Single Technology Appraisal

Eptinezumab for preventing migraine [ID3803]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Eptinezumab for preventing migraine [ID3803]

Contents:

The following documents are made available to stakeholders:

Access the final scope and final stakeholder list on the NICE website.

1. **Company submission** from Lundbeck
   a. Submission
   b. Cost comparison submission

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Migraine Trust
   b. Association of British Neurologists Headache and Pain Advisory Group
   c. British Association for the Study of Headache (BASH)

4. **Expert personal perspectives from:**
   a. Ria Bhola, Headache Nurse - Patient Expert nominated by the Migraine Trust
   b. Steph Weatherley. Information advisor - Patient Expert nominated by the Migraine Trust

5. **External Assessment Report** prepared by School of Health and Related Research (ScHARR)

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Eptinezumab for preventing migraine [ID3803]

Document B

Company evidence submission

August 2022

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ID3803_Lundbeck Eptinezumab_ STA Document B	1.0	Yes	18 August 2022

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Abbreviations

Abbreviation	Definition
AE	Adverse event
Anti-CGRPs	Anti-calcitonin gene-related peptides
BASH	British Association for the Study of Headache
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CrI	Credible interval
CM	Chronic migraine
EM	Episodic migraine
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FAS	Full analysis set
HFEM	High-frequency episodic migraine
HIT-6™	6-item Headache Impact Test
HR	Hazard ratio
HRQL	Health-related quality of life
HUNT	Norwegian Nord-Trøndelag Health
ICHD-3	International Classification of Headache Disorders (third edition)
IgG1	Immunoglobulin G1
IHS	International Headache Society
IMP	Investigational medicinal product
iNHB	Incremental net health benefit
iNMB	Incremental net monetary benefit
ITC	Indirect treatment comparison
IV	Intravenous
LFEM	Low-frequency episodic migraine
MAST	Migraine in America Symptoms and Treatment
MCS	Mental component summary
MHD	Monthly headache days
MHRA	Medicines and Healthcare products Regulatory Agency
MIDAS	Migraine Disability Assessment test
MMD	Monthly migraine days
MOH	Medication-overuse headache
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire version 2.1
NHS	National Health Service
NMA	Network meta-analysis
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PCS	Physical component summary

Abbreviation	Definition
PSA	Probabilistic sensitivity analysis
RCT	Randomised controlled trial
SF-36®	36-item Short Form Health Survey
SF-6D®	Short Form Six-Dimension
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
WPAI	Work Productivity and Activity Impairment
YLD	Years lost to disabilities

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication. A summary of how the decision problem is addressed by this submission is presented 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 who have at least 4 migraine days per month	Adults with migraine who have at least 4 migraine days per month and after at least 3 preventive drug treatments have failed	Lundbeck has focused on the population that is eligible for treatment with current anti-CGRP therapies
Intervention	Eptinezumab	As per scope	N/A
Comparator(s)	• Oral preventive treatments (such as topiramate, propranolol and amitriptyline) • Erenumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed) • Galcanezumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed) • Fremanezumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed) • Botulinum toxin A (in chronic migraine that has not responded to at least 3 prior pharmacological prophylaxis therapies) • Best supportive care	• Erenumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed) • Galcanezumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed) • Fremanezumab (4 or more migraine days per month and after at least 3 preventive drug treatments have failed) • Botulinum toxin A (in chronic migraine that has not responded to at least 3 prior pharmacological prophylaxis therapies) • Best supportive care	Oral preventive treatments were not considered a relevant comparator, consistent with previous anti-CGRP therapy appraisals. In the fremanezumab appraisal, clinicians advised that patients would have had 3 prior oral treatments, and these should have been explored before considering specialist treatments such as anti-CGRPs and botulinum toxin A[1]
Outcomes	The outcome measures to be considered include: • Frequency of headache days per month • Frequency of migraine days per month • Severity of headaches and migraines	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• 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		
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 The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be long enough 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 considered	As per the NICE reference case. In addition to the NICE reference case presented in the main submission, there is a scenario for a cost comparison in the appendices (Appendix M)	Following discussions with NICE at the decision problem meeting, we believe that this treatment may be a candidate for cost comparison. We have therefore presented this scenario in the appendices to help the Committee with its decision-making
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People with EM or CM	Lundbeck will provide a subgroup analysis for people with EM and CM The submission will focus on patients with 4 or more migraine days per	Lundbeck has aligned a subgroup analysis with the available data for a robust analysis and this is in line with previous NICE appraisals.[1-3]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Subgroups defined by the number of previous preventive treatments • Subgroups defined by the frequency of EM 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.	month after at least 3 prior preventive drug treatments have failed Scenario analyses of patients for whom 2 prior preventive treatments have failed will also be provided Subgroups defined by the frequency of EM will not be provided	High-frequency EM has not been recognised as a distinct subgroup by clinicians consulted in previous appraisals, so it has not been included[1-3]
Key: CGRP, calcitonin gene-related peptide; CM, chronic migraine; EM, episodic migraine; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.			

B.1.2. Description of the technology being appraised

A description of eptinezumab (Vyepti®) is presented in Table 2. The summary of product characteristics (SmPC) and the European Public Assessment Report (EPAR) are presented in Appendix C. The UK public assessment report is not currently available; as such the EPAR has been provided instead.

Table 2: Technology being evaluated

UK approved name and brand name	Eptinezumab (Vyepti®)
Mechanism of action	Eptinezumab is a humanised immunoglobulin G1 (IgG1) antibody that binds to α- and β- forms of the human calcitonin gene-related peptide (CGRP) ligand with low picomolar affinity (4 and 3 pM Kd, respectively). The complex eptinezumab-CGRP cannot bind to the receptor which results in the biological effects of circulating CGRP being blocked in humans. It is administered as a 30-minute intravenous infusion, so it has 100% bioavailability and maximum blood concentrations after 30 minutes.[4] As a result, eptinezumab prevents the activation of the CGRP receptors and the resultant downstream cascade of physiological events linked to initiation, frequency and severity of migraine attacks.[4] Eptinezumab is highly selective and does not bind to any of the related neuropeptides: amylin, calcitonin, adrenomedullin or intermedin.[4]
Marketing authorisation/CE mark status	Eptinezumab received marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) on 26 January 2022,[5] and from the European Medicines Agency (EMA) on 24 January 2022[6] for the prophylaxis of migraine in adults who have at least 4 migraine days per month.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Indication** Indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.[5] **Contraindications** Hypersensitivity to the active substance or to any of the excipients: sorbitol, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, water for injection.[5] **Special warnings and precautions for use** • Patients with a history of cardiovascular disease (hypertension, ischaemic heart disease) were excluded from clinical studies. Limited safety data are available in patients with cardiovascular risk factors such as diabetes, circulatory diseases and hyperlipidaemia[5] • Patients with a history of neurological diseases or psychiatric conditions that were uncontrolled and/or untreated were excluded from clinical studies. Limited safety data are available in these patients[5]

	• Serious hypersensitivity reactions, including anaphylactic reactions, have been reported and may develop within minutes of the infusion. Most hypersensitivity reactions occurred during infusion and were not serious. In the event of a serious hypersensitivity reaction, eptinezumab should be discontinued immediately and appropriate therapy initiated. If the hypersensitivity reaction is not serious, continuation of further treatment with eptinezumab is at the discretion of the treating physician, taking into account the benefits and risks for the individual patient[5] • Patients with hereditary fructose intolerance must not be given this medicinal product unless strictly necessary. A detailed history about hereditary fructose intolerance symptoms must be taken for each patient before eptinezumab is administered[5] • There is limited data from the use of eptinezumab in pregnant women, and human IgG is known to cross the placental barrier; eptinezumab may therefore be transmitted from the mother to the developing foetus. As a precautionary measure, it is preferable to avoid use of eptinezumab during pregnancy[5]
Method of administration and dosage	Administered as a 30-minute intravenous infusion every 12 weeks. The recommended dose is 100 mg.[5] Eptinezumab can be administered as a 300 mg dose, but a 300 mg vial is not available and will not be commercialised in the UK.
Additional tests or investigations	A detailed history about hereditary fructose intolerance must be taken for each patient before they are given this medicinal product.[5]
List price and average cost of a course of treatment	£1,350 per 100 mg vial
Patient access scheme (if applicable)	[redacted]

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

B.1.3.1. Disease overview

Migraine is a highly prevalent neurovascular disorder characterised by recurrent episodes of primary headache.[7] Often chronic in nature, it is ranked in the top 10 causes of disability among people aged 10–49 years in the Global Burden of Disease study (1990–2019).[8]

B.1.3.1.1. Pathophysiology of migraine

The pathophysiology of migraine is complex and involves multiple areas of the brain, and the activation of trigeminovascular pain pathways.[9] The neuropeptide calcitonin gene-related peptide (CGRP), which is found in trigeminal ganglion neurons, has been implicated in the pathophysiology of migraine and its symptoms through several mechanisms.[9]

Anti-calcitonin gene-related peptides (anti-CGRP; eptinezumab, fremanezumab, and galcanezumab) and anti-CGRP receptor antibodies (erenumab) have demonstrated the therapeutic potential of blocking CGRP signalling to prevent migraine.

B.1.3.1.2. Classification of migraine

Patients with migraine are diagnosed with migraine with or without aura, or chronic migraine (CM), based on criteria published by the International Headache Society (IHS) International Classification of Headache Disorders (third edition; ICHD-3; Table 3).[7] While episodic migraine (EM) is not an ICHD-3 diagnostic term, patients are classified as having EM or CM throughout this submission, based on migraine attack frequency.

Table 3: ICHD-3 diagnostic criteria for migraine with aura, migraine without aura and chronic migraine

Migraine without aura	A. ≥ five attacks fulfilling criteria B–D B. Headache lasting 4–72 hours (untreated or unsuccessfully treated) C. Headache with ≥ two of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate/severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity D. During headache experience of ≥ one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
Migraine with aura	A. ≥ two attacks fulfilling criteria B and C B. ≥ one of the following fully reversible aura symptoms: visual; sensory; speech and/or language; motor; brainstem; retinal C. ≥ three of the following: ≥ one aura symptom spreads gradually over ≥ 5 minutes; two or more aura symptoms last 5–60 minutes; ≥ one aura symptom is unilateral; ≥ one aura symptom is positive; the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis
Chronic migraine	A. Headache (migraine-like or tension-type-like) on ≥ 15 days/month for > 3 months B. Occurring in a patient who has had ≥ 5 attacks fulfilling criteria B–D for migraine without aura and/or criteria B and C for migraine with aura C. Headache on ≥ 8 days/month for > 3 months fulfilling any of the following: criteria C and D for migraine without aura; criteria B and C for migraine with aura; 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
Key: ICHD-3, International Classification of Headache Disorders (third edition) **Notes:** Migraine with or without aura diagnostic criteria refer to patients with episodic migraine. **Source:** International Headache Society (2018)[7]	

Based on the ICHD diagnostic criteria, EM can be defined as ≤ 14 headache days per month with ≥ 4 monthly migraine days (MMD), and CM can be defined as ≥ 15 headache days per month with ≥ 8 MMDs.

EM can be further categorised based on the frequency of migraine headache days per month: low-frequency episodic migraine (LFEM) is defined as < 8 days of migraine attacks per month, and high-frequency episodic migraine (HFEM) is defined as 8–14 days of migraine attacks per month.[10] Despite being categorised as having

EM, patients with HFEM differ from those with LFEM, and are more similar to patients with CM in terms of chronicity, disability and overall prevalence of comorbidities.[10, 11]

CM is further complicated by medication-overuse headache (MOH), with 40–70% of patients with CM also experiencing MOH.[12, 13] The IHS describes MOH as headache occurring on ≥ 15 days/month in a patient with a pre-existing primary headache, and developing MOH as a consequence of regular overuse of acute or symptomatic headache medication (on ≥ 10 or ≥ 15 days/month, depending on the medication) for > 3 months.[7] It may resolve when the medication is no longer being overused.

B.1.3.1.3. Natural history and changes in migraine frequency over time

Patients with migraine transition between EM and CM interchangeably. A large US study estimating the prevalence of CM conducted follow-up visits at 3-monthly intervals and found that headache characteristics changed substantially over the course of a year. Almost three-quarters of patients (73.4%) with CM at baseline, and who had attended four or five follow-up visits, experienced at least one 3-month period in which they did not meet the ≥ 15 monthly headache days (MHD) criteria for CM.[14]

Risk factors that can lead to increases in migraine frequency include hormonal fluctuations (such as the onset of menopause[15]), ineffective acute treatment[7, 16], obesity, craniomandibular disorders and psychological factors.[17]

Migraine chronification (the progression from EM to CM) can occur in around 3% of patients per year.[18, 19] However, rates of up to 14% have been reported in speciality headache clinics.[20]

Patients with CM can also experience remission to EM or other headache conditions, but remission rates vary. In the American Migraine Prevalence and Prevention study, one-quarter (26.1%) of patients with CM at baseline (n = 100) had ‘remitted CM’. This meant that they had other headache conditions such as LFEM, no headache, probable migraine, episodic tension-type headache, or other episodic headache in subsequent years.[21] A longitudinal cohort study using historical data from the Norwegian Nord-Trøndelag Health (HUNT) study provided 11 years of follow-up data on remission rates of chronic headache (defined as ≥ 15 headache days/month

during the last year).[22] Remission (defined as no headache or < 15 headache days per month) was observed in almost three-quarters of respondents (74.7%; n = 452). Patients with MOH were significantly less likely to experience remission than those without MOH (65.4% versus 81.5%; p < 0.001).[22]

In UK clinical practice, patients with migraine who receive effective treatment with oral preventive therapies are recommended gradual withdrawal after 6–12 months.[7, 23, 24] However, it is unclear what impact this has on the natural history of migraine. This recommendation is based on evidence from studies of topiramate demonstrating improved chances of sustained benefit following drug withdrawal, if treatment is maintained for at least 6–12 months before a treatment break.[25]

B.1.3.2. Epidemiology

Migraine has a prevalence of > 1.3 billion people, with > 110,000 people affected worldwide per year (estimation from 2017).[26]

Almost 6 million people in the UK are estimated to experience migraine attacks, with 190,000 migraine attacks occurring every day, according to a telephone survey of a random sample (n = 4,007) of individuals aged 18–65 years in England.[27] In England in 2019, age-standardised prevalence and incidence rates were reported as 14.72% of total prevalent cases and 0.26% of total new cases, respectively.[28] The prevalence peak is observed during the prime productive years (30–49 years[29, 30]), and decreases with age regardless of gender. Migraine is more common in women than men, with 18.3% of female respondents versus 7.6% of male respondents experiencing migraine within the last year.[27]

There is a lack of data regarding the relative prevalence of EM and CM, which is potentially driven by the transitioning natural history of migraine as described in Section B.1.3.1.3. Two large studies conducted in the US found that 6.8–8.8% of patients with migraine met CM criteria.[10, 31] It is therefore estimated that EM accounts for the remaining 91.2–93.2% of patients.[10, 31]

B.1.3.3. Burden of disease

B.1.3.3.1. Clinical burden

A migraine typically presents as a moderate-to-severe, unilateral, throbbing pain aggravated by routine activity and accompanied by nausea, photophobia and phonophobia, and/or cutaneous allodynia.[7] In the cross-sectional, observational Migraine in America Symptoms and Treatment (MAST) study, 64.9% of the 6,045 respondents reported experiencing nausea, photophobia and phonophobia, with 49.1% of respondents reporting photophobia as their most bothersome symptom.[32]

Patients with migraine often experience comorbidities that further contribute to the overall burden of migraine. In the MAST study, patients with migraine (n = 15,133) were significantly more likely to report insomnia, depression and anxiety, compared with people without migraine (n = 77,453; $p < 0.001$).[33] Several studies have demonstrated an association between increasing migraine attack frequency and increased risk of experiencing sleep-related problems, depression and anxiety.[10, 32-36] In a study of 11,266 people living with migraine worldwide, 85% of people with migraine said they felt helpless, depressed or misunderstood, and 83% had trouble sleeping because of their migraines.[37]

In addition to the comorbidities, migraine has been highlighted as an independent risk factor for suicidal behaviours, even after adjusting for psychiatric conditions. Increases in pain severity, intensity and frequency have increased the risk of suicidal activity among patients with migraine.[38] In an English cohort study of 147,330 people admitted to hospital with migraine from 1999 to 2011, compared with a reference cohort, migraine significantly increased the risk of suicide (relative risk: 1.3; 95% CI [confidence interval]: 1.0, 1.8).[39]

B.1.3.3.2. Humanistic burden

Migraine has a substantial societal cost as it affects patients' ability to work and/or learn effectively, with subsequent detrimental effects on their career and financial stability.[40, 41] In a longitudinal, web-based US study, around 50% (48.2–57.4%) of respondents with migraine reported reduced participation in family activities due to migraine at least once a month, and one-third worried about their family's long-term financial security as a result of their headaches.[42] As headache frequency increased,

respondents were more likely to believe that their condition was hindering their ability to care for their children (LFEM: 29.9%; HFEM: 58.0%; CM: 71.7%).[42]

B.1.3.3.2.1. Health-related quality of life versus non-migraine controls

Patients with migraine experience poorer health-related quality of life (HRQL) compared with non-migraine controls. HRQL was lower in respondents with migraine versus non-migraine controls in a retrospective cross-sectional study using data from the European 2016 National Health and Wellness Survey (n = 80,600 from France, Germany, Italy, Spain, and the UK). The study reported that various HRQL measures were significantly lower in respondents with migraine than those in non-migraine controls ($p < 0.001$) in terms of: the 36-item Short Form Health Survey (SF-36® v2) physical component summary (PCS: 46.00 versus 50.51) and mental component summary scores (MCS: 37.69 versus 44.82); the Short Form Six-Dimension (SF-6D®) health state utility score (0.62 versus 0.71); and EQ-5D® questionnaire scores (0.68 versus 0.81).[29] However, previous NICE appraisals of anti-CGRPs have found that the EQ-5D questionnaire is not sufficiently sensitive enough to capture changes in HRQL caused by migraine because of the lack of recall period, and patients do not usually complete the questionnaire on the day of a migraine.[1 3] An English population-based case-control study also reported reduced HRQL in respondents with migraine versus non-migraine controls, with significant reductions (> 5 points; $p < 0.005$) in SF-36 PCS and MCS scores.[43]

Respondents with migraine who suffered from ≥ 4 MHDs, compared with non-migraine controls, reported significantly ($p < 0.001$) higher levels of absenteeism from work (14.43% versus 9.46%; $p = 0.001$), presenteeism (35.52% versus 20.97%), overall work impairment (38.70% versus 23.27%), and activity impairment (44.17% versus 27.75%).[29]

B.1.3.3.2.2. Health-related quality of life based on headache frequency and migraine type

The detrimental impact of migraine on HRQL and migraine-related disability increases with rising migraine headache frequency.[44, 45] In two multinational web-based surveys, patients with CM reported higher levels of headache-related disability versus patients with EM.[44, 45] In the UK, most respondents with CM (73.7–82.0%)

reported having very severe disability (MIDAS [Migraine Disability Assessment test] Grade IVb).[46, 47]

CM also has a detrimental impact on patients' daily lives, as demonstrated in studies using the 6-item Headache Impact Test (HIT-6™) or the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1). These instruments assess how migraines affect daily social- and work-related activities. The HIT-6 focuses on the impact of headache on such activities, as well as pain severity, fatigue, frustration and difficulty concentrating. The MSQ v2.1 focuses more on how a migraine limits and prevents such activities, and the emotions associated with migraine. The following two studies reported such information:

- Patients with CM (n = 373) experienced a significantly greater adverse headache impact versus patients with EM (n = 6,554) in terms of the mean HIT-6 score (63.7 [severe impact] versus 58.0 [substantial impact]; odds ratio [OR]: 5.88; $p < 0.001$) in the American Migraine Prevalence and Prevention study[34]
- In a web-based survey of participants from Australia, Canada, France, Germany, Italy, Spain, the UK, Taiwan and the US, conducted between February and April 2009, respondents with CM reported significantly ($p < 0.0001$) lower MSQ v2.1 scores versus respondents with EM, even when the scores were adjusted for covariates (age, gender, country, education and comorbidities, including pain, vascular disease risk factors and events, and psychiatric disorders)[11]

Patients with HFEM often report similarly diminished HRQL outcomes as those seen in patients with CM.[10, 48, 49] As treatment decisions are based on headache frequency, patients with HFEM may not receive the same standard of care as those with CM, despite experiencing a similarly poor quality of life.

B.1.3.3.2.3. Health-related quality of life based on the number of preventive therapies used

In a real-world study, 615 physicians provided migraine and preventive treatment history for 5,785 patients in the US and Europe (France, Germany, Spain, Italy, and the UK) between August and December 2017, which highlighted greater migraine-related HRQL burden and disability among who patients received multiple preventive treatments. Preventive-treated patients experienced significantly lower HRQL

compared with preventive-naïve patients, measured by the EQ-5D-5L visual analogue scale (VAS) and the MSQ total score and subscores ($p < 0.0001$, except MSQ role function – preventive [US]: $p < 0.01$). Decreasing HRQL correlated with an increasing number of preventive therapies used.[50]

Additionally, patients treated with 3 or more preventive treatments were more likely to report moderate-to-very-severe disability than patients treated with fewer than 3 preventive treatments, with one-third (US: 35%; Europe: 33%) reporting very severe disability (MIDAS score 41+). In contrast, over half of preventive-naïve patients (US: 65%; Europe: 53%) reported little/no disability (MIDAS score 0–5), and over half of patients treated with one to two preventive therapies had little/no or mild disability (US: 75%; Europe: 57%; MIDAS score 0–10).[50]

B.1.3.3.2.4. Years lost to disabilities

Globally, migraine is the sixth leading cause of years lost to disabilities (YLD; 2017) and is the leading cause of YLD for people aged 15–49 years.[26] Migraine prevalence peaks during prime productive years (30–49 years).[29, 30]

In England, migraine is the fourth leading cause of YLD (647.95 YLD per 100,000), rising to the second leading cause in people aged 15–49 years (935.26 YLD per 100,000).[28]

B.1.3.3.3. Economic burden

Migraine is associated with substantial direct and indirect cost burdens. Direct annual expenditure for adult patients with migraine in England (n = 2,859) was estimated at £4.21 million, including general practitioner and nursing costs at £650,000, and hospitalisation costs at £1.18 million (2015 GBP) according to an observational study.[51]

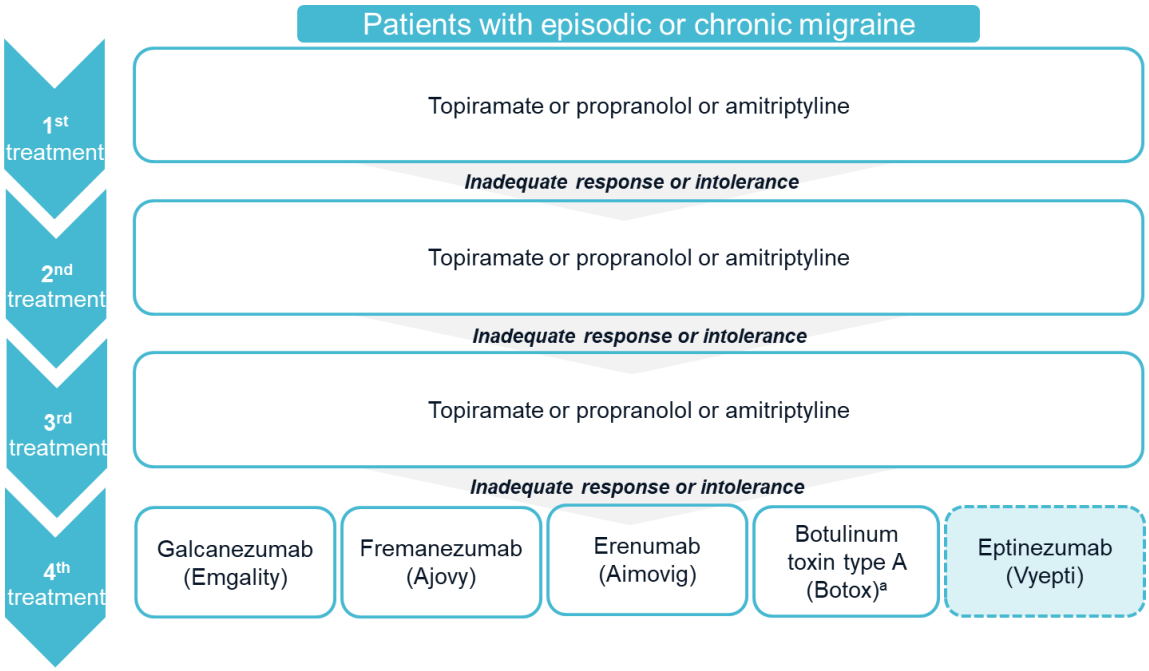
The cost of healthcare for patients with migraine in five European countries (the UK, France, Germany, Italy and Spain) was estimated based on cross-sectional data collected via a web-based survey in the International Burden of Migraine study.[46] Per-patient annual costs were highest in the UK and Spain. CM was associated with higher medical resource use and total costs compared with EM in all countries, indicating that increased headache frequency resulted in increased economic and clinical burden.

Migraine has been associated with increased absenteeism, presenteeism and overall diminished productivity, which burden employees and employers. A study conducted by the Work Foundation estimated that 86 million work days are lost to migraine-related absenteeism and presenteeism in the UK, at a cost of £8.8 billion.[52] A separate study demonstrated that patients for whom multiple lines of preventive treatment have failed experienced a lower reported work productivity, as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire. In a real-world study including patients with migraine in Europe (France, Germany, Spain, Italy and the UK), patients treated with 3 or more preventive migraine treatments had statistically significantly ($p < 0.001$) higher WPAI scores than preventive treatment-naïve patients. These scores indicated higher rates of absenteeism and presenteeism, and greater work productivity and activity impairment.[50]

B.1.3.4. Current pathway of care for prophylaxis in migraine

The current treatment pathway for preventive migraine treatment in patients with EM and CM, according to NICE guidance, is presented in Figure 1.

Figure 1: NICE recommended treatment pathway for migraine prophylaxis



Notes: [a]Botulinum toxin A is recommended for the prophylaxis of migraine in patients with CM only, as per NICE guidance recommendations.[53]
Source: NICE (2012). TA260: Botulinum toxin A for the prevention of headaches in adults with chronic migraine; NICE (2021). CG150: Headaches in over 12s: diagnosis and management; NICE (2020). TA659: Galcanezumab for preventing migraine; NICE (2021). TA682: Erenumab for preventing migraine; NICE (2022). TA764: Fremanezumab for preventing migraine.[1-3, 53, 54]

This treatment pathway is largely based on NICE Clinical Guideline (CG) 150, which recommends topiramate, propranolol or amitriptyline for the prophylactic treatment of migraine, depending on the patient's preference, comorbidities and risk of adverse events (AEs).[54] Further guidance was also reviewed regarding botulinum toxin A (technology appraisal [TA] 260) in CM, and galcanezumab (TA659), fremanezumab (TA764), and erenumab (TA682) as fourth-line preventive treatment options for patients who have tried 3 other preventive treatments that have failed.[1-3, 53]

In England, the British Association for the Study of Headache (BASH) provides guidance for managing migraine and other headache disorders.[23] This guidance provides recommended preventive treatments in EM and CM without indicating a treatment pathway. In addition to the therapies recommended in CG150 and erenumab, fremanezumab, galcanezumab, and botulinum toxin A (CM only), candesartan is recommended as a preventive treatment for EM and CM. However, it is not licensed in the UK.[23, 54] An overview of the recommendations (guidelines and TA recommendations) provided by NICE and BASH is presented in Appendix D.

Lundbeck conducted an advisory board with five UK clinicians (four from England and one from Scotland) on prescribing preferences for patients treated with anti-CGRPs.[55] These clinicians advised that they prescribe anti-CGRPs for any new patients who have tried 3 or more preventive therapies that have failed, and prescribing is based on experience and availability. The clinicians predominantly used erenumab as it was the first anti-CGRP available. The clinicians also clarified that, while subcutaneous fremanezumab is available as a 3-monthly regimen as well as a once-monthly injection, the 3-monthly regimen is not regularly used in the UK. The reason for this is the burden associated with administering three separate injections, and the potential for sub-optimal dosing as a result.

Anti-CGRPs are administered subcutaneously, usually once a month. The first two doses are typically administered by a healthcare professional and, following training from a healthcare professional, patients or caregivers can administer it at home. Clinicians consulted as part of the advisory board conducted by Lundbeck suggested that in some cases (approximately 10%), patients require support with administering subcutaneous therapies, resulting in the need for homecare.[55] They also noted that

patients treated in NHS clinical practice may be placed on waiting lists, creating issues with timely treatment access.[55]

B.1.3.4.1. Proposed positioning of eptinezumab in the treatment pathway

Eptinezumab is positioned throughout this submission as a treatment option for patients with migraine for whom ≥ 3 preventive migraine treatments have failed. These patients face a considerable humanistic and economic burden as described in Sections B.1.3.3.2.3 and B.1.3.3.3.[50] These patients may benefit from having further personalised treatment options at this stage in their treatment journey as described in the National Health Service (NHS) Long Term Plan, and the NHS Headache and Migraine toolkit.[56, 57]

B.1.3.4.2. Limitations of current treatments

Botulinum toxin A is a recommended treatment option for the prevention of CM. However, its use is limited by complex injection requirements (30–40 intramuscular injections at the head and back of the neck) and the risk of serious AEs, such as the spread of toxin effects.[58, 59] It is therefore associated with an unfavourable patient experience which, when coupled with a slow onset of action[60], often results in suboptimal efficacy and/or treatment discontinuation.[61] Access to botulinum toxin A is also limited, as administration requires a healthcare professional fully trained in botulinum toxin A for use in migraine.

The introduction of anti-CGRPs as a new drug class offers multiple advantages as migraine-preventive therapy compared with earlier lines of treatment, including improved tolerability and a significantly reduced AE profile. However, the current anti-CGRP options (galcanezumab, fremanezumab, and erenumab) are limited by their subcutaneous route of administration and monthly administration schedules. A need remains for additional anti-CGRP treatments that offer the potential for improved convenience, rapid onset of action and sustained efficacy, as detailed further below.

B.1.3.4.2.1. Convenience

Results from a US patient preference study of 300 respondents with migraine indicate that patients with migraine who are eligible for preventive treatment prefer fewer injections, with a preference for a once-monthly versus a twice-monthly injection (the treatment and route of administration [i.e. intravenous or subcutaneous] were not specified).[62] There was no significant preference for either oral or injection routes of administration.[62] In an additional US study of patient preferences towards advanced migraine prevention, a discrete choice experiment found that, of five treatment attributes tested in 604 patients, mode of administration and healthcare provider had the highest relative importance (28.8% of patients). Administration setting and frequency of administration were less often selected as the most important attributes (9.9% and 8.8%, respectively). One-fifth of patients (21%) preferred a longer lasting and intravenous treatment given by a healthcare professional, whilst another 22% favoured self-administration and a longer-lasting treatment.[63] A novel treatment with a less frequent administration burden could offer patients a more convenient option to manage their migraines, with potential benefits extending to increased treatment adherence and improved quality of life.

B.1.3.4.2.2. Rapid onset of action

In a preference-elicitation thresholding study conducted in the US between December 2019 and January 2020 in adults diagnosed with EM or CM, early onset of efficacy for preventing migraine was viewed as favourably as reductions in MMDs in the first month post-treatment.[64] However, delivery by subcutaneous route of administration (as for fremanezumab, galcanezumab, and erenumab) requires time for absorption, which is associated with a loss of active drug or reduced bioavailability.[65] Therefore, to achieve and maintain therapeutic exposure, patients are often treated with higher and/or more frequent doses of these treatments.[65] The current anti-CGRPs each report a long T_{max}, ranging from 4–11 days with erenumab, 5–11 days with fremanezumab, and 7–14 days with galcanezumab.[65] An additional US study of patient preferences about advanced migraine prevention used a discrete choice experiment method, and found that 26% of the total migraine sample (n = 604) prioritised therapies with a more rapid speed of onset.[63] A novel therapy with a rapid onset of action may translate to earlier improvements in HRQL and workplace

productivity for patients who have previously not responded and/or tolerated preventive migraine treatments.

B.1.4. Equality considerations

No equality issues are expected.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant randomised controlled trials (RCTs) describing efficacy and safety of preventive therapies for migraine in patients who have a history of prior preventive treatments failing. The SLR was conducted in May 2020 and updated in March 2022. In total, the SLR identified 680 publications describing 64 RCTs, of which four were eptinezumab studies (including PROMISE-1 and PROMISE-2, detailed in Appendix D, and two Phase II trials), and 60 were studies of relevant comparators (detailed in Appendix D).

Details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are described in Appendix D.

Three additional studies were identified as additional eptinezumab studies known to the manufacturer. These included DELIVER, PREVAIL and RELIEF. DELIVER was not captured in the SLR as primary results were published in June 2022, following the SLR update. PREVAIL was not captured due to its open-label study design, and RELIEF was not captured as it investigated eptinezumab as an acute treatment rather than a preventive treatment.

B.2.2. List of relevant clinical effectiveness evidence

This submission presents data from the following Phase III trials of eptinezumab 100 mg relevant to the population of interest (Table 4):

- **DELIVER**, an RCT that provided evidence on the clinical benefits of eptinezumab versus placebo in patients with EM or CM who have tried previous preventive treatments and had an inadequate response or intolerance

- **PROMISE-1**, an RCT that evaluated the clinical effectiveness and safety of eptinezumab versus placebo in patients with EM
- **PROMISE-2**, an RCT that evaluated the clinical effectiveness and safety of eptinezumab versus placebo in patients with CM

Additionally, two further Phase III studies investigating eptinezumab in patients with migraine were conducted. These studies were either outside the population of interest or used a dose other than the 100 mg dose of interest (Table 4):

- **PREVAIL**, an open-label, single-arm study with 104 weeks of follow-up. This trial provides long-term safety, tolerability and patient-reported outcomes data for eptinezumab 300 mg
  - Although this trial is focused on the 300 mg dose, not the 100 mg dose of interest, the long-term safety data for this higher dose provide supportive evidence for eptinezumab. Given the focus on long-term safety data, the results of this trial are presented in Appendix F
- **RELIEF**, a double-blind, placebo-controlled RCT conducted over 48 hours. This trial evaluated eptinezumab as an acute treatment rather than a preventive treatment for patients with at least a 1-year history of migraine, with 4–15 migraine days in the 3 months before screening (i.e. eligible for preventive treatment)
  - Although this trial was not conducted to support the indication of interest, these data are supportive in terms of the fast onset of migraine relief (time to headache pain freedom). These data are presented in section B.2.6

An additional RCT, Sunlight (NCT04772742), recently completed in May 2022, with a data read-out anticipated in August 2022. This was a Phase III, randomised, double-blind, parallel group, placebo-controlled study of eptinezumab in adult patients with a diagnosis of migraine and MOH. The trial population was predominantly Chinese and included patients with no previous preventive treatment failures. As a result, outcomes from the Sunlight trial have not been included in this submission as they are not representative of UK clinical practice or UK patients, and do not directly support the population of interest.

The following sections (Sections B.2.3–B.2.7) focus on the DELIVER, PROMISE-1 and PROMISE-2 RCTs. Although PROMISE-1 and PROMISE-2 were not used to populate the economic model because they did not comprise the full target

population, the results of these studies provide further support for the clinical effectiveness and safety of eptinezumab. Details of the PROMISE trials' methods and results can be found in Appendix D.

DELIVER, PROMISE-1 and PROMISE-2 provide results for the relevant dose of this submission, 100 mg, and also the higher 300 mg dose. Eptinezumab is only available in a 100 mg vial; a 300 mg vial is not available, and the 300 mg dose is not being commercialised in the UK. No significant differences were observed in efficacy endpoints between the 100 mg and 300 mg doses of eptinezumab.[65] However, for transparency, efficacy and safety results for both doses are provided in sections B.2.6 and B.2.10. Additionally, a lower dose of eptinezumab (30 mg) was investigated in PROMISE-1 only. Results supporting the 30 mg dose are not presented within this submission as it is not a licensed or recommended dose in the UK; pharmacokinetic and exposure-response analysis support 100 mg as the lowest effective dose of eptinezumab.[65]

Table 4: Clinical effectiveness evidence for eptinezumab

Study	DELIVER	PROMISE-1	PROMISE-2	PREVAIL	RELIEF
Study design	Phase III, multicentre, double-blind, placebo-controlled, parallel group RCT	Phase III, multicentre, double-blind, placebo-controlled, parallel group RCT	Phase III, multicentre, double-blind, placebo-controlled, parallel group RCT	Phase III randomised, open-label study with a primary treatment phase (4 eptinezumab infusions 12 weeks apart) followed by secondary treatment phase (< 4 additional eptinezumab infusions 12 weeks apart)	Phase III, multicentre, double-blind, placebo-controlled, parallel group RCT
Population	Patients aged 18–75 years (inclusive) with a diagnosis of migraine (onset ≤ 50 years of age) per IHS ICHD-3 and a history of EM or CM at least 12 months prior to the screening visit, with ≥ 4 migraine days per month within the past 3 months prior to screening and documented evidence of treatment failure in the past 10 years of 2-4 different migraine preventive medications. Patients with a concurrent MOH diagnosis were also included.	Patients aged 18–75 years (inclusive) with a diagnosis of migraine (onset ≤ 50 years of age) per ICHD criteria and a history of migraine for ≥ 12 months with ≤ 14 headache days per month, including ≥ 4 migraine days, in the 3 months prior to screening. Eligible patients were required to have documented ≤ 14 headache days, including ≥ 4 migraine days during the screening period	Patients aged 18–65 years (inclusive) with a diagnosis of migraine (onset ≤ 50 years of age) and history of CM for ≥ 12 months before screening and experienced ≥ 15 to ≤ 26 headache days and ≥ 8 migraine days during the 28-day screening period. Patients with a concurrent MOH diagnosis were also included	Patients aged 18–65 years (inclusive) with a diagnosis of migraine (onset ≤ 50 years of age) and history of CM for ≥ 1 year	Patients aged 18–75 years (inclusive) with ≥ 1 year history of migraine (onset ≤ 50 years of age), with or without aura, per IHS ICHD-3. A typical migraine attack, if untreated, associated with moderate to severe headache pain intensity, and MBS of nausea, photophobia, or phonophobia. Patients with migraine on 4–15 days per month in the 3 months prior to screening, with history of either previous or active use of triptans for migraine,

Study	DELIVER	PROMISE-1	PROMISE-2	PREVAIL	RELIEF
	During the screening period patients with CM must have experienced ≥ 8 migraine days and headache occurring on > 14 days, and patients with EM must have experienced ≥ 4 migraine days and ≤ 14 headache days				and headache free for at least 24 hours prior to onset of a qualifying migraine. On Day 0 patients had a moderate to severe headache associated with at least 1 of the following headache characteristics: pulsating quality, unilaterality, and aggravation by or avoidance of routine physical activity. In addition, they had during the headache at least 1 of: nausea and/or vomiting; photophobia and phonophobia
Intervention(s)	Eptinezumab 100 mg or 300 mg Q12W by IV infusion over 30 (up to 45) minutes	Eptinezumab 30 mg or 100 mg or 300 mg Q12W by IV over 1 hour (±15 minutes)	Eptinezumab 100 mg or 300 mg Q12W by IV infusion over 30 (up to 45) minutes	Eptinezumab 300 mg Q12W by IV infusion over 30 (up to 45) minutes	Eptinezumab 100 mg on Day 0 by IV infusion over 30 (up to 45) minutes
Comparator(s)	Placebo	Placebo	Placebo	NA	Placebo
Indicate if: **study supports application for marketing authorisation**	No	Yes	Yes	Yes	No

Study	DELIVER	PROMISE-1	PROMISE-2	PREVAIL	RELIEF
study used in economic model	Yes	No	No	No	No
Rationale if study not used in the model	N/A	Trial evaluated eptinezumab in only part of the population described in the decision problem (EM only) and patient histories were not recorded to a detailed enough extent to be able to ascertain how many previous treatment failures study entrants had had; therefore, we could not derive the population of interest, i.e. patients with EM or CM who had ≥ 3 prior preventive treatment failures	Trial evaluated eptinezumab in only part of the population described in the decision problem (CM only) and patient histories were not recorded to a detailed enough extent to be able to ascertain how many previous treatment failures study entrants had had; therefore, we could not derive the population of interest, i.e. patients with EM or CM who had ≥ 3 prior preventive treatment failures	Trial evaluated eptinezumab in only part of the population described in the decision problem (CM only), and at the 300 mg dose	Trial evaluated eptinezumab in an acute setting, rather than as a preventive therapy
Reported primary and secondary outcomes specified in the decision problem	<u>Primary outcome</u> • **Change from baseline in MMDs (Weeks 1 to 12)** <u>Secondary outcomes</u> • Change from baseline in MMDs (Weeks 13 to 24)	<u>Primary outcome</u> • Change from baseline in MMDs (Weeks 1 to 12) <u>Secondary outcomes</u> • Change in acute migraine medication days	<u>Primary outcome</u> • Change from baseline in MMDs (Weeks 1 to 12) <u>Secondary outcomes</u> • HIT-6 • Acute migraine medication usage	<u>Safety outcomes</u> • AEs	<u>Safety outcomes</u> AEs

Study	DELIVER	PROMISE-1	PROMISE-2	PREVAIL	RELIEF
	• Change from baseline in MHDs (Weeks 1 to 12) • Change from baseline in the percentage of migraines with severe pain intensity (Weeks 1 to 12) • Change from baseline in the number of monthly days with use of acute migraine medication (Weeks 1 to 12; 13 to 24) • Change from baseline in the number of MMDs with use of acute medication (Weeks 1 to 12; 13 to 24) • Change from baseline in number of monthly migraine headache hours (post-hoc analysis) • Health-related quality of life outcomes (HIT-6, MSQ)	<u>Safety outcomes</u> • AEs	<u>Safety outcomes</u> • AEs		

Study	DELIVER	PROMISE-1	PROMISE-2	PREVAIL	RELIEF
	Safety outcomes • **AEs**				
All other reported primary and secondary outcomes	Secondary outcomes • Migraine on the day after first dosing • Change from baseline in the number of MMDs in patients with MOH (Weeks 1 to 12) *Response* • **≥ 50% reduction from baseline in MMDs (Weeks 1 to 12;** 13 to 24) • ≥ 75% reduction from baseline in MMDs (Weeks 1 to 12; 13 to 24) • ≥ 5-point reduction from baseline to Week 12 and Week 24 in HIT-6 score	Secondary outcomes • Migraine on the day after first dosing • Time to migraine after first dosing *Response* • 75% migraine responder rate (Weeks 1 to 12) • 50% migraine responder rate (Weeks 1 to 12)	Secondary outcomes • Migraine on the day after first dosing • Reduction in migraine prevalence from baseline to week 4 • Time to migraine after first dosing *Response* • 75% migraine responder rate (Weeks 1 to 12) • 50% migraine responder rate (Weeks 1 to 12)		Co-primary outcomes • Time to headache pain freedom • Time to absence of MBS

Key: AE, adverse event; CM, chronic migraine; ECG, electrocardiogram; EM, episodic migraine; HCRU, healthcare resource utilisation; HIT-6, 6 item Headache Impact Test; ICHD-3, International Classification of Headache Disorders (3rd edition); IHS, International Headache Society; IV, intravenous; MBS, most bothersome symptom; MHD, monthly headache day; MMD, monthly migraine day; MOH, medication overuse headache; MSQ, Migraine-Specific Quality of Life; N/A, not applicable; PGIC, Patient Global Impression of Change; Q12W, every 12 weeks; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.
Notes: Outcomes in **bold** are those directly used in the economic modelling.

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

A summary of the methods used in DELIVER is presented in Table 5.

