezumab would be an option. With specific regard to galcanezumab, this will depend solely on whether there is sufficient robust evidence to support its efficacy, safety and cost-effectiveness in these positions within the treatment pathway.
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	Based on the inclusion criteria for the CONQUER trial, Teva believes that data from this trial could potentially provide some evidence for galcanezumab as a 5th line treatment for chronic migraine (*e.g.* through an analysis of patients with four failures including botulinum toxin A). Teva notes that this would be an unplanned, *post-hoc* analysis that is likely to include only a small number of

	patients; given that the CONQUER study had a total of 93 chronic migraine patients receiving active treatment, it would thus not be statistically powered to assess this question (Mulleners *et al*. Poster presented at the International Headache Congress, Dublin, September 2019). As such, any analyses are likely to be of low quality, include a high degree of uncertainty, and should be interpreted with an appropriate degree of caution. Teva is unaware of any additional evidence that could support the use of galcanezumab as a 5th line treatment.
Issue 4: Indirect treatment comparison for chronic migraine	
7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	Teva strongly believes that the indirect treatment comparison conducted for galcanezumab provides no reliable evidence that galcanezumab is more effective at preventing migraine than botulinum toxin A. [redacted], but due to the weaknesses within these analyses Teva does not believe that this provides evidence that galcanezumab is more effective at preventing migraine than botulinum toxin A. In addition, [redacted] These results must therefore be treated with extreme caution and the possibility of equal efficacy between galcanezumab and botulinum toxin A cannot be excluded, and therefore must be considered as a plausible scenario within this appraisal. These issues are explored in a little more detail below. Firstly, as noted by the ERG and the company, there are a number of weaknesses within this comparison (including differences in placebo response, differences in how placebo was administered, small sample sizes, differences in time point of analysis, differences in double-blind treatment period). These weaknesses in indirect treatment comparisons to botulinum toxin A have been discussed thoroughly during the appraisals of fremanezumab and erenumab, and the committee concluded in both cases that it was appropriate to consider a scenario of equal efficacy between the treatments. In both these former appraisals, the committee had particular concerns around the difference in placebo between treatments (intramuscular injections into 31 to 39

	different sites on the head and neck for botulinum toxin type A every 12 weeks *versus* one to three subcutaneous injections for anti-CGRPs every 4/12 weeks) and the impact that this would have on the placebo response. The final Technology Appraisal Guidance for fremanezumab stated the following, "*The committee thought the differences in administration may have influenced the placebo responses, which were substantially different in the trials.*" Similar statements were included within the Final Appraisal Document for erenumab. The appraisals of both fremanezumab and erenumab concluded that a scenario of equal efficacy between treatments was appropriate to consider. The final Technology Appraisal Guidance for fremanezumab stated "*It [the committee] agreed it was appropriate to consider a scenario in which equivalent efficacy was assumed ….*" As detailed by the ERG in the current appraisal, the indirect treatment comparison conducted for galcanezumab also had further serious limitations. There were differences in statistical methods for the analysis of results, with galcanezumab using a mixed model repeated measures approach, whilst botulinum toxin A used analysis of covariance. This difference in statistical techniques would not be expected to have a major impact on the results, but does raise questions around the direct comparability of these data. This is of particular importance here, as a [redacted] is being used as the main determinant in demonstrating a superior efficacy of galcanezumab. A major problem in this indirect treatment comparison comes from the difference in definitions for headache/migraine days, as monthly migraine days is the more important measure in this appraisal (due to its use within the economic model). The trials of galcanezumab utilised a definition of migraine days that required headache of ≥30 minutes in length (with additional migraine features); this contrasts to the trials of botulinum toxin A which utilised a definition that required headache of ≥4 continuous hours in length. This is a significant difference in definition that raises substantial questions around the comparability of these results. In addition, Teva has concerns that the definition used within the trials of galcanezumab does not match with the ICHD-3 diagnostic criteria (which require a headache of ≥4 hours with additional criteria to qualify as a migraine attack). The ICHD-3 guidelines are internationally recognised (including by the British Association for the Study of Headache). In addition, this definition of a migraine day (requiring ≥4

	hours of headache) is included within the Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults (Tassorelli *et al*. Cephalagia 2018; 38: 815-832; https://doi.org/10.1177/0333102418758283). These deviations from internationally recognised standards raise important questions on the comparability of results within an indirect comparison. Furthermore, there are additional differences in the trials of galcanezumab compared to trials of other migraine preventive therapies that limit the comparability of results; this includes the definition of treatment failure, which required a two month period at maximum tolerated dose (compared to three months in most other trials), and the data analysis methods in the REGAIN study, where we understand that responder rates were taken as monthly averages that were then averaged to produce a final figure (this differs to how these calculations were conducted in trials of other migraine preventive therapies). Given these considerable weaknesses in the indirect treatment comparison comparing galcanezumab and botulinum toxin A, the results must be treated with extreme caution and cannot be used to justify superiority of galcanezumab. Teva also notes that during the appraisal of fremanezumab and erenumab that the committee considered the UK real-world evidence available for botulinum toxin A. The final Technology Appraisal Guidance for fremanezumab noted "*The committee acknowledged this and recognised the same evidence was not available for fremanezumab (as for most new treatment options).*" This statement remains true for galcanezumab. Another key consideration is that the model produced by the company does not consider treatment with botulinum toxin A in line with published NICE guidance. The Technology Appraisal Guidance for botulinum toxin A states that response should be assessed after two treatment cycles (*i.e.* 24 weeks). However, the company's model includes this assessment at 12 weeks. In addition to the above concerns around the indirect treatment comparison itself, Teva has further concerns around how any difference in efficacy between galcanezumab and botulinum toxin A is incorporated into the economic model. Modelling of migraine within a model of the structure used by the company, where different responder and non-responder populations are considered, relies on the interplay between response rates and MMD reductions within the respective groups to accurately model the changes in migraine days seen within the overall clinical trial data. These

	two efficacy inputs can therefore be seen as co-dependent, as the modelled migraine days within the full model population results from the combination of these two inputs. It therefore makes logical sense to include both inputs within the modelling. However, there are additional problems with the evidence presented by the company that preclude this approach from being taken. The indirect treatment comparison (which has many acknowledge weaknesses, as discussed above) uses data on the full population to inform the difference in migraine days between treatments in the responder group. This assumption is illogical and not justified by the available data. Logically, it can be seen that the responder and non-responder groups are select subgroups with specific requirements for inclusion (for CM, these are whether or not there was at least a 30% reduction in monthly migraine days). This therefore acts to reduce any difference between treatments in these select subgroups, as all patients within these groups must have met the required threshold to be included within that group. This can be clearly illustrated in the data within the company submission and ERG report. The difference in migraine days between galcanezumab and BSC/placebo in the responder group of chronic migraine patients with ≥3 previous failures was [redacted] at 3 months (Table 55 of company submission and Table 21 of ERG report) and in the non-responder group was [redacted] (Table 21 of ERG report), whereas the overall results for this patient group showed an equivalent difference of [redacted] (Table 27 of company submission). This clearly demonstrates that these more homogenous groups have smaller differences in migraine days than the full population. Similar effects were seen within the fremanezumab data, where the responder and non-responder groups showed much smaller differences in monthly migraine days than the overall trial population results. This is logically explained by the selection of the responder group reducing this difference, as outlined above; and the full treatment effect being a combination of these subgroup differences and differences in response rates. This highlights that the treatment difference for the overall population cannot be logically or plausibly applied to the responder group. The application of the results of the indirect treatment comparison gathered in a full trial population cannot be used to inform the migraine day reduction within the responder subgroup. The data above demonstrates that the migraine day differences in these two distinct groups (full population and responder subgroup) cannot be considered to be equivalent. In the absence of any other data, equivalent efficacy in the migraine day reduction for the responder groups of