Table 5: Summary of DELIVER methods

Trial	**NCT04418765 (DELIVER)**
Location	96 sites across Belgium: 4; Bulgaria: 6; Czech Republic: 14; Denmark: 2; Finland: 4; France: 6; Georgia: 9; Germany: 6; Hungary: 2; Italy: 3; Poland: 18; Russian Federation: 1; Slovakia: 4; Spain: 8; Sweden: 1; UK: 5 and US: 3
Trial design	Phase III, multicentre, randomised, double-blind, parallel, placebo-controlled The study consisted of: • Screening period: 28- to 30-day period prior to randomisation • Placebo-controlled period: 24-week double-blind treatment period • Extension period: 48-week dose-blinded period with eptinezumab after completion of the placebo-controlled period
Trial intervention and comparator drugs	• Eptinezumab 100 mg (n = 299) or 300 mg (n = 294), concentrate for solution for infusion 100 mg/mL, added to 100 mL 0.9% saline solution, IV • Placebo (n = 299): 100 mL of 0.9% saline solution, IV
Permitted and disallowed concomitant medication	Concomitant medications were permitted with restrictions: • Acute treatment of migraine (prescription or over-the-counter medication recommended by a healthcare professional) was permitted, provided the dose had been stable for ≥ 12 weeks prior to screening • Barbiturates and prescription opiates were allowed for ≤ 4 days per month, provided the patient had been on a stable regimen (< 4 days per month) for at least 12 weeks prior to screening • Hormonal therapy (e.g., contraceptives, hormone replacement therapy) permitted if the dose had been stable for at least 12 weeks prior to screening • Non-pharmacological interventions including cognitive behavioural therapy were permitted provided use had been stable for at least 12 weeks prior to screening • Anti-impotence agents were allowed if the dose had been stable for ≥ 12 weeks prior to screening

Trial	NCT04418765 (DELIVER)
	Disallowed medications were as follows: • Preventive migraine treatment use <1 week prior to the screening visit and during the study was not permitted. This included daily use of beta-blockers (propranolol, metoprolol), anticonvulsants (topiramate, valproate, divalproex), tricyclics (amitriptyline), calcium channel blocker (flunarizine), angiotensin II receptor antagonist (candesartan), medication locally approved for the prevention of migraine. Other medications in the same classes but not included in this list were allowed. • Oral anti-CGRPs for acute treatment <4 weeks prior to screening and during the study were not allowed • Use of eptinezumab or other monoclonal antibody targeting the CGRP pathway <24 weeks prior to screening and during the study was not allowed • Patients for whom a previous anti-CGRP treatment failed were disallowed in the study • Botulinum toxin A for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck were prohibited from 4 months prior to screening and during the study • Devices, neuromodulation, neurostimulation or injectable therapy for headache preventive treatment were prohibited 2 months prior to screening and during the study • Monoamine oxidase inhibitors, ketamine, methysergide, methylergonovine, and nimesulide were prohibited within 3 months prior to screening and during the study • Any investigational drugs were not permitted within 30 days or 5 plasma half-lives (whichever is longest) prior to screening
Primary outcome	Change from baseline in the number of MMDs during Weeks 1 to 12
Other outcomes used in the economic model/specified in the scope	<u>Secondary outcomes</u> • Change from baseline in MMDs (Weeks 13 to 24) • Change from baseline in MHDs (Weeks 1 to 12) • Change from baseline in the percentage of migraines/headache with severe pain intensity (Weeks 1 to 12) • Change from baseline in the number of monthly days with use of acute migraine medication (Weeks 1 to 12) • Change from baseline in the number of monthly days with use of acute migraine medication (Weeks 13 to 24)

Trial	NCT04418765 (DELIVER)
	• Change from baseline in the number of MMDs with use of acute medication (Weeks 1 to 12) • Change from baseline in the number of MMDs with use of acute medication (Weeks 13 to 24) • Change from baseline in number of monthly migraine headache hours (post-hoc analysis) • Change from baseline to Week 12 in the HIT-6 score • Change from baseline to Week 24 in the HIT-6 score • Change from baseline to Week 12 in the MSQ subscores • Change from baseline to Week 12 in EQ-5D-5L VAS score • Change from baseline to Week 24 in the MSQ subscores • Change from baseline to Week 24 in EQ-5D-5L VAS score • Change from baseline to Week 12 in the WPAI questionnaire subscores • Change from baseline to Week 24 in the WPAI questionnaire subscores <u>Safety outcomes</u> • **AEs**
Pre-planned subgroups	Subgroup analyses for the primary endpoint were planned for the following subgroups: • Sex • EM (MMDs ≥ 4, MHDs ≤ 14) and CM (MMDs ≥ 8, MHDs > 14) • Age group (≤ 35 years and > 35 years) • MOH diagnosis • Number of failed previous treatments (2 and > 2) • Low frequency EM (4 ≤ MMDs < 8), high frequency EM (8 ≤ MMDs ≤ 14), and CM (MMDs ≥ 8)
Key: AE, adverse event; CM, chronic migraine; EM, episodic migraine; HIT-6; 6 item Headache Impact Test; IV, intravenous; MHD, monthly headache day; MMD, monthly migraine day; MOH, medication overuse headache; MSQ, Migraine-Specific Quality of Life Questionnaire; PGIC, Patient Global Impression of Change; SAE, serious adverse event; SF-36; 36-item Short Form; VAS, visual analogue scale; WPAI, Workplace Productivity and Activity Impairment.	

B.2.3.1. DELIVER study design

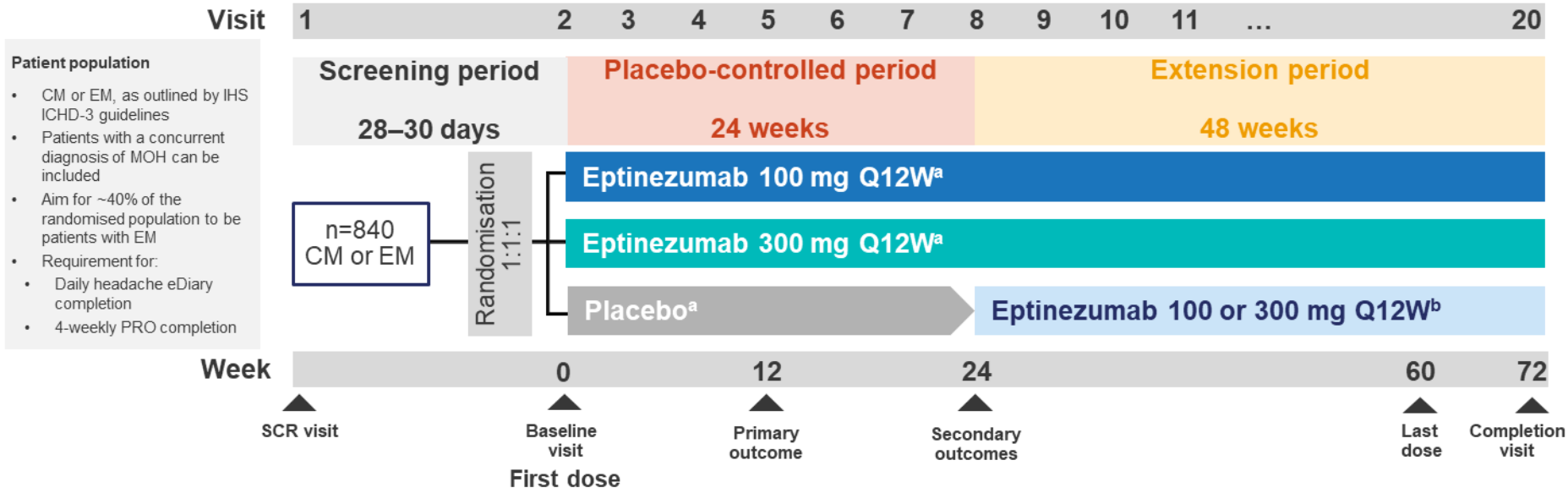
DELIVER is a multicentre, double-blind, parallel-group, placebo-controlled, randomised Phase III study of eptinezumab in adult patients with EM or CM (per IHS ICHD-3 criteria)[7] who were previously treated with 2–4 different preventive migraine treatments in the last 10 years (Figure 2). The trial was conducted at 96 sites across 17 countries, including five sites in the UK.

Patients were given an eDiary to record their migraine/headache characteristics, including severity, duration, and acute migraine medication use. The eDiary was used from the screening visit for 4 weeks (screening period) to confirm eligibility criteria and establish baseline data. Following the screening period, eligible patients completed an eDiary entry each trial day.

During the placebo-controlled phase, patients were randomised 1:1:1 to 24 weeks of double-blind treatment with placebo, eptinezumab 100 mg, or eptinezumab 300 mg. Randomisation was stratified by country and by number of MHDs at baseline (≤ 14 MHD/> 14 MHD). Patients received treatment by intravenous (IV) infusion over 30–45 minutes, starting from the baseline visit, and subsequently every 12 weeks (a total of two doses).

After 24 weeks, patients entered a dose-blinded extension period. During this period, patients originally assigned to placebo were randomised 1:1 to treatment with either eptinezumab 100 mg or eptinezumab 300 mg. Patients who were assigned to eptinezumab in the placebo-controlled phase continued their treatment at the dose they were assigned. Treatment was administered every 12 weeks starting at Week 24. Patients completing the extension period received six doses in total (two doses in the placebo-controlled period and four doses in the extension period).

Figure 2: Study design for DELIVER



Notes: [a]IV by infusion over 30 minutes (+ 15 minutes); [b]Patients who were assigned to the placebo in the placebo-controlled period will be randomly allocated to one of two treatment groups: eptinezumab 300 mg or eptinezumab 100 mg with a ratio of 1:1.
Key: CM, chronic migraine; EM, episodic migraine; ICHD-3, International Classification of Headache Disorders 3rd edition; IHS, International Headache Society; IV, intravenous; MOH, medication overuse headache; PRO, patient-reported outcome; SCR, screening; Q12W, every 12 weeks.
Source: Eptinezumab clinical study report[66]

B.2.3.2. Eligibility criteria

Table 6 presents the key inclusion and exclusion criteria for DELIVER. A summary of key definitions of headache day, migraine day and compliant day are provided in Appendix D.

Table 6: Eligibility criteria in DELIVER

Eligibility criteria	DELIVER
Key inclusion criteria	• Outpatients with a diagnosis of migraine as defined by IHS ICHD-3 criteria with a history of EM or CM ≥ 12 months prior to the screening visit • ≥ 18 and ≤ 75 years of age • Diagnosis of migraine at ≤ 50 years of age • ≥ 4 migraine days per month for each month within the past 3 months prior to the screening visit • Fulfilment of the following criteria for EM or CM in prospectively collected information in an eDiary during the screening period: – CM: migraine occurring on ≥ 8 days and headache occurring on > 14 days – EM: migraine occurring on ≥ 4 days and headache occurring on ≤ 14 days • Documented evidence of: – Treatment failure in the past 10 years of 2–4 different migraine-preventive medications (propranolol/metoprolol, topiramate, amitriptyline, flunarizine, candesartan, valproate/divalproex, botulinum toxin A/B for CM), ***and*** – Failure of two of the following of which at least one must be due to inadequate efficacy: propranolol/metoprolol, topiramate, amitriptyline, flunarizine, candesartan • History of either previous or active use of triptans for migraine
Key exclusion criteria	• Currently enrolled in this study, or has participated in another clinical trial within the last 30 days or within 5 half-lives (whichever is longer) prior to the screening visit • Failure on a previous treatment targeting the CGRP pathway • Treatment failure on valproate/divalproex or botulinum toxin A/B and the treatment is not the latest preventive medication prior to study inclusion • Confounding and clinically significant pain syndromes, such as fibromyalgia, chronic low back pain, complex regional pain syndrome • Diagnosis of acute or active temporomandibular disorder • History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), ophthalmoplegic migraine, or migraine with neurological accompaniments that is not typical of migraine aura (diplopia, altered consciousness, or long duration)

Eligibility criteria	DELIVER
	• Psychiatric condition that was uncontrolled and/or untreated for ≥ 6 months prior to the screening visit. Patients with a lifetime history of psychosis and/or mania in the last 5 years prior to screening visit were excluded
Key: CGRP, calcitonin gene related peptide; CM, chronic migraine; EM, episodic migraine; ICHD, International Classification of Headache Disorders; IHS, International Headache Society.	

B.2.3.3. Baseline characteristics

Details of key baseline demographics, clinical characteristics and previous treatments for patients included in DELIVER are presented in Table 7. The subgroup of patients who had experienced ≥ 3 preventive treatment failures were largely aligned with the full analysis set (FAS) in the DELIVER trial (n = 890) in terms of age and sex:

- Mean age: 45.2 (SD: 11.84) years (≥ 3 preventive treatment failures subgroup) versus 43.8 (10.83) years (DELIVER full analysis set)
- Female: 88.7% (≥ 3 preventive treatment failures subgroup) versus 89.9% (DELIVER full analysis set)

Table 7: Key baseline characteristics of patients in DELIVER (full analysis set)

Baseline characteristics	DELIVER (n = 890)		
	Eptinezumab		Placebo (n = 298)
	100 mg (n = 299)	300 mg (n = 293)	
Age, years (mean [SD])	44.6 (10.8)	43.1 (10.2)	43.8 (10.8)
Female (n [%])	277 (92.6)	260 (88.7)	263 (88.3)
Ethnicity (n [%]):			
• **White**	281 (95.9)	288 (96.3)	285 (95.6)
• **Other**	0	0	2 (0.7)
• **Unknown**	12 (4.1)	11 (3.7)	11 (3.7)
BMI, kg/m^2 (mean [SD])	25.2 (4.5)	25.2 (4.4)	25 (4.3)
Age at first migraine diagnosis, years (mean [SD])	26.1 (11.0)	26.3 (10.9)	26.1 (10.9)

Baseline characteristics	DELIVER (n = 890)		
	Eptinezumab		Placebo (n = 298)
	100 mg (n = 299)	300 mg (n = 293)	
Migraine diagnosis at baseline (n [%]):			
• **CM** **Duration of current CM diagnosis, years (mean [SD])**	123 (41.1) 12.9 (12.1)	107 (36.5) 10.3 (8.9)	125 (41.9) 11.0 (10.9)
• **EM** **Duration of current EM diagnosis, years (mean [SD])**	176 (58.9) 16.6 (11.3)	186 (63.5) 15.9 (11.1)	173 (58.1) 17.5 (12.1)
MOH diagnosis (n [%])[a]	38 (12.7)	35 (11.9)	37 (12.4)
Number of previous treatment failures (n [%]):			
• **0**	1 (0.3)	0	0
• **1**	0	1 (0.3)	1 (0.3)
• **2**	187 (62.5)	183 (62.5)	180 (60.4)
• **3**	92 (30.8)	95 (32.4)	90 (30.2)
• **4**	19 (6.4)	14 (4.8)	27 (9.1)
MMDs (mean [SD])	13.8 (5.6)	13.7 (5.4)	13.9 (5.7)
MHDs (mean [SD])	14.5 (5.6)	14.4 (5.4)	14.5 (5.8)
MMDs with use of acute medication	12.7 (5.5)	12.4 (5.4)	12.5 (5.6)
Days of monthly acute medication use	11.2 (5.5)	11.0 (5.3)	11.2 (5.9)
Monthly migraine attacks	11.0 (5.4)	11.0 (5.8)	11.4 (5.7)
Monthly headache episodes	[redacted]	[redacted]	[redacted]
Proportion (%) of migraine attacks with severe pain intensity (mean [SD])	47.1 (29.8)	43.9 (28.4)	40.4 (29.7)
Proportion (%) of headache episodes with severe pain intensity (mean [SD])	44.2 (28.6)	41.0 (27.0)	38.5 (29.3)
Average duration of migraine attacks, hours (mean [SD])	[redacted]	[redacted]	[redacted]

Baseline characteristics	DELIVER (n = 890)		
	Eptinezumab		Placebo (n = 298)
	100 mg (n = 299)	300 mg (n = 293)	
Average duration of headache episodes, hours (mean [SD])	[redacted]	[redacted]	[redacted]

Key: BMI, body mass index; CM, chronic migraine; EM, episodic migraine; MHD, monthly headache day; MMD, monthly migraine day; MOH, medication overuse headache; SD, standard deviation.
Notes: Baseline efficacy scores/values were based on self-reported data in the eDiary. [a]Patients with migraine, particularly CM, may also be diagnosed with MOH.
Sources: Ashina *et al.* (2022)[67]; DELIVER clinical study report (2021)[66] (supplemented by results published on ClinicalTrials.gov: NCT04418765).

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

Statistical considerations related to the DELIVER study are summarised in Table 8.

The FAS population was used for the efficacy analysis; the FAS comprised all randomised patients who received eptinezumab or placebo, depending on random assignment. Patients included in the FAS were defined as all randomised patients who had a valid baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1–12.

The safety population was defined as all randomised patients who received at least one infusion of the investigational medicinal product (IMP). Patients were included within the treatment group in which they received treatment. Patients treated with two different doses were included in the treatment arm of the highest dose received. A patient consort diagram for the DELIVER study is presented in Appendix D.

Table 8: Summary of statistical analyses in DELIVER

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
DELIVER	The primary estimand was the effect of eptinezumab on the number of MMDs that was seen in the hypothetical case where no acute medication was available if patients who withdrew due to lack of efficacy remained on their current trajectory, if patients who withdrew due to adverse events at an early stage were considered as obtaining only limited improvement in their baseline disease level, and if the effect was considered regardless of use of preventive medication and infusion interruptions or terminations.	Pre-specified comparisons between treatment groups were conducted using a REML-based MMRM of the change from baseline. The model included the fixed effects of month, country, stratification (MHDs at baseline: ≤ 14 MHDs/> 14 MHDs), and treatment as factors; baseline MMDs as a continuous covariate; treatment-by-month, baseline score-by-month, and stratum-by-month interactions. An unstructured variance structure was used to model within-patient errors. The mean difference between treatments was estimated based on the least squares means for the treatment-by-month interaction in the MMRM model. A hierarchical testing strategy was employed, either testing one endpoint at a time or using the Bonferroni-Holm method to test a group of endpoints. If the results of the first step were statistically significant, the formal testing continued, ensuring protection of the type 1 error.	With 280 patients per treatment group, (EM: 40%, CM: 60%), and 2% of patients not reaching a post-baseline assessment of the primary endpoint, simulations showed that the power for the test of the primary endpoint was approximately 94% for the comparison of eptinezumab 100 mg to placebo. The individual key secondary endpoints had a power of ≥ 68% for showing an effect, with a combined power of 58% for seeing an effect for all primary and key secondary endpoints and both doses in the testing strategy.	Kaplan-Meier plots of time to withdrawal in each period are presented by treatment group. For the Extension Period, the plot is by treatment-sequence group. The time was calculated from the date of first dose of IMP in the period to the date of completion or withdrawal from study. Patients who completed the period were regarded as censored.
Key: CM, chronic migraine; EM, episodic migraine; IMP, investigational medicinal product; MHD, monthly headache day; MMD, monthly migraine day; MMRM, mixed model repeated measures; REML, restricted maximum likelihood.				

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

The DELIVER study was a multicentre, randomised, double-blind, placebo-controlled, parallel group Phase III trial in patients with EM and CM. A summary of the quality assessment of this study is presented in Table 9 with full details in Appendix D.

Table 9: Quality assessment results

Trial number (acronym)	**DELIVER**
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[a]
Were there any unexpected imbalances in dropouts 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
Notes: [a]Three potentially unblinded patients were included in the study as they did not meet criteria for accidental unblinding. **Sources:** DELIVER clinical study report (2021)[66]	

Most patients enrolled in DELIVER were women (80.9%) with a mean age within the prevalence peak of migraine, i.e. 30–49 years (43.8 years).[29, 30] Real-world data from the UK indicate a higher prevalence of migraine in women than men, with twice as many female respondents in a random sample of the UK adult population experiencing migraine within the last year (18.3% versus 7.6%).[27] A real-world study of botulinum toxin A in CM in adults treated at the Hull Migraine Clinic included a similar proportion of female patients (81.4%) with a median age of 45 years.[68]

In DELIVER, the mean time since first migraine diagnosis (EM or CM) was 18 years, and the mean age at first diagnosis of migraine was 26 years. Enrolled patients reported a mean HIT-6 score of 66 points, indicating the severe impact of headache on the patients' abilities to function normally in daily life.

The patient baseline demographics and clinical characteristics of DELIVER align with patients treated in UK clinical practice participating in a prospective real-world analysis of erenumab in CM.[69] Patients with a mean age of 46 years and a CM diagnosis duration of 13 years reported an average HIT-6 score of 67.6,[69] which suggested a similar level of migraine-related disability to that experienced by patients in DELIVER. UK clinicians confirmed that the DELIVER trial is generalisable to UK patients and clinical practice.[55]

B.2.6. Clinical effectiveness results of the relevant trials

This section presents the primary and relevant secondary and exploratory efficacy outcomes data for the mixed EM and CM population in DELIVER.

B.2.6.1. Key clinical effectiveness results from DELIVER

Table 10 outlines the relevant primary, secondary and exploratory endpoints according to the outcomes presented in the decision problem in the combined EM and CM DELIVER trial population (i.e. patients that have been previously treated with 2–4 different preventive migraine treatments in the last 10 years).

Further subgroup analyses have been performed that focus on the population of interest to this submission, which was the population used in the economic model: patients for whom ≥ 3 prior preventive treatments have failed. The results of these analyses are presented in the subgroup section (Section B.2.7.1.1).

Table 10: DELIVER trial endpoints presented in this section

Decision problem outcomes	Endpoint	Section
Frequency of headache days per month	**Additional secondary endpoints: efficacy** • Change from baseline in MHDs (Weeks 1 to 12)	B.2.6.1.2
Frequency of migraine days per month	**Primary endpoint** • Change from baseline in the number of MMDs (Weeks 1 to 12) **Key secondary endpoints: efficacy** • Change from baseline in the number of MMDs (Weeks 13 to 24)	B.2.6.1.1 B.2.6.1.2
Severity of headaches and migraines	**Additional secondary endpoints: efficacy** • Change from baseline in the percentage of migraines with severe pain intensity (Weeks 1 to 12) **Exploratory endpoints** • Change from baseline in the percentage of migraines with severe pain intensity (Weeks 13 to 24)	B.2.6.1.2
Number of cumulative hours of headache or migraine on headache or migraine days	**Post-hoc analysis** • Change from baseline in monthly migraine hours at Weeks 1–12 • Change from baseline in monthly migraine hours at Weeks 13–24	B.2.6.1.2
Reduction in acute pharmacological medication	**Additional secondary endpoints: efficacy** • Change from baseline in the number of days using acute medication (Weeks 1 to 12) • Change from baseline in the number of MMDs with use of acute medication (Weeks 1 to 12) • Change from baseline in the number of days using acute medication (Weeks 13 to 24) • Change from baseline in the number of MMDs with use of acute medication (Weeks 13 to 24)	B.2.6.1.2
Health-related quality of life	**Key secondary endpoint: health-related quality of life** Change from baseline to Week 12 in the HIT-6 score **Health-related quality of life endpoints** • Change from baseline to Week 24 in the HIT-6 score • Change from baseline to Week 12 in the MSQ subscores • Change from baseline to Week 12 in the EQ-5D-5L VAS score	B.2.6.1.3

Decision problem outcomes	Endpoint	Section
	• Change from baseline to Week 24 in the MSQ subscores • Change from baseline to Week 24 in the EQ-5D-5L VAS score • Change from baseline to Week 12 in the WPAI questionnaire subscores • Change from baseline to Week 24 in the WPAI questionnaire subscores **Additional secondary endpoints: efficacy** • Response: proportion of patients achieving 5-point reduction in HIT-6 total score at Week 12 • Response: proportion of patients achieving 5-point reduction in HIT-6 total score at Week 24	
Additional outcomes not specified in the decision problem	**Key secondary endpoints: efficacy** • Response: ≥ 50% reduction from baseline in MMDs (Weeks 1 to 12) • Response: ≥ 50% reduction from baseline in MMDs (Weeks 1 to 12) **Additional secondary endpoints: efficacy** • Response: ≥ 50% reduction from baseline in MMDs (Weeks 13 to 24) • Response: ≥ 50% reduction from baseline in MMDs (Weeks 13 to 24) • Change from baseline in the number of MMDs in patients with MOH (Weeks 1 to 12) **Exploratory endpoints** • Change from baseline in the number of MMDs in patients with MOH (Weeks 13 to 24)	B.2.6.1.2
Key: HIT-6; 6 item Headache Impact Test; MHD, monthly headache days; MMD, monthly migraine days; MOH, medication overuse headache; MSQ, Migraine-Specific Quality of Life Questionnaire; PGIC, Patients' Global Impression of Change; VAS, visual analogue scale; WPAI, Workplace Productivity and Activity Impairment.		

B.2.6.1.1. Primary efficacy outcome

The mean change from baseline to Week 12 in the number of MMDs was -4.8 and -5.3 with eptinezumab 100 mg and 300 mg, respectively, compared with -2.1 with placebo (Table 11).[67]

Table 11: Primary efficacy outcome, change from baseline in MMDs at Week 12

Treatment arm	Baseline		Comparison to placebo				
	N	Mean	Interval	N	Mean (SE)	Diff. (95% CI)	p value
Change from baseline in MMDs							
Eptinezumab 100 mg	299	13.8	Weeks 1–12	299	-4.8 (0.37)	-2.7 (-3.4, -2.0)	< 0.0001
Eptinezumab 300 mg	293	13.7	Weeks 1–12	293	-5.3 (0.37)	-3.2 (-3.9, -2.5)	< 0.0001
Placebo	298	13.9	Weeks 1–12	298	-2.1 (0.38)	-	-

Key: CI, confidence interval; MMD, monthly migraine days; SE, standard error.
Source: Ashina *et al.* (2022)[67]

Both doses of eptinezumab demonstrated a clinically meaningful difference in the number of MMDs versus placebo (100 mg: -2.7 days; 300 mg: -3.2 days; both $p < 0.0001$).[67] Subgroup analyses (including EM versus CM, MOH diagnosis, and the number of failed previous treatments [2 and > 2]) performed on the primary endpoint resulted in estimates consistent with those for the total population (detailed in Section B.2.7).

B.2.6.1.2. Secondary and exploratory efficacy outcomes

In addition to meeting the primary endpoint, eptinezumab demonstrated statistically significant reductions in MHDs, proportion of migraines with severe pain intensity, number of days using acute medication and number of MMDs with use of acute medication, when compared with placebo ($p \leq 0.0001$; Table 12).[66] The change from baseline in MMDs in patients with MOH was also statistically significantly reduced compared with placebo ($p < 0.05$; Table 12).[66] Statistical significance was achieved for key secondary outcomes measuring response, with a significantly greater proportion of patients treated with eptinezumab (100 mg: 42.1%; 300 mg: 49.5%) achieving ≥ 50% reduction in MMDs over Weeks 1–12 compared with placebo (13.1%; $p < 0.0001$; Table 12).[67] Similar results were observed for achievement of ≥ 75% reduction in MMDs and a 5-point reduction in HIT-6 total score (Table 12).

Table 12: Select secondary and exploratory migraine-related efficacy outcomes from DELIVER

Outcome	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Change from baseline in MMDs at Weeks 13–24[a]			
Baseline N	299	293	298
Baseline mean	13.8	13.7	13.9
N	287	286	295
Mean (SE)	-5.4 (0.39)	-6.1 (0.39)	-2.4 (0.39)
Diff. vs placebo (95% CI)	-3.0 (-3.8, -2.2)	-3.7 (-4.5, -3.0)	-
p value	< 0.0001	< 0.0001	-
Proportion of patients with ≥ 50% reduction in MMDs from baseline at Week 12[a]			
N	299	293	298
Responders, n (%)	126 (42.1)	145 (49.5)	39 (13.1)
Odds ratio vs placebo (95% CI)	29.1 (3.29, 7.47)	36.4 (4.41, 10.01)	-
p value	< 0.0001	< 0.0001	-
Proportion of patients with ≥ 50% reduction in MMDs from baseline at Week 24			
N	287	286	295
Responders, n (%)	150 (52.3)	169 (59.1)	70 (23.7)
Odds ratio vs placebo (95% CI)	28.5 (2.50, 5.10)	35.4 (3.29, 6.75)	-
p value	< 0.0001	< 0.0001	-
Proportion of patients with ≥ 75% reduction in MMDs from baseline at Week 12[a]			
N	299	293	298
Responders, n (%)	47 (15.7)	55 (18.8)	6 (2.0)
Odds ratio vs placebo (95% CI)	9.19 (4.16, 24.35)	11.43 (5.22, 30.15)	-
p value	< 0.0001	< 0.0001	-

Outcome	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Proportion of patients with ≥ 75% reduction in MMDs from baseline at Week 24			
N	287	286	295
Responders, n (%)	61 (21.3)	79 (27.6)	20 (6.8)
Odds ratio vs placebo (95% CI)	3.75 (2.23, 6.55)	5.32 (3.20, 9.20)	-
p value	< 0.0001	< 0.0001	-
Proportion of patients achieving response: 5-point reduction in HIT-6 total score at Week 12			
N	280	284	288
Responders, n (%)	174 (62.1)	176 (62.0)	115 (39.9)
Odds ratio vs placebo (95% CI)	2.45 (1.74, 3.47)	2.48 (1.77, 3.50)	-
p value	< 0.0001	< 0.0001	-
Proportion of patients achieving response: 5-point reduction in HIT-6 total score at Week 24			
N	280	285	288
Responders, n (%)	202 (72.1)	204 (71.6)	133 (46.2)
Odds ratio vs placebo (95% CI)	3.06 (2.14, 4.39)	3.04 (2.14, 4.36)	-
p value	< 0.0001	< 0.0001	-
Change from baseline in MHDs at Weeks 1–12			
Baseline N	299	293	298
Baseline mean	14.5	14.5	14.5
N	299	293	298
Mean (SE)	-4.6 (0.37)	-5.1 (0.37)	-2.1 (0.38)
Diff. vs placebo (95% CI)	-2.6 (-3.3, -1.9)	-3.0 (-3.7, -2.3)	-
p value	< 0.0001	< 0.0001	-
Change from baseline in the percentage of migraines with severe pain intensity at Weeks 1–12			
Baseline N	299	293	298
Baseline mean	47.1	43.9	40.4
N	299	293	298

Outcome	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Mean (SE)	-17.9 (1.87)	-21.3 (1.87)	-10.2 (1.91)
Diff. vs placebo (95% CI)	-7.7 (-11.3, -4.1)	-11.1 (-14.7, -7.5)	-
p value	< 0.0001	< 0.0001	-
Change from baseline in the percentage of migraines with severe pain intensity at Weeks 13–24[b]			
Baseline N	299	293	298
Baseline mean	47.1	43.9	40.4
N	287	286	295
Mean (SE)	-20.5 (1.98)	-22.4 (1.98)	-12.6 (2.00)
Diff. vs placebo (95% CI)	-7.9 (-11.9, -3.9)	-9.8 (-13.8, -5.8)	-
p value	0.0001	< 0.0001	-
Change from baseline in the number of days using acute medication at Weeks 1–12			
Baseline N	298	290	298
Baseline mean	11.1	11.0	11.2
N	298	290	298
Mean (SE)	-4.1 (0.33)	-4.6 (0.34)	-1.6 (0.34)
Diff. vs placebo (95% CI)	-2.5 (-3.2, -1.9)	-3.0 (-3.6 -2.4)	-
p value	< 0.0001	< 0.0001	-
Change from baseline in the number of days using acute medication at Weeks 13–24			
Baseline N	298	290	298
Baseline mean	11.1	11.0	11.2
N	287	285	294
Mean (SE)	-4.6 (0.36)	-5.2 (0.36)	-1.7 (0.36)
Diff. vs placebo (95% CI)	-2.9 (-3.6 -2.2)	-3.5 (-4.2 -2.8)	-
p value	< 0.0001	< 0.0001	-
Change from baseline in the number of MMDs with use of acute medication at Weeks 1–12			
Baseline N	299	293	298

Outcome	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Baseline mean	12.7	12.4	12.5
N	299	293	298
Mean (SE)	-4.6 (0.36)	-5.2 (0.36)	-2.0 (0.36)
Diff. vs placebo (95% CI)	-2.7 (-3.4, -2.0)	-3.2 (-3.9, -2.5)	-
p value	< 0.0001	< 0.0001	-
Change from baseline in the number of MMDs with use of acute medication at Weeks 13–24			
Baseline N	299	293	298
Baseline mean	12.7	12.4	12.5
N	287	286	295
Mean (SE)	-4.9 (0.39)	-5.8 (0.38)	-2.1 (0.39)
Diff. vs placebo (95% CI)	-2.8 (-3.6, -2.0)	-3.7 (-4.4, -2.9)	-
p value	< 0.0001	< 0.0001	-
Change from baseline in the number of MMDs in patients with MOH at Weeks 1–12			
Baseline N	38	35	37
Baseline mean	17.0	16.1	18.9
N	38	35	37
Mean (SE)	-5.6 (1.07)	-7.3 (1.18)	-2.3 (1.12)
Diff. vs placebo (95% CI)	-3.3 (-5.9, -0.7)	-5.0 (-6.2, -0.2)	-
p value	0.0120	0.0003	-
Change from baseline in the number of MMDs in patients with MOH at Weeks 13–24[b]			
Baseline N	38	35	37
Baseline mean	17.0	16.1	18.9
N	36	35	37
Mean (SE)	-5.8 (1.21)	-6.6 (1.32)	-2.6 (1.25)
Diff. vs placebo (95% CI)	-5.0 (-7.6, -2.3)	-4.0 (-7.0, -0.9)	-
p value	0.0342	0.0106	-

Outcome	Eptinezumab 100 mg	Eptinezumab 300 mg	Placebo
Change from baseline in monthly migraine hours at Weeks 1–12[c]			
Baseline N	299	293	298
Baseline mean	133.8	129.6	132.3
Mean (SE)	-43.9 (5.70)	-52.2 (5.69)	-16.7 (5.79)
Diff. vs placebo (95% CI)	-27.3 (-38.1, -16.4)	-35.5 (-46.4, -24.6)	-
p value	< 0.001	< 0.001	-
Change from baseline in monthly migraine hours at Weeks 13–24[c]			
Baseline N	299	293	298
Baseline mean	133.8	129.6	132.3
Mean (SE)	-49.6 (6.06)	-55.7 (6.04)	-13.8 (6.12)
Diff. vs placebo (95% CI)	-35.8 (-47.9, -23.7)	-41.9 (-54.1, -29.8)	-
p value	< 0.001	< 0.001	-

Key: CI, confidence interval; diff, difference; HIT-6, 6 item Headache Impact Test; MHD, monthly headache day; MMD, monthly migraine day; MOH, medication overuse headache; PGIC, Patients' Global Impression of Change; SE, standard error.
Note: [a]Key secondary efficacy endpoints. [b]Exploratory efficacy endpoints. [c]Post-hoc analysis.
Source: Ashina *et al.* (2022);[67] Eptinezumab clinical study report[66]; Lundbeck data on file[70] (supplemented by results published on ClinicalTrials.gov: NCT04418765).

We performed an exploratory analysis to evaluate the proportion of patients with migraine on the day after first dosing in the FAS population (Table 13). A significantly lower proportion of patients receiving eptinezumab (100 mg: 27%; 300 mg: 24%) experienced migraine on the day after the initial dose, compared with those receiving placebo (44%; p < 0.0001), suggesting a rapid onset of action for eptinezumab.

Table 13: Proportion of patients with migraine on the day after first dosing

Treatment arm	Day after infusion visit		p value
	N	Migraine, %	
Eptinezumab 100 mg	299	27	< 0.0001
Eptinezumab 300 mg	293	24	< 0.0001
Placebo	298	44	-

Key: CMH, Cochran-Mantel-Haenszel; MHD, monthly headache day.
Notes: Exploratory analysis. Baseline: average percentage of patients with migraine across the first 28 days. Percentage of patients with migraine on the first day after first dose: derived based on available eDiary data on Day 1. p values were computed for each active treatment arm using extended CMH test, adjusting for the stratification factor, MHDs at baseline (≤ 14 vs > 14 days).
Source: Ashina *et al.* (2022)[67]

B.2.6.1.3. Health-related quality of life outcomes

Several HRQL instruments were used to investigate patients' quality of life in the DELIVER trial. Results from HIT-6, MSQ, EQ-5D-5L VAS and the WPAI questionnaire are presented in Table 14. Eptinezumab delivered significant improvements in HRQL versus placebo, measured by changes from baseline in HIT-6 score and MSQ subscores (p < 0.0001).[66] Significant improvements (p < 0.005) in patients' general well-being (EQ-5D-5L VAS) were also observed with eptinezumab. The WPAI instrument showed significant outcome improvements in terms of presenteeism (p = 0.0005), absenteeism (p = 0.0011), work productivity loss (p = 0.0004) and activity impairment (p < 0.0001), compared with placebo.[66]

The impact of response status (≥ 50% reduction in MMDs) on WPAI subscores was evaluated in a post-hoc analysis among patients for whom ≥ 2 previous preventive treatments failed.[71] Results indicated that patients who responded to placebo did not experience associated benefits in terms of improvements in absenteeism or presenteeism. However, patients with a response to eptinezumab did show substantial reductions compared with patients with no response. These results are presented in Section B.2.7.1.3.

Table 14: Health-related quality of life outcomes from DELIVER

Treatment arm	Baseline		Visit	Comparison to placebo			
	N	Mean		N	Mean (SE)	Diff. (95% CI)	p value
Change from baseline in the HIT-6 score							
Eptinezumab 100 mg	280	66.6	Week 12	277	-6.9 (0.61)	-3.8 (-5.0, -2.5)	< .0001
			Week 24	266	-8.9 (0.63)	-5.0 (-6.3, -3.7)	< .0001
Eptinezumab 300 mg	285	66.4	Week 12	283	-8.5 (0.60)	-5.4 (-6.7, -4.2)	< .0001
			Week 24	276	-9.9 (0.62)	-6.0 (-7.3, -4.7)	< .0001
Placebo	288	66.2	Week 12	288	-3.1 (0.61)	-	-
			Week 24	278	-3.9 (0.63)		
Change from baseline in the MSQ role function restrictive subscore							
Eptinezumab 100 mg	276	35.7	Week 12	271	25.0 (1.75)	11.3 (8.0, 14.7)	< .0001
			Week 24	259	30.1 (1.78)	15.1 (11.7, 18.5)	< .0001
Eptinezumab 300 mg	287	35.7	Week 12	283	28.7 (1.72)	15.0 (11.6, 18.3)	< .0001
			Week 24	275	30.0 (1.73)	15.0 (11.6, 18.4)	< .0001
Placebo	288	35.1	Week 12	288	13.7 (1.75)	-	-
			Week 24	278	15.0 (1.76)		
Change from baseline in the MSQ role function preventive subscore							
Eptinezumab 100 mg	276	50.2	Week 12	271	22.7 (1.64)	11.1 (8.0, 14.3)	< .0001
			Week 24	259	25.7 (1.65)	12.6 (9.4, 15.8)	< .0001
Eptinezumab 300 mg	287	51.0	Week 12	283	25.0 (1.61)	10.4 (10.4, 16.6)	< .0001
			Week 24	275	26.3 (1.61)	10.1 (10.1, 16.4)	< .0001
Placebo	288	50.5	Week 12	288	11.6 (1.63)	-	-
			Week 24	278	13.1 (1.63)		

Treatment arm	Baseline		Visit	Comparison to placebo			
	N	Mean		N	Mean (SE)	Diff. (95% CI)	p value
Change from baseline in the MSQ emotional function subscore							
Eptinezumab 100 mg	276	50.3	Week 12	271	20.6 (1.84)	11.1 (7.5, 14.6)	< .0001
			Week 24	259	24.1 (1.86)	14.1 (10.5, 17.7)	< .0001
Eptinezumab 300 mg	287	48.6	Week 12	283	23.1 (1.80)	13.5 (10.0 ,17.0)	< .0001
			Week 24	275	24.1 (1.81)	14.1 (10.6, 17.7)	< .0001
Placebo	288	48.4	Week 12	288	9.6 (1.83)	-	-
			Week 24	278	9.9 (1.84)		
Change from baseline in the EQ-5D-5L VAS score							
Eptinezumab 100 mg	276	75.9	Week 12	271	2.0 (1.40)	5.1 (2.2, 8.1)	0.0007
			Week 24	259	2.0 (1.40)	4.7 (1.8, 7.7)	0.0014
Eptinezumab 300 mg	285	74.5	Week 12	281	4.4 (1.38)	7.5 (4.5, 10.4)	< .0001
			Week 24	275	5.2 (1.37)	8.0 (5.1, 10.8)	< .0001
Placebo	287	74.0	Week 12	287	-3.1 (1.39)	-	-
			Week 24	278	-2.8 (1.38)		
Change from baseline in the WPAI questionnaire subscore: absenteeism							
Eptinezumab 100 mg	196	11.4	Week 12	174	-5.8 (1.53)	-5.7 (-9.2, -2.3)	0.0011
			Week 24	151	-5.2 (1.53)	-4.5 (-7.8, -1.1)	0.0092
Eptinezumab 300 mg	209	12.0	Week 12	183	-3.8 (1.50)	-3.7 (-7.1, -0.4)	0.0303
			Week 24	168	-5.4 (1.47)	-4.7 (-8.0, -1.5)	0.0046
Placebo	218	12.8	Week 12	196	-0.1 (1.49)	-	-
			Week 24	180	-0.7 (1.46)		
Change from baseline in the WPAI questionnaire subscore: presenteeism							
Eptinezumab 100 mg	191	50.8	Week 12	169	-19.0 (2.46)	-9.1 (-14.2, -4.0)	0.0005
			Week 24	145	-22.2 (2.59)	-14.7 (-20.1, -9.2)	< .0001

Treatment arm	Baseline		Visit	Comparison to placebo			
	N	Mean		N	Mean (SE)	Diff. (95% CI)	p value
Eptinezumab 300 mg	206	53.3	Week 12	179	-23.3 (2.40)	-13.4 (-18.5, -8.4)	< .0001
			Week 24	166	-19.3 (2.46)	-11.8 (-17.0, -6.5)	< .0001
Placebo	212	51.7	Week 12	188	-9.9 (2.42)	-	-
			Week 24	173	-7.5 (2.49)		
Change from baseline in the WPAI questionnaire subscore: work productivity loss							
Eptinezumab 100 mg	191	53.7	Week 12	169	-19.5 (2.61)	-9.8 (-15.3, -4.4)	0.0004
			Week 24	145	-22.6 (2.73)	-15.4 (-21.1, -9.7)	< .0001
Eptinezumab 300 mg	206	57.0	Week 12	179	-24.0 (2.54)	-14.3 (-19.6, -9.0)	< .0001
			Week 24	166	-20.2 (2.60)	-13.0 (-18.6, -7.5)	< .0001
Placebo	212	55.6	Week 12	188	-9.7 (2.56)	-	-
			Week 24	173	-7.2 (2.62)		
Change from baseline in the WPAI questionnaire subscore: activity impairment							
Eptinezumab 100 mg	274	58.5	Week 12	268	-21.3 (2.07)	-10.1 (-14.3, -5.9)	< .0001
			Week 24	256	-24.7 (2.09)	-14.6 (-18.8, -10.4)	< .0001
Eptinezumab 300 mg	285	59.1?	Week 12	280	-23.8 (2.05)	-12.6 (-16.8, -8.5)	< .0001
			Week 24	273	-22.6 (2.04)	-12.5 (-16.7, -8.4)	< .0001
Placebo	286	58.7	Week 12	286	-11.2 (2.07)	-	-
			Week 24	275	-10.1 (2.07)		

Key: CI, confidence interval; HIT-6; 6 item Headache Impact Test; MSQ, Migraine-Specific Quality of Life Questionnaire; SE, standard error; VAS, visual analogue scale; WPAI, Workplace Productivity and Activity Impairment.
Note: [a]Key secondary efficacy endpoints.
Source: Ashina *et al.* (2022);[67] Eptinezumab clinical study report[66] (supplemented by results published on ClinicalTrials.gov: NCT04418765).

B.2.6.2. Key clinical effectiveness results from PROMISE-1

In patients with EM, eptinezumab demonstrated a statistically significant reduction ($p < 0.05$) from baseline in the number of MMDs during Weeks 1–12 compared with placebo. Mean MMDs at baseline ranged from 8.4 (placebo) to 8.7 (eptinezumab 100 mg) days. During Weeks 1–12, the mean MMDs declined to 4.7 days with eptinezumab 100 mg and 5.4 days with placebo.[72]

Eptinezumab also demonstrated migraine-preventive effects on the first day after dosing. The average percentage of patients with a migraine on any given day at baseline was 30.7%, and on the first day post-infusion, a significantly lower proportion of patients receiving eptinezumab 100 mg had a migraine compared with placebo (14.8% versus 22.5%, respectively; $p < 0.05$).[72] Further results from PROMISE-1 are included in Appendix D.

B.2.6.3. Key clinical effectiveness results from PROMISE-2

In patients with CM, eptinezumab demonstrated a statistically significant reduction in MMDs during Weeks 1–12 ($p < 0.0001$) versus placebo. Mean MMDs at baseline ranged from 16.1 (eptinezumab 100 mg) to 16.2 (placebo) days, and during Weeks 1–12 mean MMDs were 8.5 days with eptinezumab and 10.5 days with placebo.[73]

The migraine-preventive effect of eptinezumab was observed as early as the first day after dosing. The proportion of patients with a migraine on the first day after dosing was statistically significantly lower with eptinezumab 100 mg (28.6%) versus placebo (42.3%; $p < 0.0001$).[72] Further results from PROMISE-2 are included in Appendix D.

B.2.6.4. Key clinical effectiveness results from RELIEF

In the RELIEF study, which evaluated eptinezumab as an acute treatment rather than a preventive treatment, eptinezumab treatment during an active moderate-to-severe migraine attack shortened the time to headache and migraine symptom freedom compared with placebo. The median time after start of infusion to:

- Headache freedom was 4 versus 9 hours (hazard ratio [HR]: 1.54 [95% CI: 1.20, 1.98]; $p = 0.0006$)[74]

- Absence of most bothersome symptom was 2 versus 3 hours (HR: 1.75 [95% CI: 1.41, 2.19]; p < 0.0001)[74]

B.2.7. Subgroup analysis

B.2.7.1. DELIVER

Several subgroup analyses were conducted, including:

- Analyses of the primary and key secondary endpoints in the subgroup of patients for whom ≥ 3 prior preventive treatments had failed, i.e. the population of interest for this submission, which is presented in Section B.2.7.1.1. These subgroup data have been used as inputs in the economic model (Section B.3.3.1)
  - An additional subgroup analysis was performed in the subgroup of patients with CM for whom ≥ 3 prior preventive treatments had failed, to determine the 30% migraine response rate to feed into the economic model (Section B.3.3.1.1). A 30% response rate is recommended by the BASH guidance and was deemed appropriate following discussions with the clinical community, who confirmed its use in clinical practice
- A pre-planned subgroup analysis of the primary endpoint, change from baseline in MMDs at Week 12, which is presented in Section B.2.7.1.1. This analysis investigates several subgroups
- A post-hoc analysis on the FAS (i.e. patients for whom ≥ 2 prior preventive treatments failed), which investigates the impact of response (≥ 50% reduction in MMDs) on WPAI subscores, which is presented in Section B.2.7.1.3

B.2.7.1.1. Analyses of primary and key secondary endpoints in the subgroup of patients within DELIVER for whom ≥ 3 prior preventive treatments failed

Further subgroup analyses of the primary and key secondary endpoints have been performed, and they focus on the population of interest to this submission: patients for whom ≥ 3 prior preventive treatments failed (Table 15). In the subpopulation of patients with EM or CM, and ≥ 3 prior preventive treatment failures, both doses of eptinezumab significantly reduced the overall mean number of MMDs from baseline compared with placebo ([redacted]). The outputs of these analyses were used in the indirect treatment comparison (ITC) described in Section B.2.9.