	galcanezumab and botulinum toxin A is the only plausible assumption that can be made. Furthermore, Teva has additional concerns that the ERG scenario D causes further distortion in the comparison between botulinum toxin A and galcanezumab, where a differential response rate is applied on top of the difference in migraine days in the responder group. This scenario uses the overall population difference in migraine days and applies it to the responder group (hence, as outlined above, leading to an overestimate of efficacy in this group); this is then combined with a differential response rate that further enhances the relative efficacy of galcanezumab and leads to a double counting of any treatment benefit. The overall migraine day difference used as an input can be seen to consist of a combination of the treatment benefit in responders combined with any benefit of treatment response. By applying this overall population effect to responder patients means that the benefit of any difference in response rate is already included within this calculation, and so applying a difference in response rate on top of this will clearly lead to a double counting of treatment benefit.
8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?	The indirect treatment comparison provides no evidence for a difference in response rates between galcanezumab and botulinum toxin A. The indirect treatment comparison produced [redacted] in this comparison, had wide confidence intervals and utilised a broader population than the population of interest for this appraisal. Given the well-documented weaknesses in the indirect treatment comparison (with the particular additional concerns around the results for galcanezumab), these results must be treated with caution and no difference in response rate can be assumed from the results. This is in line with the committee's judgements in the two previous appraisals of anti-CGRP therapies.
Issue 5: Long-term treatment effectiveness and discontinuation	
9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	Teva believes that the assumption of long-term efficacy is a difficult issue that is key to demonstrating cost effectiveness of migraine preventive treatments. There is currently a lack of long-term data to demonstrate whether treatment efficacy is maintained for galcanezumab over extended time periods. There is also no data available to show over what time scale and to what degree treatment efficacy may wane over time. The uncertainty related to this lack of evidence

	must be borne in mind during any consideration of the long-term modelling of galcanezumab. Teva also notes that the issue of long-term continuation of treatment in responders has been evaluated during the appraisals of fremanezumab and erenumab. In the Technology Appraisal Guidance for fremanezumab, the following was concluded, "*Therefore, taking account of what it had heard from clinical experts, the committee considered that there are no clear criteria for when people should stop treatment and understood that a positive stopping rule could be challenging to implement in clinical practice. It recognised that people may not be willing to stop treatment that is beneficial for them. It also recalled that no positive stopping criteria were used in FOCUS. Therefore, the committee concluded that it was not appropriate to apply the company's positive stopping rule in the model.*"
10. What proportion of people are expected to restart treatment after it was stopped for any reason?	Teva is not aware of any data that could directly inform this assumption. Teva notes that any decision to restart treatment would primarily depend on the number of migraine days experienced by the patient after treatment cessation; where the latter is likely to vary from patient to patient due to the natural history of the condition and the impact of exogenous factors, such as stress and hormones. During the fremanezumab appraisal, the ERG for that appraisal modelled a scenario where patients who discontinued had their treatment effect wane over time, and when the waning had reduced the treatment effect by 50% these patients restarted active treatment. Teva believes that all patients that reach a clinically relevant threshold such as this would be expected to restart treatment. However, what proportion of patients this would consist of is unclear and no data are available to inform this assumption. Teva also notes that the modelling of fremanezumab and erenumab (under the committee's preferred assumption) included no maintenance of treatment effect after treatment discontinuation; therefore, an appropriate assumption would be to consider a similar scenario for galcanezumab (*i.e.* an instantaneous reversion to baseline migraine days).
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	There is very limited evidence covering waning periods after galcanezumab discontinuation, and there are a number of weaknesses within the washout data used to inform these assumptions. The ERG raised several concerns around these data and stated that they are considered to be highly uncertain, especially regarding the generalisability of these data, as they were not produced as part of a protocol driven washout. In addition, the ERG highlighted that the data were

	extrapolated long beyond the 4 months over which data were available (data were extrapolated over [redacted] months, greatly increasing uncertainty in these analyses), and that the waning was assumed to be linear when the evidence does not fully support this assumption (especially when considering the fluctuations in disease associated with the natural history of the condition, life events or hormonal changes, with these fluctuations varying from patient to patient). Teva additionally finds that the data do not account for any placebo effect present. The washout data in CM consisted of galcanezumab treated patients only, and included no comparative data. The washout data in EM does contain a comparison to a placebo group, but these data do not support the waning implemented within the economic model. The company has taken the approach of considering waning back to baseline migraine days, but when considering potential placebo effects, a far more justified comparison would be the time taken to wane back to placebo results. The data in Figure 16 of the company submission, shows that the majority of the treatment benefit (in comparison to placebo) is dissipated within the 4 month washout data presented, such that the final data point presented shows no significant difference between placebo and galcanezumab 120mg. As noted elsewhere by the ERG, clinical trials use a comparison to identical placebos to account for any placebo effect within all arms of a trial. The comparison in this washout data must therefore be made against placebo to account for any placebo effect, and without a placebo comparison is of very questionable value. Teva therefore believes that the washout data provided is sufficient to demonstrate treatment waning over the 4 months covered by these data, but that any benefit beyond this time period cannot be demonstrated by the data presented and is highly uncertain and unproven. Teva also has further concerns around the generalisability of the washout data results to the modelled scenario, as these data were not derived within the population being considered by the economic modelling, and also these data were not reported in patients who had been specifically either positively or negatively stopped. This adds further uncertainty to these data and their use within the economic model. There is no plausible mechanism that Teva is aware of that would lead to a difference in waning period for episodic and chronic migraine patients. Combined with the additional weaknesses in the CM washout data, Teva believes that a consistent waning period based on the EM data is the

	most plausible assumption to be used. Teva is aware of no data that provides evidence on the waning period of treatment effect in botulinum toxin A after discontinuation. In the absence of any data to use for this modelling, the most reasonable assumption is that this waning is assumed to occur in an identical manner to that of galcanezumab, as the indirect treatment comparison shows similar efficacy between these treatments. Teva also has some concerns around the application of this waning within the company's model. The modelled behaviour evident in the model version supplied appears to show the efficacy of galcanezumab increases after the end of the clinical trial data. This cannot logically occur, as the efficacy of treated patients is assumed to reach a maximum at the end of the clinical trial data and is then maintained through the rest of the modelled horizon. After this point, patients can only maintain this level of response or discontinue treatment and wane back to baseline migraine days. Therefore, the maximal efficacy (and hence minimal migraine days) must occur at the end of the study data, and not significantly after this time. These concerns led Teva to undertake further inspection of the economic model. Based on this inspection, Teva has some concerns around the rigour and reliability of the economic model, as provided by NICE. As *per* the instructions from NICE, Teva has limited this to an inspection to inform an understanding of the model and an evaluation of the reliability of aspects identified during this process. Teva wishes to raise the following areas of concern: [redacted]

	[redacted]

	[redacted] Teva recognises that some of these issues may have been impacted or influenced by the redaction of certain elements in the model. However, from inspection, it does not appear that the identified deficiencies have been unduly impacted by the redaction process. Due to the restrictions placed on use of the model, Teva has not conducted any detailed analysis of these areas and wishes only to flag these concerns with NICE to ensure that the model is thoroughly evaluated and provides a robust basis for decision making.
12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	There is no published evidence to suggest that there is a difference in waning periods between botulinum toxin A and galcanezumab. Therefore, the only reasonable assumption is that this waning occurs in an identical manner for both of these treatments.
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	From conversations with UK clinical experts, patients would be assessed as to whether treatment remained necessary after a positive response. Clinicians indicated to Teva that any discontinuation would occur with agreement of the patient and initially as a trial to assess whether treatment remained necessary. The SmPC for galcanezumab includes the sentence "*Evaluation of the need to continue treatment is recommended regularly thereafter*." Importantly, available data, albeit currently limited, for anti-CGRPs and clinical expert opinion is that the treatment effect

	would not remain indefinitely. There is currently no data available to inform treatment response after positive discontinuation within normal clinical practice for galcanezumab. Teva also notes that the issue of positive stopping has been evaluated during the appraisals of fremanezumab and erenumab. In the Technology Appraisal Guidance for fremanezumab, the following was concluded, "*Therefore, taking account of what it had heard from clinical experts, the committee considered that there are no clear criteria for when people should stop treatment and understood that a positive stopping rule could be challenging to implement in clinical practice. It recognised that people may not be willing to stop treatment that is beneficial for them. It also recalled that no positive stopping criteria were used in FOCUS. Therefore, the committee concluded that it was not appropriate to apply the company's positive stopping rule in the model.*"
Issue 6: Health related quality of life	
15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	Teva believes that the largest possible dataset should be used for the evaluation of utilities, as this should provide the most robust data possible. This a particular important issue in this appraisal as the evaluation of utilities across 31 migraine day states requires a sufficiently large dataset to produce reliable data. Therefore, there are strong arguments that all relevant data should be included in this analysis.
16. Should the same utility values be used for both galcanezumab and comparators?	The company submission for the galcanezumab appraisal evaluated a differential treatment effect on utilities, but, importantly, it was not included within the company base case, concluding that, "*Even though including a treatment effect modifier was statistically significant, single pooled values were chosen based on recent NICE committee preferences from NICE technology appraisal for fremanezumab.*" There are also concerns around the application of the differential utilities, as it is unclear from the supplied documentation which utilities have been applied to botulinum toxin A. As botulinum toxin A is a proven efficacious therapy compared to placebo, this treatment should utilise the 'on treatment' utilities derived for galcanezumab. This approach was taken by Teva during the appraisal of fremanezumab. The appraisal documentation does not clearly communicate whether this has been the case in this current appraisal.

	In the fremanezumab appraisal, the committee considered all the evidence presented in this regard and came to the conclusion that "*The committee recalled that utility values were generated from MSQ data, which measured the impact of migraine on daily social and work-related activities, and emotional functioning. Therefore, it agreed that it was uncertain whether health-related quality-of-life benefits beyond those related to reducing monthly migraine days were not already adequately captured by the MSQ. … The committee concluded that the company's additional on-treatment utility value benefits should not be included in the economic model.*" The company for the current appraisal did not present any additional evidence to justify differential utilities between active treatment and best supportive care. Therefore, it is clear that the company did not believe that there was sufficient additional evidence to override the previous decision made during the fremanezumab appraisal. During that appraisal, Teva presented evidence, including clinical trial data, arguments around severity and quality of life aspects outside those captured by the MSQ, and published reports. Since the clinical trial data for both products are similar in this regard, Teva finds that there is no additional evidence presented to this appraisal that should lead to the previous decision being reconsidered.
17. Should age-related disutilities be applied?	Teva believes that the application of age-related disutilities is a sensible consideration when considering a lifetime time horizon.
18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	An equivalent question was included in the Technical engagement for the fremanezumab appraisal. This issue was then fully considered by the committee during that appraisal, with the conclusion that these factors were adequately captured by The Migraine-Specific Quality of Life Questionnaire. The following was included within the final Technology Appraisal Guidance for fremanezumab "*The committee recalled that utility values were generated from MSQ data, which measured the impact of migraine on daily social and work-related activities, and emotional functioning. Therefore, it agreed that it was uncertain whether health-related quality-of-life benefits beyond those related to reducing monthly migraine days were not already adequately captured by the MSQ.… The committee concluded that the company's additional on-treatment utility value benefits should not be included in the economic model.*" With similar MSQ data available for galcanezumab and no additional data in this regard, the same conclusion is warranted from the

	committee.
Issue 7: Resource costs	
19. What proportion of people would not be able to self-administer galcanezumab?	Teva believes that only a small proportion of patients would not be able to administer galcanezumab, but that reliable estimates for this proportion are not available. Therefore, the most appropriate assumption is to use the value of 10% as used during the appraisal of fremanezumab. The final Technology Appraisal Guidance for fremanezumab concluded, "*The committee concluded that it was unlikely that everyone having fremanezumab would be capable of self-administering treatment. It agreed that applying administration costs for 10% of people having fremanezumab was reasonable, but acknowledged that this had little effect on the model results.*"
20. Should an additional cost for people who cannot self-administer be included in the model?	As noted in the above response, the most appropriate assumption is that 10% of patients require assistance with administration. In these cases, an additional cost will be associated with this administration and so this should be incorporated into the economic modelling. The final Technology Appraisal Guidance for fremanezumab concluded, "*The committee concluded that it was unlikely that everyone having fremanezumab would be capable of self-administering treatment. It agreed that applying administration costs for 10% of people having fremanezumab was reasonable, but acknowledged that this had little effect on the model results.*"
21. Should additional monitoring costs from the 6 to 12 month patient reviews be included in the model?	The SmPC for galcanezumab includes the sentence "*Evaluation of the need to continue treatment is recommended regularly thereafter*." This implies that regular monitoring is a requirement under the SmPC of this product, although the exact details of the required monitoring are not defined. The Technical Report includes the sentence "*The ERG also noted that monitoring costs were not included as clinical advice suggested that galcanezumab patients would be reviewed every 6 to 12 months.*" This acknowledges that review of treatment every 6 months by a consultant neurologist is an appropriate assumption, and this should therefore be included within the economic evaluation. These reviews must be seen as additional costs, as such reviews would not occur in patients receiving best supportive care or those receiving botulinum toxin A. For patients not receiving active treatment (*i.e.* best supportive care), it is likely that any review will be infrequent;

	based on clinical advice received by Teva it is also likely that these patients will be discharged from headache clinics for management within primary care, as there are no additional treatments that can be supplied by the headache clinic. As patients receiving botulinum toxin A attend clinic for each administration, it is likely that the majority of monitoring will occur during these visits and any additional monitoring visits are again infrequent. Predicated on the above, the inclusion of a cost for regular monitoring of galcanezumab should be included; this would also match the approach taken by Teva during the appraisal of fremanezumab (where the costs of review appointments every 6 months were included).
22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	Teva agrees with the ERG that the National Health and Wellness Survey provide the most robust data on resource use in a UK setting. The US survey by Munakata *et al*. was considered for use by Teva during the appraisal of fremanezumab, but this was judged not to be an appropriate data source by due to the significant differences in healthcare systems between the UK and the US, and the limitations in its consideration of the impact of migraine days on resource use. Given the availability of the National Health and Wellness Survey data, Teva feels that this is a much more appropriate data source for UK resource usage and notes (as also recorded by the ERG) that the National Health and Wellness Survey data was used in both the appraisal of erenumab and fremanezumab. In both of these appraisals, the committee judged that these data were an appropriate source for use within the modelling.

Single Technology Appraisal (STA)

Galcanezumab for preventing migraine

ERG addendum: review of company's response to technical engagement

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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List of abbreviations

ABN	Association of British Neurologists
BASH	British Association for the Study of Headache
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence interval
CM	Chronic migraine
CMU	Commercial medicine unit
CS	Company submission
DTT-3-CM	Difficult to treat population of chronic migraine patients who have failed ≥ 3 previous preventive treatments for migraine
ERG	Evidence review group
HD	Headache days
HFEM	High frequency episodic migraine
HRQoL	Health related quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
LSM	Least-squares mean
MHD	Migraine headache days
MIBS	Migraine Interictal Burden Scale
NHWS	National Health and Wellness Survey
NICE	National Institute for Health and Care Excellence
PRO	Patient-reported outcome
QALY	Quality adjusted life-year
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics

1 OVERVIEW

This addendum to the Evidence Review Group (ERG) report provides the ERG critique of the additional evidence provided by Eli Lilly in their response to the draft Technical Report for the appraisal of Galcanezumab for preventing migraine.

The draft Technical Report outlined 7 key issues for consideration and provides the technical team's preliminary scientific judgement on each issue. The company's response to the draft Technical Report indicated that they accepted the technical team's preliminary judgement on a number of issues, which the ERG now considers resolved (Table 1). The company's response to all issues, along with relevant stakeholder responses, are discussed in Section 2.

The ERG also presents the probabilistic results of the Technical Team's preferred base case (Section 3.1) and additional exploratory scenarios based on information provided by stakeholders in response to technical engagement (Section 3.2).