Table 15: Subgroup analyses of patients for whom ≥ 3 prior preventive treatments failed

	EM			CM			Pooled EM and CM		
	Eptinezumab		Placebo	Eptinezumab		Placebo	Eptinezumab		Placebo
	100 mg	300 mg		100 mg	300 mg		100 mg	300 mg	
Change from baseline in MMDs: Weeks 1–12									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model estimate mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diff. vs placebo (95% CI)	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
p value	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Change from baseline in MMDs: Weeks 13–24									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model estimate mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diff. vs placebo (95% CI)	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
p value	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Proportion of patients with 75% response on MMDs:[a] Weeks 1–12									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with 75% response on MMDs:[a] Weeks 13–24									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	EM			CM			Pooled EM and CM		
	Eptinezumab		Placebo	Eptinezumab		Placebo	Eptinezumab		Placebo
	100 mg	300 mg		100 mg	300 mg		100 mg	300 mg	
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients with 50% response on MMDs: Weeks 1–12									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs placebo (95% CI)	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
p value	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Proportion of patients with 50% response on MMDs: Weeks 13–24									
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR vs placebo (95% CI)	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
p value	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-

Key: CI, confidence interval; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days; MMRM, mixed model repeated measures; OR, odds ratio; SE, standard error.
Notes: [a]No logistic regression was performed due to low 'numbers'.
Source: Lundbeck data on file[75, 76]

B.2.7.1.1.1. 30% migraine response rate in patients with CM for whom ≥ 3 prior preventive treatments failed

Clinical response in the model that is presented in Section B.3 is defined as a 30% reduction in MMDs for patients with CM. Subgroup analyses were performed on the subgroup of patients with CM with ≥ 3 prior preventive treatment failures. Response to eptinezumab 100 mg resulted in post-baseline decreases in MMD compared with baseline ([redacted]; Table 16).[77]

Table 16: Proportion of patients with CM with ≥ 3 prior preventive treatment failures and 30% response on MMDs (Weeks 1–12)

Treatment	30% response rate	Response status	N	MMD (SE)	
				Baseline	Post-baseline
Eptinezumab 100 mg	64.3%	No response	[redacted]	[redacted]	[redacted]
		Response	[redacted]	[redacted]	[redacted]
Eptinezumab 300 mg	72.2%	No response	[redacted]	[redacted]	[redacted]
		Response	[redacted]	[redacted]	[redacted]
Placebo	23.2%	No response	[redacted]	[redacted]	[redacted]
		Response	[redacted]	[redacted]	[redacted]

Key: CM, chronic migraine; MMD, monthly migraine day; SE, standard error.
Source: Lundbeck data on file[77]

B.2.7.1.2. Analyses of the primary endpoint for subgroups of the whole DELIVER population

A pre-planned subgroup analysis was performed on the primary endpoint (change from baseline in MMDs at Week 12). The primary efficacy analysis (mixed model repeated measures) was repeated for the following subgroups: EM or CM; number of failed previous treatments (2 and > 2); LFEM (≤ 4 MMDs < 8); HFEM (≤ 8 MMDs ≤ 14); and age and sex (Figure 3). Magnitudes of point estimates were consistent with those for the total population.

Exploratory investigations of an equal treatment effect across subgroups indicated no statistically significant interactions between treatment and any of the subgroups.

Figure 3: Forest plot of difference from placebo in MMDs change from baseline over Weeks 1–12 by subgroup for eptinezumab 100 mg and 300 mg in DELIVER

Key: CM, chronic migraine; EM, episodic migraine; Epti, eptinezumab; FAS, full analysis set; HFEM, high-frequency episodic migraine; LFEM, low-frequency episodic migraine; MMD, monthly migraine day; MMRM, mixed model repeated measures; MOH, medication overuse headache; no., number; PBO, placebo; trt, treatment.
Source: Lundbeck data on file[78]

B.2.7.1.3. Impact of response status on WPAI subscores among whole DELIVER population

We performed a post-hoc analysis to investigate the impact of response (≥ 50% reduction in MMDs) on WPAI subscores during Weeks 1–12 among patients in the FAS population for whom ≥ 2 previous preventive treatments had failed. Results indicated that patients with a response to placebo did not experience associated benefits in terms of improvements in absenteeism or presenteeism (Table 17), while patients with a response to eptinezumab did show substantial reductions in absenteeism and presenteeism compared with patients with no response.[71]

Table 17: Post-hoc analysis of WPAI outcomes during Weeks 1–12 in patients with ≥ 50% reduction in MMDs for whom ≥ 2 previous preventive treatments failed

Responder status	N	Absenteeism per month (hours), mean (SE)	Presenteeism per month (hours), mean (SE)	Absenteeism score	Presenteeism score
Eptinezumab 100 mg					
No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eptinezumab 300 mg					
No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo					
No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: SE, standard error; WPAI, Work Productivity and Activity Impairment.
Notes: For each patient, the average value of WPAI absenteeism and presenteeism scores taken at Week 4, 8 and 12 was calculated. Those values were assumed to be the average work impairment over Weeks 1–12. No missing data were imputed (i.e. if only one value was reported by a patient, this value was used as the average over Weeks 1–12). The individual patient values were then summarised by treatment and responder status. Monthly hours are calculated by converting WPAI scores assuming 4 weeks in a month and 36.9 working hours per week.
Source: Lundbeck data on file[71]

B.2.8. Meta-analysis

No meta-analysis of the eptinezumab studies has been performed to evaluate efficacy. DELIVER (EM and CM), PROMISE-1 (EM) and PROMISE-2 (CM) evaluated the efficacy of eptinezumab in different patient populations, rendering any pooling of these trials inappropriate. The DELIVER trial was deemed to be the most appropriate eptinezumab trial to establish comparative efficacy based on its trial design. DELIVER eligibility criteria specified that patients with between two and four documented treatment failures were eligible for inclusion, which allowed analyses by number of treatment failures to be conducted. The outputs of these analyses informed the ITC versus other placebo-controlled trials of active comparators (Section B.2.9).

A pooled safety analysis was also conducted and is detailed in Appendix F.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1. Overview

In the absence of head-to-head comparisons, an ITC was performed to provide comparative estimates in terms of efficacy, safety and HRQL for eptinezumab versus its key comparators for patients in the third and fourth lines of treatment (patients for whom ≥ 2 or ≥ 3 prior treatments had failed) for migraine prevention. This submission focuses on the results for patients in the fourth line of treatment and the eptinezumab 100 mg dose. Results of eptinezumab versus its key comparators as a third-line treatment are presented in Appendix D.

To identify comparator studies for the network meta-analysis (NMA), an SLR was conducted, as described in Section B.2.1. The full methods of the SLR are provided in Appendix D.

B.2.9.2. Included studies

64 studies were identified in the SLR, of which four were studies of eptinezumab and the remaining 60 were comparator studies. Of the 60 comparator studies identified by the SLR, ten comparator studies were deemed relevant for inclusion in the NMA. The SLR eligibility criteria were refined for the NMA to restrict the focus to preventive anti-CGRPs in both EM and CM, and additionally botulinum toxin A for CM. The refined eligibility criteria are listed in Appendix D.

Table 18 summarises the studies that were deemed suitable for inclusion in the NMA, for which primary outcomes were pre-determined. Of these 11 studies, 10 were comparator studies that were identified in the SLR and then deemed to be relevant to the NMA, and the one additional study was a study of eptinezumab, DELIVER, which was obtained from Lundbeck data-on-file, and was in addition to the studies identified in the SLR.

Table 18: Studies eligible for inclusion in the network meta-analysis

Trial	Interventions
DELIVER[66]	Eptinezumab 100 mg or 300 mg[a] versus placebo
CONQUER[79]	Galcanezumab 120 mg versus placebo
EVOLVE-1, EVOLVE-2[80, 81]	Galcanezumab 120 mg or 240 mg versus placebo
REGAIN[82]	Galcanezumab 120 mg or 240 mg versus placebo
FOCUS[83]	Fremanezumab 675/225/225 mg monthly or fremanezumab 675 mg quarterly versus placebo
LIBERTY[84]	Erenumab 140 mg versus placebo
NCT02066415[85]	Erenumab 70 mg or 140 mg versus placebo
STRIVE[86]	Erenumab 70 mg or 140 mg versus placebo
PREEMPT-1, PREEMPT-2[87, 88]	Botulinum toxin A 155-195 mg versus placebo
Note: [a]As this submission focuses on eptinezumab 100 mg, the NMA results of eptinezumab 300 mg versus comparators are not presented.	

B.2.9.3. Methodology

Full details of the methodology of this ITC are presented in Appendix D. A feasibility assessment, also presented in Appendix D, was conducted to assess availability of the following outcomes across the 11 selected studies, including DELIVER, before conducting the NMA, with the primary timepoint of interest being Week 12:

- Change from baseline in MMDs
- 50% and 75% migraine response rate
- Change from baseline in MMDs with use of acute medication
- Change from baseline in MHDs
- HRQL: change from baseline in: HIT-6; Role Function-Restrictive, Emotional Function, and Role Function-Preventive MSQ v2.1 domains; WPAI
- Safety outcomes (discontinuations due to AEs, all-cause discontinuations)

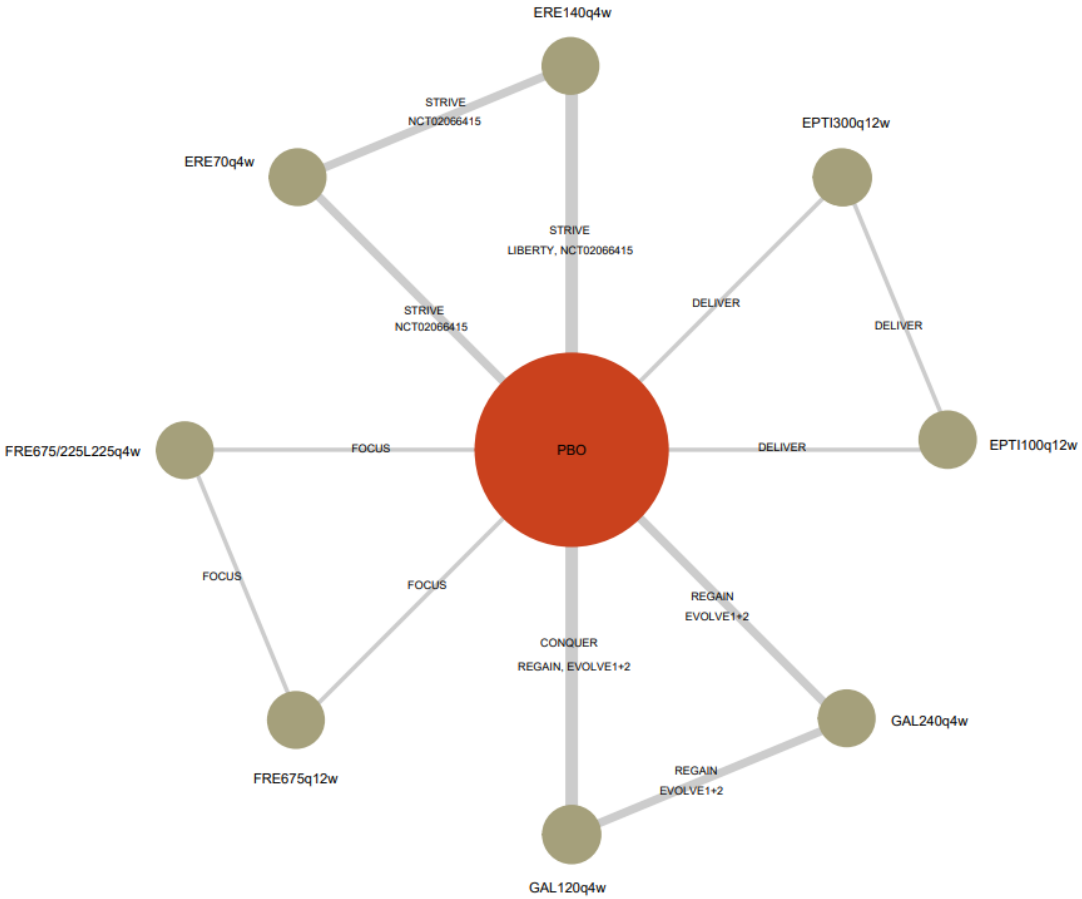
NMAs were conducted, which were stratified by EM and CM and the prior number of treatment failures (2+ and 3+) to control potential differences across studies. A pooled NMA of both EM and CM was also conducted for 50% and 75% migraine response rates and discontinuation outcomes (stratifying by 2+ and 3+ prior treatment failures). A pooled analysis of mixed anti-CGRPs was conducted to assess the suitability of pooling EM and CM for 50% migraine response rate, which demonstrated that pooling EM and CM was suitable. All results presented below use eptinezumab 100 mg as the reference treatment.

B.2.9.4. Results

Results for the fixed-effects NMAs are presented in this section. Fixed-effects models were considered to be most appropriate, as few studies per treatment comparison were available (refer to Appendix D for justification of the fixed-effects approach).

Results for patients for whom ≥ 2 prior treatments had failed (i.e. including the overall DELIVER trial population) are presented in Appendix D. These include additional efficacy outcomes (change from baseline in MMDs with use of acute medication), HRQL outcomes (change from baseline in HIT-6 and MSQ v2.1 subscores), and discontinuations (all-cause and AE-related). A summary of the NMAs conducted is presented in Table 19, and a global network plot is presented in Figure 4.

Figure 4: Global network plot for comparisons versus anti-CGRPs



Key: CM, chronic migraine; ERE70q4w, erenumab 70 mg (q4w); ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); GAL240q4w, galcanezumab 240 mg (q4w); PBO, placebo.
Note: This diagram does not include the PREEMPT-1 and PREEMPT-2 studies which informed comparisons in patients with CM versus botulinum toxin A.

Table 19: Summary of outcomes included in each fixed-effect NMA conducted

NMA	Versus anti-CGRPs				Versus botulinum toxin A	
	Pooled EM and CM NMA		Separate EM and CM NMAs		CM NMA	
Treatment failures	2+	3+	2+	3+	2+	3+
Outcomes	• 50% migraine response rate • 75% migraine response rate • All-cause discontinuations • Discontinuations due to AEs	• 50% migraine response rate • 75% migraine response rate	• Change from baseline in MMDs • Change from baseline in MMDs with use of acute medication • 50% migraine response rate • 75% migraine response rate • Change from baseline in HIT-6 • Change from baseline in MSQ subscores (RF-R, EF, RF-P)	• Change from baseline in MMDs • Change from baseline in MMDs with use of acute medication • 50% migraine response rate • 75% migraine response rate • Change from baseline in MSQ subscores (RF-R, EF, RF-P)	• Change from baseline in MMDs • 50% migraine response rate	
Relevant section	Appendix D	B.2.9.4.4 (Table 22)	Appendix D (EM: Table 25; CM: Table 26)	EM: B.2.9.4.2 (Table 20) CM: B.2.9.4.3 (Table 21)	Appendix D	B.2.9.4.3.2

Key: AE, adverse event; anti-CGRP, anti-calcitonin gene-related peptide; CM, chronic migraine; EF, emotional function; EM, episodic migraine; HIT-6, 6-item Headache Impact Test; MMD, monthly migraine day; MSQ, Migraine-Specific Quality of Life Questionnaire; NMA, network meta-analysis; RF-R, role function restrictive RF-P, role function preventive

B.2.9.4.1. Feasibility assessment

Including DELIVER, 11 studies were identified as being relevant for inclusion in the NMA. Baseline severity (EM versus CM and baseline MMD), the number of prior treatment failures and MOH were identified as potential treatment effect modifiers through a review of subgroup results captured in the SLR. Heterogeneity across studies was observed in baseline severity and in the proportion of patients with higher numbers of prior treatment failures (e.g. 3+). MOH was not well reported, making it difficult to assess heterogeneity in this characteristic.

Comparisons with botulinum toxin A in patients with CM were deemed feasible for change from baseline in MMD and 50% migraine response rate. Due to limited data availability, these comparisons included Week 24 data for botulinum toxin A and Week 12 data for eptinezumab. In addition, due to a lack of data availability, change from baseline in MHD data were used for botulinum toxin A, while change from baseline in MMD data were used for eptinezumab.

B.2.9.4.2. EM: eptinezumab 100 mg versus anti-CGRPs in patients for whom ≥ 3 prior preventive treatments failed

In EM, eptinezumab 100 mg was shown to be as effective as comparator anti-CGRPs in patients for whom ≥ 3 prior preventive treatments failed, with none of the other anti-CGRPs demonstrating a statistically superior benefit in efficacy (change from baseline in MMDs and MMDs with use of acute medication, 50% and 75% migraine response rates, and MSQ subscores) over eptinezumab (Table 20). Clinical experts who were consulted on the results of this NMA considered that the efficacy, HRQL and safety of eptinezumab were comparable to other anti-CGRPs analysed in both the third and fourth lines of treatment for migraine prevention in EM and CM.[55]

Table 20: Summary of NMA versus anti-CGRPs results: EM in patients with ≥ 3 treatment failures

Comparator	Reference treatment: eptinezumab 100 mg every 12 weeks							
	Change from baseline in MMD	Change from baseline in MMD with use of acute medication	50% migraine response rate	75% migraine response rate	Change from baseline in HIT-6	Change from baseline in RF-R MSQ	Change from baseline in EF MSQ	Change from baseline in RF-P MSQ
PBO	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
ERE70q4w	-	-	-	-	-	-	-	-
ERE140q4w	-	-	[redacted]	[redacted]	-	-	-	-
FRE675q12w	-	-	[redacted]	-	-	-	-	-
FRE675/225/225q4w	-	-	[redacted]	-	-	-	-	-
GAL120q4w	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]	[redacted]
GAL240q4w	-	-	-	-	-	-	-	-

Key: CrI, credible interval; ERE70q4w, erenumab 70 mg (q4w); ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); GAL240q4w, galcanezumab 240 mg (q4w); HIT-6, 6-item Headache Impact Test; MMD, monthly migraine days; PBO, placebo.
Notes: Change from baseline in MMDs, MMDs with use of acute medication, and HIT-6 results: mean differences in change from baseline with 95% CrIs, where results < 0 favour the comparator, results > 0 favour eptinezumab 100 mg.
Change from baseline in MSQ subscores: mean differences in change from baseline with 95% CrIs, where results > 0 favour the comparator and results < 0 favour eptinezumab 100 mg.
50% and 75% migraine response rate results: odds ratios with 95% CrIs, where results > 1 favour the comparator, results < 1 favour eptinezumab 100 mg.

B.2.9.4.3. CM: eptinezumab 100 mg versus anti-CGRPs and botulinum toxin A in patients for whom ≥ 3 prior preventive treatments failed

B.2.9.4.3.1. Eptinezumab 100 mg versus anti-CGRPs

In CM, eptinezumab 100 mg was shown to be as effective as comparator anti-CGRPs in patients for whom ≥ 3 prior preventive treatments failed, with none of the comparators demonstrating a statistically superior benefit in efficacy (change from baseline in MMDs and MMDs with use of acute medication, 50% and 75% migraine response rates, and MSQ subscores) over eptinezumab (Table 21). Clinical experts who were consulted on the results of this NMA considered that the efficacy, HRQL and safety of eptinezumab were comparable to other anti-CGRPs analysed in both the third and fourth lines of treatment for migraine prevention in EM and CM.[55] Treatment with erenumab (70 mg and 140 mg every 4 weeks) and galcanezumab (120 mg every 4 weeks) had a lower probability of achieving a 50% and 75% response rate, and galcanezumab (240 mg every 4 weeks) led to an increase in change from baseline in the MSQ Role Function-Restrictive subscore when compared to eptinezumab 100 mg. However, these differences were not statistically significant.

Table 21: Summary of NMA versus anti-CGRPs results: CM in patients with ≥ 3 treatment failures

Comparator	Reference treatment: eptinezumab 100 mg every 12 weeks							
	Change from baseline in MMD	Change from baseline in MMD with use of acute medication	50% migraine response rate	75% migraine response rate	Change from baseline in HIT-6	Change from baseline in RF-R MSQ	Change from baseline in EF MSQ	Change from baseline in RF-P MSQ
PBO	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
ERE70q4w	-	-	[redacted]	[redacted]	-	-	-	-
ERE140q4w	[redacted]	-	[redacted]	[redacted]	-	-	-	-
FRE675q12w	-	-	[redacted]	-	-	-	-	-
FRE675/225 /225q4w	-	-	[redacted]	-	-	-	-	-
GAL120q4w	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
GAL240q4w	[redacted]	[redacted]	[redacted]	-	-	[redacted]	-	-

Key: CrI, credible interval; ERE70q4w, erenumab 70 mg (q4w); ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); GAL240q4w, galcanezumab 240 mg (q4w); HIT-6, 6-item Headache Impact Test; MMD, monthly migraine days; PBO, placebo.
Notes: Change from baseline in MMDs, MMDs with use of acute medication, and HIT-6 results: mean differences in change from baseline with 95% CrIs, where results < 0 favour the comparator, results > 0 favour eptinezumab 100 mg.
Change from baseline in MSQ subscores: mean differences in change from baseline with 95% CrIs, where results > 0 favour the comparator and results < 0 favour eptinezumab 100 mg.
50% and 75% migraine response rate results: odds ratios with 95% CrIs, where results > 1 favour the comparator, results < 1 favour eptinezumab 100 mg.

B.2.9.4.3.2. Eptinezumab 100 mg versus botulinum toxin A

In patients with CM for whom ≥ 3 prior preventive treatments failed, eptinezumab 100 mg was shown to be as effective as botulinum toxin A, as the latter did not demonstrate a statistically superior benefit in efficacy (change from baseline in MMDs, and 50% migraine response rate) over eptinezumab 100 mg:

- Botulinum toxin A led to an increase in change from baseline MMD versus eptinezumab 100 mg ([redacted])
- Botulinum toxin A had a lower probability of a 50% response rate when compared to eptinezumab 100 mg ([redacted])

Additional outcomes were not available for this analysis.

B.2.9.4.4. Pooled EM and CM: eptinezumab 100 mg versus anti-CGRPs in patients for whom ≥ 3 prior preventive treatments failed

In the pooled EM and CM population, eptinezumab 100 mg was shown to be as effective as comparator treatments in patients for whom ≥ 3 prior preventive treatments failed, with no comparator demonstrating a statistically superior benefit in efficacy (50% and 75% migraine response rates) over eptinezumab 100 mg (Table 22).

Table 22: Summary of NMA versus anti-CGRPs results: pooled EM and CM with ≥ 3 treatment failures

Comparator	**Reference treatment: eptinezumab 100 mg every 12 weeks**	
	50% migraine response rate	**75% migraine response rate**
PBO	[redacted]	[redacted]
ERE70q4w	[redacted]	[redacted]
ERE140q4w	[redacted]	[redacted]
FRE675q12w	[redacted]	-
FRE675/225/225q4w	[redacted]	-
GAL120q4w	[redacted]	-
GAL240q4w	[redacted]	-

Key: CrI, credible interval; ERE70q4w, erenumab 70 mg (q4w); ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); GAL240q4w, galcanezumab 240 mg (q4w); HIT-6, 6-item Headache Impact Test; MMD, monthly migraine days; PBO, placebo.
Notes: 50% and 75% migraine response rate results: odds ratios with 95% CrIs, where results > 1 favour the comparator, results < 1 favour eptinezumab 100 mg.

B.2.9.5. Uncertainties in the indirect and mixed treatment comparisons

Several limitations of this analysis were identified, with the primary limitation being the sparsity of available data for some combinations of outcomes and populations. Data were not well-reported for all outcomes of interest across migraine classifications and treatment failure subgroups, so analyses were not feasible for all outcomes of interest. Few studies were available per treatment comparison, and so random effect models were inappropriate for the majority of outcomes.

The feasibility assessment (presented in Appendix D) identified that MOH at baseline was a potential treatment effect modifier. However, the proportion of patients with MOH diagnosis at baseline was poorly reported across CM studies and therefore could not be adjusted for in the pooled or CM comparisons. This may have resulted in an unbalanced influence of MOH on the treatment effect across studies. In addition, the difference in placebo effect between different routes of administration was only adjusted for in secondary analyses for MMD.

The primary timepoint of interest was Week 12 for the analyses. However, differences in comparator dosing led to differences in reporting of outcomes at this timepoint, which resulted in 4-week interval data being combined with 12-week interval data for the analyses. As the monthly dosing may have led to an improved response on receipt of the second dose before Week 12, there were limitations in terms of comparability between 4-week and 12-week interval data.

The available timepoints were also a limitation for the analysis comparing eptinezumab with botulinum toxin A. Due to the sparsity of botulinum toxin A data, a comparison was performed using Week 24 botulinum toxin A and Week 12 eptinezumab data. In addition, MMD was not reported for botulinum toxin A, and therefore MHD data for botulinum toxin A was considered comparable with MMD data for eptinezumab. After evaluating the definition of a headache day in the PREEMPT trials (defined as a calendar day [00:00–23:59] when the patient reported ≥ 4 continuous hours of headache, per the patient diary) and the secondary efficacy variable: frequency of migraine days (defined as a calendar day with ≥ 4 continuous hours of headache meeting ICHD-II criteria for migraine [Criteria 1.1, 1.2 or 1.6]), it was deemed appropriate to compare MMD data from DELIVER with MHD data from

the PREEMPT trials. During the 28-day baseline period, mean MHD and mean MMD were similar in both treatment arms:

- Mean (SD) MHD: botulinum toxin A, 19.9 (3.68) days; placebo, 19.8 (3.68) days
- Mean (SD) MMD: botulinum toxin A, 19.1 (3.99) days; placebo, 18.9 (4.05) days[89]

Furthermore, within each migraine classification (EM and CM), baseline MHD and MMD were similar across the trials included within the NMA (see Appendix D). As such, MHD data from the PREEMPT trials were considered migraine days rather than headache days as suggested in previous appraisals.[1-3]

B.2.10. Adverse reactions

B.2.10.1. Summary of safety from SmPC

Over 2,000 patients have been treated with eptinezumab in clinical studies, and approximately 1,000 of these patients were exposed for 48 weeks (four doses).[5] The most common AEs were nasopharyngitis and hypersensitivity.

Approximately 6% of patients receiving eptinezumab 100 mg and 6% of patients on placebo in the PROMISE trials experienced nasopharyngitis.[5] Nasopharyngitis was most frequent following the first dose of eptinezumab and incidence decreased notably with subsequent doses and remained fairly steady thereafter.

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported and may develop within minutes of infusion.[5] The reported anaphylactic reactions have included symptoms of hypotension and respiratory difficulties and have led to discontinuation of eptinezumab. Other hypersensitivity reactions, including angioedema, urticaria, flushing, rash and pruritus, were reported in approximately 3% of patients on 100 mg and 1% of patients on placebo in the PROMISE studies.

Other symptoms reported in association with eptinezumab infusion include respiratory symptoms (nasal congestion, rhinorrhoea, throat irritation, cough,

sneezing, dyspnoea) and fatigue.[5, 6] Most of these events were non-serious and transient in nature.

Approximately 3% of patients on eptinezumab (any dose) and 2% of patients on placebo in the placebo-controlled PROMISE trials experienced fatigue. Fatigue was most frequent on the day of the first infusion. Following the first week and with subsequent infusions, fatigue was reported in lower incidences and the incidences were comparable to placebo.

A summary of common and very common AEs observed with eptinezumab and comparators, as reported in their SmPCs, is presented in Table 23.

Table 23: Summary of very common and common adverse events by treatment

Intervention	Key adverse events	
	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**
Eptinezumab	• None reported	• Nasopharyngitis • Hypersensitivity reactions • Infusion-related reactions • Fatigue
Erenumab	• None reported	• Hypersensitivity reactions, including anaphylaxis, angioedema, rash, swelling/oedema, and urticaria • Constipation • Pruritis (including generalised pruritis and pruritic rash) • Muscle spasms • Injection site reactions
Fremanezumab	• Injection site pain • Injection site induration • Injection site erythema	• Injection site pruritis
Galcanezumab	• Injection site pain • Injection site reactions	• Vertigo • Constipation • Pruritus
Source: eptinezumab UK SmPC (2022);[5] erenumab SmPC (2021);[90] fremanezumab SmPC (2021);[91] galcanezumab SmPC (2021)[92]		

B.2.10.2. DELIVER

B.2.10.2.1. Summary of adverse reactions reported in DELIVER

Similar proportions (eptinezumab 100 mg: 42%; eptinezumab 300 mg: 41%; placebo: 40%) of patients across eptinezumab and placebo arms reported a treatment-emergent adverse event (TEAE; Table 24).[67]

Table 24: Summary of TEAEs reported in DELIVER (safety population)

	Eptinezumab 100 mg (N = 299)	Eptinezumab 300 mg (N = 294)	Placebo (N = 298)
Patients with TEAEs, n (%)	127 (42)	120 (41)	119 (40)
Patients with SAEs, n (%)	5 (2)	7 (2)	4 (1)
Patients with TEAEs leading to infusion interruption/ termination, n (%)	1 (< 1)	3 (1)	0
Patients with TEAEs leading to withdrawal, n (%)	1 (< 1)	6 (2)	1 (< 1)
Deaths	0	0	0
Total number of TEAEs, n	[redacted]	[redacted]	[redacted]
Total number of SAEs, n	5	7	4
Total number of TEAEs leading to infusion interruption / termination, n	1	3	0
Total number of TEAEs leading to withdrawal, n	1	6	1

Key: SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Source: Ashina *et* al. (2022);[67] Eptinezumab clinical study report[66] (supplemented by results published on ClinicalTrials.gov: NCT04418765).

A summary of the most common TEAEs (≥ 1.5% of subjects) is provided in Table 25. The most common TEAE was COVID-19, with an incidence of approximately 6% across treatment arms.[67] Nasopharyngitis was the next most common TEAE, with an incidence ranging from 1% (placebo) to 3% (eptinezumab 300 mg).[66]

Table 25: Most common TEAEs by preferred term with an incidence of ≥ 1.5% in any treatment arm in DELIVER (safety population)

Preferred term	Eptinezumab 100 mg (N = 299)	Eptinezumab 300 mg (N = 294)	Placebo (N = 298)
COVID-19, n (%)	20 (7)	17 (6)	16 (5)
Nasopharyngitis, n (%)	5 (2)	9 (3)	3 (1)
Fatigue, n (%)	2 (1)	6 (2)	4 (1)
Diarrhoea, n (%)	0	5 (2)	5 (2)
Nausea, n (%)	4 (1)	5 (2)	4 (1)
Urinary tract infection, n (%)	1 (< 1)	5 (2)	4 (1)
Abdominal pain upper, n (%)	5 (2)	4 (1)	2 (1)
Arthralgia, n (%)	5 (2)	4 (1)	0
Dizziness, n (%)	2 (1)	4 (1)	5 (2)
Back pain, n (%)	5 (2)	3 (1)	4 (1)

Key: TEAE, treatment-emergent adverse event.
Source: Ashina et al. (2022)[67]

Hypersensitivity and anaphylactic reactions occurred in six (2%) patients in the eptinezumab 100 mg arm, 10 (3%) patients in the eptinezumab 300 mg arm, and six (2%) patients in the placebo arm.[67] The majority of hypersensitivity and anaphylactic reaction TEAEs were mild or moderate in severity, and two serious adverse events of anaphylactic reaction in the eptinezumab 300 mg arm were considered eptinezumab-related. The only other hypersensitivity and anaphylactic reaction TEAE that led to withdrawal from the study was one event of moderate hypersensitivity in a patient treated with eptinezumab 100 mg. Two patients treated with eptinezumab (treated with 100 mg and 300 mg) had mild circulatory collapse which led to interruption of the infusion. Neither of these events were considered to be allergic reactions and both patients received their second infusion without any AEs.[67]

Overall, five (1%) patients in the eptinezumab 100 mg arm, seven (2%) patients in the eptinezumab 300 mg arm, and two (1%) patients in the placebo arm experienced AEs potentially related to the IMP infusion (selected TEAEs with onset within 24 hours of 7 days after the IMP infusion, depending on the type of event).[67] All events were mild or moderate in severity, and none led to withdrawal from the study.

B.2.10.2.2. Treatment exposure

Most of the safety population ([redacted]) received two infusions of eptinezumab during the placebo-controlled period.[66] A total of [redacted] across both eptinezumab groups did not complete their infusion as planned and, therefore, did not receive the full dosage. For further information regarding exposure, please refer to Appendix F.

B.2.10.3. Supportive safety data

The PROMISE trials, PREVAIL and a pooled analysis provide further supportive evidence for the manageable tolerability profile of eptinezumab:

- In PROMISE-1, the incidence of TEAEs was similar across the eptinezumab (100 mg: 63.2%; 300 mg: 57.6%) and placebo (59.5%) arms. 29 patients with EM (3.3%) experienced a TEAE that resulted in study drug withdrawal, including six patients in the eptinezumab 100 mg arm, and five in the placebo arm[72]
- In PROMISE-2, the incidence of TEAEs was similar across treatment arms (eptinezumab 100 mg: 43.5%; placebo: 46.7%). 13 patients with CM (1.2%) experienced a TEAE resulting in study drug withdrawal, including three patients in the eptinezumab 100 mg arm and two patients in the placebo arm[73]
- PREVAIL provided long-term safety data for eptinezumab 300 mg over a 2-year study period, with a greater duration of exposure than for the DELIVER, PROMISE-1, and PROMISE-2 trials. These data, although for the 300 mg dose, are included as supportive evidence of eptinezumab over the long term. Overall, 18 patients experienced at least one TEAE that was considered related to eptinezumab, with the most frequently reported TEAEs being hypersensitivity (3.9%) and fatigue (3.1%)[93]
- A pooled analysis including patients with migraine treated with eptinezumab (n = 2,076) or placebo (n = 791) in four RCTs, including PROMISE-1, PROMISE-2, a Phase I study (NCT01772524), a Phase II study (NCT02275117), and an open-label study (PREVAIL; primary treatment phase only) reported that administering either eptinezumab 100 mg or eptinezumab 300 mg every 12 weeks demonstrated a favourable safety and tolerability profile.[94] A similar proportion of patients between treatment groups experienced at least one TEAE (100 mg: 52.2%; 300 mg: 56.7%; placebo: 52.3%); serious TEAEs (100 mg: 1.6%; 300 mg:

2.1%; placebo: 1.4%), and TEAEs leading to discontinuation (100 mg: 1.3%; 300 mg: 2.3%; placebo: 1.0%).

Further information regarding the safety reported in these trials is included in Appendix F.

B.2.11. Ongoing studies

There are no further studies investigating eptinezumab in the population of interest to this submission (i.e. studies that may report data within the next 12 months).

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the clinical evidence

Eptinezumab offers patients with migraine a treatment option with a less frequent dosing regimen (12-weekly) than available anti-CGRP treatments, in addition to fast preventive migraine efficacy. Eptinezumab also provides similar efficacy to current treatments, a well-tolerated safety profile and demonstrable improvements in patient quality of life.[95]

Eptinezumab delivered significant reductions in MMDs among other outcomes in patients with EM and CM. Statistically significant treatment effects ($p < 0.0001$) favouring eptinezumab 100 mg versus placebo were seen for all efficacy analyses that were included in the testing strategy in the DELIVER study. In the primary analysis of the primary endpoint (mean change from baseline in the number of MMDs from Weeks 1–12), eptinezumab 100 mg demonstrated a clinically meaningful and significant difference versus placebo (-2.7 days; $p < 0.0001$).[67]

The results of the sensitivity analyses and the supplementary analyses of the primary endpoint were consistent with the results of the primary analyses.[66] In addition, the improvement with eptinezumab in change from baseline in the number of MMDs during Weeks 1–12 was sustained during Weeks 13–24.[66]

In separate studies of patients with EM (PROMISE-1) and CM (PROMISE-2), eptinezumab 100 mg also demonstrated efficacy by providing a statistically

significant reduction in the number of MMDs over Weeks 1–12 compared with placebo ($p < 0.0001$).[72, 73]

The principal findings from the clinical evidence can be grouped as follows.

Eptinezumab is an effective treatment for patients with migraine for whom ≥ 3 prior preventive treatments have failed

Patients with migraine for whom ≥ 3 prior preventive treatments have failed represent a population with considerable humanistic and economic burden, as described in Sections B.1.3.3.2.3 and B.1.3.3.3.

In patients for whom ≥ 3 prior preventive treatments failed, eptinezumab 100 mg demonstrated significant reductions in mean change from baseline in the number of MMDs from Weeks 1–12 versus placebo ([redacted]).[75, 76] This improvement was sustained during Weeks 13–24 following the second infusion of eptinezumab ([redacted]).[75, 76] Similar results were observed for a 50% migraine response rate in patients for whom ≥ 3 prior treatments failed (OR [95% CI] versus placebo: [redacted]), and sustained during Weeks 13–24 (OR [95% CI] vs placebo[redacted]).

In an ITC, eptinezumab 100 mg was also shown to be as effective as other anti-CGRPs (erenumab, fremanezumab and galcanezumab) in reducing MMDs and achieving 50% migraine response rate for patients with EM or CM for whom ≥ 3 prior preventive treatments had failed, as described in Section B.2.9.

IV treatment with eptinezumab provided migraine relief as early as the first day post-infusion

Migraine-preventive effects were observed with eptinezumab on the first day after dosing. Significantly fewer patients with EM or CM in DELIVER who received eptinezumab 100 mg experienced a migraine on the first day post-infusion compared with placebo (eptinezumab 100 mg: 27%; placebo: 44%; $p < 0.0001$).[67] Similar results were achieved in the PROMISE studies (PROMISE-1 [EM]: eptinezumab 100 mg: 15%; placebo: 23%;[72] PROMISE-2 [CM]: eptinezumab 100 mg: 29%; placebo: 42%; $p < 0.0001$).[73]

The RELIEF trial provided further support of the fast onset of migraine relief with eptinezumab. Acute treatment with eptinezumab during an active moderate-to-severe migraine attack significantly more than halved the time to headache freedom compared with placebo (4 hours versus 9 hours; p = 0.0006).[74]

Eptinezumab's treatment effect was sustained with quarterly dosing frequency

The early therapeutic effect observed with eptinezumab was maintained through Weeks 1–12, as eptinezumab met its primary endpoint across all three trials. This suggests that eptinezumab provided a durable response despite less frequent treatment administration (i.e. quarterly rather than monthly as with other anti-CGRPs). This aligns with the preferences of patients with migraine who value treatments with a lower administration frequency and a durability of prevention.

Migraine-related HRQL improved with eptinezumab treatment

Eptinezumab has also demonstrated significant ($p < 0.0001$) improvements in patients' HRQL, based on MSQ subscores, and their ability to function normally in daily life (based on changes in the HIT-6 total score).[66] Eptinezumab 100 mg also resulted in workplace productivity benefits for patients, leading to significant ($p < 0.05$) reductions in absenteeism, presenteeism, work productivity loss and activity impairment across the 24-week treatment period.[66]

Eptinezumab administered by IV infusions has demonstrated an acceptable safety profile across several RCTs

Eptinezumab administered by IV infusions every 12 weeks demonstrated a well-tolerated safety profile for the preventive treatment of migraine in patients with EM and CM in DELIVER and PROMISE trials.[67, 72, 73] The proportion of patients experiencing any TEAE was similar across treatment arms, and no dose response patterns for safety endpoints were identified across eptinezumab doses. Most TEAEs were mild or moderate in severity and no deaths were reported during the studies. A pooled analysis of four RCTs and the PREVAIL study, including 2,076 patients treated with eptinezumab and 791 patients treated with placebo, provided further support as they showed similar rates of TEAEs, serious TEAEs and TEAEs leading to discontinuation between the eptinezumab and placebo groups.[94]

DELIVER employed broader selection criteria than previous trials of eptinezumab without new safety concerns emerging, providing further support for the well-tolerated safety profile of eptinezumab.

B.2.12.2. Strengths and limitations of the evidence base

DELIVER, PROMISE-1 and PROMISE-2 were all multicentre, double-blind RCTs that were designed to investigate the efficacy and safety of eptinezumab for the prevention of migraine. These trials were conducted in compliance with *Good Clinical Practices* as referenced in the *International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E6*, and were of good quality, which provides confidence in their internal validity.

As described in Section B.2.5, the patients included in these trials had similar baseline demographics and clinical characteristics, compared with patients treated in UK clinical practice who have participated in a prospective real-world analysis of erenumab in CM. Most patients included in DELIVER were from Europe (n = 993; 93%), including 20 patients from 5 UK sites. PROMISE-1 included patients from Georgia and the US, and PROMISE-2 included patients from 128 sites in 13 countries in the US and Europe, including five sites in the UK.

Limitations of the clinical evidence base for eptinezumab include the lack of a direct comparison with an active comparator used in UK clinical practice. To address this limitation, an ITC was conducted (Section B.2.9). The results of the ITC should be interpreted with caution, owing to the sparsity of data available for some combinations of outcomes and populations (Section B.2.9.4.3). However, clinical experts who were consulted on the results of this NMA considered the efficacy of eptinezumab to be equal to other anti-CGRPs that were analysed.[55]

Another key limitation of the DELIVER trial was that the FAS population was not limited to the population of interest (i.e. patients for whom ≥ 3 prior preventive treatments failed) outlined in the decision problem, and this was not a pre-specified subgroup. As a result, supporting data from DELIVER that are relevant to the decision problem are post-hoc. However, results were consistent with the overall results obtained in the trial, which supports the robustness of this analysis.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology evaluation).
- See section 3.1 of the user guide for full details of the information required in appendix G.

An SLR of cost-effectiveness studies relating to EM and CM was conducted in February 2021, and updated in April 2022, in line with NICE guidelines.[96] For full details of the SLR methods and outcomes, please see Appendix G. The SLR identified 16 studies from 26 reports that met the inclusion criteria (studies assessing populations with 3 prior preventive treatment failures). Of these studies, 15 were cost–utility analyses and one was a cost-effectiveness analysis.[97] A list of the identified studies may be seen in Table 26.