Table 1 Questions for engagement and current status regarding issue resolution

Issue 1: Time horizon	
1. Will all the costs and benefits of galcanezumab be captured over 25 years?	Resolved
2. Is a lifetime time horizon more appropriate than 25 years?	Resolved
Issue 2: High frequency episodic migraine	
3. Is high frequency episodic migraine a clinically distinct subgroup?	Resolved
4. If yes, what definition of "high-frequency" is used in clinical practice?	Resolved
Issue 3: Position of galcanezumab in the treatment pathway	
5. Would galcanezumab be considered as an option once botulinum toxin A has failed, is not considered to be appropriate or has not been tolerated?	Resolved
6. Is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A?	Resolved but uncertainty remains
Issue 4: Indirect treatment comparison for chronic migraine	
7. Is galcanezumab more effective at preventing migraines than botulinum toxin A?	Unresolved
8. In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?	Unresolved
Issue 5: Long-term treatment effectiveness and discontinuation	
9. Is it reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds?	Resolved
10. What proportion of people are expected to restart treatment after it was stopped for any reason?	Resolved but uncertainty remains
11. After negative discontinuation, what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A)?	Resolved but uncertainty remains

12. Is it justified to have different waning periods for galcanezumab and botulinum toxin A?	Resolved
13. In UK clinical practice, would treatment be stopped if people respond positively and migraine frequency decreases? Would treatment effect be maintained indefinitely after positive discontinuation?	Resolved
Issue 6: Health related quality of life	
15. Should relevant utility data from the EVOLVE and REGAIN trials be included?	Resolved
16. Should the same utility values be used for both galcanezumab and comparators?	Resolved but uncertainty remains
17. Should age-related disutilities be applied?	Resolved
18. Are there other factors that impact on HRQoL and costs, aside from frequency of migraine?	Resolved
Issue 7: Resource costs	
19. What proportion of people would not be able to self-administer galcanezumab?	Resolved
20. Should an additional cost for people who cannot self-administer be included in the model?	Resolved
21. Should additional monitoring costs from the 6 to 12-month patient reviews be included in the model?	Unresolved
22. Does the data from the US survey (Munakata et al) adequately estimate resource use costs in a population with migraine?	Resolved

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Issue 1: Time horizon

Two questions were raised by the technical team: whether all the costs and benefits of galcanezumab would be captured over 25 years (***Question 1***) and whether a lifetime time horizon is more appropriate than 25 years (***Question 2***)?

The company's preference, as outlined in the original submission and in response to technical engagement, is to use a 25-year time horizon. The company state that this is preferable to a 45-year (lifetime) time horizon, as increasing the length of the time horizon increases uncertainty in the economic results owing to the absence of long-term data on the effectiveness of galcanezumab, and the omission of the potentially dynamic natural history of migraine in the economic model. A number of responses from stakeholders agreed with this position, for example responses from the British Association for the Study of Headache (BASH) and Abbvie.

A number of responses, however, considered the lifetime time horizon to be more appropriate for the economic model to fully capture the costs and benefits. In addition, a longer time horizon was

preferred for consistency with the committee preferences in the appraisal of erenumab and fremanezumab for a lifetime time horizon.[1, 2]

The company accepted the technical team's preferred scenario of using a 45-year modelled time horizon in their response. As stated in the original critique, the ERG considers that a 45-year time horizon increases uncertainty and is unnecessary in the modelled population given the natural history of migraine. However, the ERG considers the use of a lifetime time horizon to be acceptable in the base-case and notes it has limited impact on the incremental cost-effectiveness ratio (ICER) (see Technical Report, Tables 1a, 1b and 1c).

2.2 Issue 2: High frequency episodic migraine (HFEM)

Two questions were raised by the technical team: whether HFEM was a clinically distinct subgroup (***Question 3***) and, if so, what definition of "high-frequency" is used in clinical practice ***(Question 4***)?

Firstly, the company acknowledged in their response that HFEM is not currently classified as a clinically distinct subgroup in the International Classification of Headache Disorders, Third Edition (ICHD-3)[3] and has not been considered as such in previous NICE appraisals.[1, 2] However, the company reiterated their view that HFEM should be treated as a clinically distinct subgroup citing their recently sponsored (June 2020) advisory board meeting with neurologists who supported this view. The ERG report recognised that this remains an important topic of debate within migraine research. These uncertainties are reflected in responses from other stakeholders. For example, BASH's response similarly argued that HFEM patients should be treated either as a distinct clinical subgroup or in a similar manner to patients with chronic migraine (CM). In contrast, the Migraine Trust argued that there is currently insufficient evidence to consider HFEM a clinically distinct subgroup.

Secondly, the company argued that HFEM should be defined as 8-14 migraine headache days (MHDs) per month reflecting the definition used in the galcanezumab trials, whilst acknowledging the lack of consensus on the definition of HFEM in migraine research. Most technical engagement responses also reflected this lack of consensus in migraine research and in clinical practice.

Given the lack of consensus within the field on the clinical distinctiveness of HFEM and the lack of consensus on how to define it, the ERG maintains there is insufficient evidence that HFEM is a clinically distinct subgroup.

2.3 Issue 3: Position of galcanezumab in the treatment pathway

Two questions were raised by the technical team: would galcanezumab be considered as an option once botulinum toxin A has failed, is not considered to be appropriate or has not been tolerated

(***Question 5***), and is there any evidence to support the use of galcanezumab as a 5th line treatment following failed treatment with botulinum toxin A (***Question 6***)?

Firstly, the company's response states that galcanezumab would be considered an option when botulinum toxin A has failed, is not considered to be appropriate or has not been tolerated. The company response highlights feedback from BASH during the appraisal of fremanezumab in which it was stated that treatment options at fifth line following botulinum toxin A failure are needed. Evidence provided by the company in response to technical engagement from research conducted by The Migraine Trust, estimates the proportion of botulinum toxin A failures in the chronic migraine population to be 15.7%.[4] Technical engagement responses from almost all stakeholders consider galcanezumab to have a potential role following botulinum toxin A failure.

The ERG report highlights the fifth line positioning of Calcitonin Gene-Related Peptides (CGRPs) to be a plausible treatment sequence and outlines the lack of modelling of alternative treatment sequencing in the company submission (CS) to be an important limitation (see ERG Report, Section 4.2.4). This is particularly the case in light of the successful appeal in the appraisal of erenumab[5] which upheld that the committee should have considered erenumab as a 5th line therapy for patients who had failed botulinum toxin A.

A key point in the consideration of treatment sequencing is the availability of botulinum toxin A treatment. Comments from the ERG's clinical advisor highlighted the limited availability of botulinum toxin A and the more burdensome administration associated with it, concluding the preferred position for galcanezumab and other CGRPs in the incident population would be as a 4th line treatment. In response, AbbVie disagreed that access to botulinum toxin A treatment is restricted. In addition, AbbVie's response highlighted the nurse-led migraine onabotulinumtoxinA service implemented to facilitate access to botulinum toxin A; the ERG considers the economic implications of this nurse-led service in Section 2.7.4.

Uncertainty remains of the clinical and cost-effectiveness of different treatment sequences due not only to the failure of the economic model to consider sequencing, but also the lack of clinical evidence to support the use of galcanezumab as a 5th line treatment following botulinum toxin A. In the company's response, patient numbers for this population from CONQUER are too small (Galcanezumab, N=[redacted]; Placebo, N=[redacted]) to provide any robust, meaningful or clinically interpretable results.

Both BASH and the Association of British Neurologists (ABN) highlight a recent publication by Ailani et al.[6] in which pooled data from EVOLVE-1, EVOLVE-2 and REGAIN showed 50% responder rates for chronic migraine patients treated with different doses of galcanezumab following

botulinum toxin A failure. Response rates of 41.3% (120 mg) and 47.5% (240 mg) were observed for patients treated with galcanezumab, compared to 9.4% for placebo. As this patient population was not in the 5th line of therapy, the ERG concluded that these data do not substantially change conclusions around the lack of clinical evidence in the 5th line setting.

The ERG maintains that the lack of treatment sequencing in the company's economic model is an important limitation and remains an area of uncertainty. In the absence of such analysis it may be appropriate to include a provision in any guidance outlining that patients should receive the cheapest treatment option appropriate to their line of treatment. This will minimise use of more expensive treatment options where acceptable clinical outcomes can be achieved on cheaper treatments.

2.4 Issue 4: Indirect treatment comparison for chronic migraine

Two questions were raised by the technical team: is galcanezumab more effective at preventing migraines than botulinum toxin A (***Question 7***)? And, in chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A (***Question 8***)?

2.4.1 Is galcanezumab more effective at preventing migraines than botulinum toxin A?

Firstly, the company's response acknowledged the limitations of the indirect treatment comparison (ITC) comparing galcanezumab and botulinum toxin A for preventing migraines already discussed in the CS and ERG report. However, the company's response highlighted that their analyses were likely to be conservative citing sensitivity analyses previously reported in the CS. Technical engagement responses from other stakeholders also reiterated the limitations of the ITC analyses. These limitations (e.g. small sample sizes, differences in placebo response rates, differences in measuring key outcome measures) were discussed in detail in the CS and ERG reports.

Since no new data were provided, and no additional limitations of the ITC were identified by other stakeholders, the ERG will not comment further on these responses (please see section 3.4 of the ERG report for a detailed critique of the indirect comparison analyses).

Secondly, the company cited a new publication[7] to support the generalizability of the CONQUER trial to a real world population (using data from InovPain, a registry of French patients with migraine). In this company sponsored analysis, patient-level data from the CONQUER trial were weighted to match aggregated InovPain registry data for patients with a history of ≥ 2 failed prior preventative therapies. The weighted CONQUER analyses were similar to those of patients identified in the InovPain registry for most study characteristics (e.g. monthly MHDs). The main difference was that the weighted analyses still had a greater proportion of patients with ≥ 4 failed preventive treatments compared with the InovPain sample. This imbalance is unlikely to impact interpretations on the effectiveness of galcanezumab given the focus of the company submission on difficult-to-treat populations. Mean

effect estimates were similar in the primary and weighted analyses of the CONQUER trial (least-squares mean [LSM] difference from placebo in primary analysis: -3.12, 95% confidence interval [CI] (-3.92 to -2.32), $p < 0.0001$; LSM difference from placebo in weighted analysis: -3.13, (-4.02 to -2.24), $p < 0.0001$). However, the company acknowledged these data were not directly relevant to the UK population.

The ERG also noted that this study matched to patients with ≥ 2 failed prior preventatives rather than patients with ≥ 3 failed prior preventatives (DTT-3-CM), the target population for the CS. The ERG concluded that these data do not substantially change conclusions of the ERG report or CS.

2.4.2 In chronic migraine, are the response rates for galcanezumab equivalent to botulinum toxin A?

The company accepted the technical team's preferred scenario to apply a treatment effect to the response rate outcome as estimated from the indirect comparison to botulinum toxin A from the 'all-comers' population.

However, some stakeholders did not agree with the technical team's preferred scenario. Stakeholder comments mainly fell into two categories: disagreement that response rates should differ between galcanezumab and botulinum toxin A in the economic model, and disagreement that data from the 'all-comers' population should be used to inform response rates for these treatments in the economic model. The ERG report clearly stated the limitations of using data from the 'all-comers' population (i.e. lack of applicability to the target population of patients who received at least 3 prior prophylactic medications (DTT-3-CM)).

Some stakeholders questioned the use of ITC data in scenario 11b from the 'all-comers' population comparing 50% response rates between galcanezumab and botulinum toxin A. One stakeholder response argued scenario 11b should have used data from a Scottish Medicines Consortium (SMC)[8] report in the ITC analyses. The ERG considered the data reported in the SMC report with interest. However, the SMC report provided response rate data on headache days (HDs) for botulinum toxin A vs placebo but the CS provided response rate data on *migraine* headache days (MHDs) for galcanezumab vs placebo. Therefore, the ERG concluded that the response rate data in the SMC report for botulinum toxin A, although relevant to the DTT-3-CM population, were not comparable with the response rate data for galcanezumab in that same population reported in the CS. The ERG maintains that scenario 11b was based on the best available data, whilst fully acknowledging its limitations.

The ERG further notes that Teva's submission suggests that the treatment effect between botulinum toxin A and galcanezumab was double counted in scenario 11d. The ERG can confirm that this is not

the case and that the modelled treatment effect in this scenario is drawn primarily from the ITC of MHDs with a number of assumptions made to model the potential for differences in response rates between treatments.

2.5 Issue 5: Long-term treatment effectiveness and discontinuation

The technical team asked a number of questions regarding long-term treatment and discontinuation.

2.5.1 Lifetime treatment and treatment restart

The issues of whether it is reasonable to assume that treatment with galcanezumab would continue for the lifetime of the model for people whose migraine responds (***Question 9***), and what proportion of people would be expected to restart treatment after it was stopped for any reason (***Question 10***) were raised by the technical team.

The company's technical engagement response agreed with the ERG's assessment that the assumption of indefinite treatment with galcanezumab for responders is unrealistic. The ABN and BASH submissions agreed, stating that only a small proportion of patients will continue preventive therapy indefinitely. AbbVie outlined evidence that a high proportion of patients relapse to a chronic pattern.[9]

Without long-term evidence on the duration of treatment and durability of any continued benefits post-discontinuation, modelling discontinuation scenarios including positive discontinuation, would present highly uncertain results. This was also reiterated by Teva in their response to technical engagement. The ERG maintains that the omission of positive discontinuation scenarios is the most appropriate approach given the limitations of available evidence. The company outlined their agreement with this approach in their model response. This is also consistent with the committee preferences in the appraisal of fremanezumab.[2]

Regarding the question of what proportion patients would be expected to restart galcanezumab, the ERG agrees with the company that inclusion of restarting treatment in the economic model is inappropriate. This is because no data are currently available from clinical trials or real-world studies on the proportion of patients expected to restart treatment after stopping for any reason, and there is a lack of long-term washout data to determine at what point patients would return to pre-treatment baseline levels and restart treatment. Novartis also highlighted that treatment restart was not considered in the erenumab or fremanezumab appraisals. The ERG agrees that consistency should be applied unless there is clinical evidence for retreatment with galcanezumab that allows such a scenario to be reliably modelled.

2.5.2 Galcanezumab waning period

The question of what are the galcanezumab waning periods for episodic migraine, chronic migraine (vs BSC) and chronic migraine (vs botulinum toxin A) after negative discontinuation (***Question 11***) was raised by the technical team.

The ERG considers there are two issues to discuss. First, should consistent waning be assumed across chronic migraine and episodic migraine populations? And secondly, what should the modelled waning period be?

Regarding consistent galcanezumab waning across chronic and episodic migraine populations, the ERG report highlighted that the assumption of differential waning lacked face validity. The company accepted the ERG's and technical team's preference for a consistent waning period. Response to technical engagement by Teva stated there is no plausible mechanism that they are aware of that would lead to a difference in waning period for episodic and chronic migraine patients.

The second issue of what the length of the waning period should be, generated mixed responses. The company agreed with the technical team's preference for a 13-month waning period following galcanezumab discontinuation. This was based on the washout data showing up to 4 months after galcanezumab discontinuation, patients had not reverted back to baseline (see CS, Section B.3.3.2). The exact time to revert back to baseline beyond 4 months is unknown, therefore the approach taken by the company was to assume a linear waning rate based on the rate observed. This resulted in a 13-month waning period to reach baseline levels. However, a number of stakeholders considered that the waning period should be less than 13 months, with BASH estimating 2-3 months, ABN estimating 1 month, and Teva suggesting their preference for 4 months. In addition, AbbVie highlighted the uncertainty around the waning period based on 4-months of washout data. Novartis highlighted the committee preferred assumption in the appraisal of fremanezumab was that waning back to baseline occurred immediately. The ERG notes that this assumption formed the base case in the appraisal of fremanezumab as no evidence was provided of a washout period. However, evidence of a waning in reduction from baseline at 4-months post galcanezumab discontinuation in REGAIN and EVOLVE-2 was presented in the CS (see CS, Section B.3.3.2).