Most of these studies followed a Markov (n = 7) [1, 98-102] or semi-Markov (n = 3) [2, 103, 104] structure. Most of the studies focused on a short-term time horizon of 10 years or less (n = 13) [1, 3, 97-107], and only three of the studies considered life-long horizons[1, 2, 108]. Most studies originated from Europe (n = 12) [1-3, 53, 99, 100, 102-104, 106-108] and focused on the following treatments:

- Botulinum toxin A (n = 11) [1-3, 99-103, 105, 107]
- Erenumab (n = 6) [3, 97, 105-108]
- Fremanezumab (n = 4) [1, 97, 103, 104]
- Galcanezumab (n = 3) [2, 97, 98]

Of the 16 included studies, nine studies[1-3, 97, 103, 104, 106-108] assessed both EM and CM populations (eight studies reported separate data for EM and CM populations[1-3, 97, 103, 104, 106, 107], while one study reported combined data for the entire population[108]), six studies investigated CM population only[53, 99-102, 105], and one study assessed EM population only.[98]

Table 26: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Mahon[106]	2021	Hybrid decision-tree (responders vs non-responders) plus Markov model: • On treatment • Re-evaluation period • Negative discontinuation • Positive discontinuation	• Adult patients aged ≥ 18 years with migraine who have ≥ 4 MHDs per month • Patients for whom 2 or more previous preventive treatments have failed	Incremental QALYs: • EM and CM: 0.2583 • CM: 0.3290 • EM: 0.1416	Incremental costs: • EM and CM: 12,668 • CM: -1,834 • EM: 35,124 Cost year: 2019 Currency: Swedish krona (SEK)	Erenumab vs placebo: • EM and CM: 49,043 • CM: dominant • EM: 248,128
NICE erenumab (TA682) [3]	2021	Decision tree and Markov: • Responders (on treatment) • Responders (off treatment) • Non-responders (off treatment) • 28 MMD health states	• Whole population (66% CM, 34% EM) • CM • EM (for whom 3 or more prior prophylactic treatments have failed)	Redacted	Redacted Cost year: 2017 Currency: Pound sterling (£)	ICER vs BSC: • Whole population: – £22,446 (blended dose) – £19,872 (140 mg dose) • CM: – £17,212 (blended dose) – £13,340 (140 mg dose)

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			Mean age: 42.25 years Percentage of female patients: 84.51%			– Versus botulinum toxin A: £18,893 (70 mg dose); £17,832 (140 mg dose) • EM: – £35,787 (blended dose) – £40,662 (140 mg dose) • Full incremental analysis (with PAS) – £18,824 (blended dose) – £17,795 (140 mg) – Versus botulinum toxin A: £15,953 (70 mg dose); £17,795 (140 mg dose); versus BSC £10,601
CADTH Botulinum toxin A[101]	2006	Markov model with seven health states,	Adult patients who had	NR	NR	Botulinum toxin A vs BSC: CAN$34,407

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		six of which were based on the number of headache days experienced per 28-day period (0–3; 4–9; 10–14; 15–19; 20–23 and 24 or more days), and one discontinuation state.	experienced 15 or more headache days per four-week period for whom 3 or more preventive treatments have failed. Baseline characteristics are taken from PREEMPT-1 and PREEMPT-2.		Cost year: 2019 Currency: Canadian dollar (CAN$)	
Hansson-Heldblom[100]	2020		Patients with CM for whom 3 of more preventive treatments had failed	Sweden: • Total QALYs: – Botulinum toxin A: 6.505 – Placebo: 6.257 • Discounted QALYs: – Botulinum toxin A: 5.711	Sweden: • Total costs: – Botulinum toxin A: €23,293 – Placebo: €18,846 • Discounted costs: – Botulinum toxin	Sweden: • Botulinum toxin A vs placebo: €18,506 Norway: • Botulinum toxin A vs placebo: €19,954

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				– Placebo: 5.488 Norway: • Total QALYs: – Botulinum toxin A: 6.503 – Placebo: 6.255 • Discounted QALYs: – Botulinum toxin A: 5.480 – Placebo: 5.264	A: €20,700 – Placebo: €16,574 Norway: • Total costs: – Botulinum toxin A: €13,297 – Placebo: €8,524 • Discounted costs: – Botulinum toxin A: €11,501 – Placebo: €7,200 Cost year: 2019 Currency: Euro (€)	
Hollier-Hann[99]	2020	CUA: By health state:	• Patients with CM	Total QALYs: • Botulinum toxin A: 1.23	Cost year: 2017	Botulinum toxin A versus placebo: £16,306

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• 0–3 migraines per 28 days • 4–9 migraines per 28 days • 10–14 migraines per 28 days • 15–19 migraines per 28 days • 20–23 migraines per 28 days • 24+ migraines per 28 days	• Mean age: 41.3 • Percentage of female patients: 86.4%	• Placebo: 1.15 Total (discounted): • Botulinum toxin A: 1.21 • Placebo: 1.13	Currency: Pound sterling (£) Total cost: • Botulinum toxin A: £2,861 • Placebo: £1,649 Total (discounted): • Botulinum toxin A: £2,827 • Placebo: £1,623	
Batty[109]	2013	CUA: By health state: • 0–3 migraines per 28 days • 4–9 migraines per 28 days • 10–14 migraines per 28 days • 15–19 migraines per 28 days	• Patients with CM • Mean age: 41.3 • Percentage of female patients: 86.4%	Discounted QALYs • Botulinum toxin A: 1.30 • Placebo: 1.20	Total costs (discounted): • Botulinum toxin A: £2,997 • Placebo: £1,630 Cost year: 2010	Botulinum toxin A versus placebo: £15,028

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• 20–23 migraines per 28 days • 24+ migraines per 28 days			Currency: Pound sterling (£)	
NICE fremanezumab (TA631)[1]	2020	Semi-Markov: • Response (on treatment), no response (on treatment) and off treatment, and 28 MMD health states	• Patients with EM and CM • Mean age: 42 years • Percentage of female patients: 87.5%	Redacted	Redacted Cost year: NR Currency: Pound sterling (£)	ICER versus BSC: • Base case results in EM: £13,954 • Base case results in CM: – Botulinum toxin A vs BSC: £6,777 – Fremanezumab vs BSC: £11,825 – Fremanezumab vs Botulinum toxin A: £16,227 • EM fremanezumab blended utility results (ICER versus BSC): £16,142
NICE fremanezumab (TA764)[1]	2022	Decision tree analysis and Markov model Decision tree:	• Patients with EM • Mean age: 42 years	Redacted Incremental QALYs	Redacted Incremental costs	EM: fremanezumab vs BSC: £17,172

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• Responded (defined as a 50% reduction for episodic migraine or a 30% reduction for chronic migraine in monthly migraine days from baseline) and who remained on treatment. • Did not respond and who stopped treatment. Markov: Used to model the distribution of monthly migraine days in each health state	• Percentage of female patients: 87.5%	(fremanezumab vs BSC: 0.315	(fremanezumab vs BSC: £5,402 Cost year: NR Currency: Pound sterling (£)	
NICE galcanezumab (TA659)[2]	2020	Markov: • On treatment, off treatment, • Responder, • Non-responder	Patients with EM or CM	Redacted	Redacted Cost year: NR Currency: Pound sterling (£)	Base case results in EM: • Updated (corrected) base case results vs BSC:*

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• 28 MHD health states				– Galcanezumab 120 mg vs BSC ICER (£/QALY): £29,230 Base case in CM: • Galcanezumab 120 mg vs BSC: £8,077 • Galcanezumab 120 mg vs Botulinum toxin A: £2,595 • Updated company base case results of CM:* – Galcanezumab 120 mg vs BSC ICER (£/QALY): £8,080 • Updated company base case results of CM:* – Galcanezumab 120 mg vs Botulinum toxin A ICER (£/QALY): £2,560

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						Summary: • EM (vs BSC): £26,847 • CM (vs BSC): £7,421 • CM (vs Botulinum toxin A): £2,352 **Note***: The company presented an updated base case analysis using the amended model. The error identified in the model was that patients do not return to baseline monthly migraine days, but to a slightly higher value
PBAC Galcanezumab[98]	2020	Markov model health states: • On treatment/responder (after 12-week assessment) • Discontinued (due to poor response)	Adult patients with EM who have experienced an inadequate response, intolerance, or a contraindication to ≥ 3 prophylactic	Galcanezumab: 3.002 BSC: 2.807	Galcanezumab: Redacted BSC: $28,270 Cost year: NR Currency: Australian dollar (AUD$)	Redacted

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• Discontinued (due to adverse events) • Dead	migraine medications			
Sehgal[97]	2020	NR	Adult patients with EM and CM. Patients were either treatment-naïve, or had received 3 prior therapies that had not worked'	NR	NR Cost year: NR Currency: CAN$	Private payer perspective: • EM: – Fremanezumab: CAN$12,572 – Erenumab: CAN$13,388 – Galcanezumab: CAN$13,019 • CM: – Botulinum toxin A: CAN$27,741 – Fremanezumab: CAN$30,275 Public payer perspective • EM: – Fremanezumab: CAN$6421 – Erenumab: CAN$6,738

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						– Galcanezumab: CAN$6,697 • CM: – Botulinum toxin A: CAN$13,192 – Fremanezumab: CAN$14,568
Silva[108]	2020	Hybrid decision-tree and Markov model	Adults in Portugal for whom 3 previous treatments had failed	Incremental QALYs: • Discounted: 0.28 • Undiscounted: 0.60	NR Cost year: 2019 Currency: Euro (€)	Erenumab dominates
SMC Fremanezumab[103]	2019	Semi-Markov with decision treat for response.	Patients with EM and CM for whom 3 or more preventive migraine treatments had failed Mean age: • EM: 43 years • CM: 41 years	NR	NR Cost year: 2019 Currency: pound sterling (£)	EM: • Fremanezumab vs BSC: £10,300 CM: • Fremanezumab vs BSC: £8,824 • Fremanezumab vs Botulinum toxin A: £10,627

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
SMC Erenumab[107]	2019	Decision tree for response, followed by Markov model where responders could transition between 'on treatment' and 'discontinuation' states	Patients with EM and CM for whom ≥ 3 preventive migraine treatments had failed	NR	NR Cost year: 2019 Currency: Pound sterling (£)	EM: • Erenumab blended vs BSC: £35,810 • Erenumab 140 mg vs BSC: £40,667 CM: • Erenumab blended vs Botulinum toxin A: £18,883 • Erenumab 140 mg vs Botulinum toxin A: £17,823 • Erenumab blended vs BSC: £17,217 • Erenumab 140 mg vs BSC: £13,345
SMC botulinum toxin A[102]	2017	Markov model • On- and off-treatment health states	Adults with CM whose condition has failed to respond to ≥ 3 prior oral prophylactic treatments, where medication overuse has been	Incremental QALYs: 0.12	Incremental costs: £1,301 Cost year: 2016 Currency: Pound sterling (£)	Botulinum toxin A vs BSC: £10,816

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			appropriately managed			
PBAC botulinum toxin A[105]	2012	Markov model with six health states	Adult patients with CM for whom ≥ 2 preventive migraine treatments had failed.	NR	NR Cost year: NR Currency: Australian dollar (AUD$)	AUD$15,000 to AUD$45,000
NICE botulinum toxin A (TA260)[53]	2012	Markov: • On/off treatment • Number of MHD (0–3, 4–9, 10–14, 15–19, 20–23 and 24–28)	Patients with CM	Total QALYs: • Botulinum toxin A: 1.32 • Placebo: 1.23 Discounted total QALYs • Botulinum toxin A: 1.29 • Placebo: 1.20	Cost year: 2010 Currency: Pound sterling (£) Total costs: • Botulinum toxin A: £2,471 • Placebo: £1,936 Discounted total costs: • Botulinum toxin A: £2,438 • Placebo: £1,895	Botulinum toxin A vs placebo: £6,083

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Key: BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; CM, chronic migraine; CUA, cost–utility analysis; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; MHD, migraine headache days; MMD, monthly migraine days; NICE, National Institute for Health and Care Excellence; NR, not reported; PAS, patient access scheme; PBAC, Pharmaceutical Benefits Advisory Committee; QALYs, quality-adjusted life years; SMC, Scottish Medicines Consortium; TA, technology appraisal. **Note:** Previous migraine appraisals are mixed and the meanings of MHD and MMD have been used interchangeably in places. In this submission, MMD (monthly migraine days) is used consistently. The only places where the term MHD is used refer specifically to monthly headache days, i.e. days when the headache does not have features of a migraine.						

B.3.2. Economic analysis

B.3.2.1. Patient population

Eptinezumab (Vyepti®) is indicated for the prevention of migraine in adults with 4 or more migraine days per month. It is expected to be used in England in the same place in the treatment pathway as other anti-calcitonin gene-related peptides (anti-CGRPs), so the population of interest for the economic analysis is patients for whom 3 or more prior preventive treatments have failed. In addition to the base case population, two subpopulations (EM and CM) are included in the analyses. The population is referred to in short as 4 or more monthly migraine days (4M) TF3+, and subpopulations as EM TF3+ and CM TF3+.

Patients in the model are based on the key characteristics from the full analysis set of patients in the DELIVER trial, as presented in Table 27. However, the distribution of patients between EM and CM in DELIVER was not reflective of clinical practice. Consequently, Lundbeck conducted a survey in collaboration with the Migraine Trust to collect appropriate data inputs.[110]

Table 27: Baseline patient characteristics used in the economic analysis

Characteristic	Value	Source
Age, mean (SD)	45.2 (11.84)	DELIVER (TF3+)[111]
Female	88.7%	DELIVER (TF3+)[111]
Chronic migraine at baseline	46%	Lundbeck in collaboration with the Migraine Trust survey[110]
MMD at baseline, CM subgroup, mean (SD)	19.09 (3.97)	DELIVER (TF3+)[75]
MMD at baseline, EM subgroup, mean (SD)	9.79 (2.53)	DELIVER (TF3+)[76]
Key: FAS, full analysis set; MMD, monthly migraine days; SD, standard deviation; TF3+, ≥3 prior treatment failures.		

Previous NICE appraisals for migraine have used the terms Migraine Headache Days (MHD) and Monthly Migraine Days (MMD). In the current submission, MMD is used consistently in the description migraine frequency within the economic analysis, and it is the primary characteristic tracked within the model. MHDs are not tracked in the model, but when the acronym MHD is used, it refers specifically to monthly headache days, i.e. days when the headache does not have any features of a migraine.

Previous NICE appraisals have also analysed EM and CM separately, so for consistency these sub-populations are also analysed separately here (Section B.3.12), however, they are not mutually exclusive (refer to Section B.3.2.3.4).

B.3.2.2. Model structure

As discussed in Section B.3.1, there have been several previous UK HTA appraisals for preventive migraine products[1-3, 53, 102, 103, 107, 112], all using a similar (semi-)Markov modelling approach for the economic evaluation. Key issues noted in these appraisals are summarised in Table 28.

Considering the critique on previous model structures, which included the lack of natural history, treatment holidays and general flexibility, an individual patient simulation model using a discrete event simulation (DES) has been selected in preference to a Markov approach. Individual patient models generate a virtual cohort of patients who each follow an individualised disease pathway. This is determined according to baseline characteristics, sampled or fixed-time events relevant to clinical management (including treatment), and in this case the natural history of disease. The DES approach has been adopted for the current de novo model, with the intent of reducing the previously highlighted uncertainty in NICE appraisals of anti-CGRPs. Most notably by tackling the assumption of migraines for life by considering the natural history of the disease, including a clinical framework of treatment holidays for testing for changes in underlying status.

Whilst previous models have been judged sufficient in certain ways, consistent criticism of some aspects is a call for improved sophistication to match progress with evidence and consistency across assumptions. This evaluation of cost-effectiveness therefore builds on the previous NICE migraine appraisals, specifically the most recently completed, that of galcanezumab.[1-3, 53] The DES approach allows to respond to the stated challenge of including the natural history of migraine. This analysis is offered as an alternative to the base case, achieved by including two natural history events marking improvement. These are first considered within a clinical schedule of annual treatment holidays, during a period of five years on-treatment. The inclusion of treatment holidays is based on the need to ‘unmask’ the underlying condition to test for change. Beyond five years, these events are considered without the treatment holiday framework.

NICE Decision Support Unit (DSU) Technical Support Document (TSD) 15 describes the general advantage of patient-level modelling for flexibility but more importantly it describes specific situations where cohort models become problematic.[113] The situation when ‘patient flow [is] determined by time since last event or history of pervious events’ becomes relevant here because the clinical framework of treatment holiday ‘tests’ in the natural history model creates a high level of temporal complexity in respect to tracking migraine frequency. The solution offered for avoiding excessive tunnel states in a cohort context is retaining the state transition framework but switching to a patient level simulation in which a single patient moves between states stochastically. However, as the current model needs the flexibility to allow risks to change over time, a DES framework is more appropriate, this allows ‘sampling a single time to event estimate from a non-exponential time-to-event distribution which is easier and more efficient than calculating time-dependent transition probabilities for each cycle in a patient-level state-transition model.’

Table 28: Key issues from previous migraine NICE appraisals

Issue	TA764 (fremanezumab)[1]	TA682 (erenumab)[3]	TA659 (galcanezumab)[2]	TA260 (botulinum toxin A)[53]
Time horizon	A lifetime time horizon is necessary to capture all relevant costs and benefits associated with fremanezumab. Because there is no long-term natural history data, any long-term modelling beyond 10 years would be highly uncertain	A lifetime time horizon is necessary to capture all relevant costs and benefits associated with erenumab, as recommended by the ERG		
Placebo effect		It is acceptable to account for a loss of the placebo effect when migraine responds to best supportive care	Placebo (BSC) effect dissipates when migraine responds to best supportive care. The rate is from full effect to baseline over 12 one-month cycles from the end of assessment.	The benefits of botulinum toxin A include a significant placebo effect. It would therefore be wrong to retain the placebo effect when receiving botulinum toxin A but not when receiving the placebo
Relative effectiveness	It is uncertain whether fremanezumab is more clinically effective than botulinum toxin A. The Committee agreed that it was appropriate to consider a scenario in which equivalent efficacy was assumed and another scenario in which the results of the network meta-analysis were incorporated	Including a treatment effect for erenumab compared with botulinum toxin A is acceptable Because of the uncertainty in the results of the ITC, the Committee considered it appropriate to consider cost-effectiveness analyses in which erenumab and botulinum toxin A were assumed to have similar effectiveness	It was appropriate to use clinical effectiveness estimates from the ITC for CM. It was appropriate to consider a scenario in which equivalent efficacy was assumed and another scenario that included the results of the ITC	

Issue	TA764 (fremanezumab)[1]	TA682 (erenumab)[3]	TA659 (galcanezumab)[2]	TA260 (botulinum toxin A)[53]
Treatment waning and discontinuation	The fremanezumab all-cause discontinuation rate is higher than expected and could affect the cost-effectiveness results Assuming that migraine frequency would revert to the frequency of best supportive care after discontinuation from all causes was overly optimistic. A scenario where people revert to baseline MMDs is more in line with clinical expert expectations	While people stay on treatment, it is reasonable to assume that the treatment effect does not wane over time An annual discontinuation rate of 10% caused by loss of efficacy, in addition to the 2.38% all-cause discontinuation rate, was not appropriate. Loss of efficacy may result in treatment discontinuation, but the company's scenario did not reflect the gradual loss of effectiveness that would occur before treatment was stopped		
Negative stopping rule	Applying a negative stopping rule was appropriate. Any treatment benefit seen while on treatment (during the initial 12 weeks) would not be maintained after stopping the treatment	The Committee concluded that it was appropriate to include a negative stopping rule at 3 months in the economic model if there was no response to treatment. No response was defined as less than a 30% reduction (for CM) or 50% reduction (for EM) in MMDs at the 12-week assessment	The Committee concluded that it was appropriate to include a negative stopping rule at 3 months if there was insufficient response to treatment based on the agreed thresholds (having less than a 50% reduction in MMDs for EM, and less than a 30% reduction in MMD in CM)	The manufacturer and the clinical community agreed that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice
Positive stopping rule	Positive stopping rule assumptions, where 20% of people whose migraine responded to treatment would	The company's positive stopping rule scenarios assumed that people staying on treatment would be	The Committee did not consider it appropriate to include positive discontinuation because there	The Committee concluded that a positive stopping rule in which patients stop treatment if their condition has changed

Issue	TA764 (fremanezumab)[1]	TA682 (erenumab)[3]	TA659 (galcanezumab)[2]	TA260 (botulinum toxin A)[53]
	discontinue every 64 weeks despite treatment effect being maintained, were not appropriate The Committee acknowledged that, without long-term natural history data, this could not be fully understood The Committee acknowledged that treatment may not continue indefinitely after successful treatment and took this into account for decision-making	reassessed after 64.5 weeks. After that, 20% of people would stop treatment, while the remainder would resume treatment and be reassessed at 76.5-week intervals. These scenarios were not appropriate The clinical experts explained that in practice, if migraine responds to treatment, some people may try a treatment break	are no clear criteria for when people should stop treatment	to EM (that is, fewer than 15 headache days per month) for 3 consecutive months was the most clinically relevant The Committee also noted that the marketing authorisation for botulinum toxin A does not include use in people with EM
Utility mapping	The Committee concluded that the rationale for using MSQ data was reasonable because the EQ-5D-5L was not sufficiently sensitive to changes in quality of life caused by migraine The company's approach to calculating model utility values is reasonable but still uncertain	The Committee noted that the utility data were a key driver of the cost-effectiveness estimates. It was concerned about the reliability of the values given the uncertainty of using data from a broader population and mapping this to EQ-5D-3L. On balance, the Committee concluded that the utility values used in the model may be reasonable but were uncertain Applying a mode of administration utility decrement to botulinum toxin A was not appropriate		The Committee noted the ERG's concern that the non-MSQ parameter values were different in the botulinum toxin A and placebo utility mapping functions. The Committee noted that when the ERG equalised the non-MSQ parameter values, less non-monotonicity was observed. The Committee concluded that this was the most plausible scenario

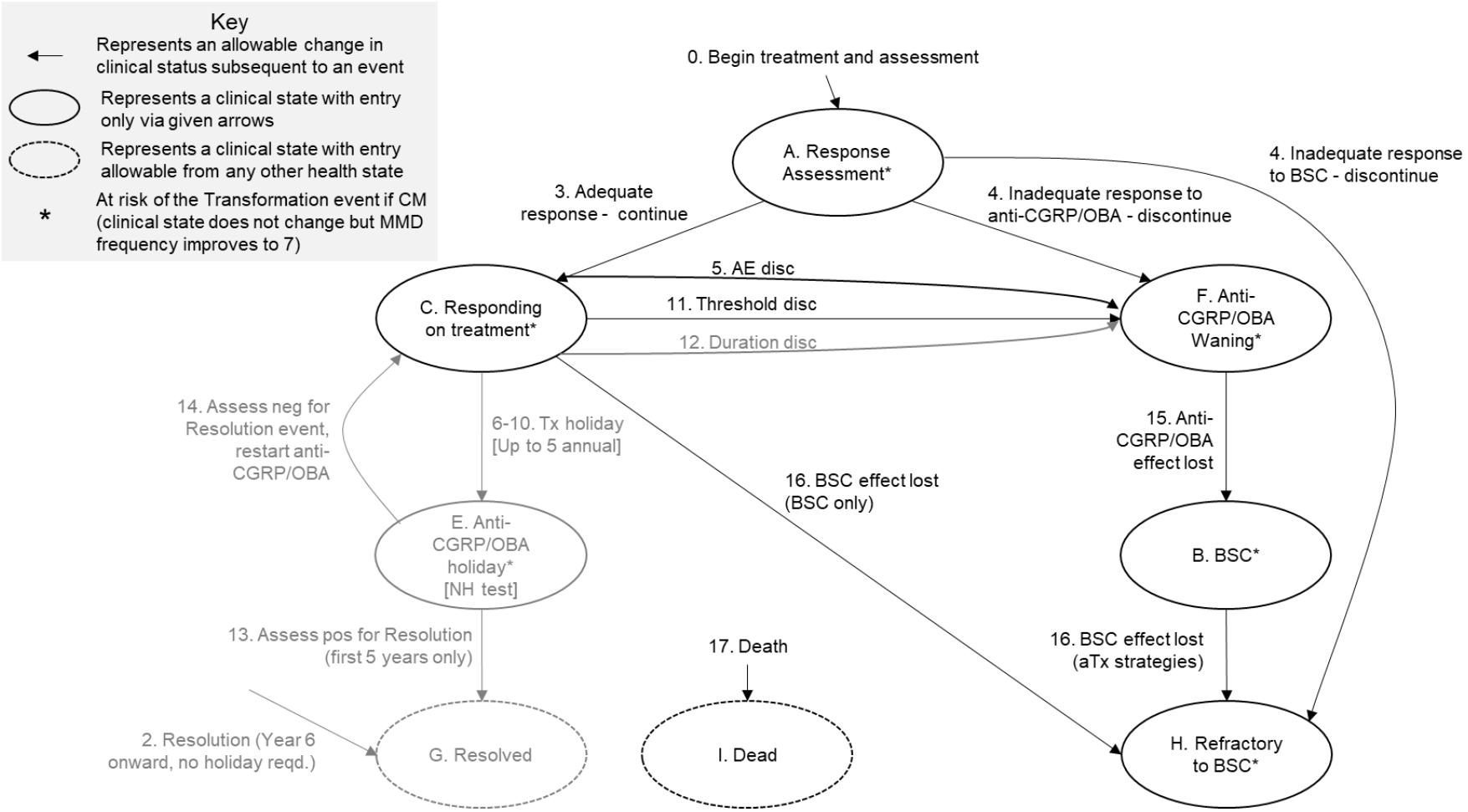
Issue	TA764 (fremanezumab)[1]	TA682 (erenumab)[3]	TA659 (galcanezumab)[2]	TA260 (botulinum toxin A)[53]
Differential utilities	There was a clinical rationale for using differential utilities for on- and off-treatment health states The company's new approach to modelling differential utility for people on and off treatment was acceptable	It was acceptable to use differential utilities in the modelling The Committee recognised that there was some evidence of a treatment effect for erenumab beyond a decrease in MMDs	There was evidence for using differential utility values for treatments, which was the preference of the committee Applying differential utilities to galcanezumab and comparators would allow improvements in migraine severity to be captured beyond the number of MHDs	The Committee noted comments from consultees and commentators that treatment with botulinum toxin A is associated with a range of clinical and non-clinical benefits, which are not included in the reduction in the number of headache days per month The Committee concluded that although using differential utilities was plausible, there was still considerable uncertainty around the degree to which differential utilities existed within each health state
Lack of natural history data	The lack of long-term natural history data and simplicity of the model causes a high level of uncertainty	The model structure proposed by the company did not fully capture natural progression of migraine. The impact of this simplification is not fully known and hence increases the uncertainty regarding the cost effectiveness results	There are 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	

Key: CM, chronic migraine; EM, episodic migraine; ERG, Evidence Review Group; ITC, indirect treatment comparison; MHD, monthly headache days; MMD, monthly migraine days; MSQ, Migraine-Specific Quality-of-Life Questionnaire; TA, technology appraisal.

B.3.2.3. Model diagram

The model diagram for the DES is presented in Figure 5 and shows clinical states and the events that trigger transition between them. Patients enter the model in the 'response assessment' clinical state when they start treatment, which is a clinical period of 12 weeks for anti-CGRP strategies and 24 weeks later for the botulinum toxin A strategy. After that, patients can then occupy one of five further clinical states (in base case of no natural history). There are six possible events individuals are at risk of in the base case, where natural history is not considered. Table 29 and Table 30 present all the clinical states and the events that dictate transitions between them. The states presented in this figure and tables are referred to as 'clinical states' rather than health states, as the MMD frequency is what dictates the utility, and therefore should be considered as the health states in this model. There are 31 health states, representing the full range of monthly migraine day (MMD) frequency of 0–30. States and events in grey apply when natural history and treatment holidays are included. Individuals with CM are at risk of Transformation in any clinical state whilst alive, except for when 'resolved'.

Figure 5: Model diagram of clinical states



Key: AE, adverse event; anti-CGRP, anti-calcitonin gene-related peptides; aTx, active treatments (anti-CGRPs or botulinum toxin A); BSC, best supportive care; MMD, monthly migraine days; NH, natural history; OBA, Onabotulinum toxin A; Tx, treatment (BSC, anti-CGRPs or botulinum toxin A
Notes: Clinical states are presented here. The health 'state' is the MMD level, which is dependent on clinical status and treatment strategy. MMDs are tracked through time. Text and figures in grey only feature in scenario analyses. Letters and numbers match explanations in Table 29 and Table 30.

Table 29: Clinical states

State ID	Clinical state name	Treatment status	Description
A	Response assessment	On-treatment (anti-CGRP/ botulinum toxin A/BSC)	A fixed 12-week period (24 weeks for botulinum toxin A) following commencement of treatment. Treatment effect (CFB) is applied as a linear ascent from baseline MMDs to full effect through 4 weeks, for responders and non-responders alike. Full treatment effect (CFB) is applied for the remainder of the assessment period. Non-responders discontinue at the end of initial assessment.
B	BSC (after anti-CGRP/ botulinum toxin A)	BSC	Follows the failure of anti-CGRP/botulinum toxin A. Response to BSC is sampled and treatment effect (CFB) is awarded after an anti-CGRP/botulinum toxin A treatment effect waning period (F). BSC treatment effect dissipates over one year in responders and non-responders alike.
C	Responding on anti-CGRP/botulinum toxin A	On-treatment (anti-CGRP/ botulinum toxin A /BSC)	The period for responders when the treatment effect (CFB) is maintained (anti-CGRP/botulinum toxin A/BSC). Interruption may occur on treatment discontinuation or death.
D	Responding off anti-CGRP/botulinum toxin A	Off-treatment (anti-CGRP/ botulinum toxin A)	Super-responder scenario only (not represented in the model diagram). When full treatment effect is awarded to anti-CGRP/botulinum toxin A despite treatment discontinuation. Described in previous TAs as 'super-response'.[+] May only occur (be unmasked) following a treatment holiday (when natural history is included).
E	Anti-CGRP/botulinum toxin A holiday	Off-treatment (anti-CGRP/ botulinum toxin A)	Natural history scenario only. When anti-CGRP/botulinum toxin A treatment is discontinued for 12 weeks to check for any changes in the underlying frequency of migraine. By the end of this period the treatment effect is waned to baseline in a linear fashion.
F	Anti-CGRP/botulinum toxin A waning	Off-treatment	When anti-CGRP/botulinum toxin A treatment is discontinued a 4-month period of waning effect follows. Through this period the treatment effect (CFB) declines linearly, returning to baseline MMD frequency.[114]
G	Resolved (no Tx)	Off-treatment (anti-CGRP/ botulinum toxin A)	Natural history scenario only. A period triggered by the natural resolution event, causing MMD frequency to improve to 3 MMDs and therefore below the lower defining threshold for the 4M population. Anti-CGRP/botulinum toxin A treatment is discontinued (low level disease monitoring costs remain). This is threshold discontinuation.
H	Refractory to BSC	Off-treatment (anti-CGRP/ botulinum toxin A/BSC)	Follows 1 year of BSC, through which the full BSC CFB has linearly waned to no effect, reaching this period when BSC is no longer effective. Individuals

			experience their underlying/baseline frequency of MMDs.
I	Dead	N/A	Life years not accumulated, zero utility.
J	Left model*	None	A time horizon truncation for scenario and accrual analyses.

Key: BSC, best supportive care; CFB, change from baseline; anti-CGRP, anti-Calcitonin gene-related peptide monoclonal antibody; IV, intravenous; MMD, monthly migraine days; N/A, Not applicable
Notes: [+]Super responders discontinue treatment permanently following the treatment holiday, irrespective of whether a natural history event occurred.
*Not featured in Figure 5
Clinical states in grey only feature in scenario analyses

Table 30: Events

Event ID	Event name	Description (in base case analysis)
0	Begin assessment	Triggers model entry.
1	Transformation (NH scenario only)	A natural history event in chronic migraine where there is a natural improvement to 7 MMDs. I.e., the individual improves to episodic migraine status. As a result, botulinum toxin A (used in CM only) is discontinued, subject to selected level of 'leeway' (a 4 MMD leeway in the base case triggers botulinum toxin A discontinuation at 3 MMDs). Time to event is sampled. Represented as an 'asterisk' in the model diagram – it is allowable from multiple clinical states but triggers no clinical state movement only a reduced MMD.
2	Resolution (NH scenario only)	A natural history event in episodic migraine where there is a natural improvement to 3 MMDs. I.e., the individual experiences migraine frequency below 4M (and EM) classification (sampled time to event). As a result, anti-CGRP treatment is discontinued. In the first 5 years of treatment, a resolution event can only occur within a treatment holiday. Time to event is sampled. This event triggers movement to the Resolved clinical state (G).
3	Adequate response - continue	The decision to continue an individual on anti-CGRP/botulinum toxin A/BSC having been judged to have responded following initial assessment. I.e., attained at least the minimum required response (50% reduction in baseline MMDs of 50% if episodic status, or 30% if chronic status). This event triggers movement to the Responding on-treatment clinical state (C).
4	Inadequate response - discontinue	The decision to discontinue an individual on anti-CGRP/botulinum toxin A/BSC having been judged not to have responded during assessment. I.e., failed to attain at least the minimum required response (50% reduction in baseline MMDs of 50% if episodic status, or 30% if chronic status). This event triggers movement to the anti-CGRP/botulinum toxin A waning clinical state (F).
5	AE disc	The occurrence of treatment-emergent adverse event. The risk is fixed during the assessment period, and sampled for any time on-treatment (anti-CGRP/botulinum toxin A) beyond that. Treatment is discontinued immediately subsequent to this event and the treatment

Event ID	Event name	Description (in base case analysis)
		effect begins to wane to baseline. This event triggers movement to the anti-CGRP/botulinum toxin A waning clinical state (F).
6 - 10	Anti-CGRP/ botulinum toxin A holiday 1 to 5	Clinical decision at the end of a 9-month course to proactively discontinue anti-CGRP/botulinum toxin A for 3 months to assess the underlying frequency of migraine. If a natural history event has occurred then the anti-CGRP/ botulinum toxin A remains discontinued, otherwise a new course is started. 1. occurs 9 months of the commencement 2. after 9 months of the second course (21 months after first commencement) 3. after 9 months of the third course (33 months after first commencement) 4. after 9 months of the fourth course (45 months after first commencement) 5. after 9 months of the fifth course (57 months after first commencement). This event triggers movement into the anti-CGRP/botulinum toxin A holiday clinical state (E).
11	Threshold disc	Discontinuation of anti-CGRP/botulinum toxin A when migraine frequency falls below the clinical justification for intervention. Applied in the model at the licensed or recommended lower range limit plus a clinical 'real-world' leeway of 4 MMDs (base case estimate, 2 MMDs in scenario analysis). In the base case, threshold discontinuation is a reality for botulinum toxin A given its restriction to chronic migraine status. It is not possible for threshold discontinuation for anti-CGRPs because the leeway would require the impossibility of on-treatment MMDs improving to below zero. This event triggers movement to the anti-CGRP/botulinum toxin A waning clinical state (F).
12	Duration disc	Scenario only. A discontinuation event which occurs when the accumulated time on eptinezumab treatment surpasses a given maximum allowable total or cap. This event triggers movement to the anti-CGRP/botulinum toxin A waning clinical state (F).
13	Assess positive super resp	Super-responder scenario only (not represented in the model diagram). When during a treatment holiday an individual is found to maintain anti-CGRP/botulinum toxin A treatment effect. I.e., treatment effect is maintained despite treatment discontinuation. These individuals are 'super-responders'. The base case probability of super-response is zero, in the scenario it is fixed at 0.2. This event triggers movement to the Responding off anti-CGRP/botulinum toxin A clinical state (D).
14	Assess negative and restart	Natural history scenario only. The event of a negative assessment during a treatment holiday for a natural improvement in underlying migraine frequency during the latest course of anti-CGRP/botulinum toxin A. Given the negative 'test' treatment is re-started with immediate onset of effect. This event triggers movement to the Responding on anti-CGRP/botulinum toxin A clinical state (C).
15	Anti-CGRP/botuli	The event at the end of a fixed treatment effect waning period that signals the loss of all treatment effect (CFB) and the move to BSC as the remaining interventional option. Distinct from the BSC strategy, in

Event ID	Event name	Description (in base case analysis)
	num toxin A effect lost	which BSC serves as an alternative to anti-CGRP/botulinum toxin A. This event triggers movement to the BSC clinical state (B).
16	BSC effect lost	The event that signals the loss of all BSC effect (CFB) at the end of a fixed treatment of BSC (during which the BSC effect diminishes). This event triggers movement to the Refractory clinical state (H).
17	Death	Costs and QALYs no longer accumulated.
18	Truncate horizon	Costs and QALYs no longer accumulated. Event is triggered only by the automated 'accruals' analysis that runs alternative time horizons.
Key: AE, adverse event; anti-CGRP, anti-Calcitonin Gene Receptor Protein; BSC, best supportive care; CFB, change from baseline; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days; NH, natural history; QALY, quality-adjusted life year; Tx, treatment. **Note:** Events in grey only feature in scenario analyses		

B.3.2.3.1. Simulation of individual patients

The model uses sampling to sequentially simulate individual patients' lives based on a set of baseline characteristics which impact, or may potentially impact, the course of medical management through the simulated patient's lifetime. Baseline characteristics (age at entry, gender, severity subpopulation, and MMD frequency) are informed by the TF3+ cohort of the DELIVER trial except that survey data is used to generate severity subpopulation status (EM or CM) since DELIVER did not randomly stratify this characteristic (see Section B.3.2.1). It should be noted that this means that MMD is the single characteristic that defines the patient's health state throughout the model. The model does not sample or track headache frequency, as is discussed in Section B.3.2.3.4

Based on the individual patient characteristics and the treatment strategy, the model samples the following events:

- Response to treatment, and based on that, MMD changes from baseline (CFB)
- Time to discontinuation (if not during initial assessment, then afterwards)
- Time to any-cause death

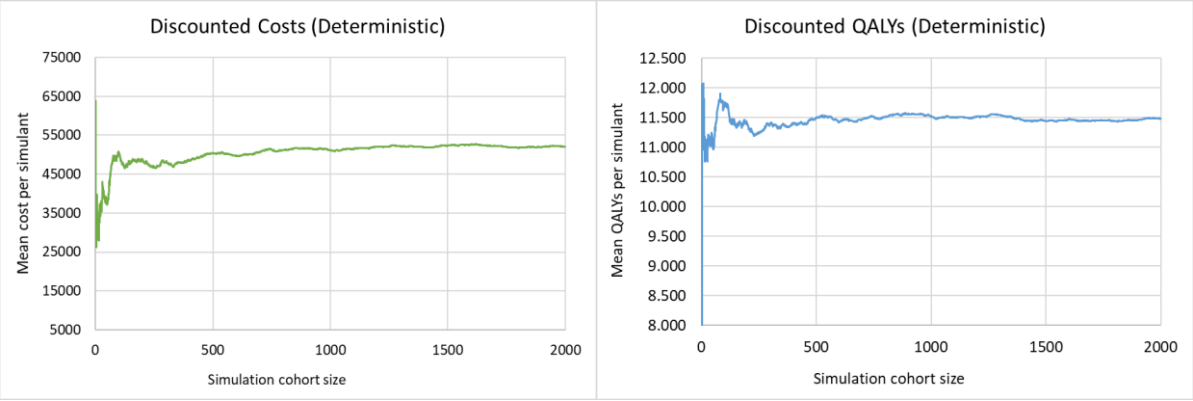
The optional natural history component of the model includes the additional sampled events of time to transformation (allowable in chronic migraine only), and time to resolution (allowable in episodic migraine only).

The relative timing of events, either fixed or sampled, dictate how a patient moves through the clinical states for each of the different treatment strategies (the earliest predicted allowable event given the sampled patient's current clinical state is the one that occurs). Output data per simulated patient, including the occurrence and timing of key events, duration of specified clinical periods, cost of resources consumed and quality of life within clinical periods, are recorded for each treatment strategy. Results are computed by calculating the mean across all simulated patients specified as included in the analysis.

In order to eliminate unwanted variation between repeated microsimulations of the pseudo-deterministic analysis, the model stores and reuses random numbers. This allows the same simulated patients to be included in one-way sensitivity analyses (OWSA) and scenario analyses. The probabilistic sensitivity analysis (PSA) overrides this restriction, allowing fresh sampling with each run of the microsimulation.

The selected cohort size was 2,000 patients, which balances stochastic stability and running time (see Figure 6).

Figure 6: Stability plot of deterministic analysis (4M TF3+, fremanezumab strategy)



Key: QALY, quality-adjusted life year.

B.3.2.3.2. Sampling of gender

The proportion of males in the DELIVER TF3+ population was 11.28%. This is the basis of the sampling threshold and was considered by consulted clinical experts as generalisable to the decision problem population.

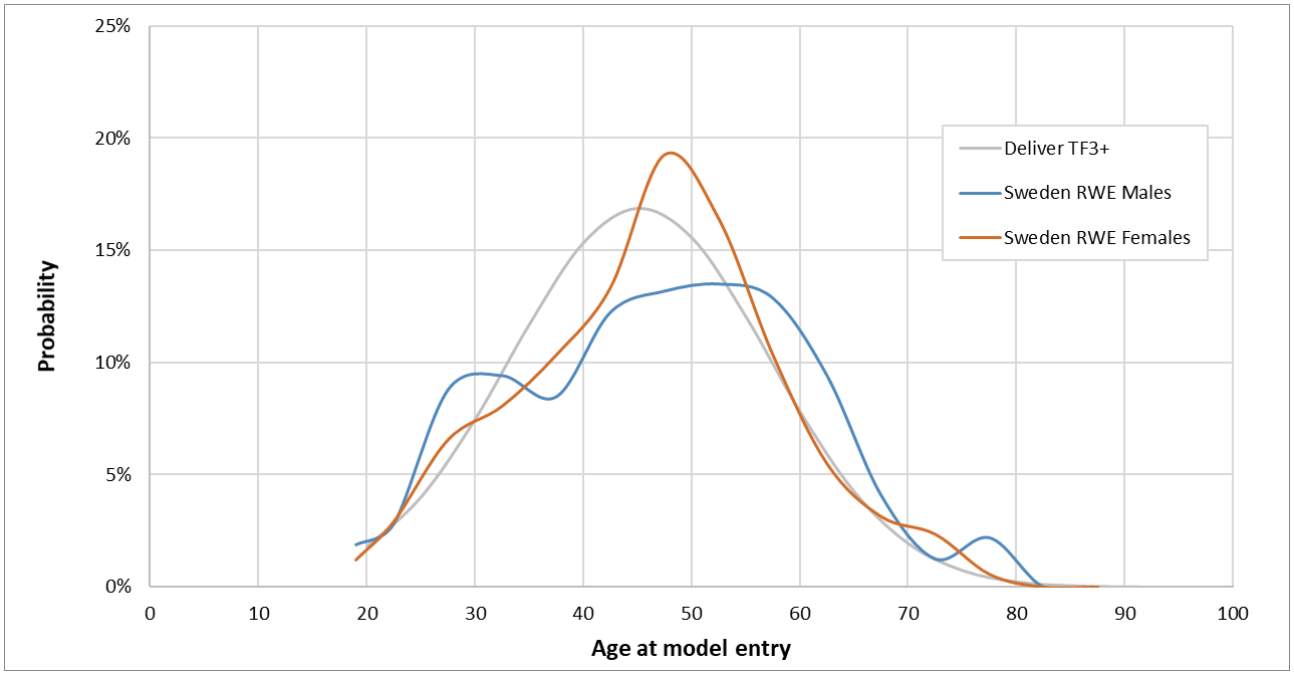
B.3.2.3.3. Sampling of age

The mean (45.2 years) and standard deviation (11.8 years) of TF3+ participants of the DELIVER trial were used in a normal distribution to define a cumulative distribution from which the age of each simulated patient is sampled. This distribution was considered by consulted clinical experts as generalisable to the population defined in the decision problem.

Examination of age in a cohort of a Swedish registry of people using anti-CGRPs for chronic migraine after 2 or more prior prophylactic treatment failures, showed a possible bimodal distribution. So, a scenario was tested in which age was sampled from this real-world data.

Age profiles from both sources are shown in Figure 7 for comparison.

Figure 7: Age at entry, comparison by gender and source



Key: TF3+, patients for whom 3 or more prior preventive treatments have failed; RWE, real-world evidence.
Note: Sweden RWE age profiles are based on patients with CM only.

B.3.2.3.4. Sampling of EM or CM status and baseline MMD

All simulated patients in the model are sampled as either EM or CM, so that the appropriate response thresholds are applied and response rates awarded. Also, which natural history event is applicable is conditional on the subpopulation at model

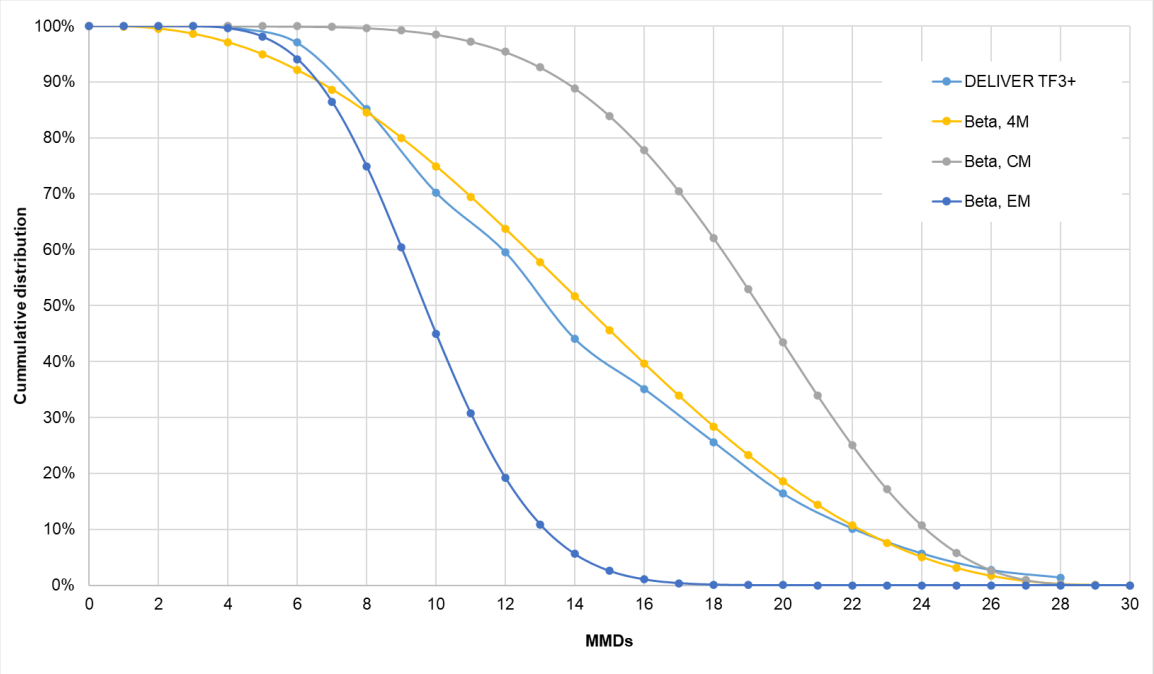
entry. The sampling threshold was 46% chronic migraine in a 4M TF3+ population, sourced from a survey of diagnosed migraine patients, conducted in collaboration with the Migraine Trust.[110] This real-world source was preferred to the DELIVER TF3+ CM proportion of 85% because requirements for statistical power in the DELIVER trial necessitated pre-specified numbers of EM and CM participants. A focussed literature search did not identify alternative sources for a TF3+ population in a clinical setting. The outcomes of the subpopulation analysis are not impacted by uncertainty within this estimate.