It is unclear whether a linear waning rate occurs after 4 months post-galcanezumab. The non-linear functional form of the REGAIN and EVOLVE-2 washout data makes the assumption of a linear waning effect over time unlikely to hold. For the purpose of the economic model, the ERG accepts the waning period likely exceeds 4 months but is uncertain as to the exact length beyond this. Therefore, the ERG accepts the technical team's preference for a 13-month waning period but highlights this remains an area of uncertainty.

2.5.3 Differential waning periods for galcanezumab and botulinum toxin A

The technical team asked if it is justified to have different waning periods for galcanezumab and botulinum toxin A (***Question 12***)?

In the ERG report, the lack of evidence justifying differential waning periods applied to galcanezumab and botulinum toxin A was highlighted. To address this, the ERG and technical team's preferred assumption is for the same waning period to be applied to both. Following the uncertainty around the length of the galcanezumab waning period (see ***Question 11***), a 13-month waning period was applied to both galcanezumab and botulinum toxin A.

In response to technical engagement, the company accept the accepts the technical team's preference to assume a consistent waning period back to baseline MHDs post-discontinuation for galcanezumab and botulinum toxin A. The company do, however, highlight the lack of data describing a sustained effect of botulinum toxin A for patients discontinuing.

Both BASH and ABN in their response to technical engagement state a differential waning period is justified, with ABN outlining the waning period should be longer for botulinum toxin A. AbbVie, Novartis and Teva all highlight a lack of evidence justifying a differential waning assumption in their response. The ERG considers that without evidence in the relevant population to justifying differential waning periods, the assumption of consistent waning is a more conservative assumption.

2.5.4 Positive discontinuation

The technical team asked whether in the UK treatment would be stopped if people respond positively and migraine frequency decreases, and whether treatment effect would be maintained indefinitely after positive discontinuation (***Question 13***).

As outlined in Issue 5, Questions 9 and 10 (Section 2.5.1), the ERG, company and stakeholders do not consider treatment with galcanezumab will be continued indefinitely. In their response, BASH and ABN highlighted current clinical practice for all oral preventive therapies is to wean off the treatment after 6-12 months with only a very small percentage (10-20%) requiring indefinite treatment.

The ERG considers this an important issue and one which should be reflected in the economic evidence. However, without long-term evidence on the duration of treatment and durability of any continued benefits post-discontinuation, modelling discontinuation scenarios, including positive discontinuation, would present highly uncertain results. In addition, the company highlight in their response that in past technology appraisals, clinical experts indicated it would be difficult to implement a positive rule in practice.[1, 2] For parity with the appraisals of fremanezumab and erenumab, the ERG does not consider positive discontinuation scenarios.

2.6 Issue 6: Health related quality of life

The technical team asked a number of questions regarding health-related quality of life (HRQoL) implemented in the economic model.

2.6.1 Relevant utility data

The technical team asked whether relevant utility data from the EVOLVE and REGAIN trials should be included (***Question 15***). The company agrees with the ERG's and technical team's preference for using utility values estimated for the specific population of patients with a history of ≥ 3 failed prior preventatives from the relevant clinical trials (CONQUER, EVOLVE-1, EVOLVE-2 and REGAIN). Responses from stakeholders agreed that utility values should be from the relevant population. The ERG considers this issue resolved.

2.6.2 Consistent utility values across galcanezumab and comparator

The technical team asked whether the same utility values should be used for both galcanezumab and comparators (***Question 16***)?

In the ERG report, the ERG's preference was for the use of differential utilities across galcanezumab and comparator, despite the company's conservative assumption of using a single set of utility values. The company's original approach was for consistency with the committee determinations in the appraisals of fremanezumab and erenumab.[1, 2] As highlighted by Novartis in their technical engagement response, differential utilities were considered by committee in the two anti-CGRP appraisals, however they were rejected. The ERG contends that clear empirical or clinical evidence in the support of differential utilities was not presented for either fremanezumab or erenumab. However, the ERG considers the CS to contain compelling clinical evidence for the use of differential utilities (see ERG Report, Section 4.2.7). In addition, this approach allows the potential for improvements in migraine severity to be captured beyond the measure of migraine headache days (see ERG Report, Section 4.2.2 and 4.2.7).

Additional information presented by the company in response to technical engagement outlines additional factors beyond migraine frequency that can impact HRQoL which lends further support to the use of differential utilities (see ***Question 18***, Section 2.6.4, for a discussion of the additional information). As part of the additional information, the company present the results of a correlation study conducted on patient-reported outcomes (PROs) collected in the CONQUER study to assess whether the interictal burden (i.e. migraine-related impairment between attacks) was adequately captured in other measures included in the study. Results show that patients treated with galcanezumab experienced statistically significant reductions in interictal burden, as measured on the Migraine Interictal Burden Scale (MIBS-4) (mean change, -1.8 point reduction on the MIBS-4 scale)

compared to placebo (-0.8 point reduction on the MIBS-4 scale). [redacted] The ERG considers this to provide weight to the argument that basing results entirely on MHD has the potential to miss important aspects impacting the burden of migraine, such as interictal burden. However, none of the methods, data and results presented in the company's response to technical engagement have been verified by the ERG, meaning the magnitude to which MHD captures the full burden of disease remains unknown.

2.6.3 Age-related disutilities

The technical team raised the issue of whether age-related disutilities should be applied in the economic model (***Question 17***)?

The company accepted the technical team's preference for the inclusion of age-related disutility to be used in the economic model to account for the likelihood of increased morbidity and frailty with age. The ERG considers this inclusion to be particularly important when a lifetime time horizon is assumed. Both AbbVie and Teva accepted the implementation of age-related disutility.

A number of stakeholders raised the important issue of the natural history of migraine when considering the effect of increased age. The natural history is for migraine to improve with age, as outlined by the company, BASH and ABN. A number of studies identified by the ERG and described in the ERG report concurred with this assessment.[10-13] Despite the agreement that the tendency of patients with migraine is to improve over time, the ERG and Technical team's preferred base case does not include the ERG's illustrative scenario of including natural history in the economic model. This is due to lack of data on the long-term effects of migraine and in particular how this might impact upon active treatments.

However, the ERG reiterates the importance of natural history on the cost-effectiveness of galcanezumab. As described in the ERG report, the inclusion of natural history has important consequences for the cost-effectiveness of any active migraine treatment as natural history will tend to erode the benefits of treatment, rending continued treatment increasingly less cost-effective. The ERG emphasises the importance of clinicians complying with the summary of product characteristics

(SmPC) recommendation that patients be regularly reviewed to assess the need for continued treatment.[14] This will ensure that patients only continue to receive treatment where it is both beneficial and cost-effective.

2.6.4 Additional factors influencing HRQoL

The technical team asked if there are other factors that impact on HRQoL and costs, aside from frequency of migraine (***Question 18***).

As described in the ERG report, the ERG considers the omission of migraine severity from the company's economic model to be an important limitation (see Section 4.2.2). BASH, ABN and The Migraine Trust indicated in their response that severity can play a role in patients' quality of life.

The company's response to technical engagement described the complex nature of migraine and the nature of the ictal burden (that is, the experience of the migraine attack itself) and interictal burden, which impacts HRQoL and is unlikely captured through reduction in MHDs alone. The additional analyses describing the correlation between interictal burden and MHDs provided in the company's response is discussed in Section 2.6.2 (***Question 16***). Results from the EuroLight Project and presented by the company show the extent of the interictal burden on patients with headache and migraine.[15, 16] Additional information provided by the company describes pain intensity and non-pain symptoms such as photo-/phonophobia, throbbing/aggravation, prodrome and nausea and vomiting (amongst others) as potentially impacting HRQoL. However, the ERG notes these symptoms may also be related to migraine frequency.