MMD frequency at baseline is sampled secondary to the sampling of subpopulation. The EM MMD range is 4 –15 inclusive, and the CM MMD range is 8 – 30 inclusive. These ranges and the distribution within are based on the baseline distribution of MMDs amongst participants of the TF3+ subgroup of the DELIVER trial. The overall 4M range is therefore 4-30 MMDs. The MMD frequency ranges overlap so subpopulations are not mutually exclusive across this single dimension. This is a direct reflection of the participant profile at baseline in the DELIVER trial. The measurement of headache frequency in combination with migraine frequency is the basis of exclusivity between subpopulations in the trial, but headache frequency is not modelled here, and has not been modelled in any prior anti-CGRP appraisal. Whilst this approach is broadly inconsequential, the lower bound of chronic migraine sets the threshold for botulinum toxin A discontinuation and also determines the MMD frequency after NH transformation from CM to EM (i.e. 7 MMDs). It was elicited from clinical experts in a UK advisory board that 8 MMDs is the most reasonable equivalent definition of the EM-CM boundary usually described as 15 MHDs with at least 8 of migraine character.[55] The lower bound of episodic migraine in the model (4 MMDs) is aligned to the IHS ICHD-3 and decision problem definition, as well as the marketing authorisations for all four anti-CGRPs.

The mean and standard deviation of the distribution of baseline MMDs for the EM and CM TF3+ subgroups of DELIVER were used to describe the alpha and beta parameters of beta distributions, representing the respective cumulative distribution functions (sampling distributions). Figure 8 shows the EM and CM baseline MMD sampling distributions, and for reference the empirical and fitted combined 4M TF3+ population distribution. The reasonable fit of the beta distribution to the combined

data of the subpopulations provides support for the approach and selection of the beta curve.

Figure 8: Baseline MMD sampling through anti-CGRP therapeutic range, DELIVER (TF3+), by subgroup



Key: anti-CGRP, anti-calcitonin gene-related peptides, CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days; TF3+, patients for whom 3 or more prior preventive treatments have failed.

B.3.2.3.5. Natural history of migraine

NICE appraisals of anti-CGRPs have not always assessed treatment cost-effectiveness across the full migraine population (patients who have ≥ 4 MMDs and for whom at least 3 prior preventive therapies have failed), but have instead assessed EM and CM subpopulations separately, as defined by identity at model entry. Consequently the impact of changes in the underlying natural history of migraine has not been explored. The current DES provides the framework to both change the underlying MMD frequency (on which treatment effect is applied), and implement a clinical schedule of treatment holidays by which to test for change in natural history. It therefore goes beyond the simplifying assumption of the past where migraines are experience for life at a fixed underlying frequency. This natural history and testing component is not activated in the base case in order to provide consistency with reference to previous results, but is included as a standard

scenario. Instead, the subgroup identity is assumed to be unchanged throughout the model horizon, and where natural improvement is not included, migraine is assumed to be experienced for life at an unchanged frequency.

Evidence exists for both short-term frequency fluctuation and long-term fluctuation, but appropriate parameters were required for a practical implementation.[14] Therefore, a targeted literature search was performed to identify outcomes signifying a change in natural history.[115] The most common relevant outcomes were transformation (CM to EM), chronification (EM to CM), partial remission and complete remission. To simplify the modelling approach, the assumption was made that in this treatment experienced population it is reasonable to model only natural history improvement rather than bi-directional change. This assumption was justified on the basis of age, time since migraine diagnosis (16 years EM, 11 years CM), and the significant treatment history of participants in the DELIVER trial (B.2.3.3).

A large US prevalence study shows a decrease in prevalence in the age categories above 40 years, indicating this is the age from which new cases are outnumbered by resolved cases.[116] The mean age of the DELIVER TF3+ subpopulation was 45.2 years, and 46.5 years in real-world anti-CGRP users in Sweden, so there can be assumed to be a natural decline in prevalence over time in this population. Also, Ashina and colleagues (2010) showed a low chronification rate.[117]

Therefore, forming the basis of the NH model were the two improvement outcomes of transformation and resolution, each triggering a migraine frequency improvement to a fixed level (from any given prior frequency). Neither prevalence studies nor longitudinal outcome studies identified information to inform the scale of improvement at an MMD level, so improvements were attained to fixed levels, ratified by clinical experts. By definition, transformation was permitted only in chronic migraine and reduced MMDs into the EM range, to 7 MMDs. Resolution was permitted only in episodic migraine, and reduced MMDs to below the EM range, 3 MMDs. Since botulinum toxin A is not licensed for people with EM, the transformation event in this strategy also triggers discontinuation (with 4 MMDs leeway to account for real-world caution). The resolution event triggers discontinuation of the anti-CGRPs. BSC is not discontinued owing to resolution.

Natural history events do not directly impact the treatment effect size (MMD CFB), but only indirectly when a treatment is discontinued as a result of improvement. Similarly, the treatment effect size in CM patients is maintained in instances of transformation and subsequent change in severity subpopulation status. Evidence was not collected within DELIVER to support any alternative approach.

A treatment holiday can be considered a test, where a positive result is an improvement in underlying disease followed by a change in clinical management. A negative test is no underlying improvement, in which case simulants were assumed to restart treatment. When treatment is stopped at the start of a holiday, treatment effect is waned (at a rate common to all reasons for discontinuation and all active comparators) and when treatment is restarted, treatment effect is resumed immediately and in full. In the base case, simulants cannot experience full treatment effect without being on-treatment; there is no account for 'super-response' following positive stopping. However, this scenario has featured in previous NICE migraine appraisals, so a scenario analysis examines the impact of 20% annually positive stopping with full treatment effect.

B.3.2.3.5.1. Sampling of time to resolution

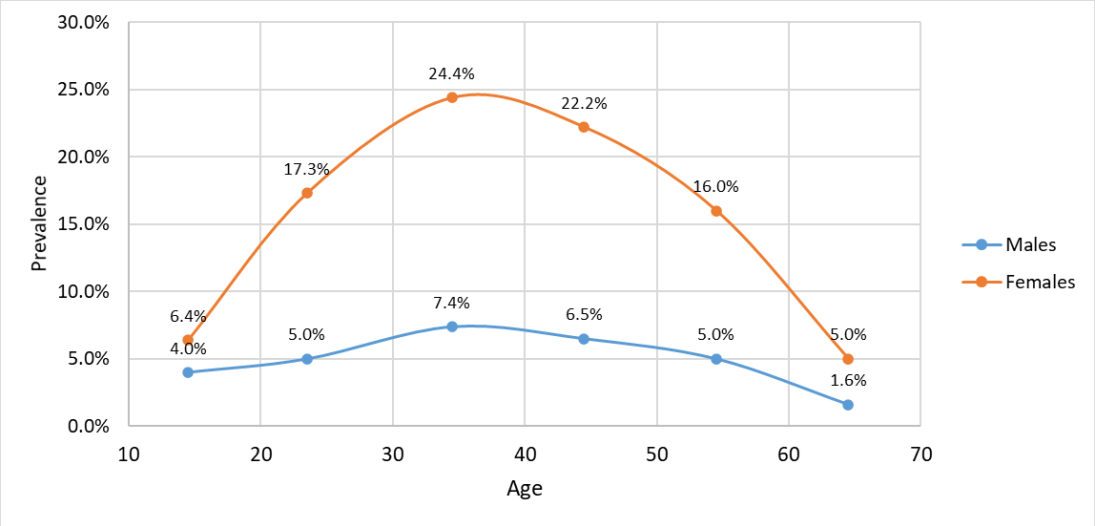
The large US prevalence study by Lipton and colleagues (2009) was used to estimate the time to resolution.[116] Samples were taken from a polynomial curve fitted to a curve of the scaled and gender-weighted estimates of migraine prevalence from the point decline in prevalence. Using the midpoint (34.5 years) of the most frequent age decile (30–39 years), the decline in prevalence was plotted and a polynomial trendline was added using Microsoft Excel® (Figure 10). The quadratic formula of the fitted curve was used to sample the time-to-resolution event. Microsoft Maths Solver was used to rearrange the formula to solve for x (time to event).

$y = -0.009x^2 + 0.0006x + 0.997$ is rearranged to $x = \frac{\sqrt{(9978-10000y)+1}}{3}$, where y is the randomly generated survival function and x is the time to resolution.

Sampled times to resolution, converted to age at the event, were rounded to the nearest year from model entry in order that its occurrence falls within a treatment holiday in a fixed five-year schedule. This is based on the idea that only during a

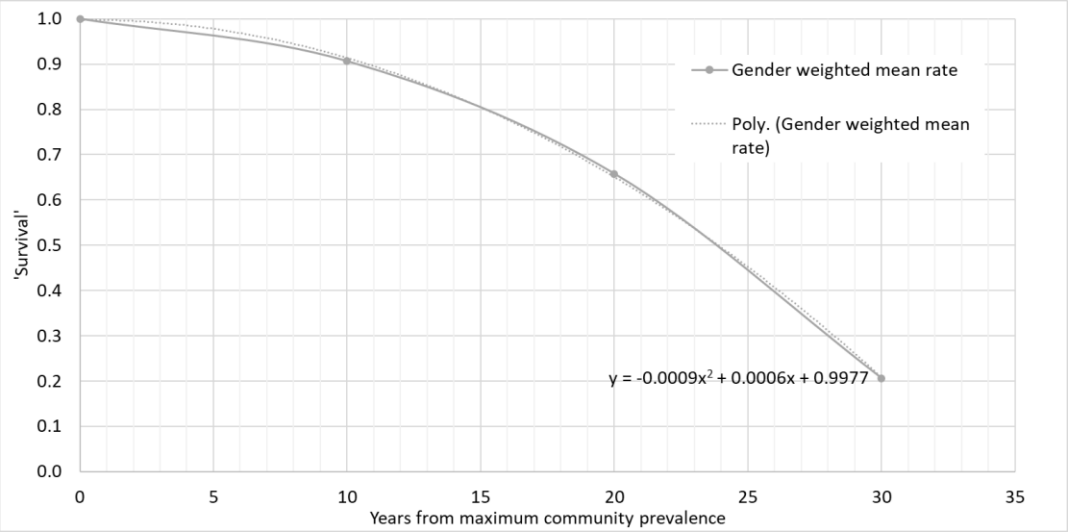
treatment holiday, when the underlying migraine frequency is observable, a natural history event can be identified.

Figure 9: 1-year period prevalence of migraine in American men and women (ICHD-2 criteria)[116]



Key: ICHD-2, International Classification of Headache Disorders (second edition).

Figure 10: Decline in migraine prevalence according to Lipton study[116]



B.3.2.3.5.2. Sampling of time to transformation

No similar evidence to that used for modelling time to resolution was identified to inform transformation. However, it may be reasonable to assume a relationship between transformation and resolution. Therefore a hazard ratio was applied to the

resolution baseline to produce a dependent transformation distribution. Two out of nine studies included in the targeted literature search[115] were selected to calculate the hazard ratio. To be selected, a confirmatory period needed to be included in the study design, as this showed that the event was sustained. Studies by Manack 2011 and Roy 2011 provided the required outcome (albeit they measured headaches and not explicitly migraines), time horizon, and confirmatory period.[21, 118] However, for the resolution outcome (improvement to 3 MMDs in the model), the study outcome was zero headaches in the past year, so the extracted estimate represented a necessary approximation which might over-estimate the time to resolution, on the basis that in reality an improvement to 3 MMDs might be reached sooner than complete resolution. The resultant hazard ratio was applied to the time to resolution curve and is illustrated in Figure 11. The survival point estimates for natural history events are presented in Table 31.

Table 31: Literature sources of proportions transforming and resolving

Study author/year	Outcome	Sample size	Experienced event	Follow-up (years)	Proportion without outcome
Manack 2011[21]	CM→EM	383	26.1 (n = 100)	1	0.74
Roy 2011[118]	EM→CR^	162,562	4.6%	1	0.954*
Hazard ratio					1.29

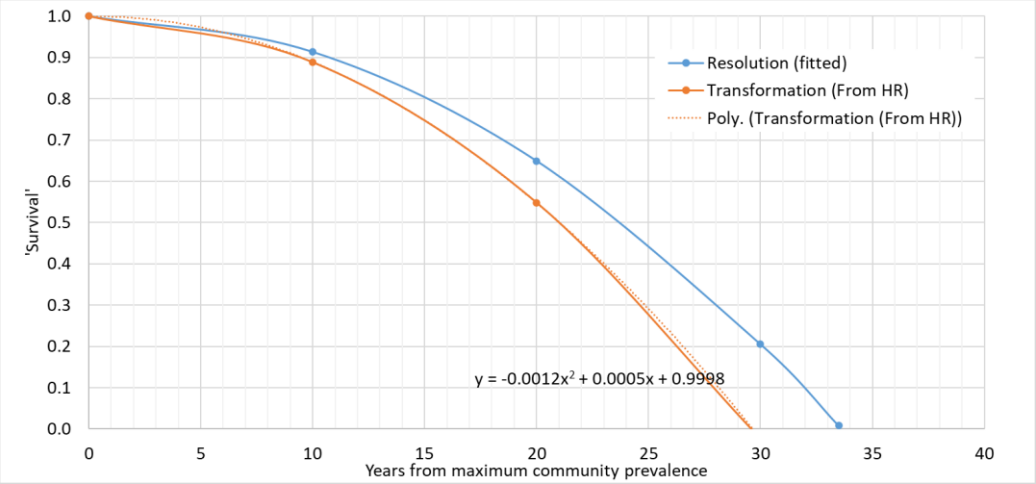
Key: CM, chronic migraine; CR, complete remission; EM, episodic migraine
Note: *Annual rate weighted by age and gender. ^CR defined as no attacks in the past year.

Roy et al. defined EM as at least one severe attack of headache in the last year, but fewer than 15 severe attacks. The study by Manack et el. examined a CM sample population, defined as having ≥ 15 headaches per month for at least the previous 3 months. Transformation (termed 'transition' in this study) required headache frequency to fall below and stay below 15 headaches per month. In using this study we must assume that 15 MHDs reasonably equate to 8 MMDs in the context of transformation (validated by a UK specific clinical advisory board).

Formula for the distribution curve for time to transformation:

$y = -0.0012x^2 + 0.0005x + 0.9998$ is rearranged to $x = \frac{\sqrt{(479929 - 480000y) + 5}}{24}$, where y is the randomly generated survival function and x is the time to transformation.

Figure 11: Sampling distributions for natural history events



Key: HR, hazard ratio.

B.3.2.3.6. Time horizon

The time horizon of the model is set to 'lifetime' in the base case. This is an 82-year horizon for individuals generated at the minimum allowable age of 18. Previous NICE TA models have used a variety of time horizons, ranging from 2 years in the appraisal of botulinum toxin A, to 10 years in the appraisals of erenumab and fremanezumab, and a lifetime horizon in the appraisal of galcanezumab. Committees in all appraisals preferred a lifetime horizon, but acknowledged the uncertainty associated with it given the lack of modelling of natural history of the disease.[1-3, 53] The current DES approach allows the incorporation of natural history, offering a means to decrease the uncertainty associated with long time horizons.

B.3.2.3.7. Model perspective

The perspective was that of the UK NHS and Personal Social Services (PSS) in accordance with the NICE reference case. A societal perspective which includes productivity gain from treatment has been explored as a scenario analysis.

B.3.2.3.8. 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.

Table 32 summarises the differences between key features of the economic analyses in previous NICE appraisals in migraine and the current analysis.

Table 32: Features of the economic analysis

	Previous evaluations				Current evaluation	
Factor	**TA659[2] Galcanezumab**	**TA682[3] Erenumab**	**TA764[1] Fremanezumab**	**TA260[53] Botulinum toxin A**	**Chosen values**	**Justification**
Time horizon	Lifetime (25 years)	10 years	10 years	2 years	Lifetime (82 years)	Individuals are modelled from mean entry age (minimum 18 years) until death, creating a lifetime horizon. Life expectancy is limited to 100 years, so this is effectively an 82-year horizon
Cycle length	Monthly (30 days)	12 weeks	4 weeks	12 weeks	N/A	Discrete event simulation models do not consider model cycles
Treatment waning effect?	No waning effect considered	No waning effect considered	Considered as a scenario	No waning effect considered	Explicitly included in the base case	• 4-month period of waning to baseline following discontinuation of anti-CGRP or botulinum toxin A; 1-year on-treatment waning to baseline on BSC • Discontinuation may be due to a negative stop following initial assessment, an adverse event, a natural history event (scenario), or a stopping rule (scenario)
Source of utilities	Patient-level MSQ v.2.1 data from CONQUER (for patients with history of treatment failure) mapped onto	Patient-level MSQ v.2.1 data from Study 295, STRIVE and ARISE mapped onto EQ-5D utility scores	Patient-level MSQ data from FOCUS trial mapped to EQ-5D-3L	Patient-level MSQ data from clinical trials	Patient-level MSQ data from DELIVER trial mapped onto EQ-5D-3L utility scores	Consistent with previous migraine appraisals. EQ-5D is not sensitive enough to capture changes in HRQL in migraine because of the requirement to report HRQL on the day of questionnaire

	Previous evaluations				Current evaluation	
Factor	**TA659[2] Galcanezumab**	**TA682[3] Erenumab**	**TA764[1] Fremanezumab**	**TA260[53] Botulinum toxin A**	**Chosen values**	**Justification**
	EQ-5D-3L utility scores using an existing mapping function	(values ranged from 0.383 to 0.839)				completion, which is typically not a migraine day
Source of costs	• Based on one 200 IU vial of botulinum toxin A 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 is based on Lilly's price for galcanezumab	• Erenumab costs were based on Novartis' price for erenumab in the UK • Botulinum toxin A costs were taken from the BNF and NHS National Tariff	BNF, PSSRU and NHS reference costs	Based on one 200 IU vial of botulinum toxin A at £276.40 and an administration cost of £116.00, leading to a total cost of £392.40 per 12-week cycle	• Eptinezumab costs were based on Lundbeck's UK price for eptinezumab • Costs of comparator treatments were taken from BNF and NHS National Tariff	Established sources of drug costs within the NHS
Source of other costs	BNF, NHS Tariff and PSSRU	National Tariff, PSSRU 2016, National Health and Wellness Survey (NHWS) survey, BNF		International Burden of Migraine study, PSSRU, NHS reference	PSSRU, NHS reference Costs.	Established sources for UK costs.

	Previous evaluations				Current evaluation	
Factor	**TA659[2] Galcanezumab**	**TA682[3] Erenumab**	**TA764[1] Fremanezumab**	**TA260[53] Botulinum toxin A**	**Chosen values**	**Justification**
				costs, Annual Survey on Hours and Earnings and IBMS study		
Resource use	Trial-specific data and Lipton et al. (2018)	NHWS survey (2017)	Vo et al. publication of NHWS	IBMS	NHWS EU (2021)	• The NHWS and IBMS surveys are similar, and TA260, TA682 and TA764 used the resource-use assumptions from these surveys. The current evaluation administers a cross-sectional questionnaire over the Internet to patients with migraine, in the same way that the NHWS and IBMS surveys did • The analysis of the migraine subset of the NHWS survey was commissioned by Lundbeck to inform the inputs to the economic model for eptinezumab. It provides more up-to-date data on resource use compared to the IBMS study (2020 versus 2010)
Health effects measure	QALYs	QALYs	QALYs	QALYs	QALYs	NICE reference case
Discount rate for	3.5% per year	3.5% per year	3.5% per year	3.5% per year	3.5% per year	NICE reference case

	Previous evaluations				Current evaluation	
Factor	**TA659[2] Galcanezumab**	**TA682[3] Erenumab**	**TA764[1] Fremanezumab**	**TA260[53] Botulinum toxin A**	**Chosen values**	**Justification**
costs and benefits						
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	NHS	NHS/PSS	NICE reference case
Half-cycle correction applied	No	• Yes for disease management and indirect costs • No for treatment costs	Not reported	Yes	No	Not applicable in DES modelling

Key: BNF, British National Formulary; BSC, best supportive care; IBSU, International Burden of Migraine; IU, international units; MMD, monthly migraine days; MSQ, Migraine-Specific Quality-of-Life Questionnaire; NHS, National Health Service; NHWS, National Health and Wellness Survey; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

B.3.2.4. Intervention technology and comparators

B.3.2.4.1. Intervention

Eptinezumab is a monoclonal antibody specifically designed to target and inhibit the calcitonin gene-related peptide (CGRP) receptor, which is believed to have a critical role in mediating the pain associated with migraine. Eptinezumab is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.[5, 6] The recommended dose is 100 mg administered by intravenous (IV) infusion every 12 weeks, which is also the dose modelled.

DELIVER trial participants in the eptinezumab arm could access the same supporting acute care and medications as those in the placebo arm; the eptinezumab strategy modelled was therefore effectively eptinezumab 100 mg and BSC, but is referred to as the eptinezumab strategy. Data informing the eptinezumab strategy was based on the TF3+ subpopulation of DELIVER.

B.3.2.4.2. Comparators

Comparators included in the model are those used in the current standard of care in England for the migraine population described above (4M TF3+):

- Best supportive care (BSC)
- Erenumab
- Fremanezumab
- Galcanezumab
- Botulinum toxin A (also known as 'Botox')

BSC is not referred to as an 'active' treatment whereas all the others are. Each of them have been the subject of previous NICE single technology appraisals in their own right, except for BSC.[1-3, 53] Each active treatment is licensed and reimbursed in England for the 4M TF3+ population, except for botulinum toxin A, which is restricted to the CM subpopulation. They are each modelled here according to their licensed use and the following dosing and administration regimens:

- Erenumab 140 mg, once every 4 weeks via subcutaneous (SC) administration

- Fremanezumab, 225 mg once every month for 90% of patients and 675 mg once every 3 months for the remaining 10% of patients, via SC administration
- Galcanezumab, starting with a single loading dose of 240 mg for 1 dose followed by 120 mg administered once every month, via SC administration
- Botulinum toxin A 200 international units (IU), once every 12 weeks via healthcare professional (HCP) SC administration

As with eptinezumab, each of the active treatment comparators are modelled in combination with BSC, and therefore include the cost acute care and medications at a rate of consumption commensurate with migraine frequency.

A blended comparator has been included in the 4M analysis based on the weighted outcomes of the anti-CGRPs. This has been provided as an additional comparator, not to substitute any of the other comparators.

B.3.3. Clinical parameters and variables

B.3.3.1. Treatment effects

B.3.3.1.1. Probability of response

A positive clinical response was applied for each strategy of the model according to an improvement from baseline MMDs of 50% or more reduction in MMDs for patients with EM, or 30% or more for CM. The response rates (by severity subgroup EM/CM) for the eptinezumab 100 mg strategy and the comparators were informed by subpopulation level (EM/CM) ITCs including all comparators (see section B.2.9). ORs for eptinezumab versus active treatments were not statistically significant, so a cost-comparison analysis is provided in addition to this cost-utility analysis (see Appendix M for results). In this analysis the response rates of eptinezumab have been applied across all comparators except BSC. Response rates applied in the base case model are presented in Table 33. Appendix Q presents alternative response rates, which are explored in scenario analyses.

Table 33: Response rates applied in the health economic model

Statistic	BSC	Eptinezumab 100 mg	Erenumab 140 mg	Fremanezumab 225 mg	Galcanezumab 120 mg	Botulinum toxin A
Base case odds ratios (see Section B.2.9)						
EM (50% threshold)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
CM (30% threshold)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case response rates (calculated)						
EM (50% threshold)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
CM (30% threshold)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-comparison scenario response rates[75, 76]						
EM (50% threshold)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
CM (30% threshold)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; CM, chronic migraine; EM, episodic migraine.
Note: *In the absence of 30% response rate data from comparator treatments, the odds ratios for CM are based on 50% response rates. These are then applied to 30% CM response rates from the DELIVER trial.

B.3.3.1.2. MMD change from baseline at Week 12

Mean MMD CFB were awarded for each strategy according to response status, however relative effects between strategies were not applied in the base case since evidence was not available for viable EM and CM ITCs (CFB data by response status were not publicly available for comparator strategies). Instead, CFB of eptinezumab 100 mg observed in responder and non-responder groups in the DELIVER TF3+ subgroup were applied equally to all active treatment comparators. The directly observed effect sizes in responders and non-responders to BSC in DELIVER TF3+ were used for the BSC strategy. CFB values applied in the model base case are presented in Table 34. Appendix Q presents alternative CFB values, which are explored in scenario analyses.

Table 34: MMD CFB applied in the health economic model.[75, 76]

Statistic	Responders		Non-responders	
	BSC	**Active treatment**	**BSC**	**Active treatment**
EM, CFB (SE)	[redacted]	[redacted]	[redacted]	[redacted]
CM, CFB (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Key: BSC, best supportive care; CFB, change from baseline; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days; SE, standard error.				

B.3.3.1.3. Onset of effect

In the absence of direct comparative evidence to support differential speeds of onset despite alternative modes of administration, the time to attainment of full effect size was assumed equal across all comparators. This may be a conservative assumption given the IV route of administration of eptinezumab. However, the initial assessment period is conducted over a relatively short period of 12 weeks, except botulinum toxin A which requires a longer 24-weeks of assessment. In all strategies the treatment effect during assessment was linearly graduated from zero to full CFB (responders and non-responders) by the end of 4 weeks (approximating empirical trends and matching the waning period). A scenario analysis is provided where onset of effect is assumed to be immediate in the case of eptinezumab. When active treatment was re-started, which can occur when treatment holidays end, full CFB was returned without delay

B.3.3.1.4. Waning of effect

Treatment effect was assumed to wane following any event leading to discontinuation of treatment (insufficient response, adverse event-related or death in the base case, also resolution and transformation with natural history in scenario analyses). The rate of waning was equally applied across active treatment strategies, irrespective of attainment of the response threshold, linear, and fixed in rate. Rate was based on the findings of a recent cohort study of migraine evolution after cessation of anti-CGRPs, which found that MMDs in weeks 13-16 post cessation approached baseline values.[114] Since the study found that the ligand class of anti-CGRP appeared to retain effect for longer compared to the receptor class (of the included anti-CGRPs, erenumab is of the receptor class) a fixed period of four months (0.33 years) dissipation was selected.

For the strategy of BSC, when the placebo effect is applied, full CFB was assumed to dissipate at a linear rate from commencement of treatment over a period of one year, when baseline is reached. This assumption is supported by the NICE committee preference in the appraisal of galcanezumab (TA659).[2] A scenario is presented in which this period is doubled. Table 35 presents the CFB considerations for the clinical states, taking account of rate and any fixed period length.

Table 35*:* Application of CFB MMDs by clinical state

Clinical state ID	Health state name	Method of application of CFB MMDs in base case
A	Initial assessment	Enter model. Period of assessment of 12 weeks for BSC and anti-CGRPs, and 24 weeks for botulinum toxin A. Linear increase from baseline to full CFB effect over 4 weeks for responders and non-responders, followed by full CFB. BSC and anti-CGRPs: (4/12)*(CFB*0.5)+(8/12)*CFB Botulinum toxin A: (4/24)*(CFB*0.5)+(20/24)*CFB
B	BSC after aTx	Arrival from State F during which CFB has waned to zero/baseline. BSC responder or non-responder CFB applied in full initially, but waned linearly to zero/baseline over 1 year. (CFB*0.5*1)
C	Responding on Tx	Responders only. Application of full CFB for duration of response. (CFB)
D	Responding off aTx	Scenario analysis only (super-responders). CFB applied in full. (CFB)
E	Tx holiday (off aTx)	Full CBF wanes for 3 months at the 4-month wane period rate. (CFB*[3/12]/[4/12]*0.5)

F	Waning (off aTx)	Responder or non-responders: reduction (waning) from full CFB to baseline over fixed 4-month period. (CFB*0.5)
G	Resolved (no Tx)	No CFB. MMD = 3
H	Tx-resistant (no Tx)	CFB not applied, migraine frequency at baseline.
Key: anti-CGRP, anti-calcitonin gene-related peptides; aTx, active treatment (anti-CGRPs and botulinum toxin A); BSC, best supportive care; CFB, change from baseline; MMD, monthly migraine days; Tx, treatment (anti-CGRPs, botulinum toxin A and BSC). **Note:** Clinical states in grey only feature in scenario analyses		

B.3.3.2. Adverse events

Adverse events are not explicitly modelled outside their causation of treatment discontinuation. The infrequency of severe AEs together with similarities in AE profiles between comparators means that any impact HRQL and resource consumption is expected to be minimal. This approach is consistent with previous NICE appraisals in migraine.[1-3, 53]

B.3.3.3. Treatment discontinuation

There are several reasons a patient can discontinue treatment, each discussed below.

B.3.3.3.1. Discontinuation due to inadequate response after initial assessment

All individuals are at risk of treatment discontinuation ('negative discontinuation') at the end of the initial assessment due to an inadequate level of effect (less than 30% for CM or 50% for EM reduction in MMDs). For each simulated patient, this is determined by whether or not a randomly generated number falls above or below the response rate for the given strategy.

B.3.3.3.2. Discontinuation due to an 'adverse event'

All individuals on treatment with anti-CGRPs or botulinum toxin A are at risk of discontinuing treatment due to treatment-emergent adverse events (TEAEs). The model implements both short-term discontinuation (during initial assessment) and long-term discontinuation (subsequent to initial assessment). The risk of AE discontinuation was equally applied to all anti-CGRP strategies (class effect assumed), with a dedicated risk for botulinum toxin A, and no risk for BSC. The

short-term risk was added to the risk of discontinuing due to insufficient response at the end of assessment, so they were sampled as a combined risk. Long-term discontinuation was independently sampled from a time-to-event distribution.

B.3.3.3.2.1. Short-term discontinuation risk

For anti-CGRPs this was based on a weighted average of the proportion of patients who discontinued due to TEAEs in the pivotal trials of the respective therapies. As presented in Table 36, the risk of discontinuing an anti-CGRP due to TEAEs during the initial assessment period of 12 weeks is 1.06%.

Table 36: Short-term TEAE discontinuation risk of anti-CGRPs

Trial	Treatment	Treatment period (weeks)	N	N discontinued due to TEAEs	Proportion discontinued due to TEAEs
DELIVER[66]	Eptinezumab	12	299	1	0.33%
CONQUER[119]	Galcanezumab	12	232	1	0.43%
FOCUS[120]	Fremanezumab	12	561	5	0.89%
HALO EM[121]	Fremanezumab	12	581	10	1.72%
HALO CM[122]	Fremanezumab	12	755	3	0.40%
ARISE EM[123]	Erenumab	12	283	5	1.77%
STRIVE EM[86]	Erenumab	12	319	7	2.19%
Study 295 CM[124]	Erenumab	12	188	2	1.06%
Weighted average			3218	34	1.06%
Key: anti-CGRP, anti-calcitonin gene-related peptides; CM, chronic migraine; EM, episodic migraine; N, number; TEAE, treatment-emergent adverse event					

For botulinum toxin A this was based on a weighted average of the proportion of patients who discontinued due to TEAEs in the two pivotal trials for this therapy. As presented in Table 37, the risk of discontinuing botulinum toxin A due to TEAEs during the initial assessment period of 24 weeks is 3.20%.

Table 37: Short-term TEAE discontinuation risk of botulinum toxin A

Trial	Treatment	Treatment period (weeks)	N	N discontinued due to TEAEs	Proportion discontinued due to TEAEs
PREEMPT 1[87]	Botulinum toxin A	24	340	14	4.12%
PREEMPT 2[88]	Botulinum toxin A	24	347	8	2.31%
Weighted average			687	22	3.20%
Key: N, number; TEAE, treatment-emergent adverse event					

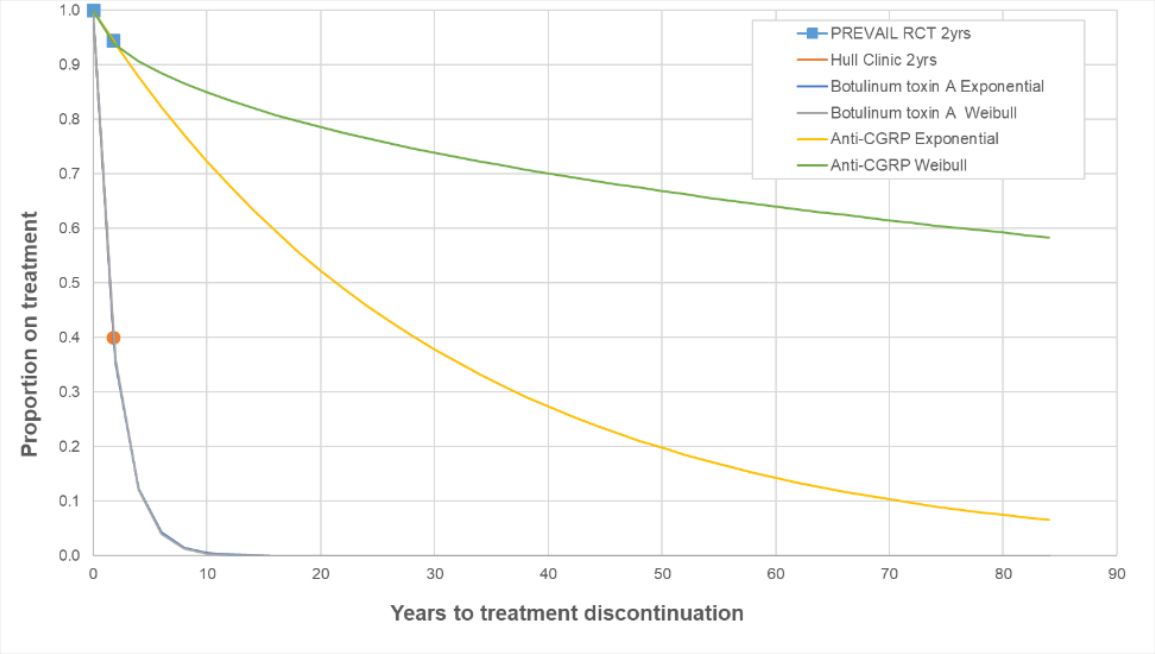
B.3.3.3.2.2. Long-term discontinuation risk

A method for sampling time-to-event was considered the best method of implementation, so data-points were sought from the long-term evidence base for eptinezumab. The PREVAIL study is a 2-year open-label phase 3 trial assessing long-term safety and tolerability of eptinezumab in patients with CM.[93] In this trial 8 out of 128 patients discontinued treatment with eptinezumab due to TEAEs. However one of these patients was excluded, since their treatment was withdrawn within the 12-week assessment period. Therefore, 5.51% (7/127) of patients discontinued treatment through 21 months following initial assessment and 94.49% remained on treatment.

For botulinum toxin A, a 2-year prospective follow up of patients attending the Hull migraine clinic was an applicable source. This study included 655 patients, 98.2% of whom had failed 3 or more previous preventive therapies.[68] 275 of 655 patients stopped treatment with botulinum toxin A due to a negative stopping rule. Of the remaining 380 patients, 152 received 9 cycles of treatment, 27 months of therapy. Therefore, the survival on botulinum toxin A at 21 months post-assessment was 44.7% (152/380).

Weibull and exponential curves were manually fitted to the respective 21 month datapoints. Following side-by-side examination from clinical experts, the exponential curve was chosen for the base case because of its face validity and simplicity in the context of scarce data. The Weibull curve was applied in a scenario analysis to explore a model of diminishing risk. Both curves are presented in Figure 12. A further scenario analysis assumes all patients discontinue treatment due to TEAEs by 5 years after commencing treatment (the base case exponent was increased to one).

Figure 12: Time to long-term TEAE discontinuation



Key: anti-CGRP, anti-calcitonin gene-related peptides; RCT, randomized clinical trial; TEAE, treatment-emergent adverse event

B.3.3.3.3. Discontinuation due to natural improvement (natural history events)

This type of discontinuation is only applied in the model when natural history and treatment holidays are included. As described in B.3.2.3.5, a treatment holiday is a clinical test for changes in underlying disease. If, in any given year, there is a natural history event (i.e., transformation or resolution), then discontinuation will continue indefinitely beyond the end of the holiday. If neither event occurs, active treatment is restarted after the 3-month break. During the holiday the treatment effect is waned. A maximum of five annual treatment holidays are implemented as a fixed clinical schedule, beyond this natural history events are permitted without treatment breaks.

There are multiple sources that recommend stopping treatment to allow for the review of the need of continuing migraine prophylaxis. However, there is some inconsistency in how they might be scheduled:

- NICE CG150 recommends to review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment[54]
- BASH guidelines recommend gradual withdrawal after 6-12 months of effective preventive therapy[23, 25]

- The European Headache Federation Guideline on use of anti-CGRPs recommends continuing treatment for at least 6-12 months in patients who have beneficial effects with those drugs[24]
- A position statement from the IHS states that when treatment is determined to be effective and well tolerated for the prevention of migraine attacks, it should be continued for at least 12 months. After 12 months, medication can be paused for 4–8 weeks to evaluate whether treatment is still necessary[125]

The mid-point of this range of recommendations, 9 months, has been selected to be applied for this model.

B.3.3.3.4. Discontinuation due to stopping rule

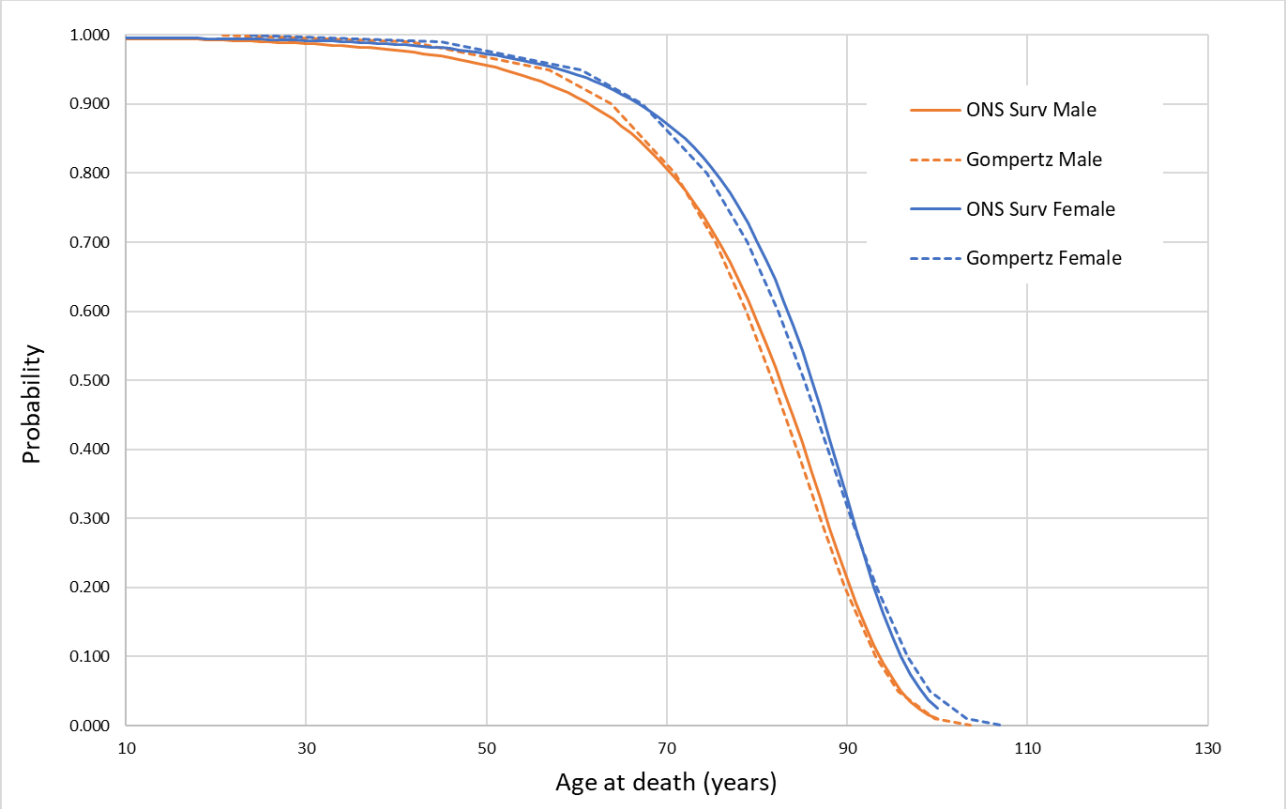
A scenario analysis is included where a maximum treatment duration of 5 years is assumed for eptinezumab

B.3.3.4. Survival

Time to death was estimated for each simulant according to their age at entry and their gender. Standard Gompertz distributions were fitted to data for England and Wales from the Office of National Statistics (Life expectancy at birth [years] with 95% confidence intervals, by sex and country, 1991–1993 to 2012–2014)[126], using Microsoft Excel's Solver functionality (see Figure 13). The mean expectancy of remaining life years at 45 years (mean age at baseline in DELIVER TF3+) in men is 35.94 years (resulting in a mean age at death of 80.9), and 39.19 years in women (resulting in a mean age of death of 84.2) (

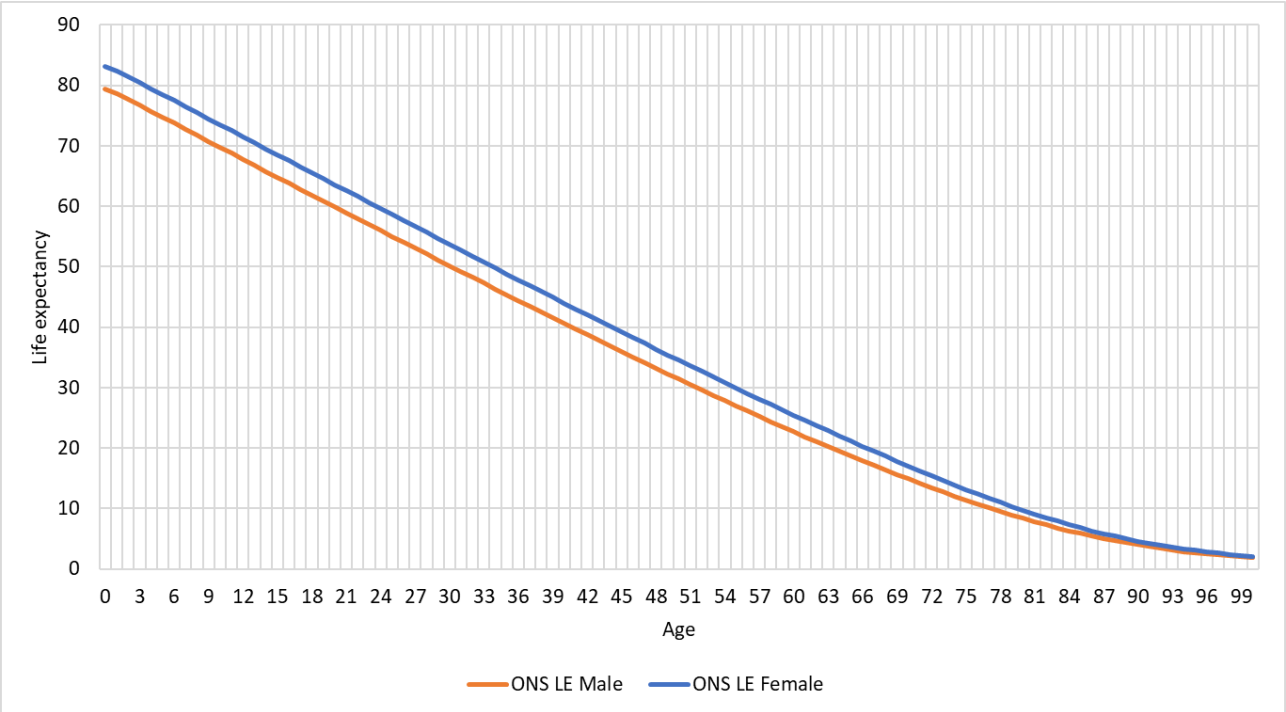
Figure 14). This correlates well with the DES model output of weighted mean age at death (80.6 years).

Figure 13: Life expectancy in men and women in England



Key: ONS, Office for National Statistics.

Figure 14: Period life expectancy in men and women in England



Key: LE, life expectancy; ONS, Office for National Statistics.

B.3.4. Measurement and valuation of health effects

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

The NICE reference case prefers the EQ-5D-3L patient-reported questionnaire to measure HRQL in adults, noting that HRQL valuation should reflect the preference of a representative sample of the UK population.[96] Previous NICE TAs of CGRP inhibitors have relied on a published mapping of responses to the Migraine Specific Quality-of-Life Questionnaire (MSQ) to EQ-5D-3L-derived utility values.[127]

Patients in the DELIVER study all completed patient-reported HRQL questionnaires, including EQ-5D-5L, MSQ and the Headache Impact Test™ (HIT-6). Questionnaires were completed at baseline, as well as at 12 and 24 weeks. As noted in Section B.2.6, changes from baseline to Week 12 in the HIT-6 score is a key secondary endpoint in the DELIVER study. Compared to EQ-5D-5L, MSQ is a more appropriate disease-specific HRQL measure for migraine, as it includes a 4-week recall period for all items and therefore assesses the patient's overall HRQL, including the impact of migraines that happened over the preceding month. Similarly, for HIT there is a 4-week recall period for 3 of the 6 evaluated items. For the other 3 items there is no specified recall period.[125, 128]

The EQ-5D-5L was used to capture patient HRQL in DELIVER, following the NICE reference case.[96] For DELIVER, the EQ-5D-5L was preferred to the EQ-5D-3L as the EQ-5D-5L increases sensitivity and precision in health measurements.[129] The previous NICE appraisal for erenumab (TA682) found that EQ-5D was insensitive to any reduction in migraine days because of the lack of recall period in EQ-5D.[3] To address this issue, a post-hoc analysis was performed for the DELIVER study, which separated the EQ-5D ratings by whether the questionnaire was taken on a migraine day or not. For patients who completed the questionnaire on a migraine day, the utility estimates are separated by degree of pain severity. Mean utility estimates (by study arm and EM/CM status at baseline) are therefore obtained for days with no migraine, and for days with mild, moderate and severe migraine pain. The number of days in each category (no migraine, mild, moderate or severe migraine pain) are then calculated for each patient for each 4-week period and multiplied with the estimated mean utility for each category, and then divided by 28.