Teva noted that determinations from the committee in the fremanezumab appraisal indicated that other factors were adequately captured by The Migraine-Specific Quality of Life Questionnaire. The ERG considers other factors may well have been captured in the Migraine-Specific Quality of Life Questionnaire data, but the assumption of using a single set of utilities then has the potential to negate improvements in factors such as interictal burden as a result of galcanezumab. The ERG considers factors other than frequency of migraine do have an impact HRQoL and costs. As described in the ERG's response to ***Question 16***, the use of differential utilities to represent a treatment effect allows improvements in migraine severity to be included in the economic evidence.

2.7 Issue 7: Resource costs

The technical team asked a number of questions regarding resource use and costs implemented in the economic model.

2.7.1 Galcanezumab self-administration

The technical team asked what proportion of people would not be able to self-administer galcanezumab (***Question 19***) and whether an additional cost for people who cannot self-administer should be included in the model (***Question 20***).

In the ERG's original critique, we highlighted that the omission of any administration costs for galcanezumab beyond the first cycle and the implicit assumption that all patients will be able to self-administer was unreasonable. For the purpose of parity with previous appraisals[1, 2] it was assumed that 10% of patients could not self-administer.

The majority of responses from stakeholders agreed the assumption that 100% will self-administer to be optimistic and that the technical team's preferred assumption of 10% not able to self-administer was reasonable. However, some responses from stakeholders questioned the exact figure. For example, Abbvie stated there is no evidence to support the assumption of 10%, and in their opinion, this is conservative when compared to other chronic conditions such as rheumatoid arthritis. In contrast, BASH felt only a very small number of patients (< 5%) that are needle-phobic would require assistance.

The company accepts the technical team's and ERG's preferred scenario of applying an administration cost for 10% of galcanezumab patients to reflect those who would not be capable of self-administering. However, the inclusion of a 10% administration cost for these patients has a limited impact on the ICERs (Technical Report, Tables 1a, 1b and 1c). The ERG considers this issue resolved.

2.7.2 Additional monitoring costs from the 6 to 12-month reviews

The question of whether additional monitoring costs from the 6 to 12-month patient reviews should be included in the model (***Question 21***) was raised by the technical team.

The company's response outlined their position that additional monitoring costs should not be included in the economic model. The ERG's position, as described in the ERG report, is that the company's omission of additional monitoring costs from the economic model is a potentially important one. However, the ERG also highlighted that positive discontinuation was not included in the economic model, removing the justification for additional monitoring costs.

Almost all stakeholder responses considered additional monitoring costs should be included in the economic model. BASH and ABN outlined monitoring should occur at 3-months and 6-month post-treatment initiation, with BASH suggesting a further assessment at 12-months. Both agreed

monitoring could be conducted virtually. Teva highlighted an assessment at 6 months and 12 months is appropriate and would be consistent with the appraisal of fremanezumab.

As outlined above, the ERG does not consider the inclusion of additional monitoring to be a reasonable assumption for inclusion in the base case. The incorporation of the costs of monitoring without the benefits of monitoring (i.e. positive discontinuation) results in overestimates of the ICERs. However, to demonstrate the impact on the ICER and for parity with previous appraisals, a scenario is implemented in which additional monitoring costs are included for patients treated with galcanezumab, see Section 3.2.1 for results.

2.7.3 Migraine population resource use

The technical team asked whether the data from the US survey (Munakata et al[17]) adequately estimated resource use costs in a population with migraine (***Question 22***). In the ERG's original critique, resource use estimated from the National Health and Wellness Survey (NHWS)[18] was preferred as the source of the most robust data on resource use in a UK setting. In addition, the use of these data creates parity with the technology appraisals of fremanezumab and erenumab. Responses from stakeholders agree with the use of the NHWS resource use data.

The ERG considers the NHWS to be appropriate and agree with the company and technical team's preference for this to be used to inform the base case. The ERG considers this issue resolved.

2.7.4 Specialist nurse-led OnabotulinumtoxinA administration

In response to the technical team's question regarding treatment sequencing of galcanezumab and botulinum toxin A (***Issue 3***), Abbvie outlined the nurse-led onabotulinumtoxinA initiative in which a specialist nurse administers treatment rather than a neurology consultant. It was stated that the majority of UK centres now use administration by specialist nurses, based on a personal communication as detailed in Hollier-Hann et al.[19] To assess the impact of this on the technical team's preferred base case, the ERG implemented a scenario analysis in which botulinum toxin A is administered by nurse specialists. The results are presented in Section 3.2.2.

3 ERG ADDITIONAL ANALYSES

3.1 Probabilistic results

To reflect uncertainty in the technical team's preferred base case assumptions, the ERG performed a probabilistic sensitivity analysis, running 5,000 iterations of the economic model.

3.1.1 Episodic Migraine

In the episodic migraine population, the mean probabilistic ICER of galcanezumab compared to BSC was £22,573 per quality adjusted life-year (QALY, see Table 2). The probability of galcanezumab being cost-effective at a threshold of £20,000 and £30,000 is [redacted] and [redacted], respectively. The cost-effectiveness acceptability curve (CEAC) showing the probability of galcanezumab being cost-effective at a range of thresholds can be seen in Figure 1. The results show that there remains a small degree of uncertainty regarding the cost-effectiveness of Galcanezumab at a threshold of £20,000 to £30,000.

Table 2 Probabilistic results of Technical Team's preferred base case (Episodic migraine, vs BSC)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,573

Figure 1 Cost-effectiveness acceptability curve (Episodic migraine vs BSC)

3.1.2 Chronic migraine

The pairwise probabilistic results of the economic analysis for chronic migraine are presented for both galcanezumab vs BSC and galcanezumab vs Botulinum toxin A. As outlined in the ERG report (Section 4.2.6.2), the company model does not present the chronic migraine results as a fully incremental analysis, in which the cost-effectiveness of BSC, galcanezumab and botulinum toxin A

are compared together. The ERG considers this a significant limitation of the model. Owing to time constraints, the ERG is unable to generate probabilistic results of a fully incremental analysis. Results are therefore only presented for the pairwise analyses.

3.1.2.1 Chronic migraine vs. BSC

In the chronic migraine vs. BSC population, the mean probabilistic ICER of galcanezumab compared to BSC was £8,838 per QALY (see Table 3Table 2). The probability of galcanezumab being cost-effective at a threshold of £20,000 and £30,000 is [redacted] and [redacted], respectively. The CEAC showing the probability of galcanezumab being cost-effective at a range of thresholds can be seen inFigure 1 Figure 2.

Table 3 Probabilistic results of Technical Team's preferred base case (Chronic migraine, vs BSC)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]			
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,838

Figure 2 Cost-effectiveness acceptability curve (Chronic migraine vs BSC)

[redacted]

3.1.2.2 Chronic migraine vs. Botulinum toxin A

In the chronic migraine vs. Botulinum toxin A population, the mean probabilistic ICER of galcanezumab compared to BSC was £16,922 per QALY (see Table 4Table 2). The probability of galcanezumab being cost-effective at a threshold of £20,000 and £30,000 is [redacted] and [redacted], respectively. The CEAC showing the probability of galcanezumab being cost-effective at a range of

thresholds can be seen inFigure 1 Figure 3. As can be seen from Figure 3, the cost-effectiveness of galcanezumab is subject to considerable uncertainty and there is a non-negligible risk that the ICER in this population is greater than the typical thresholds of £20 to £30k per QALY gained.

Table 4 Probabilistic results of Technical Team's preferred base case (Chronic migraine, vs Botulinum toxin A)

Treatment	Total cost	Total life years	Total QALYs	Incremental Cost	Incremental QALY	ICER
Galcanezumab 120mg	[redacted]	[redacted]	[redacted]			
Botulinum toxin type A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,922

Figure 3 Cost-effectiveness acceptability curve (Chronic migraine vs Botulinum toxin A)

3.2 Scenario Analyses

3.2.1 Additional galcanezumab monitoring costs

For parity with previous appraisals,[2] treatment monitoring was assumed to require a 15-minute appointment with a consultant every 6 months (unit cost of £27.25).[20] This was adjusted to a per cycle cost of £4.54 for patients responding to galcanezumab.

The results of this scenario on the technical team's preferred assumptions for episodic migraine resulted in a small increase in the ICER, from £22,663 to £23,211. For the full results, see Table 5.

The results of this scenario on the technical team's preferred assumptions for CM, showed increases in the ICERs for comparison with BSC (£8,796 to £9,062) and botulinum toxin A (£15,636 to £16,776). The full results of the pairwise and fully incremental analyses can be seen in Table 6. Note

these results are exclusive of confidential commercial medicine unit (CMU) discount for botulinum toxin A. Results inclusive of this discount are include in a confidential appendix.

3.2.2 Nurse-led botulinum toxin A administration

A nurse-led administration cost of £28.25 was used and was taken from the Personal Social Services Research Unit.[20] This was based on 15 minutes of patient contact time of a Band 6, hospital-based nurse as per Hollier-Hann et al.[19] Appointments were assumed to happen at the same frequency as those with a consultant neurologist. For the purpose of this scenario, it is assumed that this is the approach taken in 100% of UK treatment centres. The result of this scenario on the technical team's preferred base case is an increase in the ICER of galcanezumab compared to botulinum toxin A in the chronic migraine population from £15,636 to £22,579. The full results of the pairwise and fully incremental analyses can be seen in Table 6 and Table 7, respectively. Note these results are exclusive of CMU discount for botulinum toxin A. Results inclusive of this discount are include in a confidential appendix.

The ERG considers this an illustrative analysis given the assumption of neurologist-led administration included in the company, ERG and technical team's base case matches the assumption included in the appraisals of erenumab and fremanezumab.[1, 2] In addition, the ERG considers the ICER to be overestimated as the assumptions that all patients would have galcanezumab administered by a nurse and that all appointments are 15 minutes are strong assumptions. In reality, there may be difficult to treat patients requiring a neurologist and patients may require up to 30 minutes appointments.[21]

Table 5 Additional exploratory ERG analyses (episodic migraine)

Analysis	Discounted costs		Discounted QALYs		ICER	Change from company base case ICER
	Galcanezumab	BSC	Galcanezumab	BSC		
Technical team's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	£22,633	-
6-monthly Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	£23,211	+ £578

Table 6 Additional exploratory ERG analyses - Chronic migraine pairwise analyses (separate models for comparison to BSC and botulinum toxin)

Analysis	Comparator	Discounted Costs		Discounted QALYs		Pairwise	
		Galcanezumab	Comparator	Galcanezumab	Comparator	ICER	Change from technical team's base case
Technical team's preferred base case	**BSC**	[redacted]	[redacted]	[redacted]	[redacted]	£8,796	-
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£15,636	-
6-month monitoring costs	**BSC**	[redacted]	[redacted]	[redacted]	[redacted]	£9,062	+ £266
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£16,776	+£1,140
Nurse-led botulinum toxin A administration	**BSC**	[redacted]	[redacted]	[redacted]	[redacted]	£8,796	-
	Botulinum toxin A	[redacted]	[redacted]	[redacted]	[redacted]	£22,579	+ £6,943

Table 7 Additional exploratory ERG analysis - Chronic migraine fully incremental analyses (separate models for comparison to BSC and botulinum toxin)

Analysis	Discounted Costs			Discounted QALYs			Incremental ICER (Galcanezumab)	Change from technical team's base case
	BSC	Botulinum toxin A	Galcanezumab	BSC	Botulinum toxin A	Galcanezumab		
Technical team's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,636	-
6-month monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,776	+£1,140
Nurse-led botulinum toxin A administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,579	+ £6,943

References

1. National Institute for Health and Care Excellence. *Erenumab for preventing migraine. Final appraisal document*. London: NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/html-content-2

2. National Institute for Health and Care Excellence. *Fremanezumab for preventing migraine. Final appraisal document [ID1368]*. NICE; 2020. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10339/documents [accessed 17th April 2020].

3. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;**38**:1-211. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29368949

4. National Institute for Health and Care Excellence. *Galcanezumab for preventing migraine [ID1372]*. London: NICE; 2020.

5. National Institute for Health and Care Excellence. *Single Technology Appraisal. Appeal Hearing. Advice on erenumab for preventing migraine [ID1188]* NICE; 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10302/documents/appeal-decision [accessed 20th April 2020].

6. Ailani J, Pearlman E, Zhang Q, Nagy AJ, Schuh K, Aurora SK. Positive response to galcanezumab following treatment failure to onabotulinumtoxinA in patients with migraine: post hoc analyses of three randomized double-blind studies. *Eur J Neurol* 2019;**27**:542-9.

7. Paget M-A, Tockhorn-Heidenreich A, Belger M, Chartier F, Lanteri-Minet M. EPO3109: Generalisability of the CONQUER trial results to routine clinical practice: galcanezumab versus placebo in patients with inadequately controlled migraine. *Eur J Neurol* 2020;**27**:1082.

8. Scottish Medicines Consortium. *2nd resubmission. Botulin toxin A 50 Allergan units, 100 Allergan units, 200 Allergan units, powder for solution for injection (Botox). SMC No 692/11*. Glasgow: SMC; 2017.

9. Andreou AP, Trimboli M, Al-Kaisy A, Murphy M, Palmisani S, Fenech C, et al. Prospective real-world analysis of OnabotulinumtoxinA in chronic migraine post-National Institute for Health and Care Excellence UK technology appraisal. *Eur J Neurol* 2018;**25**:1069-e83.

10. Merikangas KR, Cui L, Richardson AK, Isler H, Khoromi S, Nakamura E, et al. Magnitude, impact, and stability of primary headache subtypes: 30 year prospective Swiss cohort study. *BMJ* 2011;**343**:d5076.

11. Hagen K, Kristoffersen E, Winsvold B, Stovner L, Zwart J. Remission of chronic headache: An 11-year follow-up study. Data from the Nord-Trøndelag Health Surveys 1995–1997 and 2006–2008. *Cephalagia* 2018;**38**:2026-34.

12. Bigal M, Lipton R. The prognosis of migraine. *Curr Opin Neurol* 2008;**21**:301-8.

13. Lyngberg A, Rasmussen B, Jørgensen T, Jensen R. Prognosis of migraine and tension-type headache: a population-based follow-up study. *Neurology* 2005;**65**:580-5.

14. European Medicines Agency. *EMGALITY (galcanezumab). United Kingdom. Summary of Product Characteristics*. 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/emgality-epar-product-information_en.pdf [accessed 16th March 2020].

15. Lampl C, Thomas H, Stovner LJ, Tassorelli C, Katsarava Z, Lainez JM, et al. Interictal burden attributable to episodic headache: findings from the Eurolight project. *J Headache Pain* 2016;**17**:9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26879832

16. Steiner TJ, Stovner LJ, Katsarava Z, Lainez JM, Lampl C, Lantéri-Minet M, et al. The impact of headache in Europe: principal results of the Eurolight project. *The journal of headache and pain* 2014;**15**:31-. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24884549

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4045992/

17. Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, Tierce J, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2009;**49**:498-508. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19245386

18. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain* 2018;**19**:82. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30203163

19. Hollier-Hann G, Curry A, Onishchenko K, Akehurst R, Ahmed F, Davies B, et al. Updated cost-effectiveness analysis of onabotulinumtoxinA for the prevention of headache in adults with chronic migraine who have previously received three or more preventive treatments in the UK. *J Med Econ* 2020;**23**:113-23.

20. Curtis L, Burns A. *Unit Costs of Health and Social Care 2019*. Canterbury, Kent: Personal Social Services Research Unit, University of Kent 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/

21. Jones S, Zermansky A, Szpakowski J, Button P, Button J. Improved efficiency of a nurse–led Migraine Botox service by implementation of a 'lean' management approach. *Cephalalgia* 2017;**37**.