B.3.4.2. Mapping

B.3.4.2.1. Mapping from MSQ and HIT to EQ-5D-3L

Gillard (2012) provides mapping algorithms from the MSQ and the HIT-6 to the EQ-5D-3L utilities (UK population-based tariffs), and these algorithms have been used in other migraine NICE appraisals.[1-3, 53, 127]

Each mapping algorithm is provided in two versions, and each version has two different formulas for patients with EM or CM:

1. Model 1: MSQ and HIT scores as independent variables
2. Model 2: Includes additional covariates, such as:
   - Age
   - Sex
   - Ethnicity (white versus other)
   - Current work status (full- or part-time)
   - Current use of headache medication
   - Comorbidities (pain disorders, vascular disorders, psychiatric disorders or other disorders)

Based on baseline MMDs in DELIVER, it was decided which of the two models (EM or CM) to use at the individual patient level. This model is then used for all study visits for that patient (i.e. the utility of patients with CM who become patients with EM is still informed by the CM formula). The utilities are calculated at each visit by using the number of migraine days in the previous 4-week period, but the choice of formula (EM versus CM formula) remains the same for each patient across visits. This approach is consistent with other anti-CGRP evaluations by NICE.[1] Full details of the methodology of mapping from MSQ and HIT-6 to EQ-5D-3L can be found in Appendix N.

In the model base case, the utilities are calculated for each patient and each visit by using the Model 1 MSQ mapping outlined above, as was done for the previous migraine NICE appraisals.[1-3, 53]

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

In line with the NICE guidance for methods of technology appraisal, an SLR to identify relevant utility studies was performed. Full details of the SLR search strategy can be found in Appendix H. A summary of the key findings is presented in Appendix H (section H.7).

B.3.4.4. Adverse reactions

Impact of adverse events on HRQL was not considered in the cost-effectiveness model for eptinezumab (see Section B.3.3.2). This is in line with previous NICE appraisals.[1-3, 53]

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

Total migraine days experienced is the primary determinant of QALY accumulation in the model, given that migraine is assumed not to impact mortality and therefore life years.

The model includes five different sets of utility values that calculate the MMD utility value from the treatment differential parameters (Table 38). Utility values based on treatment differentials were included in the model. This is because treatments may not only affect the number of MMDs but also the intensity of migraines, which may result in an additional utility benefit apart from that resulting from a reduction in MMDs. This is in line with previous migraine NICE appraisals. Age adjustment has been applied to the utility values to account for the fact that QoL for the general population declines with age. Age adjustment was performed in accordance with the latest NICE DSU guidelines.[130]

The model base case uses the DELIVER MSQ, TF3+ with treatment effect utility values, and applies an age adjustment based on general population utility values. The MMDs used in the model are displayed in Table 39.

Finally, a scenario analysis is included where a disutility of 0.005 is assumed for each IV infusion of eptinezumab.[3]

Table 38: Utility models included in the cost-effectiveness model

Utility model	Utility decrement		
	Intercept	On active treatment	Migraine day
DELIVER MSQ, TF3+, with treatment differential	[redacted]	[redacted]	[redacted]
DELIVER MSQ, TF3+, no treatment differential	[redacted]	N/A	[redacted]
DELIVER MSQ, TF2+, with treatment differential	[redacted]	[redacted]	[redacted]
DELIVER MSQ, TF2+, no treatment differential	[redacted]	N/A	[redacted]
DELIVER EQ-5D-5L, TF3+ (Canadian tariffs), no treatment differential	[redacted]	N/A	[redacted]
NICE TA659 (galcanezumab), no treatment differential	0.2143	N/A	0.0132

Key: MSQ, Migraine Specific Quality-of-Life Questionnaire; N/A, not applicable; PBO, placebo; TA, technology appraisal.

Table 39: Utility values in the economic model

MMDs	Utility	
	On treatment	Off treatment
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]
19	[redacted]	[redacted]
20	[redacted]	[redacted]
21	[redacted]	[redacted]
22	[redacted]	[redacted]
23	[redacted]	[redacted]

24	[redacted]	[redacted]
25	[redacted]	[redacted]
26	[redacted]	[redacted]
27	[redacted]	[redacted]
28	[redacted]	[redacted]
29	[redacted]	[redacted]
30	[redacted]	[redacted]
Key: MMD, monthly migraine days.		

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

Base case costs in model reflect the UK NHS and PSS perspective, and consist of the drug acquisition costs, drug administration costs and disease monitoring costs. A scenario analysis taking a societal perspective includes a further category of productivity loss.

The model used a 2020 cost year. Resource use and unit costs for the economic model were obtained from the National Schedule of Reference Costs 2019/2020, Personal Social Services Research Unit (PSSRU) 2020, as well as previous TAs in migraine.[1-3, 131, 132] These are described in more detail below. Where required, the CCEMG – EPPI-Centre cost converter inflation tool was used to inflate costs to 2021.[133]

An SLR conducted to identify relevant cost and resource use evidence identified 11 unique studies that met the inclusion criteria. These studies were extracted from 14 reports and included four HTAs. Full details can be found in Appendix I.

B.3.5.1. Intervention and comparators' acquisition and administration costs

B.3.5.1.1. Intervention

As per the recommended licence, the 100 mg dose of eptinezumab is modelled, with administration via IV infusion every 12 weeks.[5] The list price for a vial of 100 mg of eptinezumab is £1,350, which is a cost per year of £5,870. A patient access scheme (PAS) [redacted] applies, decreasing the vial cost to [redacted], equivalent to [redacted] per year.

B.3.5.1.2. Comparators

The drug acquisition costs of comparator treatments were sourced from the British National Formulary (BNF) and are presented in Table 40.[134-137]

Table 40: Drug acquisition costs

Drug	Unit	Unit cost (list price)	Dosing frequency	Cost per year	Reference
Eptinezumab	100 mg	£1,350.00	Every 12 weeks	£5,870	Lundbeck
Erenumab	140 mg	£386.50	Every 4 weeks	£5,042	BNF[134]
Fremanezumab	225 mg	£450.00	Monthly	£5,400	BNF[135]
Galcanezumab	120 mg	£450.00	Monthly, with 240 mg loading dose	£5,400[+]	BNF[136]
Botulinum toxin A	200 IU*	£276.40	Every 12 weeks	£1,202	BNF[137]

Key: BNF, British National Formulary; IU, international units.
Note: *Botulinum toxin A is dosed at 155-195 IU per administration. One unit of 200 IU is assumed per dose; [+]Costs in the first year are £5,850

B.3.5.1.3. Treatment administration costs

The route of administration varied between treatments and included IV, SC and IM administrations. SC delivery could be either by self-administration or HCP administration. Details are outlined in Table 41.

Table 41: Drug administration costs

Treatment	Admin type	Unit cost	Proportion with costs	Frequency per year	Annual cost	Reference
Eptinezumab	IV 30 min	£174.04	100%	4.3	£756.76	NICE MTA 195 DMARDs using the BRAM model. Administration cost assumed for IFX, RTX and ABT = £141.83. Inflated from 2008 to 2020[133, 139]
Erenumab	SC self-admin	£20	10%	13.0	£26.09	PSSRU 2020 and TA682[3, 131]
Fremanezumab	SC self-admin	£20	10%	11.2	£22.40	PSSRU 2020 and TA764[1, 131]
Galcanezumab	SC self-admin	£20	10%	12.0	£24.00	PSSRU 2020 and TA659[2, 131]
Botulinum toxin A	HCP admin IM	£187.17	100%	4.3	£813.86	NHS ref costs 2019/20 WF01A[132]

Key: ABT, abatacept; admin, administration; HCP, healthcare professional; IFX, infliximab; IM, intra-muscular; IV, intravenous; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; RTX, rituximab; SC, subcutaneous; TA, technology appraisal.

B.3.5.2. Health-state unit costs and resource use

Resource use consumption estimates are directly linked to the 31 health states reflecting the range of migraine possible in a 30-day month. The greater the MMD, the greater the requirement of migraine-related sources. This is the same approach as adopted in each of the previous NICE appraisals of anti-CGRPs. Included in the disease-related resources, measured in average annual cost, are general physician visits, accident and emergency (A&E) visits, hospitalisations, nurse visits and specialist neurologist or psychiatrist consultations. The measurement of consumption of this set of resources is the objective of the National Health and Wellbeing survey (NHWS) of migraine patients, an update commissioned by Lundbeck.[138] The previous version of the NHWS was published by Vo et al in 2018 and was used in the appraisal of galcanezumab.[29] It is also used here in a scenario analysis. Note however that both survey versions consider a headache and not a migraine scale. Additionally, only 4.1% (n = 129) of the surveyed population met the ≥ 3 prior preventive treatment failures criteria, and only 17.3% (n = 691) of the survey participants were UK based. Therefore, results are uncertain but probably underestimates of resource use and therefore conservative. In any case, this is the preferred of the available sources. The ERG and committee appraising galcanezumab (TA659) considered an alternative US survey source inferior to the NHWS used in the prior appraisals of fremanezumab and erenumab, on the basis that resource consumption was measured against migraine frequency. Detailed cost and resource use frequencies used in the model are presented in Table 43 and Table 42, respectively. Appendix Q presents the annual resource use from the previous version of this survey, which is used for a scenario analysis.[2, 29]

Table 42: Annual resource use by MMD frequency[138]

MMD frequency	Hospitalisation	A&E visits	GP visits	Neurologist visits	Psychiatrist visits	Nurse practitioner
0	0	0	0	0	0	0
1–3	0.132	0.258	0.747	0.083	0.056	0.100
4–7	0.157	0.303	0.751	0.107	0.076	0.137
8–14	0.188	0.299	0.769	0.158	0.079	0.116
15–30	0.204	0.349	0.827	0.232	0.131	0.181
Key: A&E, accident and emergency; GP, general practitioner; MMD, monthly migraine days.						

Table 43: Monitoring costs

Resource	Detail	Unit cost	Reference
GP consultation	Single 9.2-minute consultation	£39.23	PSSRU 2020, GP consultation, with indirect care staff costs and qualification costs[131]
A&E visit	HRG VB08Z, Emergency medicine, Category 2 Investigation with Category 1 Treatment, Admission Unknown	£196.63	NHS Ref costs 2019/20[132]
Hospitalisation	Non-elective tariff for AA31E (Headache, Migraine or Cerebrospinal Fluid leak, with CC Score 0-6) Weighted short stay and long-stay	£567.99	NHS Ref costs 2019/20[132]
Nurse practitioner	1 hour GP nurse	£40.00	PSSRU 2020. Cost per hour, including cost of qualifications[131]
Neurologist	WF01A Follow-up attendance - single professional for Neurology outpatient, service code 400	£187.17	NHS Ref costs 2019/20 WF01A Follow-up Attendance - Single Professional Code 400 = Neurology) [132]
Psychiatrist	WF01A Follow-up attendance - single professional for Neurology outpatient, service code 400	£187.17	NHS Ref costs 2019/20 WF01A Follow-up Attendance - Single Professional Code 400 = Neurology) [132]
Triptan*	Inflated 2018 (assumption) to 2020	£7.28	NICE TA631 PenTAG ERG unit cost of IV and oral combined (£7.01, cost year 2018)[1]

Key: A&E, accident and emergency; CC, complexity and comorbidity; ERG, evidence review group; GP, general practitioner; HRG, healthcare resource group; IV, intravenous; NHS, National Health Service; PenTAG, Peninsula Technology Assessment Group; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.
Note: *Assumed to be taken on each migraine day

B.3.5.3. Adverse reaction unit costs and resource use

Resources consumed subsequent to treatment-related adverse events were not considered in this model because serious TRAEs were infrequent and the safety profiles of comparators were similar. Further, resources associated with non-serious adverse events were assumed to be already included within the monitoring resource category.

B.3.5.4. Miscellaneous unit costs and resource use

Migraines have a large and tangible impact on work productivity, and it has been found that individuals' capacity to work improves as a result of treatment (see Section B.1.1). To examine this impact of migraine, productivity losses are assessed using the human capital approach as an alternative scenario. The scenario follows the methodology in Linde et al. 2012 who assumed that absenteeism and presenteeism are each costed as a day lost, stating that 'Reduced productivity was estimated from days at work when the amount done was ≥50% reduced, each such day counting as a full day lost, balanced by ignoring days in which the reduction was <50%'.[140] The inputs for this scenario analysis are presented in Table 44 and Table 45. The cost of absenteeism and presenteeism per MMD is listed as £56.27.

Table 44: Loss of productivity model parameters

Parameter	Value	Source
Hourly earnings (UK 2018)	€15.20	Eurostat median hourly earnings 2018[141]
Inflated and converted to pound sterling (2020)	£14.17	Calculated
UK employment rate 16–64 years old	76.3%	ONS Jan 2020[142]
UK weekly working hours	37	Cabrita 2017[143]
Proportion of population aged under 66	95%	DELIVER[111]
Key: ONS, Office for National Statistics.		

Table 45: Absenteeism and presenteeism by MMD frequency[138]

MMD frequency	Absenteeism (%)	Presenteeism (%)
0	0.0%	0.0%
1–3	12.2%	30.7%
4–7	13.6%	35.2%
8–14	15.7%	39.2%
1–30	21.0%	42.9%
Key: MMD, monthly migraine days.		

B.3.6. Severity

Previous NICE appraisals of anti-CGRPs have not reported on proportional QALY shortfall. The nature of the model (variable periods bounded by discrete events, rather than discrete cycles) means that utility values and total LYs for each individual health state are not readily computable, so these breakdowns are not provided here. Table 46 summarises the key features of the QALY shortfall analysis. The expected remaining QALYs for the general population are 17.22.[126, 130]

Table 47 summarises the QALY shortfall analysis for the current submission. From this, we can conclude that eptinezumab 100 mg does not meet the criteria for a severity weighting.

Table 46: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	89% female	B.3.2.1
Starting age	45 years old	B.3.2.1
Key: QALY, quality-adjusted life year.		

Table 47: Summary of QALY shortfall analysis

Comparator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
BSC	17.22	10.194	7.03 QALYs / 40.81%
Erenumab	17.22	11.042	6.18 QALYs / 35.88%
Fremanezumab	17.22	11.481	5.74 QALYs / 33.33%
Galcanezumab	17.22	11.261	5.96 QALYs / 34.61%
Key: BSC, best supportive care; QALY, quality-adjusted life year.			

B.3.7. Uncertainty

We are confident that we have generated high-quality evidence. The nature of migraine does not impact the ability to generate high-quality evidence.

B.3.8. Managed access proposal

Not applicable.

B.3.9. Summary of base-case analysis inputs and assumptions

B.3.9.1. Summary of base-case analysis inputs

Table 48 summarises the variables applied in the economic model and their base case input values.

Table 48: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Mean age at baseline	45.2	40.68, 49.72 (normal)	B.3.2.1
Proportion of female patients	0.887	0.876, 0.898 (beta)	B.3.2.1
Proportion of anti-CGRP population who experience CM	0.46	0.410, 0.501(beta)	B.3.2.1
Alpha constant of beta distribution informing MMDs at baseline for EM	9.762	N/A*	B.3.2.3.4
Beta constant of beta distribution informing MMDs at baseline for EM	20.150	N/A*	B.3.2.3.4
Alpha constant of beta distribution informing MMDs at baseline for CM	7.772	N/A*	B.3.2.3.4
Beta constant of beta distribution informing MMDs at baseline for CM	4.445	N/A*	B.3.2.3.4
Lambda (Gompertz) for other cause mortality, females	0.000	N/A*	B.3.3.4
Gamma (Gompertz) for other cause mortality, females	0.105	N/A*	B.3.3.4
Lambda (Gompertz) for other cause mortality, males	0.000	N/A*	B.3.3.4
Gamma (Gompertz) for other cause mortality, males	0.105	N/A*	B.3.3.4
Response rate for BSC 50% response rate at 12 weeks, EM	[redacted]	[redacted] (normal)	B.3.3.1.1
Response rate for BSC 30% response rate at 12 weeks, EM	[redacted]	[redacted] (normal)	B.3.3.1.1
Response rate for erenumab 50% response rate at 12 weeks, EM	[redacted]	[redacted] (normal)	B.3.3.1.1
Response rate for erenumab 30% response rate at 12 weeks, CM	[redacted]	[redacted](normal)	B.3.3.1.1
Response rate for fremanezumab 50% response rate at 12 weeks, EM	[redacted]	[redacted] (normal)	B.3.3.1.1

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Response rate for fremanezumab 30% response rate at 12 weeks, CM	[redacted]	[redacted](normal)	B.3.3.1.1
Response rate for galcanezumab 50% response rate at 12 weeks, EM	[redacted]	[redacted](normal)	B.3.3.1.1
Response rate for galcanezumab 30% response rate at 12 weeks, CM	[redacted]	[redacted](normal)	B.3.3.1.1
Response rate for botulinum toxin A 30% response rate at 12 weeks, CM	[redacted]	[redacted](normal)	B.3.3.1.1
Response rate for eptinezumab 50% response rate at 12 weeks, EM	[redacted]	[redacted](normal)	B.3.3.1.1
Response rate for eptinezumab 30% response rate at 12 weeks, CM	[redacted]	[redacted] (normal)	B.3.3.1.1
MMD reduction for EM 50% responders, BSC	[redacted]	[redacted] (normal)	B.3.3.1.2
MMD reduction for EM 50% non-responders, BSC	[redacted]	[redacted] (normal)	B.3.3.1.2
MMD reduction for EM 50% responders, aTX	[redacted]	[redacted] (normal)	B.3.3.1.2
MMD reduction for EM 50% non-responders, aTX	[redacted]	[redacted] (normal)	B.3.3.1.2
MMD reduction for CM 30% responders, BSC	[redacted]	[redacted] (normal)	B.3.3.1.2
MMD reduction for CM 30% non-responders, BSC	[redacted]	[redacted] (normal)	B.3.3.1.2
MMD reduction for CM 30% responders, aTX	[redacted]	[redacted](normal)	B.3.3.1.2
MMD reduction for CM 30% non-responders, aTX	[redacted]	[redacted](normal)	B.3.3.1.2
Years of MMD waning of aTx effect	0.33	0.297, 0.363 (normal)	B.3.3.1.4
Years of MMD waning of BSC effect	1.0	0.90, 1.10 (normal)	B.3.3.1.4

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Probability during initial assessment of experiencing a TEAE leading to anti-CGRP withdrawal	0.0106	0.0095, 0.0116 (normal)	B.3.3.3.2
Probability during initial assessment of experiencing a TEAE leading to botulinum toxin A withdrawal	0.0320	0.0288, 0.0352 (normal)	B.3.3.3.2
Exponent of the exponential distribution describing anti-CGRP disc due to AEs post initial assessment	0.0324	0.0292, 0.0356 (normal)	B.3.3.3.2
Exponent of the exponential distribution describing botulinum toxin A disc due to AEs post initial assessment	0.5236	0.4712, 0.5760 (normal)	B.3.3.3.2
MMD leeway below licensed MMD range before discontinuation	4.0	3.60, 4.40 (normal)	B.3.2.3
Utility, on anti-CGRPs or botulinum toxin A – intercept	[redacted]	(Multi-normal)	B.3.4.5
Utility, on anti-CGRPs or botulinum toxin A – slope	[redacted]	(Multi-normal)	B.3.4.5
Utility, no anti-CGRPs or botulinum toxin A – intercept	[redacted]	(Multi-normal)	B.3.4.5
Utility, no anti-CGRPs or botulinum toxin A – slope	[redacted]	(Multi-normal)	B.3.4.5
Annual acquisition cost of eptinezumab 100mg	£5870.09	5283.080, 6457.098[+]	B.3.5.1.2
Annual acquisition cost of erenumab 140 mg	£5041.75	4537.579, 5545.930[+]	B.3.5.1.2
Annual acquisition cost of fremanezumab 225 mg	£5400	4860.00, 5940.00[+]	B.3.5.1.2
Annual acquisition cost of galcanezumab 120 mg	£5400	4860.00, 5940.00[+]	B.3.5.1.2
Annual acquisition cost of botulinum toxin A 200 IU	£1201.85	1081.662, 1322.031[+]	B.3.5.1.2
Administration cost – eptinezumab IV	174.04	156.636, 191.444 (Gamma)	B.3.5.1.3
Administration cost – erenumab SC	£2.0	1.80, 2.20 (Gamma)	B.3.5.1.3
Administration cost – fremanezumab SC	£2.0	1.80, 2.20 (Gamma)	B.3.5.1.3
Administration cost – galcanezumab SC	£2.0	1.80, 2.20 (Gamma)	B.3.5.1.3
Administration cost – botulinum toxin A IM	£187.17	168.453, 205.887 (Gamma)	B.3.5.1.3

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Cost of GP consultation	£39.23	35.307, 43.153 (Gamma)	B.3.5.2
Cost of A&E visit	£196.63	176.967, 216.293 (Gamma)	B.3.5.2
Cost of hospitalisation	£567.99	511.191, 624.789 (Gamma)	B.3.5.2
Cost of nurse practitioner	£40.00	36.000, 44.000 (Gamma)	B.3.5.2
Cost of neurologist	£187.17	168.453, 205.887 (Gamma)	B.3.5.2
Cost of psychiatrist	£187.17	168.453, 205.887 (Gamma)	B.3.5.2
Cost of triptan (per MMD)	£7.28	6.552, 8.008 (Gamma)	B.3.5.2
Annual number of hospitalisations – 1–3 MMD	0.132	0.119, 0.145 (normal)	B.3.5.2
Annual number of hospitalisations – 4–7 MMD	0.157	0.141, 0.173 (normal)	B.3.5.2
Annual number of hospitalisations – 8–14 MMD	0.188	0.169, 0.207 (normal)	B.3.5.2
Annual number of hospitalisations – 15–30 MMD	0.204	0.184, 0.224 (normal)	B.3.5.2
Annual number of A&E visits – 1–3 MMD	0.258	0.232, 0.284 (normal)	B.3.5.2
Annual number of A&E visits – 4–7 MMD	0.303	0.273, 0.333 (normal)	B.3.5.2
Annual number of A&E visits – 8–14 MMD	0.299	0.269, 0.329 (normal)	B.3.5.2
Annual number of A&E visits – 15–30 MMD	0.349	0.314, 0.384 (normal)	B.3.5.2
Annual number of GP visits – 1–3 MMD	0.747	0.672, 0.822 (normal)	B.3.5.2
Annual number of GP visits – 4–7 MMD	0.751	0.676, 0.826 (normal)	B.3.5.2
Annual number of GP visits – 8–14 MMD	0.769	0.692, 0.846 (normal)	B.3.5.2
Annual number of GP visits – 15–30 MMD	0.827	0.744, 0.910 (normal)	B.3.5.2
Annual number of neurologist visits – 1–3 MMD	0.083	0.075, 0.091 (normal)	B.3.5.2
Annual number of neurologist visits – 4–7 MMD	0.107	0.096, 0.118 (normal)	B.3.5.2

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Annual number of neurologist visits – 8–14 MMD	0.158	0.142, 0.174 (normal)	B.3.5.2
Annual number of neurologist visits – 15–30 MMD	0.232	0.209, 0.255 (normal)	B.3.5.2
Annual number of psychiatrist visits – 1–3 MMD	0.056	0.050, 0.062 (normal)	B.3.5.2
Annual number of psychiatrist visits – 4–7 MMD	0.076	0.068, 0.084 (normal)	B.3.5.2
Annual number of psychiatrist visits – 8–14 MMD	0.079	0.071, 0.087 (normal)	B.3.5.2
Annual number of psychiatrist visits – 15–30 MMD	0.131	0.118, 0.144 (normal)	B.3.5.2
Annual number of nurse practitioner visits – 1–3 MMD	0.100	0.090, 0.110 (normal)	B.3.5.2
Annual number of nurse practitioner visits – 4–7 MMD	0.137	0.123, 0.151 (normal)	B.3.5.2
Annual number of nurse practitioner visits – 8–14 MMD	0.116	0.104, 0.128 (normal)	B.3.5.2
Annual number of nurse practitioner visits – 15–30 MMD	0.181	0.163, 0.199 (normal)	B.3.5.2

Key: A&E, accident and emergency; anti-CGRP, anti-calcitonin gene-related peptide; aTx, active treatment; BSC, best supportive care; CM, chronic migraine; EM, episodic migraine; GP, general practitioner; IM, intramuscular; IU, international units; IV, intravenous; MMD, monthly migraine days; NH, natural history; NICE, National Institute for Health and Care Excellence; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SC, subcutaneous; SD, standard deviation.
Notes: *not varied in OWSA because inputs are correlated, and not varied in PSA because baseline patient characteristics are not included in PSA. [+]Varied in OWSA but not PSA.

B.3.9.2. Assumptions

Table 49 summarises the key assumptions made in the health economic model.

Table 49: Key assumptions of the health economic model

Assumption	Justification	Reference to section in submission
Population		

Assumption	Justification	Reference to section in submission
Gender and age at entry are based on evidence from TF3+ subgroup of the DELIVER trial, and this reflects the migraine population in the UK.	• DELIVER TF3+ population data are used to make sure efficacy data in the model reflect the population entering the model. A UK advisory board confirmed that the population reflects the UK migraine population • As the age and gender profile in recruited trial participants may not reflect the ultimate profile of recipients, a scenario analysis is provided using RWE evidence from a Swedish anti-CGRP registry	B.3.2.1
Chronic migraine is defined as 8 or more MMDs, yet episodic migraine has a migraine frequency range of 4 to 15 MMDs.	Headache frequency is not modelled so the EM-CM boundary – transitioned by individuals whose underlying condition improves - must be defined in terms of MMDs only. 8 MMDs is the preferred clinical equivalent of 15 MHDs with 8 MMDs, the classic definition. Some participants of DELIVER with >8 MMDs were classified as EM.	B.3.2.3.4
The split between patients with EM and CM of those that have completed the Migraine Trust Survey is reflective of the split between EM and CM in patients that would be treated with eptinezumab in UK clinical practice. The beta distribution describes the dispersion of MMD at model entry, which is based on the DELIVER trial population stratified by EM and CM status at baseline.	• The proportion of patients with EM in the DELIVER trial was relatively high compared to the proportion of patients with EM of those that would be expected to be treated with eptinezumab. Therefore the Migraine trust survey results were used to assign patients an EM or CM status at baseline[110] • Since treatment effect is applied according to subpopulation, bias in these estimates will bias the cost-effectiveness estimate in the whole population if the results differ between groups. Anti-CGRP strategies would benefit most from a higher proportion of EM, since the NMA finds that BSC has the largest relative response rate improvement from EM to CM. Acquisition cost is not subgroup sensitive, and monitoring costs are small and nearly linear through the MMD range	B.3.2.3.4
Neither migraine nor migraine treatment have any impact on mortality.	• This is in line with TA764, TA682, TA659 and TA260, none of which assume excess mortality associated with migraine • If years of migraine did reduce survival, then the DES model estimates of cost-effectiveness are likely to be conservative given that anti-CGRPs and botulinum toxin A reduce the burden of disease. There is no evidence for either	B.3.3.4

Assumption	Justification	Reference to section in submission
Anti-CGRPs and botulinum toxin A		
The onset of response for all treatments is assumed to be 4 weeks	This assumption facilitates consistency within the model, despite variation in administration techniques. Based on trial data this may overestimate time of response of eptinezumab and underestimate the comparators hence making it a conservative assumption	B.3.3.1.3
Anti-CGRPs do not modify disease.	There is no evidence for anti-CGRPs inducing a prolonged and sustained effect after discontinuation.[3, 106] However, a scenario analysis is provided where 20% of individuals who positively discontinue eptinezumab or other aTx sustain CFB	B.3.2.3.5
The relative effect in 50% response in CM, as seen from the NMA, also applies for the 30% response definition as applied in the model for CM	This is in line with TA659, and was also confirmed during a UK advisory board[2]	B.3.3.1.1
Treatment effectiveness is stratified by migraine subpopulation, and all patients without a 30% or 50% reduction in their MMDs at 12 weeks (dependent on the subpopulation) after the start of their treatment, discontinue anti-CGRPs or botulinum toxin A.	This follows previous NICE guidance for TA764, TA682 and TA659, where a 50% MMD reduction was classified as response for EM, and a 30% MMD reduction was classified as response for CM[1-3]	B.3.3.1.1
Weighting CFB by response status is based on DELIVER for all treatments.	Estimates of CFB according to response status are not publicly available for comparator treatments, so uncertainty is unavoidable given the approximation of awarding the eptinezumab CFBs to all comparator anti-CGRPs or botulinum toxin A	B.1.1.1.1
Treatments are not discontinued outside their recommended MMD threshold for commencement.	The base case assumption is that in responders, treatment with anti-CGRPs will be continued for as long as they are deriving clinical benefit. This is applied by including a discontinuation leeway of 4 MMDs, which allows for treatment discontinuation due to this reason in the botulinum toxin A strategy (as it is only available for CM patients), but not anti-CGRPs. A scenario analysis is provided where this leeway is reduced to 2 MMDs (i.e. discontinuation at 2 MMDs)	B.3.3.3

Assumption	Justification	Reference to section in submission
The effect of anti-CGRPs or botulinum toxin A lasts beyond discontinuation, waning away linearly over 4 months.	This estimate is supported by recent clinical evidence.[114] A longer period (1 year) of waning is explored in a scenario analysis	B.3.2.3
Utility		
On-treatment utility is higher than off-treatment utility because anti-CGRPs and botulinum toxin A reduce not only MMDs, but also migraine duration and intensity.	This position is supported by precedence (TA764, TA682 and TA659), and the same utility treatment effect is observed in participants of the DELIVER study (both in the FAS as well as the population who tried at least 3 prior preventive therapies that failed).[1-3, 53] This is further supported by the differences between eptinezumab and placebo responders in WPAI scores (See Section B.1.1)	B.3.4.5
MSQ is the best utility instrument to measure change in MMD in patients with migraine.	This is in line with TA764, TA682 and TA659[1-3]	B.3.4.2.1
The impact of AEs on costs and HRQL is low, so these are not included in the model.	This is in line with TA764, TA682 and TA659[1-3]	B.3.3.2
Costs and resource use		
The update of the NHWS best reflects HCRU in migraine.	Builds upon previous TAs' use of the 2018 NHWS to include more recent data that are reflective of the population	B.3.5.2
Best supportive care		
Individuals may be classified as responders and non-responders to BSC.	This is in line with TA764, TA682 and TA659[1-3]	B.3.3.1.1
The CFB derived by BSC lasts only 1 year, with all effect waning away linearly over that time.	The accepted period of effect of BSC in the NICE appraisal of TA659 was 1 year, a period through which the size of effect diminishes to nothing.[2] A scenario analysis is provided where a 2-year diminishing effect is applied	B.3.3.1.4
Response to BSC after aTX is independent of response to aTx.	No evidence has been identified to correlate responsivity between sequential lines of treatment	B.3.3.1.1

Assumption	Justification	Reference to section in submission
Intravenous administration does not increase the significance of the placebo effect compared to subcutaneously administered placebo.	This is a conservative assumption. A scenario analysis is provided that includes an additional 1.3 MMD CFB for eptinezumab, which is the calculated level of adjustment for non-comparable placebo in the NMA	B.3.3.1.1
Botulinum toxin A		
Response rate over 24 weeks is used in the 12-week response rate NMA, but is then applied at 24 weeks in the model.	Use of the 24-week botulinum toxin A estimate in the 12-week NMA introduces uncertainty into the generation of the botulinum toxin A response rate whether applied at 12 or 24 weeks. Each of the previous three anti-CGRP NICE appraisals (TA764, TA682 and TA659) encountered the same challenge	B.3.3.1.1

Key: AE, adverse event; aTx, active treatment; BSC, best supportive care; CFB, change from baseline; CGRP, calcitonin gene-related peptide; CM, chronic migraine; DES, discrete event simulation; EM, episodic migraine; FAS, full analysis set; HCRU, healthcare resource utilisation; HRQL, health-related quality of life; IV, intravenous; MMD, monthly migraine days; MSQ, Migraine Specific Quality-of-Life Questionnaire; NH, natural history; NHWS, National Health and Wellness Survey; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RWE, real-world evidence; TA, technology appraisal; WPAI, Work Productivity and Activity Impairment scale.

B.3.10. Base-case results

The results presented in this document (Sections B.3.10 to B.3.12) are the cost-utility results, and represent the list price for eptinezumab and its comparators. The results with PAS discount applied for eptinezumab would not be informative, as the PAS discounts for the other anti-CGRPs are unknown to Lundbeck, and therefore eptinezumab would appear more cost effective than it is when PAS discounts for all therapies would be considered.

We also assessed the impact of the equal efficiency assumption. Appendix M presents cost-comparison results, using the format suggested in the user guide for cost-comparison analyses.[144] These are also presented without any PAS discounts applied.

B.3.10.1. Base-case incremental cost-effectiveness analysis results

A summary of the base case results for the overall population is presented in Table 50. As discussed above, these results do not consider PAS discounts for eptinezumab or the other anti-CGRPs. Lundbeck's expectation is that, if the PAS discounts for all treatments would be applied, and PAS discounts for the comparator anti-CGRPs were in the range of [redacted], eptinezumab would be [redacted] compared to the other anti-CGRPs. The incremental QALYs versus BSC for all anti-CGRP therapies are very similar. The incremental QALYs for eptinezumab (1.103) are a bit higher compared to those associated with erenumab and galcanezumab (0.848 and 1.067 respectively), and a bit lower than those associated with fremanezumab (1.286). Incremental costs compared to BSC are highest with eptinezumab (£42,025 vs BSC, compared to £23,921 - £38,030 for the other anti-CGRPs). This is mostly a result of the higher administration costs associated with eptinezumab (see Appendix J).

Similarly, from Table 51 it can be seen that the incremental net health benefit (iNHB) versus BSC for all anti-CGRPs is very similar. If all PAS discounts would be considered, these are expected to be higher.

For completeness, the ICER and incremental net benefit of eptinezumab versus each comparator (Table 52) and eptinezumab versus a blended anti-CGRP

comparator (Table 53) are presented as well. The blended anti-CGRP comparator is based on market shares of the anti-CGRPs in the UK, which are assumed as follows based on market sales data:[145]

- Erenumab 140 mg: 14%
- Fremanezumab 225 mg: 76%
- Galcanezumab 120 mg: 10%

The clinical outcomes modelled, alongside the disaggregated results of the base case ICER analyses, are presented in Appendix J.

Table 50: Base-case results (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	£14,015	35.1	10.194				
Erenumab 140mg	£37,936	35.1	11.042	£23,921	0.848	£28,221	Extendedly dominated
Galcanezumab 120mg	£47,301	35.1	11.261	£33,287	1.067	£31,206	Extendedly dominated
Fremanezumab 225mg	£52,044	35.1	11.481	£38,030	1.286	£29,566	£29,566
Eptinezumab 100mg	£56,040	35.1	11.297	£42,025	1.103	£38,102	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.							

Table 51: Incremental net health benefit all anti-CGRPs vs BSC for the full population (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	iNHB at £20,000 vs BSC	iNHB at £30,000 vs BSC
BSC	£14,015	35.1	10.194				
Erenumab 140mg	£37,936	35.1	11.042	£23,921	0.848	-0.348	0.050
Galcanezumab 120mg	£47,301	35.1	11.261	£33,287	1.067	-0.598	-0.043
Fremanezumab 225mg	£52,044	35.1	11.481	£38,030	1.286	-0.615	0.019
Eptinezumab 100mg	£56,040	35.1	11.297	£42,025	1.103	-0.998	-0.298
Key: LYG, life years gained; iNHB, incremental net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.							

Table 52: ICER and incremental net health benefit for eptinezumab vs all comparators for the full population (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Eptinezumab vs comparator				
				Incremental costs	Incremental QALYs	ICER	iNHB at £20,000	iNHB at £30,000
Eptinezumab 100mg	£56,040	35.1	11.297					
BSC	£14,015	35.1	10.194	£13,107	1.103	£38,102	-0.998	-0.298
Erenumab 140mg	£37,936	35.1	11.042	£4,133	0.255	£70,905	-0.650	-0.348
Fremanezumab 225mg	£52,044	35.1	11.481	-£1,138	-0.183	-£21,801	-0.383	-0.316
Galcanezumab 120mg	£47,301	35.1	11.261	£558	0.036	£240,839	-0.401	-0.255
Key: LYG, life years gained; iNHB, incremental net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.								

Table 53: ICER and incremental net health benefit for eptinezumab versus blended anti-CGRP comparator (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Eptinezumab vs comparator				
				Incremental costs	Incremental QALYs	ICER	iNHB at £20,000	iNHB at £30,000
Eptinezumab 100mg	£56,040	35.1	11.297					
Blended anti-CGRPs	£49,592	35.1	11.400	£6,448	-0.103	£62,753	-0.425	-0.318
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; iNHB, incremental net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.								

B.3.11. Exploring uncertainty

To assess the level of uncertainty surrounding the model parameters, sensitivity analyses in the form of univariate deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were undertaken. Additionally, a broad range of scenario analyses were undertaken to examine the uncertainty surrounding the model assumptions.

Appendix M contains uncertainty analyses for the cost-comparison analysis.

B.3.11.1. Probabilistic sensitivity analysis

A PSA was undertaken to assess the uncertainty surrounding model parameters. Cost and QALY outputs of base case analyses were collected for each strategy of multiple microsimulations. Each microsimulation contained simulated patients created from a unique parameter set, and point estimates were randomly sampled from the parameter distributions. Where distribution parameters were not known, the standard error was approximated to 20% of the mean. The unit costs of anti-CGRPs and botulinum toxin A acquisition were excluded from the PSA as they are known and certain. Also excluded from variation in the PSA were the parameters informing baseline variation between individuals (as these are varied at a patient-simulation level), so that the emphasis is placed on testing treatment effectiveness, utility, cost, and resource estimates. Cost and QALYs across the repeated microsimulations were averaged to inform probabilistic outcomes, which are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) in Figure 15 and Figure 16, respectively.

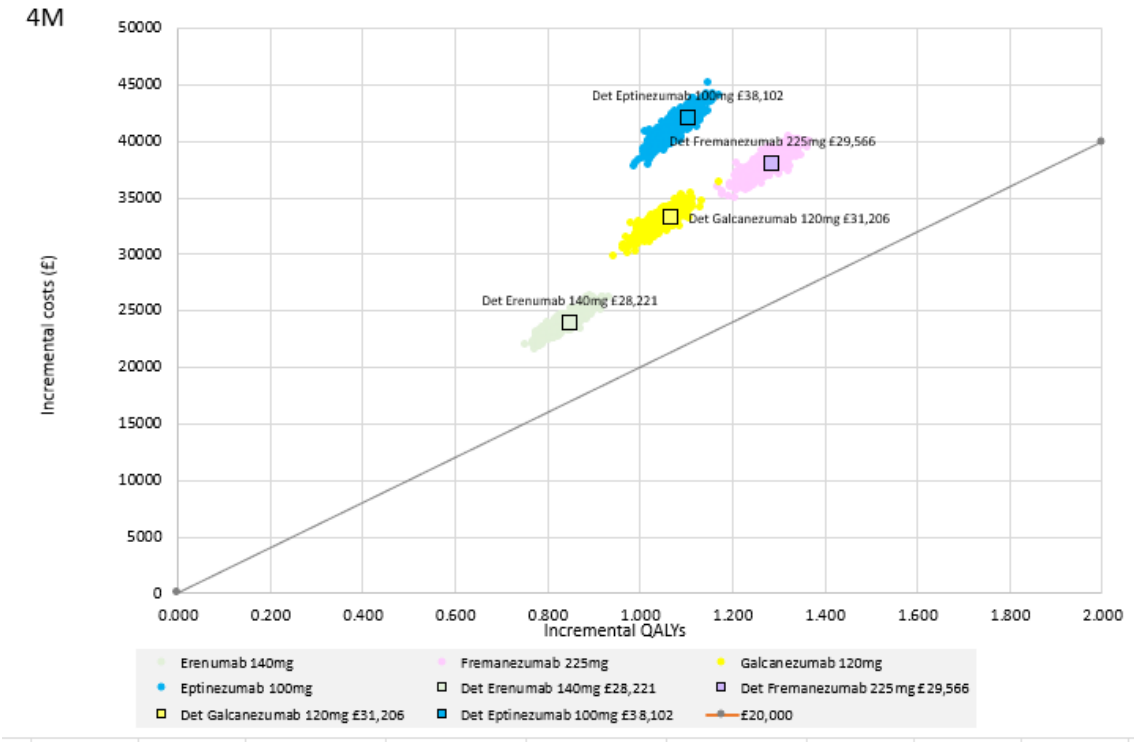
Figure 15, Figure 16 and Table 54 demonstrate that the findings from the PSA are not significantly different compared with the deterministic base case analysis. Table 55 and Figure 16 show the probability of each treatment being the most cost-effective option at various WTP thresholds.

Table 54: Probabilistic base-case results (no PAS considered)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	£14,151	10.193				
Erenumab 140 mg	£38,168	11.038	£24,016	0.845	£28,420	Extendedly dominated
Fremanezumab 225 mg	£47,062	11.243	£32,910	1.050	£31,357	Extendedly dominated
Galcanezumab 120 mg	£51,836	11.463	£37,684	1.270	£29,678	£29,678
Eptinezumab 100 mg	£55,284	11.269	£41,132	1.076	£38,226	Dominated

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IU, international units; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 15: Cost-effectiveness plane, incremental versus BSC (no PAS considered)



Key: Det, deterministic; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 16: Cost-effectiveness acceptability curve (no PAS considered)

Key: CE, cost-effectiveness; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 55: Probability of being most cost effective at different WTP thresholds (no PAS considered)

WTP	Eptinezumab 100 mg	Erenumab 140 mg	Galcanezumab 120 mg	Fremanezumab 225 mg
£0	0%	100%	0%	0%
£2,000	0%	100%	0%	0%
£4,000	0%	100%	0%	0%
£6,000	0%	100%	0%	0%
£8,000	0%	100%	0%	0%
£10,000	0%	100%	0%	0%
£12,000	0%	100%	0%	0%
£14,000	0%	100%	0%	0%
£16,000	0%	100%	0%	0%
£18,000	0%	100%	0%	0%
£20,000	0%	100%	0%	0%
£22,000	0%	100%	0%	0%
£24,000	0%	100%	0%	0%
£26,000	0%	100%	0%	0%
£28,000	0%	100%	0%	0%
£30,000	0%	100%	0%	0%
£32,000	0%	61%	0%	39%
£34,000	0%	3%	0%	97%
£36,000	0%	0%	0%	100%
£38,000	0%	0%	0%	100%
£40,000	0%	0%	0%	100%
£42,000	0%	0%	0%	100%
£44,000	0%	0%	0%	100%
£46,000	0%	0%	0%	100%
£48,000	0%	0%	0%	100%
£50,000	0%	0%	0%	100%

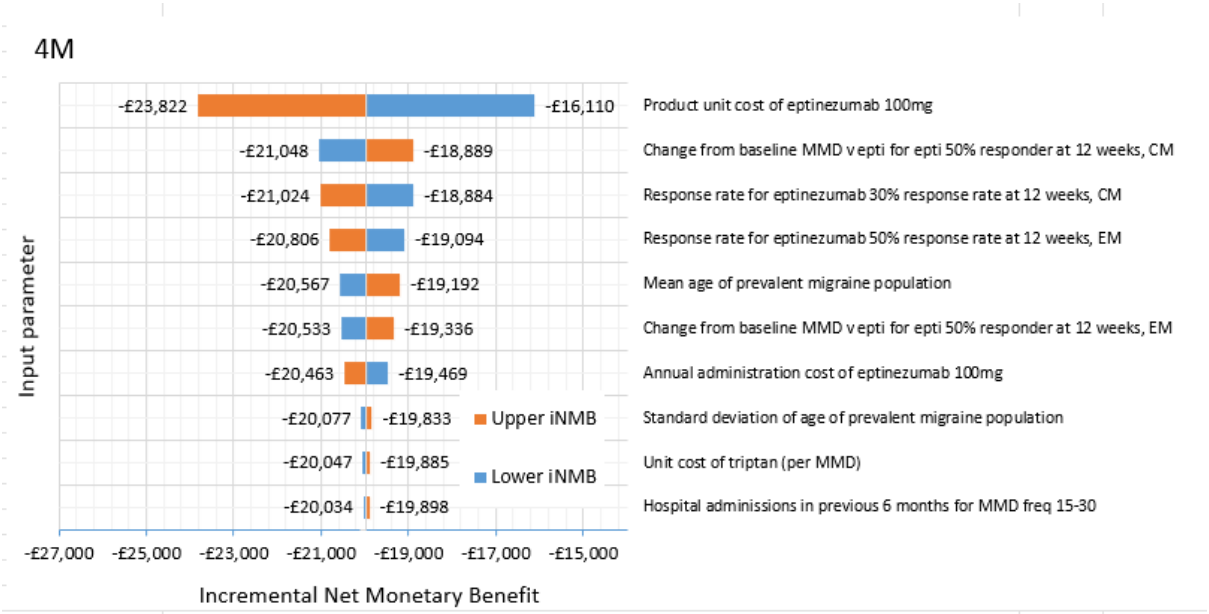
B.3.11.2. Deterministic sensitivity analysis

A deterministic sensitivity analysis was undertaken in the form of an OWSA. Drug unit costs were included to comprehensively explore the sensitivity of incremental net monetary benefit (iNMB) to fixed variation in every independent parameter. This included the drug unit costs and excluded any correlated input estimates (i.e., parametric survival models for lifespan and natural history, and utility regression models). Subsequently, the included parameters were tested by varying them 10% either side of the point estimate of the mean. The 10 most influential parameters

have been presented in a tornado diagram (Figure 17). The analysis examines sensitivity in the comparison of eptinezumab versus BSC in the 4M population.

The most impactful parameters for the modelled population were the product unit cost of eptinezumab 100mg, and change from baseline MMD versus eptinezumab for 50% response at 12 weeks in the CM subgroup.

Figure 17: OWSA tornado diagram, eptinezumab vs. BSC (no PAS considered)



Key: BSC, best supportive care; CM, chronic migraine; EM, episodic migraine; iNMB, incremental net monetary benefit; MMD, monthly migraine days; OWSA, one-way sensitivity analysis; PAS, patient access scheme.

B.3.11.3. Scenario analysis

Table 56 shows the ICERs derived from the scenario analyses for the overall population. The scenario analysis assesses 30 alternative structural and parameter scenarios compared to the base case. The scrutinised pairwise comparisons in this population are versus BSC.

For each population, the scenario analysis that assessed the mean MMD improvement in comparison with BSC appeared to have the most significant impact on the ICER.

Table 56: Scenario analysis results, eptinezumab vs BSC (no PAS considered)

Scenario	Details provided in	ICER
Base case; eptinezumab vs BSC; overall population	N/A	£38,102
Time horizon 10 years	Table 32	£38,387
No discounting future costs and benefits	Table 32	£38,146
Taking a societal perspective (including indirect costs of lost productivity)	B.3.5.4	£37,909
Switch from RCT to real-world registry data for age at entry	B.3.2.3.3	£38,150
Include natural history (transformation and resolution) and positive stop assessments (treatment holidays)	B.3.2.3.5	£36,529
Include NH events but exclude treatment holidays	B.3.3.3.3	£38,746
Include NH events but having 2 years between positive stop assessments	B.3.3.3.3	£35,916
NMA odds ratio TF3+ at the 50% threshold for EM, and at the 50% threshold for CM	Appendix Q	£39,636
NMA odds ratio TF3+ at the 50% threshold, pooled EM and CM	Appendix Q	£39,040
NMA TF3+ EM and CM (BSC-galcanezumab-eptinezumab), both stratified at 50% threshold	Appendix Q	£33,741
Directly using TF2+ DELIVER data, both stratified at 50% thresholds	Appendix Q	£34,078
Directly using TF2+ DELIVER data, No stratification for response	Appendix Q	£54,231
NMA TF2+ pooled (BSC-erenumab-fremanezumab-galcanezumab-eptinezumab), No stratification for response	Appendix Q	£76,618
Assume immediate onset of response for eptinezumab	B.3.3.1.3	£38,009
All patients discontinued due to TEAEs by 5 years	B.3.3.3.2.2	£32,757
Weibull distribution extrapolation of long-term TEAE discontinuation	B.3.3.3.2.2	£38,559
MMD leeway of 2 days before threshold/licence discontinuation	Table 30	£37,900
20% 'super-responding' with sustained aTx CFB post-discontinuation	Table 30	£29,359

Scenario	Details provided in	ICER
2 years of on-treatment BSC waning following response (time to reach baseline MMDs)	Table 30	£38,373
1 year of post-discontinuation waning for anti-CGRPs and botulinum toxin A (time to reach BSC MMDs)	Table 30	£36,877
5 years until maximum treatment duration stop (eptinezumab only)	B.3.3.3	£36,052
Excluding age adjustment of utility	B.3.4.5	£38,048
DELIVER MSQ, TF3+; no treatment differential	B.3.4.5	£40,362
DELIVER MSQ, TF2+ treatment differential	B.3.4.5	£37,455
DELIVER MSQ, TF2+; no treatment differential	B.3.4.5	£39,936
NICE TA659 (galcanezumab); no treatment differential	B.3.4.5	£56,890
Using EQ-5D DELIVER results, no treatment differential	B.3.4.5	£139,374
Including disutility for eptinezumab IV infusion	B.3.4.5	£43,582
Using NHWS resource use data from before update (NICE galcanezumab TA; Vo 2018)	Appendix Q	£38,500

Key: anti-CGRPs, anti-calcitonin gene-related peptides; aTx, active treatment; BSC, best supportive care; CFB, change from baseline; CM, chronic migraine; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; IV, intravenous; MMD, monthly migraine days; MSQ, Migraine Specific Quality-of-Life Questionnaire; NH, natural history; NHWS, National Health and Wellness Survey; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; TA, technology appraisal.

B.3.12. Subgroup analysis

The population described in the NICE scope is referred to as the 4M TF3+ population, or ‘whole population. EM and CM populations are presented as subgroups and the results of their analysis are presented in B.3.12.1 (CM) and B.1.1.1 (EM).

B.3.12.1. Chronic migraine population

A summary of the base case results for the CM population is presented in Table 57. As for the full population, these do not consider any PAS discounts for eptinezumab or the other anti-CGRPs.

The incremental QALYs versus BSC for all anti-CGRP therapies are very similar, while QALYs associated with botulinum toxin A are lower than those associated with any of the anti-CGRPs. The incremental QALYs for eptinezumab (1.571) are a bit higher compared to those associated with erenumab (1.393), and a bit lower than those associated with fremanezumab and galcanezumab (1.630 and 1.756

respectively). Incremental costs compared to BSC are highest with eptinezumab (£71,559 vs BSC, compared to £53,731 - £67,616 for the other anti-CGRPs). This is mostly a result of the higher administration costs associated with eptinezumab. When PAS discounts are applied for all treatments, and PAS discounts for the comparator anti-CGRPs would be in the range of [redacted], the expectation is that total costs associated with eptinezumab are [redacted] those associated with other anti-CGRPs.

Similarly, from Table 58 it can be seen that the incremental net health benefit (iNHB) versus BSC for all anti-CGRPs is very similar. If all PAS discounts would be considered, these are expected to be higher.

For completeness, the ICER and incremental net benefit of eptinezumab versus each comparator (Table 59) is presented as well.

Table 57: Base case results for CM subgroup (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	£16,840	35.7	8.825				
Botulinum toxin A 200 IU	£18,817	35.7	8.988	£1,977	0.164	£12,093	£12,093
Erenumab 140 mg	£53,731	35.7	10.217	£36,892	1.393	£26,486	Extendedly dominated
Fremanezumab 225 mg	£60,058	35.7	10.455	£43,219	1.630	£26,510	£28,117
Galcanezumab 120 mg	£67,616	35.7	10.581	£50,777	1.756	£28,913	£60,034
Eptinezumab 100 mg	£71,559	35.7	10.396	£54,719	1.571	£34,830	Dominated
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.							

Table 58: Net health benefit for CM subgroup (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	iNHB at £20,000 vs BSC	iNHB at £30,000 vs BSC
BSC	£16,840	35.7	8.825				
Botulinum toxin A 200 IU	£18,817	35.7	8.988	£1,977	0.164	0.065	0.098
Erenumab 140 mg	£53,731	35.7	10.217	£36,892	1.393	-0.452	0.163
Fremanezumab 225 mg	£60,058	35.7	10.455	£43,219	1.630	-0.531	0.190
Galcanezumab 120 mg	£67,616	35.7	10.581	£50,777	1.756	-0.783	0.064
Eptinezumab 100 mg	£71,559	35.7	10.396	£54,719	1.571	-1.165	-0.253
Key: LYG, life years gained; iNHB, incremental net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.							

Table 59: ICER and incremental net health benefit for eptinezumab vs all comparators for the CM subgroup (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Eptinezumab vs comparator				
				Incremental costs	Incremental QALYs	ICER	iNHB at £20,000	iNHB at £30,000
Eptinezumab 100 mg	£71,559	35.7	10.396					
BSC	£16,840	35.7	8.825	£54,719	1.571	£34,830	-1.165	-0.253
Erenumab 140 mg	£53,731	35.7	10.217	£17,828	0.178	£100,060	-0.713	-0.416
Fremanezumab 225 mg	£60,058	35.7	10.455	£11,501	-0.059	-£194,138	-0.634	-0.443
Botulinum toxin A 200 IU	£18,817	35.7	8.988	£52,742	1.408	£37,472	-1.230	-0.351
Galcanezumab 120 mg	£67,616	35.7	10.581	£3,943	-0.185	-£21,296	-0.382	-0.317
Key: LYG, life years gained; iNHB, incremental net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.								

B.3.12.2. Episodic migraine population

A summary of the base case results for the EM population is presented in Table 60. As for the full population, these do not consider any PAS discounts for eptinezumab or the other anti-CGRPs.

The incremental QALYs versus BSC for all anti-CGRP therapies are very similar. The incremental QALYs for eptinezumab (0.726) are a bit higher compared to those associated with erenumab and galcanezumab (0.409 and 0.512 respectively), and a bit lower than those associated with fremanezumab (1.009). Incremental costs compared to BSC for eptinezumab (£43,547) are somewhat lower than those associated with fremanezumab (£43,592) and somewhat higher than those of erenumab and galcanezumab (£25,220 and £30,946 respectively). When PAS discounts are applied for all treatments, and PAS discounts for the comparator anti-CGRPs would be in the range of [redacted], the expectation is that total costs associated with eptinezumab are [redacted] than those associated with other anti-CGRPs.

Similarly, from Table 61 it can be seen that the incremental net health benefit (iNHB) versus BSC for all anti-CGRPs is very similar. If all PAS discounts would be considered, these are expected to be higher.

For completeness, the ICER and incremental net benefit of eptinezumab versus each comparator (Table 62) is presented as well.

Table 60: Base case results for EM subgroup (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	£11,740	34.6	11.297				
Erenumab 140 mg	£25,220	34.6	11.706	£13,480	0.409	£32,981	Extendedly dominated
Galcanezumab 120 mg	£30,946	34.6	11.809	£19,206	0.512	£37,540	Extendedly dominated
Eptinezumab 100 mg	£43,547	34.6	12.023	£31,806	0.726	£43,801	Extendedly dominated
Fremanezumab 225 mg	£45,592	34.6	12.306	£33,852	1.009	£33,540	£33,540

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 61: Net health benefit for EM subgroup (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	iNHB at £20,000 vs BSC	iNHB at £30,000 vs BSC
BSC	£11,740	34.6	11.297				
Erenumab 140 mg	£25,220	34.6	11.706	£13,480	0.409	-0.265	-0.041
Galcanezumab 120 mg	£30,946	34.6	11.809	£19,206	0.512	-0.449	-0.129
Eptinezumab 100 mg	£43,547	34.6	12.023	£31,806	0.726	-0.864	-0.334
Fremanezumab 225 mg	£45,592	34.6	12.306	£33,852	1.009	-0.683	-0.119

Key: LYG, life years gained; iNHB, incremental net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 62: ICER and incremental net health benefit for eptinezumab vs all comparators for the EM subgroup (no PAS considered)

Technologies	Total costs	Total LYG	Total QALYs	Eptinezumab vs comparator				
				Incremental costs	Incremental QALYs	ICER	iNHB at £20,000	iNHB at £30,000
Eptinezumab 100 mg	£43,547	34.6	12.023					
BSC	£11,740	34.6	11.297	£31,806	0.726	£43,801	-0.864	-0.334
Erenumab 140 mg	£25,220	34.6	11.706	£18,327	0.317	£57,732	-0.599	-0.293
Fremanezumab 225 mg	£45,592	34.6	12.306	-£2,046	-0.283	£7,225 (Dominated)	-0.181	-0.215
Galcanezumab 120 mg	£30,946	34.6	11.809	£12,600	0.215	£58,730	-0.415	-0.205
Key: LYG, life years gained; iNHB, incremental net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.								

B.3.13. Benefits not captured in the QALY calculation

In the DELIVER trial, Work Productivity and Activity Impairment (WPAI) was measured at Weeks 4, 8 and 12. The WPAI is a patient self-rated scale and is designed to provide a quantitative measure of patients' work productivity and activity impairment due to a specific health problem (WPAI:M). The WPAI assesses activities over the preceding 7 days and consists of six questions. The first question addresses whether the patient is currently employed. The next three questions assess the number of hours worked, the number of hours missed from work due to the patient's condition or due to other reasons; and two visual numerical scales assess how much the patient's condition affects their productivity at work and their ability to complete normal daily activities.[146]

Table 63 presents the analysis of the WPAI scores reported in the DELIVER trial. For each patient, the average value of the WPAI absenteeism and presenteeism scores taken at Weeks 4, 8 and 12 was calculated. The absenteeism score represents the proportion of worktime that was not spent working, while the presenteeism score represented the percentage of time not being productive whilst working. These values were assumed to be the average work impairment over Weeks 1–12. No missing data were imputed (i.e. if only one value was reported by a patient, this value was used as the average over Weeks 1–12). The individual patient values were then summarised by treatment and responder status (i.e. a 50% reduction in MMDs). Monthly hours were calculated by converting WPAI scores, assuming 4 weeks in a month and 36.9 working hours per week.

Absenteeism and presenteeism (i.e. being at work, but not being productive) rates decreased for patients treated with eptinezumab when compared to placebo. This happened in the responder and non-responder groups. When comparing responders on eptinezumab to responders on placebo, all of whom experienced a 50% reduction in MMDs, the patients treated with eptinezumab had a much greater reduction in absenteeism and presenteeism than those on placebo. Patients who responded to treatment with placebo still had high scores despite having at least a 50% reduction in MMDs. This further validates the use of differential utilities, as discussed in Section B.3.4.5.

Table 63: Analysis of WPAI scores in FAS of DELIVER, by 50% response status

Patient group	N	Absenteeism score	Presenteeism score
Placebo 100 mg baseline	212	12.8	51.7
Eptinezumab 100 mg baseline	161	11.4	50.8
Placebo 100 mg non-responder	204	11.5	42.1
Eptinezumab 100 mg non-responder	135	7.6	37.3
Placebo 100 mg responder	34	9.1	32.7
Eptinezumab 100 mg responder	95	2.1	16.9
Key: FAS, full analysis set; WPAI, Work Productivity and Activity Impairment.			

B.3.14. Validation

B.3.14.1. Validation of cost-effectiveness analysis

The model was quality controlled (QCed) by an experienced, unconflicted health economist who has not been involved in developing the model. An internally developed QC checklist was followed, which uses publicly available checklists such as the Drummond and the Philips checklists as a guide. The internal checklist also includes all checks listed in the published Technical Verification (TechVER) checklist.[147-149]

The model inputs and outputs were tested in a local advisory board, and an attempt was made to be closely aligned to previous migraine NICE appraisals in the base case analyses with regards to inputs and assumptions, despite the difference in model structure.[55]

B.3.14.2. Internal validation

To internally validate the model, a comparison was made between a selection of inputs and outputs. As presented in Table 64, the patient characteristics of the cohort of individual patients modelled matched very well with the patient characteristics inputted into the model.

Table 64: Internal validation of patient characteristics

Characteristic	Input	Output
Minimum starting age	18.0	18.2
Mean age at entry, 4M	45.2	45.3
Max age in model	100.0	105.7
Proportion female	89%	89%
Proportion male	11%	11%
Mean baseline MMDs, 4M	14.4	14.2
Mean baseline MMDs, EM	9.8	9.2
Mean baseline MMDs, CM	19.1	20.3
Mean age at death from any cause	83.8	80.9
Key: 4M, ≥4 MMDs; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days		

B.3.14.3. External validation

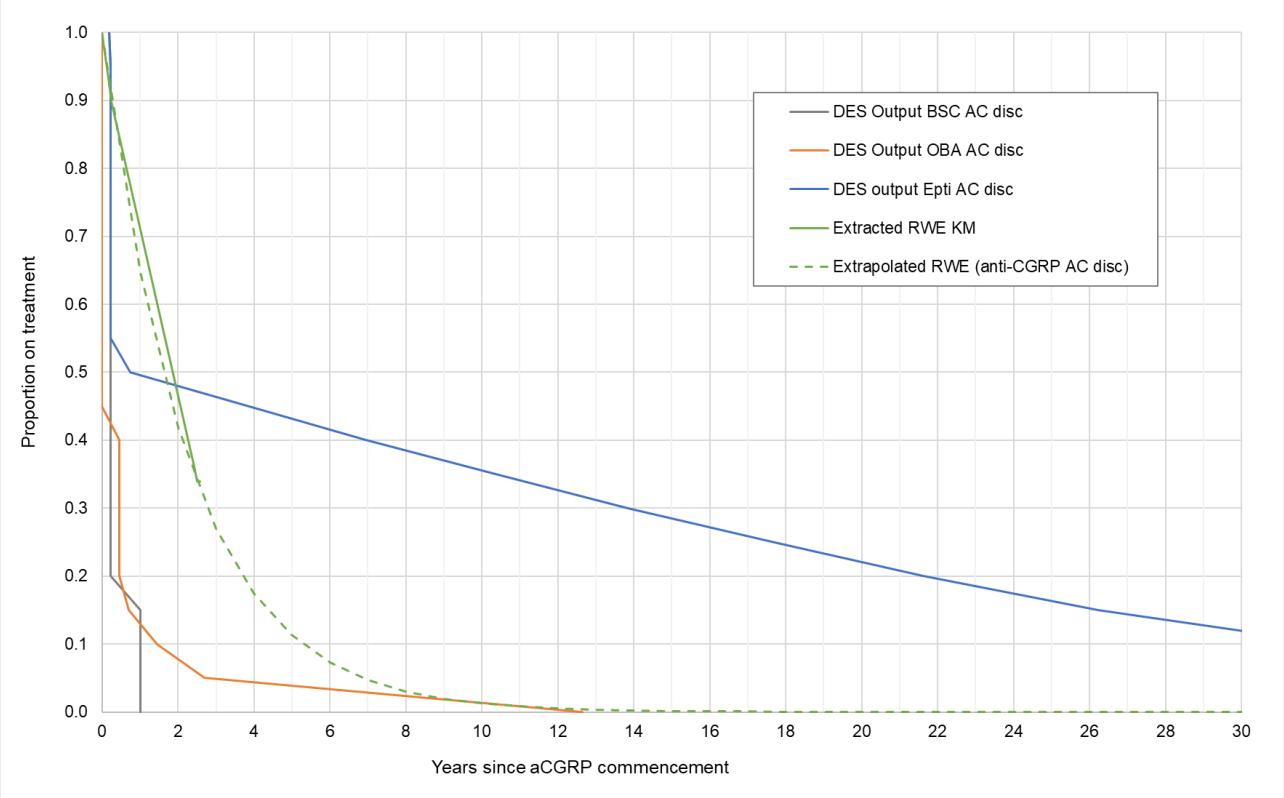
A number of external validations were carried out to compare model outcomes to other published sources.

B.3.14.3.1. Time on treatment

Time on treatment in the model is a composite of treatment discontinuation due to insufficient response (negative discontinuation), adverse events, death and threshold discontinuation (botulinum toxin A only). A real-world evidence source from Sweden was identified that reported any-cause discontinuation of anti-CGRPs in chronic migraine.[150] An exponential curve was fit to these time on treatment data, to be able to extrapolate beyond 30 months.

Figure 18 shows that the model initially overestimates treatment discontinuation, but the rate of discontinuation declines after the initial assessment at 12 weeks for eptinezumab (and other anti-CGRPs), resulting in longer time on treatment compared to the extrapolated RWE data. Early differences may be due to the less stringent negative stopping in Sweden, where response assessment is recommended but isn't a condition of treatment continuation as it is in England. Later differences maybe conservative in the comparison versus BSC since the 5-year maximum treatment scenario produces a lower ICER.

Figure 18: Modelled any-cause discontinuation rates compared to real-world data



Key: AC, any cause; anti-CGRP, anti-calcitonin gene-related peptides; BSC, best supportive care; DES, discrete event simulation; KM, Kaplan-Meier; OBA, onabotulinum toxin A; RWE, real world evidence.

B.3.14.3.2. Comparison to previous migraine NICE TAs

Although the majority of the outcomes of the models used in previous migraine NICE appraisals were redacted, and therefore unavailable to use for validation purposes, an attempt has still been made to compare outcomes of the current model to those of previous appraisals. As is presented in Table 65, Table 66 and Table 67, the ICERs produced in the current model are somewhat lower to the ICERs reported for the scenarios with the most equivalent assumptions in the galcanezumab appraisal. It was not possible to make a similar comparison using the other previous TAs, as the relevant information was redacted. Because of the redacting of intermediate outcomes, it is also impossible to explain exactly what causes the difference in ICERs with those presented for galcanezumab.

Table 65: Comparison of current model ICERs versus BSC to previous NICE TAs in EM subpopulation

	ICER vs BSC				Reference to previous NICE TA
Strategy	**Eptinezumab**	**Erenumab**	**Fremanezumab**	**Galcanezumab**	
Current model (Eptinezumab)	£43,902	£33,143	£33,558	£37,594	
Galcanezumab				£34,370	ERG ICER with most equivalent assumptions (ERG report Table 40)[2]
Key: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; TA, technology appraisal					

Table 66: Comparison of current model ICERs versus BSC to previous NICE TAs in CM subpopulation

	ICER vs BSC					Reference to previous NICE TA
Strategy	**Eptinezumab**	**Erenumab**	**Fremanezumab**	**Botulinum toxin A**	**Galcanezumab**	
Current model (Eptinezumab)	£34,897	£26,542	£26,589	£12,154	£29,025	
Galcanezumab					£22,344	ERG ICER with most equivalent assumptions (ERG report Table 40)[2]
Key: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; TA, technology appraisal						

Table 67: Comparison of current model ICERs versus botulinum toxin A to previous NICE TAs in CM subpopulation

	ICER vs botulinum toxin A				Reference to previous NICE TA
Strategy	**Eptinezumab**	**Erenumab**	**Fremanezumab**	**Galcanezumab**	
Current model (Eptinezumab)	£37,723	£28,579	£28,301	£30,861	
Galcanezumab				£26,648	ERG ICER with most equivalent assumptions (ERG report Table 40)[2]
Key: BSC, best supportive care; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; TA, technology appraisal					

B.3.15. Interpretation and conclusions of economic evidence

The difference in QALYs between eptinezumab and other anti-CGRPs is small. When not considering any PAS discounts (for eptinezumab or its comparators), eptinezumab results in 1.071 additional QALYs compared to BSC. This is offset by incremental costs of £40,657, resulting in a deterministic ICER of £37,956 compared to BSC. The probabilistic ICER is very similar, £38,284. As we do not know about confidential discounts for comparator products, but have estimated these to be in the range of [redacted], it is expected that a strategy of eptinezumab results in [redacted] compared to other anti-CGRP therapies. Results for the EM and CM subgroups, without any PAS discounts, show an ICER versus BSC of £43,688 and £34,868, respectively. When looking at the cost–comparison analysis results, eptinezumab is associated with additional discounted costs versus galcanezumab of £7,014 in the whole (4M) population, and £5,067 and £9,432 for the EM and CM populations, respectively. Again, these results do not consider any PAS discounts.

The current DES model allows addressing of the key issues discussed in previous migraine NICE appraisals, including the lack of consideration of natural history of the disease. To be as consistent as possible with previous appraisals, these natural history events were however not included in the base case analyses. If natural history events were considered, the ICER for eptinezumab compared to BSC would be similar to the base case ICER (-4% versus base case). The key uncertainty in the current model is associated with the relative effectiveness, as none of the NMA outcomes applied to the model showed any statistically significant difference between the different anti-CGRPs. For that reason, cost-comparison results were also provided. Clinicians that attended the UK specific advisory board all agreed that all anti-CGRP therapies have comparable efficacy, HRQL and safety for TF3+ patients, justifying further the cost-comparison analyses.[55]

Overall, for patients impacted by migraine, eptinezumab is the only IV preventive treatment that offers a rapid reduction in the frequency of monthly migraine days from the first day after infusion and comparable efficacy to other anti-CGRPs at the same, or lower, cost once confidential discounts are applied.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Eptinezumab for preventing migraine [ID3803]

Appendix M- Cost comparison results

October 2022

File name	Version	Contains confidential information	Date
ID3803_Lundbeck Eptinezumab_ STA Appendix M	**1.0**	**Yes**	**17 October 2022** *(originally submitted with Document B appendices 18 August 2022)*

Contents

Abbreviations

Abbreviation	Definition
Anti-CGRP	Anti-calcitonin gene-related peptide antibodies
BSC	Best supportive care
CM	Chronic migraine
EM	Episodic migraine
MMD	Monthly migraine day
MSQ	Migraine-Specific Quality of Life Questionnaire
NICE	National Institute for Health and Care Excellence
OWSA	One-way sensitivity analysis
PAS	Patient access scheme

Appendix M: Cost-comparison results

As for the base case results presented in Document B, section B.3.10, the results presented here represent the list price for eptinezumab and its comparators. The results with patient access scheme (PAS) discount applied for eptinezumab would not be informative as the PAS discounts for the other anti-CGRP antibodies are unknown to Lundbeck, and therefore eptinezumab would appear much cheaper than other anti-CGRPs.

Results presented here represent undiscounted costs over a lifetime time horizon.

M.1 Base case results

Table 1 presents the base case results for the full population. From this table it can be seen that total costs associated with eptinezumab are higher than those for all comparator strategies. When comparing to BSC, the higher costs associated with eptinezumab are caused by the acquisition and administration costs, and partly offset by the lower monitoring and concomitant medication costs. When comparing to other anti-CGRP therapies, the higher costs for eptinezumab are caused by higher acquisition and administration costs. Incremental discounted costs compared to galcanezumab (the comparator associated with highest costs) are £7,014. If PAS discounts would be applied, and PAS discounts for the comparator anti-CGRPs would be in the range of [redacted], Lundbeck expects eptinezumab to be associated with [redacted] compared to other anti-CGRPs.

Table 1: Base case results, undiscounted costs (No PAS considered)

Technologies	Costs						
	Acquisition	Administration	Monitoring	Concomitant medication	Total undiscounted	Total discounted	Incremental (Eptinezumab vs comparator)
BSC	£0	£0	£20,473	£8,038	£28,512	£14,879	£43,398
Erenumab 140 mg	£54,092	£280	£19,326	£6,695	£80,393	£47,841	£10,437
Fremanezumab 225 mg	£54,247	£241	£19,326	£6,695	£80,508	£47,982	£10,296
Galcanezumab 120 mg	£58,934	£258	£19,326	£6,695	£85,213	£51,264	£7,014
Eptinezumab 100 mg	£62,755	£8,090	£19,326	£6,695	£96,866	£58,277	

Key: BSC, best supportive care; PAS, patient access scheme.

M.2 Exploring uncertainty

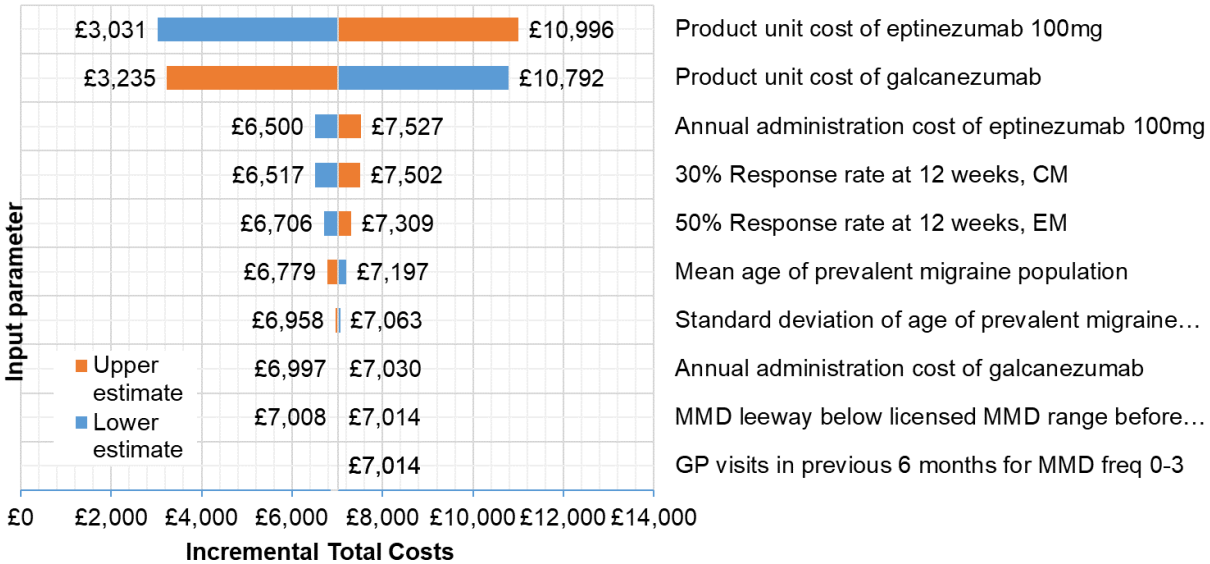
To assess the level of uncertainty surrounding the model parameters, sensitivity analyses in the form of univariate deterministic sensitivity analyses were undertaken. Additionally, a broad range of scenario analyses were undertaken to examine the uncertainty surrounding the model assumptions.

M.1.1 Deterministic sensitivity analysis

A deterministic sensitivity analysis was undertaken in the form of a one-way sensitivity analysis (OWSA). Drug unit costs were included to comprehensively explore the sensitivity of total undiscounted costs to fixed variation in every independent parameter. Subsequently, the included parameters were tested by varying them 10% either side of the point estimate of the mean. The 10 most influential parameters have been presented in a tornado diagram (Figure 1). The analysis examines sensitivity in the comparison of eptinezumab versus galcanezumab (the next most expensive strategy) in the overall population.

The most impactful parameters were the response rates for eptinezumab and galcanezumab in patients with EM and CM.

Figure 1: OWSA tornado diagram (No PAS considered)



Key: BSC, best supportive care; CM, chronic migraine; EM, episodic migraine; INMB, incremental net monetary benefit; MMD, monthly migraine days; OWSA, one-way sensitivity analysis; PAS, patient access scheme.

M.1.2 Scenario analyses

Table 2 shows the incremental discounted costs derived from the scenario analyses for the overall population. The scenario analysis assesses 17 alternative structural and parameter scenarios compared to the base case. The scrutinised pairwise comparisons in this population are versus galcanezumab (the next most expensive strategy). The scenario analysis that used the Weibull distribution extrapolation of long-term adverse events has the most significant impact on the incremental costs compared to galcanezumab.

Table 2: Scenario analysis results, eptinezumab vs galcanezumab (No PAS considered)

Scenario	Incr disc costs
Base case; eptinezumab vs BSC; overall population	£7,014
Time horizon 10 years	£3,353
No discounting of future benefits and costs	£11,651
Taking a societal perspective (including indirect costs of lost productivity)	£7,014
Switch from RCT to real-world registry data for age at entry	£6,721
Including natural history (transformation and resolution)	£4,065
Include NH events but exclude treatment holidays	£5,495
Include NH events but having 2 years between positive stop assessments	£3,436
NMA odds ratio TF3+ at the 50% threshold for EM, and at the 50% threshold for CM	£4,609
NMA odds ratio TF3+ at the 50% threshold, pooled EM and CM	£7,014
NMA TF3+ EM and CM (BSC-galcanezumab-eptinezumab), both stratified at 50% threshold	£4,490
All discontinued due to adverse events by 5 years	-£278
Weibull distribution extrapolation of long-term adverse events (from exponential)	£9,611
MMD leeway of 2 days before threshold/licence discontinuation	£6,623
20% 'super-responding' with sustained aTx CFB post-discontinuation	£4,388
2 years of on-treatment BSC waning following response (time to reach baseline MMDs)	£7,014
1 year of post-discontinuation waning for anti-CGRPs and botulinum toxin A (time to reach BSC MMDs)	£7,014
Using NHWS resource use data before update (NICE galcanezumab TA; Vo 2018)	£7,014

Key: aTx, active treatment; BSC, best supportive care; CFB, change from baseline; CM, chronic migraine; EM, episodic migraine; ICER, incremental cost-effectiveness ratio; IV, intravenous; MMD, monthly migraine days; MSQ, Migraine Specific Quality-of-Life Questionnaire; NH, natural history; NHWS, National Health and Wellness Survey; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; TA, technology appraisal.

M.3 Subgroup analyses

The population described in the NICE scope is represented by the 'whole' population of patients who have failed treatment three or more prior preventive treatments. EM and CM populations are presented as subgroups. The DES (discrete event simulation) model produces results for all three populations in equal detail. Analyses relating to the bespoke subgroups is presented in M.3.1 (CM) and M.3.2 (EM).

M.3.1 Chronic migraine population

Table 3 presents the base case results for the CM population. From this table it can be seen that total costs associated with eptinezumab are higher than those for all comparator strategies. As for the full population, when comparing to BSC or botulinum toxin A, the higher costs associated with eptinezumab are caused by the acquisition and administration costs, and partly offset by the lower monitoring and concomitant medication costs. When comparing with other anti-CGRP therapies, the higher costs for eptinezumab are caused by higher acquisition and administration costs. If PAS discounts would be applied, Lundbeck expects eptinezumab to be associated with similar costs or to be cost-saving compared with other anti-CGRPs.

M.3.2 Episodic migraine population

Table 4 presents the base case results for the EM population. As for the other populations, total costs associated with eptinezumab are higher than those for all comparator strategies. When comparing with BSC, the higher costs associated with eptinezumab are caused by the acquisition and administration costs and partly offset by the lower monitoring and concomitant medication costs. When comparing with other anti-CGRP therapies, the higher costs for eptinezumab are caused by higher acquisition and administration costs. If PAS discounts would be applied, Lundbeck expects eptinezumab to be associated with similar costs or to be cost-saving compared with other anti-CGRPs.

Table 3: Base case results for CM subgroup, undiscounted costs (No PAS considered)

Technologies	Costs						
	Acquisition	Administration	Monitoring	Concomitant medication	Total undiscounted	Total discounted	Incremental (Eptinezumab vs comparator)
BSC	£0	£0	£22,778	£11,601	£34,378	£17,873	£56,427
Erenumab 140 mg	£70,593	£365	£21,448	£9,579	£101,985	£60,714	£13,586
Fremanezumab 225 mg	£70,737	£314	£21,448	£9,579	£102,078	£60,840	£13,460
Botulinum toxin A	£1,827	£1,237	£22,650	£11,384	£37,098	£20,445	£53,855
Galcanezumab 120 mg	£76,606	£336	£21,448	£9,579	£107,969	£64,868	£9,432
Eptinezumab 100 mg	£81,899	£10,558	£21,448	£9,579	£123,484	£74,300	
Key: BSC, best supportive care; CM, chronic migraine; PAS, patient access scheme.							

Table 4: Base case results for EM subgroup, undiscounted costs (No PAS considered)

Technologies	Costs						
	Acquisition	Administration	Monitoring	Concomitant medication	Total undiscounted	Total discounted	Incremental (Eptinezumab vs comparator)
BSC	£0	£0	£18,618	£5,170	£23,789	£12,470	£32,909
Erenumab 140 mg	£40,808	£211	£17,618	£4,372	£63,009	£37,477	£7,901
Fremanezumab 225 mg	£40,971	£182	£17,618	£4,372	£63,143	£37,630	£7,748
Galcanezumab 120 mg	£44,708	£195	£17,618	£4,372	£66,893	£40,312	£5,067
Eptinezumab 100 mg	£47,344	£6,103	£17,618	£4,372	£75,438	£45,379	
Key: BSC, best supportive care; EM, episodic migraine; PAS, patient access scheme.							

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost-comparison evaluation

Eptinezumab for preventing migraine [ID3803]

Clarification questions

September 2022

File name	Version	Contains confidential information	Date
ID3803 eptinezumab clarification letter to PM	v1.0	Yes	7 September 2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority question: Please provide all relevant data used to perform the network meta-analyses (NMAs) for the two priority outcomes (change from baseline in monthly migraine days [MMD] and 50% migraine response rate [MRR]), sufficient to permit the EAG to check and/or reanalyse the NMAs, including:

a) **all BUGS model code files (including both fixed effect and random effects model)**

b) **all data files (in a format ready to be loaded into R) and the treatment coding (e.g., 1 for placebo) for the episodic migraine (EM) patient population with 3+ prior treatment failures and chronic migraine (CM) patient population with 3+ prior treatment failures**

c) **all BUGS "initial value" files**

All files are included in the folder labelled A1.

The root folder contains the R scripts to run the NMA for 50% responders ("NMA for responders -FE and RE.R") and for change from baseline (CFB) in monthly migraine days ("NMA for MMD - FE and RE.R") . Both files can run fixed-effects and random-

effects models. In the R script “FE” or “RE” has to be inputted to select the model type.
The “data” folder contains the data for ≥3 treatment failures . There are four files to capture the required endpoints (50% responders and CFB in MMD) and the type of migraine (chronic vs. episodic).
The “outputs” folder contains the outputs of the fixed-effects and random-effects models in sub-folders labelled “FE” and “RE”, respectively.
The “programs” folder contains two sub-folders:

- The “functions” sub-folder - the list of initial values can be found in the function fn_call_BUGS.R located in this sub-folder,
- The “bayesian” sub-folder - the NMAs were conducted with a Bayesian generalised linear model framework using arm-level data. Supporting files can be found in this sub-folder.

A2. Priority question: Appendix D.1.3.6.2 provides random effects NMA results for 50% MRR in patients with EM/CM and 2+ treatment failures, but no random effects NMA results were presented for change from baseline MMD. Please provide the random effects NMA results for change from baseline in MMD for patients with EM/CM and 3+ treatment failures, and for 50% MRR for patients with EM/CM and 3+ treatment failures.

The output files for the random effect models can be found in the folder labelled A2, including those for change from baseline in MMD for patients with EM/CM and 3+ treatment failures, for 50% MRR for patients with EM/CM and 3+ treatment failures, and for change from baseline in MMD for patients with EM/CM and 2+ treatment failures. The code used to produce those files is located in the folder labelled A1.

A3. Priority question: Please check the NMA input for FOCUS. In Table 21 of Appendix D, the 50% MRR and discontinuations data for fremanezumab monthly and fremanezumab quarterly data appear to have been transposed for

FOCUS (when compared with Ferrari 2019). If the NMA input was incorrect, please correct and re-run NMAs and provide updated results.

Files relating to this question can be found in the folder labelled A3.

Regarding discontinuations, the reviewer is correct: the labelling in table 21 was erroneous and the monthly and quarterly fremanezumab labels for discontinuations were inverted, however the NMA input for discontinuations was correct. Please note that the summary of NMA results in table 27 are properly labelled and the results are correct.

For 50% MRR, in our pooled responder analysis, we added EM and CM responders as well as the total number of patients per arm. Ferrari 2019 did not separately report the number of responders for EM or CM for either ≥ 2 treatment failures or $\underline{\geq}$ 3 treatment failures. The publication only reported the percentage of responders for 2, 3 and 4 treatment failures and the total number of previous failures. Therefore, we had to make assumptions to include fremanezumab into the network. More specifically, we assumed that the distribution of patients with 2 treatment failures, 3 treatment failures or 4 treatment failures was the same between EM and CM. This allowed us to estimate the proportion of responders for EM and for CM. Numbers were then rounded, converted back to patient numbers and summed across EM and CM. This was to verify if our assumptions were realistic. Calculations can be seen in the “additional_calculations.xls” file contained in folder A3.

For monthly fremanezumab, we obtained 97 responders with ≥ 2 treatment failures (the same as Supplemental Table 5 in Ferrari 2019). For quarterly fremanezumab, we obtained 97 patients instead of 95 patients as reported in Ferrari 2019. This figure was used for the NMA and therefore the input used for the pooled analysis is more favourable for fremanezumab quarterly than the reported value in Ferrari 2019.

Due to time available and limited internal resources Lundbeck have not re-run the analysis at this stage as it would only marginally improve the efficacy in favour of

eptinezumab, however if the EAG would like the NMA to be updated and re-run with the correct input Lundbeck would be happy to do so.

A4. Priority question: Please add a column to present the information on baseline medication-overuse headache (MOH) (or medication overuse status as reported by trials) for the studies contained in Table 20 of Appendix D.

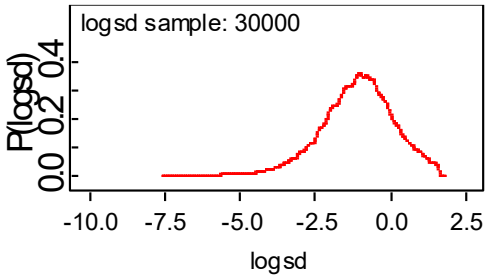
DELIVER and REGAIN were the only trials included in the NMA that reported the proportions of patients with MOH at baseline. Table 20 of Appendix D has been updated to include a column presenting baseline MOH to reflect this. This updated table can be found in a file saved in the folder A4 + A5.

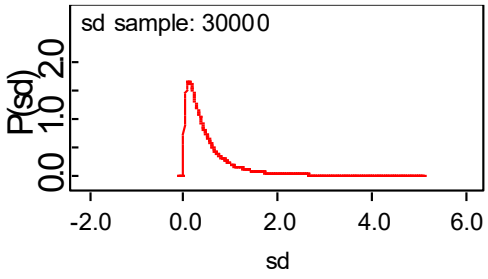
A5. Priority question: Please provide citations to references for all the data contained in Tables 20-23 of Appendix D. It is currently unclear where some data are sourced. If any of these references have not been supplied, please provide them. For example, please provide the reference for Okonkwo R, Tockhorn-Heidenreich A, Stroud C, et al. Efficacy of galcanezumab in patients with migraine and history of failure to 3-4 preventive medication categories: subgroup analysis from CONQUER study. *The journal of headache and pain*. 2021; 22(1):113. (The reference labelled as number 79 from the company submission [document B] is instead Ruff et al 2019).

Updated versions of Table 18 (list of studies eligible for inclusion in the NMA) of Document B and Tables 20-23 (providing baseline characteristics across studies and NMA inputs) of Appendix D can be found in a file saved in the folder A4 + A5. Several references were used per trial to provide inputs for the 2+ treatment failures and 3+ treatment failures population. As such, each datapoint in Tables 21-23 of Appendix D is referenced. References are provided in a subfolder within the folder A4 + A5.

A6. Appendix D.1.3.2. states that the posterior distribution of an NMA conducted for Phase 3 trials in EM was used to inform the prior distribution of the between-study variance. Please list the studies included in this NMA and clarify how the approximation to a log-normal distribution was achieved.

We have added the OpenBugs odc file used to estimate the informative prior; this is included in the folder labelled A6.
The trials used are ARISE, EVOLVE 1, EVOLVE 2, HALO EM, STRIVE and PROMISE 1.
The posterior distribution of the between-trial standard deviation was skewed. Therefore, we analysed the posterior distribution of the logarithmic of standard deviation (logsd in the graph below). Logsd posterior distribution look more similar to a normal distribution even though a long left tail remained. The median value of logsd was -1.1. To estimate the standard deviation of logsd we calculated the difference between the 97.5th (1.146) percentile and the 2.5th percentile (-4.276) and divided by 2*1.96. This resulted in a sd of 1.37 for the logsd variable.





Section B: Clarification on cost-effectiveness data

B1. Priority question: The costs associated with a 30-minute infusion are considerably dated having been taken from NICE technology appraisal (TA) 195 and then inflated from 2008 to 2020. Please clarify what search strategies were undertaken to find the most appropriate value. The EAG is aware that NICE TA247 included a cost of £154 for a similar infusion to NICE TA195, but more recent values may exist. It would be helpful to attempt to find a more

recent value and seek clinical input if needed. As this cost only applies to eptinezumab the EAG believes that it may be a key consideration for the NICE Appraisal Committee.

In order to ascertain the most appropriate unit cost for the 30-minute infusion associated with eptinezumab's administration, an advisory board meeting was held on the 27th May 2022 to seek expert advice and clinical input [Reference 55 in Doc B reference pack]. Professor Stephen Palmer highlighted that there is no NHS reference cost for IV infusion of biologicsso when looking at IV treatment costs, chemotherapy is commonly used as a reference, with a cost of £142 from TA195 inflated to current year. This approach was supported by the clinical experts.

A simple search of previous NICE appraisals was also conducted and this approach to calculating the administration cost was used in TA247 (February 2012) to provide a figure of £154 after inflation. TA375 (January 2016) also used an administration cost of £154, based on TA247.

TA397 (June 2016) initially used an administration cost of £126 based on 2 hours of nurse time at £63 per hour (assuming one hour infusion time and one hour for patient preparation and monitoring). After appeal, the manufacturer submitted an administration cost of £154, based on TA247.

Eptinezumab is a simple 30-minute infusion without complex patient preparation or monitoring requirements. Lundbeck took the original £142 cost used in TA195 and inflated this to 2020 to provide a cost of £174.04.

A search of more recent appraisals has identified a number of technologies with a 30-minute IV administration. The administration cost included in the Resource Impact Reports and Resource Impact Templates are shown below:

- Resource impact report: Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma (August 2022) [TA818]
    - Nivolumab and ipilimumab require a 30-minute infusion
    - Deliver simple parenteral chemotherapy at first attendance £162

- Resource impact template: Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence (August 2022) [TA817]
    - Nivolumab requires a 30-minute infusion
    - Deliver simple parenteral chemotherapy at first attendance £161
- Resource impact template: Cemiplimab for treating advanced cutaneous squamous cell carcinoma (June 2022) [TA802]
    - Cemiplimab requires a 30-minute infusion
    - Deliver simple parenteral chemotherapy at first attendance £161
- Resource impact template: Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation (June 2022) [TA798]
    - Durvalumab requires a 30-minute infusion
    - Deliver simple parenteral chemotherapy at first attendance £161

For information, Lundbeck received the Budget Impact Assessment from PASLU on the 14th September 2022. PASLU have applied a £[redacted] per month (£[redacted] per annum) administration cost to the comparator sub-cutaneous anti-CGRP treatments. This cost is described as “Homecare delivery - monthly admin charge of £[redacted] assumed”. This cost was higher than that included in Lundbeck’s submission, which assumed annual administration costs between £22.40 - £26.09 for the sub-cutaneous anti-CGRPs. The annual administration costs for erenumab, fremanezumab and galcanezumab in Lundbeck’s submission may therefore be underestimates when costs associated with services such as homecare are considered.

Section C: Textual clarification and additional points

C1. Please check the data reported for the proportion of patients with ≥ 50% reduction in MMDs from baseline at week 12 in Table 12 of the company submission and amend if appropriate. The midpoint odds ratios versus placebo do not lie within

their 95% confidence intervals. From Ashina 2022, the EAG believes that the midpoints should be 4.9 and 6.6.

The EAG are correct, this was a typo. The correct values for odds ratios (95% CI) vs placebo are:

- Eptinezumab 100 mg: 4.9 (3·3 to 7·5)
- Eptinezumab 300 mg: 6.6 (4·4 to 10·0)

C2. The same issue described in C1 appears to be present in the odds ratio vs placebo for the proportion of patients with ≥ 50% reduction in MMDs from baseline at week 24 in Table 12 of the company submission. Please check and amend if appropriate.

This was also a typo; the correct values for odds ratios (95% CI) vs placebo are:

- Eptinezumab 100 mg: 9.2 (4·2 to 24·4)
- Eptinezumab 300 mg: 11.4 (5·2 to 30·2)

C3. In Table 7 of the company submission, the values for migraine diagnosis at baseline (n [%]) for CM and EM do not match the percentages reported in in Ashina 2022. This paper reports 46% (eptinezumab 100mg), 46% (eptinezumab 300mg), and 45% (placebo) for CM, and 54%, 54% and 55% respectively for EM. Please clarify this discrepancy.

This was due to figures from the incorrect table in the Clinical Study Report being included in Table 7. The figures included are for “Current migraine diagnosis” from the Clinical Study Report for DELIVER, shown below:

Panel 16 Migraine History (FAS)

		Treatment Group			
		PBO	EPTI 100 mg	EPTI 300 mg	Total
Current migraine diagnosis, n (%)	EM	173 (58.1)	176 (58.9)	186 (63.5)	535 (60.1)
	CM	125 (41.9)	123 (41.1)	107 (36.5)	355 (39.9)

These are different to the figures for “migraine diagnosis at baseline” reported in Ashina 2022. The correct table for “Baseline migraine characteristics” from the CSR, matching Ashina 2022, is shown below:

Table 10 Baseline Migraine Characteristics, eDiary (FAS)

		Treatment Group							
		PBO		EPTI 100 mg		EPTI 300 mg		Total	
Number of Patients		298		299		293		890	
Episodic/chronic migraine group*, n (%)	EM	164	(55.0)	162	(54.2)	158	(53.9)	484	(54.4)
	CM	134	(45.0)	137	(45.8)	134	(45.7)	405	(45.5)
	Not applicable					1	(0.3)	1	(0.1)

The reason for the discrepancy is because the figures included in Table 7 (Current migraine diagnosis) are the reported migraine diagnosis for each study participant at their screening visit. Participants were then provided an eDiary to record their migraine characteristics, including MMDs and MHDs, over the following 4 week screening period to confirm eligibility and establish baseline data. There is a difference between the diagnosis reported at screening and the diagnosis based on 4 weeks eDiary data following completion of the screening period, with the latter being considered “baseline”. As such, the EM/CM diagnosis figures from Table 10, above, should have been included in Table 7 of the company submission and these are consistent with those reported in Ashina 2022.

C4. Please clarify whether the values in Table 42 of the company submission relate to annual resource use as implied by the title, or whether this is a 26-week period as implied by cell A72 in the ‘resource and costs’ sheet in the model.

This is a mislabelling of Table 42; the figures included in Table 42 are for the 26-week period as per cell A72 in the ‘resource and costs’ sheet.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Eptinezumab for preventing migraine [ID3803]
Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	The Migraine Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Migraine Trust is dedicated to helping the 10 million people affected by migraine. We are the only UK migraine charity providing information and support, campaigning for awareness and change, and funding and promoting research. One in seven people in the UK live with migraine, and this complex and debilitating neurological disorder significantly affects their lives. We have been leading and bringing the migraine community together to change this since 1965. Every year over two million people visit our website and thousands contact our helplines and other support services for information and support on all aspects of migraine and for help in managing it at work, in education, and in accessing healthcare. We campaign for increased awareness and understanding of migraine, and national policy change to improve the lives of people who get it. We have funded over 140 medical research projects and hold an international symposium every two years to bring together the world's leading experts on migraine. We are funded through legacies, individual donations, community and event fundraising, corporate partnerships, trusts and foundations, and industry. We are not a membership organisation. We have over 30,000 people signed up to receive our monthly e-bulletin.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	We have received the following funding in the last twelve months • £22,605 from Abbvie to support our work in devolved nations • £20,000 from Lundbeck for our support services. • We also received £20,000 from Allergan just over a year ago to support the development of new resources on migraine in children and young people.
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 regularly run surveys of people affected by migraine to understand their experience and identify gaps of unmet needs in order to obtain information on their experience of the impact of migraine and treatments on their symptoms and ability to function. None were specifically in relation to the use of Eptinezumab, which is not available in the UK but some did cover other CGRP mAbs. We feel there are parallels that can be drawn from this data. Surveys we have run include: **1 CGRP user survey 2022** We received 304 responses from active users of CGRP mAbs. Of those 30-50% found it had improved their quality of life in some aspect namely: the treatment was effective, well tolerated with manageable or no side effects and by its impact on their quality of life. However, 26% felt it did not meet their expectation. **2 Women's survey Jan-Mar 2022** We received over 700 responses on the impact of migraine on their lives and relationships.

	>75% felt that there was a negative impact on their family, social life, work and general health and their ability to exercise. A similar number said it made them anxious and worried. Many women noted that their migraine has worsened over time; 34% said their symptoms have worsened or remained worse, while 35% said their attacks have become more frequent. **3 Men's survey 2021** We surveyed 350 men and found similar results to those in our Women's survey. This demonstrates the impact of migraine upon both men and women and the need to provide treatments that work and access to all who need it. **4 Migraine community survey 2019** This 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. One responder said: "*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*." **5 CGRP Patient Experience Survey (2019)** We received 203 responses from patients who were 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. This survey showed that for patients who had tried both botox and a cgrp monoclonal antibody at different times, 78% agreed or strongly agreed that the CGRP drug was more effective at controlling their migraine and 76% felt it had improved their quality of life. **6. Dismissed for too long** In September 2021 we launched our 'Dismissed for too long' report into migraine care across the UK, this included a nationally representative commissioned censuswide poll in July 2021 and FOI requests to NHS Trusts across the UK in May 2021, which included questions around access to CGRP mAbs. These have provided context and information for this response.

	7. Impact of Covid The charity ran three surveys around the impact of Covid, with over 1,000 responses. Below are some of the main results. • 68% reported their migraine had worsened • 57% were more stressed – this is a migraine trigger • There was increased frequency and worsening of symptoms • 30% were taking more medication which increases the risk of medication overuse headache • More were managing self-care as they struggled to access treatments or appointments

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?	Migraine 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 (aged 15-69) living with migraine. Migraine can have a huge toll on the lives of those living with it as well as on their family and carers. Migraine is a chronic long term disorder for which there is no cure and which affects people at their most productive years of life. It is costly to the individual, their family and society. People living 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. It is estimated that there could be up to 86m workdays a year lost to migraine (Work Foundation 2018). Our Migraine Community Survey (2019) found that nearly half (47%) of respondees consider themselves to have a disability as defined by the Equality Act 2020 because of their migraine. 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***." "***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.***" "***I was harassed and bullied in the workplace of my chronic migraine condition. This led me to having to leave my career prematurely***." The 2022 women's survey responses included; "***I lost my job as I was told I was taking too much time off due to migraines***." Another said: "***I'm a teacher, and the general attitude is that we should just soldier on through illness – it took for me to have a hemiplegic attack at work for my migraines to be taken seriously***."

	Recent pro-bono research undertaken for The Migraine Trust showed that the cost of loss of productivity and absenteeism due to migraine is estimated at £9 billion a year. **b. Family relationships** Over half (54%) of respondees to our CGRP Patient Experience Survey (2019) 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." **c. Social life** Migraine can be a very isolating condition, with 83% of respondees to our CGRP Patient Experience Survey (2019) 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. Over the past few months the charity has seen a marked rise in calls to our helpline, often being for longer and more emotional around the impact of mental health as they are unable to get the support, and care they desperately need. Our more recent surveys support these findings:

	○ A Censuswide survey that we ran this summer found that almost a third (32%) of those with migraine said that their migraine negatively affected their mental health and almost a third (32%) said that their migraine negatively affected their overall health ○ Three in ten (30%) of those with migraine said that their migraine negatively affected their working life. ○ A quarter (25%) of those with migraine said that their migraine negatively affected their family life and 27% said it negatively affected their social life. ○ Our recent survey responses (5. Above), described some of the negative impact of migraine on work, education, family and social life, general health and mental well-being. Gender differences In terms of gender the numbers affected are similar until puberty and we then we see significantly greater numbers of women affected, with around 24% of women and 12% of men affected. For more than half of women aged between 18 and 60, the onset and timing of migraines is connected with their menstrual cycle. Our

research has shown that many of the impacts affect everyone in the same way, but that there are also differences.

- Men are more likely to "struggle on" in an illness and may view it as a sign of weakness.
- Men are also 35% more likely to report physical exertion as a migraine trigger
- Women are 50% more likely to experience weather as a migraine trigger

Our recent research showed that there were similar levels of impact in general and across work, social life, family and mental health, but all significantly high.

	Men	Women
General	75%	80%
Work	84%	85%
Social	82%	88%
Family	71%	76%
Mental health	73%	65%

For men, there's a concern that migraine is viewed as a woman's disorder and our 2021 men's survey received responses such as:
*"**[Migraine] needs to be seen as a real and debilitating condition that affects both sexes not just women. Migraine also needs to stop being stigmatised and seen as an excuse to skive off work. Men get chronic migraine too and the effects can be devastating on all aspects of life**."*

For women our research has show that migraine has influenced them on life decisions such as:

- 40% limit the environments they work in
- 31% limit type of work
- 22% not seek a promotion
- 17% not work
- 9% about having children

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Migraine cannot be cured, and it is therefore crucial that appropriate and effective treatments are made available. 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. This makes it time consuming and puts them and increased risk of unwanted medication side effects and drug interactions. **Preventive treatments** 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, tricyclic antidepressants 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 some people they are ineffective. 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." After trying a range of oral preventive treatments patients should have access to further preventive treatment options, including other medications (e.g. flunarizine), Greater Occipital Nerve (GON) blocks, Botox (for chronic migraine), new CGRP mAbs and devices. However, access to these is patchy and not everyone who is eligible can access them. There are also issues around side effects and suitability. • Patients, carers and people using our helpline and support services tell us about a range of experiences. They frequently report difficulty to access treatments or specialists, obtain a diagnosis, debilitating treatment side effects. There is difficulty in accessing the newer treatments such as CGRP mAbs. • Only 33% of men who took part in the survey had found a treatment that consistently improves their migraine. This may be due to the treatments not working or lack of access to the right care or treatment. • Of those who have used a newer treatment some have reported side effects and lack of benefit or adequate benefit.

8. Is there an unmet need for patients with this condition?	There continues to be inadequate access to specialists, too long a wait for a diagnosis, uneven access to new treatments, lengthy wait times for specialists, struggles in getting help for mental well-being and coping with the debilitating symptoms, high levels of anxiety, medication overuse and support to treat or prevent this There is an unmet need for patients with migraine, particularly those who: • are unable to tolerate existing treatments. • don't meet eligibility criteria for treatments. • are unable to access specialist clinics (made worse during the COVID-19 pandemic). • have other health conditions. As highlighted above there is unmet need for both acute and preventive treatment options for migraine. **Preventive** There is also unmet need for patients in need of preventive treatment, specifically those who fail to respond to current preventive treatments. Many patients struggle to find an effective preventive treatment, or fail to access appropriate preventive treatments. The COVID-19 pandemic has compounded access issues to migraine treatment and led to an increase in unmet need. For example, one in eight (12%) people accessing support for their migraine said they had been unable to access treatment and / or medication for their migraine over the last year, according to our survey run in July 2021. The censuswide survey found that over half of people (55%) said that the changes to the healthcare system since the beginning of the pandemic had affected the management of their migraine.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	• As this treatment is not yet available in the UK, and patients have not had the opportunity to use it, many people contacting us are seeking new effective treatments. • Current preventives are not adequately effective for many.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	• As above; there is lack of experience with the treatment in the UK. However, based on what we know from other NICE approved CGRP mAbs we would hope / expect there to be few disadvantages to the treatment.

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.	• We know that those most impacted by the condition are those with frequent episodic attacks, chronic migraine, medication overuse, rare forms of migraine, or have other comorbidities. Some people already take a number of oral medications and would like to reduce or avoid these due to undesirable side effects or drug interactions.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• We strongly believe there should be equality of access to anyone who has debilitating migraine and that resorting to best supportive care should not be the default option due to geographical location. It should be made available to everyone who meet the treatment criteria regardless of their age, gender, disability, ethnicity, religion or location.

Other issues

13. Are there any other issues that you would like the committee to consider?	Access to appropriate treatment for patients with migraine is an issue. Despite new migraine treatments that have recently been approved (CGRP mAbs), there are significant issues with access to these treatments. We know many people who are eligible for these treatments are unable to access them. Either because they are unable to access a specialist who can prescribe them, or because there is no provision or funding in place to provide them. When reviewing Eptinezumab the committee should consider how people will be able to access these treatments if approved. As part of our dismissed for too long report we submitted an FOI to NHS Trusts in all four nations asking for more information around how migraine is managed and access to headache specialists, and appropriate treatment. In England, just 16% (n=15) of all NHS Trusts responding to the FOI said eligible patients could access CGRP mAb treatment, while another 15 explicitly said they could not. • People with migraine have largely been offered treatments that were designed for other conditions which were often difficult to tolerate, often with disabling side effects and variable benefit. • Many people with migraine still rely on best supportive care, which includes the currently available options. For patients who either do not benefit or have no access to current migraine-specific treatments, additional options are needed. • We would urge the committee to consider recommending this treatment based on the evidence of effectiveness and tolerability.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is still a large unmet need in this population who are typically impacted during their most productive years, making non-treatment very expensive. • Migraine impacts individuals and the health of society as a whole. Effective, targeted migraine treatments are needed. • Migraines can worsen over time and become more debilitating, costly and difficult to treat; early targeted treatment is needed. • An estimated 16,500 emergency admissions for headache and migraine attacks could be avoided if patients are on the right treatment. • Patients should not have to try every recommended treatment before being offered access to a targeted cgrp mAb treatment, such as eptinezumab.

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

Single Technology Appraisal

Eptinezumab for preventing migraine [ID3803]

Professional organisation submission

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.

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

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 select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No 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
5b. 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.**	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 mean headache day reduction v. 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?	we believe there is a very significant unmet need • Migraine affects 15% of the general population (22% women and 8% men). 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 UK economy run into 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 an unmet need in both research and education on the disorder in primary and secondary care • 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 episodic and chronic 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 (beta-blockers, 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. CGRP monoclonal antibodies (CGRP mAbs) (erenumab, galcanezaumab and fremanezumab) are approved by NICE for those with episodic and chronic migraine (>4 migraine days per month) who have tried and failed at least 3 other preventive treatments. These therapies are currently used only in specialist settings. 4. 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 5. 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
9a. 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/
9b. 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.)	NICE and BASH guidelines provide a comprehensive care pathway and management guidelines for care of a headache patient. However, 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.
9c. What impact would the technology have on the current pathway of care?	There are 3 CGRP mAbs (erenumab, fremanezumab, galcanezumab) currently available recommended for those who have failed at least three first line treatments. All of these are subcutaneous injections self-

	administered by patients. Eptinezumab is a three monthly intravenous infusion which will provide an additional option with better compliance as this will be delivered in the day-care settings. This treatment would be particularly useful in those with severe migraine attacks presenting to Accident and Emergency department as there is evidence of its efficacy in treating status migrainosus and may well be initiated as a preventive measure. The use of eptinezumab will require human and financial resources as the treatment requires attendance to the hospital and an infusion as day-case.
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, and may be considered for those with compliance issues
10a. How does healthcare resource use differ between the technology and current care?	The three currently available CGRP mAbs are subcutaneous injections that are self-administered by patients. The treatment with eptinezumab will require a day-care set up so the infusions are delivered every three months. Additional considerations for eptinezumab are the resources required to administer a 12 weekly intravenous infusion
10b. 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 secondary care, preferably specialist headache centres, with facilities for intravenous infusion
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Infusion training and day case infusion facilities in secondary care 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.

11a. Do you expect the technology to increase length of life more than current care?	Improve quality rather than length of life.
11b. 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 appropriate) than the general population?	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 eptinezumab 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 affecting patient acceptability or ease of use or additional tests or monitoring needed.)	For patients: easier, eptinezumab is a 12 weekly intravenous infusion that has side effect comparable to placebo. For healthcare professionals: more difficult, due to infrastructure and administrative tasks of organising intravenous infusions

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting and stopping criteria would be in line with those recommended for other CGRP monoclonal antibodies. Its placement with the current treatment will really be based on the cost of the technology, including day case infusion costs We suggest: **Starting criteria**: failed 3 standard migraine preventive mediations (at sufficient dose and for at least 2 months) **Stopping criteria:** ***'Negative':*** assessment 3 months after initiating treatment and stopping if there is lack of therapeutic response (at least 50% reduction in mean monthly migraine days for episodic and 30% in chronic migraine), ***'Positive':*** if effective in achieving the desired level of response consider discontinuing treatment after 6-12 months No additional testing required
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: PROMISE 1 Phase 3 study (Ashina et al Cephalalgia 2020) showed at least a 50% reduction in mean monthly migraine days (MMDs) of 50% 100mg dose, 56% 300mg v 37% placebo over 1-12 weeks. The 75% reduction in MMDs was 22% (100mg), 30% (300mg) v 16% placebo Chronic Migraine: PROMISE 2 Phase 3 study (Lipton et al Neurology 2020) showed at least a 50% reduction in MMDs of 58% (100mg), 61% (300mg), v placebo 39% over 1-12 weeks treatment. The 75% reduction in MMDs was 27% (100mg), 33 % (300mg) v 15% placebo Chronic and Episodic treatment resistant migraine DELIVER Phase 3 study (Ashina et al Lancet Neurol 2022) patients who had previously failed 2-4 preventative treatments showed a reduction in MMDs of 4.8 (100mg) , 5.3 (300mg) v 2.1 placebo
16. Do you consider the technology to be innovative in its potential to make a significant and	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.

substantial impact on health-related benefits 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.
16a. Is the technology a 'step-change' in the management of the condition?	Potentially yes: eptinezumab 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. It is the first of its kind to be offered as a 12 weekly infusion
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, by improving compliance
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 Phase 3 clinical trial of episodic and chronic migraine patients included patients who had tried other preventive medications for migraine but the results did not stratify response according to previous medications failed. Only the DELIVER Phase 3 study was designed to study those who had previously failed 2-4 preventative treatments In UK clinical practice many such high cost treatments are restricted to use in those who have failed at least 3 preventatives.

18a. 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 eptinezumab would be used in patients refractory to at least three preventive treatments
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	• Reduction in frequency or severity of headache (50% in episodic and 30% in chronic) • Percentage of patients with sustained headache response • Reduction in acute analgesic intake • % of patients with 75% and 100% response rate • Significant reported change in patient quality of life measures e.g.HIT6, MIDAS, EQ5D, MSQ (validated quality of life measure in migraine) The current data is only for three months (chronic migraine) and six months (episodic migraine) and long term follow up is awaited.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge
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	No

comparator treatments since the publication of NICE technology appraisal guidance TA764, TA682, TA659, TA260?	
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No real world data yet available
22b. Consider whether these issues are different from issues with current care and why.	Migraine is more common in women (22%) compared to men (8%).

Key messages

23. 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 • The treatment is well tolerated and safe with a side effect profile similar placebo • Three monthly infusion will improve compliance and facilitate good monitoring. • Intravenous infusions to be delivered in a day-care setting. • Particularly effective in those with prior 2-4 treatment failure relevant to the UK population treatment strategy

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Eptinezumab for preventing migraine [ID3803]
Professional organisation submission

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.

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- 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	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Association for the Study of Headache (BASH) is a professional body representing healthcare professionals interested in the field of headache. The organisation has 182 members who pay annual subscription. The organisation promotes research and education in the field of headache among primary and secondary care doctors and other healthcare professionals working in the field. The organisation often ask for unrestricted educational grants from the industry partners to organise teaching courses and educational events countrywide within the United Kingdom. The executives are chair, vice chair, secretary and treasurer along with educational and scientific officers. There are 12 council members who oversee the day to day running of the organisation. The executives and council members offer their services voluntarily and may only receive reimbursement for out of pocket expenses.
5b. 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 organised webinars in the year 2021 for which it received unrestricted educational grants of 4K each from: Allergan, TEVA, Eli Lily and Lundbeck The organisation received unrestricted educational grant of £ 8K from TEVA for a teaching course in Aviemore in May this year and another 8K from Eli Lily for the teaching course to be organised in Belfast in November 2022.

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.)	Migraine is not curable and hence treatments are aimed towards treatment of acute attacks and prevention in those with frequent attacks. The main aim of a preventive treatment (such as this one) is: • Reduce the frequency of migraine attacks to improve the quality of life of patient suffering from this condition. • Reduce the severity of attacks to minimise its impact on activities of daily living. • To reduce the need for acute treatments by reducing the frequency and severity of individual attacks. • To provide a treatment that is well tolerated and safe.
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.)	A 50% reduction in the frequency or severity of headaches in those with episodic form of migraine – defined as headaches on < 15 days of headaches per month A 30% reduction in the frequency or severity of headaches in those with chronic form of migraine – defined as headaches on ≥ 15 days of headaches per month for at least three months. An improvement in quality of life measured through many validated measures e.g., EQ – 5D, HIT-6, MIDAS or MSQ.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Migraine is a highly prevalent disorder that affects 15% of the general population (22% women and 8% men) and has impact worse than diabetes, epilepsy and asthma put together. Around 2-5% of the population suffers from migrainous headaches on more than 15 days per month (Chronic Migraine) with significant morbidity and has a major impact on healthcare resources directly and indirectly to the general economy that runs in billions (euros/£)with 20 millions lost days a year (UK /Europe?). In the UK there is shortage of general neurologist and those with interest in headache medicine are scarce. Hence the condition is under-recognised, under-resourced and under-diagnosed. There is lack of education and research in this field.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Migraine is under-diagnosed due to lack of specialist care, hence many sufferers self-manage through over the counter analgesics. Those with severe but infrequent migraine attacks are given prescribed analgesics such as non-steroidal anti-inflammatory drugs (NSAID) or triptans for the acute attacks. Those with frequent episodes that require regular preventive therapy are given lifestyle advice and may get referred to secondary care for advice. Due to shortage of headache specialist, many patients are given lifestyle advice by the specialist nurses, although there are only 70 nurses in the UK. Psychologists might be helpful but such services are not linked to headache clinics in most of the UK centres. Acute treatments are usually offered in the primary care. Some of the preventive treatments are offered in primary care including tricyclic anti-depressants, beta-blockers and anti-epileptics and/or angiotensin receptor blockers. Those refractory to first line treatments are referred to secondary care for more specialised treatment that include OnabotulinumtoxinA (for chronic migraine only), CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab) that are licensed for both chronic and episodic migraine (> 4 days / month). There are transitional treatments such as cranial nerve blocks offered in headache centres and in refractory cases patients may be offered intravenous dihydroergotamine infusion in no more than 2-3 centres in the UK. There are non-invasive neuro-modulation devices such as gammacore, transcranial magnetic stimulation and cephaly device but these are not funded through the NHS. In intractable cases patients may be referred for invasive neuromodulation such as occipital nerve stimulator although this is only available in three UK centres based in London and are hugely expensive.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	In the UK, healthcare professional follow the NICE CG150 (2012 & updates) https://www.nice.org.uk/guidance/cg150 Or the British Association for the Study of Headache (BASH) National Management System for adults 2019 https://www.bash.org.uk/fuidelines/ Or the SIGN guidelines (2018) http://www.sign.ac.uk/sign-155-migraine.html
9b. 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	NICE and BASH guidelines provide a comprehensive care pathway and management guidelines for care of a headache patient. However, there is regional variation determined by the access to specialist care. The headache services in the UK are patchy with population nearer a headache centre receiving extremely good care and those without access to specialised care receiving extremely poor care. There is lack of headache education right from the medical school and those serving in primary care have very little awareness of the condition.

experience is from outside England.)	
9c. What impact would the technology have on the current pathway of care?	There are 3 CGRP mAb (erenumab, fremanezumab, galcanezumab) currently available recommended to those with failure of at least three first line treatments. All of these are subcutaneous injections self-administered by patients. Eptinezumab is a three monthly intravenous infusion which will provide an additional option with better compliance as this will be delivered in the day-care settings. This treatment would be particularly useful in those with severe migraine attacks presenting to Accident and Emergency department as there is evidence of its efficacy in treating status migrainosus and may well be initiated as a preventive measure. The use of Eptinezumab will require human and financial resources as the treatment requires attendance to the hospital and an infusion as day-case.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Eptinezumab provides an additional tool in the current pathway and may well be considered for those with compliance issues.
10a. How does healthcare resource use differ between the technology and current care?	The three CGRP mAb are subcutaneous injections that are self-administered by patients. The treatment with Eptinezumab will require a day-care set up so the infusions are delivered every three months.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Like other CGRP mAb, this treatment is best initiated in secondary care preferably the specialist headache centres.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Provision of beds at the day-care or programmed investigation units to accommodate these patients for three monthly infusions. • Training of nursing staff on infusions and monitoring • Administrative costs towards setting up of the service.
11. Do you expect the technology to provide	Patients with poor compliance will be well suited to this technology.

clinically meaningful benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	Migraine is a lifelong illness and preventive treatments improve quality of life and reduce disability rather than increasing life expectancy.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Like other CGRP MAB, this treatment will improve health-related quality of life, particularly in those with poor compliance to current therapy choices.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with status migrainosus or those with prolonged severe migraine attacks may benefit more than those with continuous disabling headaches where home therapy may well be better with subcutaneous self-administered injections.

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	As the treatment is intravenous and require administration in day care, this may well be reserved for those with poor compliance to the currently available subcutaneous self-administered options.

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?	In line with other CGRP mAb and OnabotulinumtoxinA, the treatment should have defined starting and stopping criteria. BASH recommends that treatment be given to those with failure of three first line treatments and given for an initial period of six months (2 infusions three months apart). It should be stopped if there is lack of response (negative stopping rule) 50% in episodic and 30% in chronic migraine population. Those with positive response should continue for at least 12 months following which the patient is evaluated for further continuation of therapy.
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?	PROMISE 1 STUDY (N = 888) (Ashina et al Cephalalgia 2020) - Phase three study on episodic migraine showed 50% reduction in the mean monthly migraine days (MMD) of up to 56% compared to 37% in placebo and 75% reduction in MMD of up to 33% (check this) compared to 16% in placebo. PROMISE 2 STUDY (N = 1072) (Lipton et al Neurology 2020) – Phase three study on chronic migraine showing 50% reduction in MMD of up to 61% compared to placebo 39% and 75% reduction in MMD of up to 33% compared to 15% in placebo. DELIVER STUDY (N = 891) (Ashina et al Lancet Neurology 2022) – Phase three study on chronic and episodic migraine who previously failed 2-4 treatments with reduction of up to 5.3 headache days compared to 2.1 with placebo.
16. Do you consider the technology to be innovative in its potential to make a significant and	We have seen significant improvement of up to 80% in the current CGRP mAb and anticipate a similar response to Eptinezumab. Like other CGRP MAB, it is a migraine specific preventive treatment that is

substantial impact on health-related benefits and how might it improve the way that current need is met?	well tolerated and have a side effect profile similar to placebo. The three monthly dosing is easier and will improve compliance and better monitoring would be possible.
16a. Is the technology a 'step-change' in the management of the condition?	Like other CGRP MAB, this is a significant paradigm shift towards using a migraine-specific prophylaxis that is well tolerated and safe in comparison to all first line treatments that were used for other conditions and were accidentally found to be effective in migraine but have a poor side effect profile and a higher dropout rate.
16b. Does the use of the technology address any particular unmet need of the patient population?	Patients with poor compliance are more suited to this treatment
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?	Side effect profile is similar to placebo in clinical trials.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Deliver study particularly addresses treatment efficacy on those with previous 2-4 failure. Currently high cost therapies are restricted to those who failed three first line treatments.

18a. If not, how could the results be extrapolated to the UK setting?	Many high cost treatment options are restricted to failure of three first line treatments and hence data from Deliver study would demonstrate its superiority in this group of patients.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	• Reduction of severity or frequency of at least 30% in those with chronic migraine and 50% in those with episodic migraine • Reduction in acute analgesic intake • 50%, 75%, 100% responder rate • Improved quality of life measures – HIT-6, MIDAS, MSQ, EQ 5D etc The long term efficacy data on this treatment are lacking and real-life data should be collected to substantiate three and 6 month clinical trial data.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a	Long term efficacy and tolerability

systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA764, TA682, TA659, TA260?	NO
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Migraine is more common in females of fertile age group.
22b. Consider whether these issues are different from issues with current care and why.	No

Key messagesOF

23. In up to 5 bullet points, please summarise the key messages of your submission.	• CGRP mAb is the first migraine specific preventive treatment • The treatment is well tolerated and safe with a side effect profile similar placebo • Three monthly infusion will improve compliance and facilitate improved monitoring. • Intravenous infusions to be delivered in a day-care setting. • Particularly effective in those with prior 2-4 treatment failure relevant to the UK population treatment strategy.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Single Technology Appraisal

Eptinezumab for preventing migraine [ID3803]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with migraine or caring for a patient with migraine. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Patient expert statement

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Tuesday 1 November 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with migraine

Table 1 About you, migraine, current treatments and equality

1. Your name	Ria Bhola
2. Are you (please tick all that apply)	☐ A patient with migraine? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with migraine? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	THE MIGRAINE TRUST
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference The Migraine Trust / myself, did not receive an invitation to participate in the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with migraine? **If you are a carer (for someone with migraine) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for preventing migraine on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	***The current treatments / care is inadequate. Based on communication through the Helpline and survey responses we received at The Migraine Trust:*** ***Migraine specialist preventive treatments such as mAbs and botulinum toxin A, have helped many people with migraine but access to a specialist and specialist preventive treatments, has been uneven and inadequate across parts of the country.***
8. If there are disadvantages for patients of current NHS treatments for preventing migraine (for example, how they are given or taken, side effects of treatment, and any others) please describe these	***The main disadvantages patients have told us include:*** ***Lack of access to treatment, the presence of side effects with current treatments, waiting times for specialist reviews and lack of benefit with their current treatment***.
9a. If there are advantages of eptinezumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	*a.**For patients who have not had benefit or adequate benefit, some potential advantages may be:*** ***Having a treatment that is beneficial and specifically targets the range of migraine symptoms with minimal side effects would be welcomed.*** ***b.Having an effective treatment will improve the quality of life and ability to function which will hugely impact work, education, family and social life and***

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does eptinezumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	***reduce the demand for healthcare services (eg GP, emergency, specialist services).*** ***c.Eptinezumab has the potential to help a range of people with migraine including those who already take oral medicines for other conditions and do not wish to have more, as it makes them more prone to side effects; as well as those who have not found benefit with oral treatments.*** ***Eptinezumab as a treatment with an intravenous route, could be more effective due to the more direct route of administration.*** ***It will help to meet the unmet need for patients who cannot self inject (eg mAbs), or cannot tolerate multiple injections (eg Botulinum toxin A).***
10. If there are disadvantages of eptinezumab over current treatments on the NHS please describe these. For example, are there any risks with eptinezumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	***There may be a longer wait time for a clinician-administered treatment.***
11. Are there any groups of patients who might benefit more from eptinezumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity, or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering migraine and eptinezumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	***We need to ensure that appropriate treatments are available for everyone including those who cannot self-administer due to physical, cognitive or other disability and those who may have additional disability due to side effects when taking multiple oral medications.***

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Additional treatment options are required for people with migraine.
- Access to treatment should be equitable.
- Not everyone has benefit or adequate benefit with currently available options.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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Single Technology Appraisal

Eptinezumab for preventing migraine [ID3803]

Patient expert statement

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with migraine

Table 1 About you, migraine, current treatments and equality

1. Your name	Steph Weatherley
2. Are you (please tick all that apply)	☒ A patient with migraine? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with migraine? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Migraine Trust
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I work for the migraine trust as an information and support advisor. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference because I was not invited to this ☐ I have not completed part 2 of the statement
6. What is your experience of living with migraine? **If you are a carer (for someone with migraine) please share your experience of caring for them**	I was diagnosed with migraine as a child, I would miss numerous days off school, wore tinted glasses and carried medication with me. My migraine stopped when I was approx. 19yrs old and reduced down to one or two a year. This did not last and my migraine returned 4 years ago when I was 34. It went from twice a year to everyday, I was later diagnosed with chronic migraine and chronic daily headache at Kings College Hospital in 2020. I tried preventive medications, candesartan, propranolol, topiramate, duloxetine, gabapentin and pregabalin and these made no difference to my migraine condition at all. Many I could not tolerate due to being sensitive to medications and having side effects. I was then offered a GON injection which after 2 years provided some relief, although this was short lived and interrupted by the Covid pandemic. I relocated to another part of the country where is was referred to a different hospital and neurologist. The level of care was exceptional and I was then offered either CGRP medication or Botox. Botox had a longer waiting list so I opted for the CGRP medication and was prescribed Ajovy 4 months later. Unfortunately after 6 weeks I get an all over body rash. The hives were deemed a side effect or allergic reaction to the Ajovy and I was no longer able to take this. I am now back on duloxetine which is also for my TMD and to date this is not helping. Aimovig may be considered next and I have a review next year for this, The lengthy time frame in between appointments makes things difficult as I have a family to look after, a full time job and I am also studying part time as well. My migraine impacts all of these, it causes issues within my personal life and affects my quality of life. I have found that it has been a lengthy journey accessing and trialling medications and 4 years on its still not controlled.

7a. What do you think of the current treatments and care available for preventing migraine on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. I think the current pathway for treatment is too long. It takes approx. 3 months to trial each preventive medication via the GP and after 9 months of this and them not working you then need to wait approx. 1 year to be seen by a neurologist and fight to access CGRP or Botox treatment. Which you then have to wait a further 3-6 months (possibly longer) to start. We can go over 2 years waiting to access the right treatment which caused depression, impacts my quality of life and for some people prevents them for working and supporting themselves and their families. The preventive medications do not appear to work and have far too many side effects. The CGRP medications have great reviews but are very difficult to get on prescription. Botox has a strange criteria and when you drop below 15 migraines a month it is reviewed and stopped although you may still be having up to 14 migraines which is still debilitating. 7b. I feel my views are fair and similar compared to others with migraine. As a chronic migraineur I work for the migraine trust on the helpline and I speak to many other migraineurs daily that struggle with their GP's, struggle in getting a diagnosis and have many delays and issues in accessing treatment. It has a large impact on the quality of life when a person is waiting over a year to see a neurologist and despite informing a HCP that they cannot tolerate a preventive medication or it has not worked in the 6 months they have been on it they are told to take more painkillers and get on with it. There seems to be a large issue with medication overuse headache as well due to the lengthy timescales in accessing appropriate treatment.
8. If there are disadvantages for patients of current NHS treatments for preventing migraine (for example,	Many of the preventive medications are designed for other medical conditions but have seen to be beneficial for migraine, however this only appears to work for a small number of people. I have had side effects to every preventive medication I

how they are given or taken, side effects of treatment, and any others) please describe these	have tried including Ajovy. The only thing that I tolerated was a GON block but neurologist do not seem to like this treatment and prefer not to give it. I am now due to try Aimovig in the near future however there is a high chance that I will also have a reaction to this. Side effects can be just as debilitating as the migraine, however it can not be helped if a person is not able to tolerate a treatment. Through speaking to others with migraine I have noticed that with the current CGRP treatments being self-injectable many people find it hard to inject themselves or have a needle phobia and need someone to do this for them,. Their current neurology clinics do not provide a service for them to go visit the clinic for their injection monthly. Due to this issue some patients miss out on having the treatment. It would be useful if there were other methods of taking the CGRP treatments such as tablets or nasal sprays etc. All of the treatments after the standard preventive medications include needles.
9a. If there are advantages of eptinezumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does eptinezumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a. Eptinezumab is another treatment option that might help those that have not responded to other treatments. It will also enable those with a needle phobia to receive CGRP medication in allowing them to attend a clinic, receive support and have someone manage the needle for them- this will open the doorway to many that avoid treatments due to issues with injections. Those of us with migraine might have the chance to continue working and not struggling on reduced hours, be able to spend time with our families and have a better quality of life. Migraine is debilitating and so much time is missed when you spend it laying in bed for days unable to function. 9b. The most important advantage is the improvement in quality of life. I have spent many days and evenings laying in a dark room, away from any noise, light and people. I have had issues with depression caused by my migraine which has affected my mental health. I have continued working but this has in the past been very difficult but when you have a house and children to support there is no other option. I tried to claim for PIP benefit but was not successful despite an inability to

	be able to function, cook, socialise etc. Many people struggle with all of these aspects in life and the life they have is not good quality, it is not even basic compared to others and if a treatment is available that can help improve the health, mental wellbeing and functional abilities of a person with migraine it should be an available option for them, but not be ridiculously difficult to access with a complicated criteria. 9c. Yes it would, it will be a CGRP option for those unable to self-administer the injection at home. It is also another treatment option for those that have not had any success with previous treatments. Providing the criteria is a sensible criteria and there are not continuous funding issues like other CGRP treatments.
10. If there are disadvantages of eptinezumab over current treatments on the NHS please describe these. For example, are there any risks with eptinezumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I can not see any current disadvantages, all treatments come with side effects and when you have chronic migraine you are willing to accept side effects to relieve the horrendous pain you are in and debilitating consequences it has on your quality of life.
11. Are there any groups of patients who might benefit more from eptinezumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity, or cognitive impairments) that affect the suitability of different treatments	It may benefit those with allergies to certain ingredients in standard tablets, this is usually the fillers like lactose etc, it will enable those with needle phobia to have support during the infusions when done in a clinic with a nurse. It will be beneficial for those with other medical conditions and co morbidities and allow them to be able to have a treatment for their migraine condition. It can help those that are unable to swallow tablets as well.
12. Are there any potential equality issues that should be taken into account when considering migraine and eptinezumab? Please explain if you think any groups of people with this condition are particularly disadvantage	I do not feel that there are any equality issues with this treatment.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	I think consideration around access and funding should take place. Many people are still struggling to access other CGRP treatments despite them being licensed over 2 years ago. New treatments are great but can cause just as much stress when they are not accessible.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Eptinezumab will provide an additional treatment option for those that have not responded to others.
- Epitnezumab is an infusion and will be a CGRP option for those unable to self-inject at home.
- Migraine is a debilitating condition and access to treatment is very difficult.
- If Eptinezumab is improved it needs a sensible criteria, to be accessible and to not have funding issues like other CGRP medications available.
- Epitnezumab can give a person their quality of life back, support their mental health and general wellbeing.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Eptinezumab for preventing migraine [ID3803]: A cost-comparison technology appraisal.

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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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.

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Kate Ren critiqued the statistical aspects of the submission. Matt Stevenson and Andrew Rawdin critiqued the economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

CGRP	Calcitonin gene-related peptide
CS	Company Submission
CSR	Clinical study report
EAG	Evidence assessment group
FTA	Fast Track Appraisal
HRQoL	Health related quality of life
ITC	Indirect treatment comparison
MCMC	Markov chain Monte Carlo
MHDs	Monthly headache days
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intent to treat analysis
MMD	Monthly migraine days
MOH	Medication overuse headache
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PAS	Patient Access Scheme
RCT	Randomised controlled trial
STA	Single technology appraisal
TA	Technology appraisals

1. Introduction and the External Assessment Group's view of whether the appropriate pathway for this appraisal

This appraisal pilots a new process, agreed by the National Institute for Health and Care Excellence (NICE) the company (Lundbeck), and the External Assessment Group (EAG) in deciding whether an appraisal should be a single technology appraisal (STA), or a cost-comparison fast-track appraisal (FTA). The company provided sufficient information such that the decision on whether it was an STA, or an FTA would be made by NICE early in the appraisal, having reviewed evidence provided by the EAG. For this appraisal, NICE considered that this topic meets the criteria for cost-comparison. A summary of the EAG's view of the appropriateness of undertaking an FTA is contained below.

The company has provided estimates of comparative efficacy for eptinezumab in patients with episodic or chronic migraine who have had at least three prior preventative drug treatments. This is the positioning of the three anti-CGRP (Calcitonin gene-related peptide) therapies, galcanezumab, fremanezumab, and erenumab which have been previously approved by NICE.

The indirect comparisons provided by the company suggest similar effectiveness, as measured by migraine response rate at week 12, of eptinezumab compared with the three anti-CGRP treatments. This conclusion was supported by the clinical advisors to the EAG. Eptinezumab was well tolerated, as were galcanezumab, fremanezumab, and erenumab.

This report summarises the clinical data and provides the list prices for the three anti-CGRP drugs along with administrative costs. Eptinezumab has a patient access scheme (PAS) which is a simple discount on the list price. PASs have also been agreed for the three anti-CGRP drugs which the company wants to be compared with in the cost-comparison analyses. Passes are not considered in this report but are contained in a confidential appendix that is provided to the NICE Appraisal Committee.

2. Critique of the decision problem in the company's submission

Eptinezumab received marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) for the prophylaxis of migraine in adults who have at least 4 migraine days per month.[1] The marketing authorisation is broader than the population considered in the decision problem which is "*Adults with migraine who have at least four migraine days per month and after at least three preventive drug treatments have failed*". This positioning is consistent with the placement of the three anti-CGRP therapies in the treatment pathway, as is required for a cost-comparison FTA.

Eptinezumab is administered as 30-minute intravenous infusion every 12 weeks. The recommended dose is 100 mg; it can be administered as a 300mg dose, but the company states that this will not be '*commercialised in the UK*.'

Studies used in the company's indirect comparisons had populations broader than the decision problem. Subgroup analyses were reported to match the decision problem in the company submission.

3. Critique of the clinical effectiveness evidence submitted

3.1 Summary of company's systematic review methods

To identify all clinical effectiveness and safety studies of preventative treatments for adult migraine patients who had previously failed preventative treatments, the company conducted an initial systematic literature review in May 2020, followed by two updates in June 2021 and March 2022. The company searched several electronic bibliographic databases: MEDLINE, MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations [via Ovid], EMBASE [via Ovid], Cochrane Library Cochrane Database of Systematic Reviews (CDSR) or Cochrane Central Register of Controlled Trials (CENTRAL), and the Database of Abstracts of Reviews [Centre for Reviews and Dissemination platform, York University]. All database searches were undertaken simultaneously by the company on a single platform (Ovid). The company hand searched the bibliographies of relevant systematic reviews to identify other studies for inclusion.

The company searched several key conference abstract websites covering the last three years (2020-2022): American Academy of Neurology, American Headache Society, European Academy of Neurology, and European Headache Federation. The company searched the websites of six health technology assessment agencies: National Institute for Health and Care Excellence; Scottish Medicines Consortium; All Wales Medicines Strategy Group, National Centre for Pharmacoeconomics, Pharmaceutical Benefits Advisory Committee; and the Canadian Agency for Drugs and Technologies in Health in July 2021. This search was updated in April 2022. The company searched the clinicaltrials.gov registry in May 2020, July 2021, and April 2022 for ongoing or completed or unpublished trials, although two further trials registries could be searched, namely the World Health Organization International Clinical Trials Registry Platform and the European Union Clinical Trials Register.

The reported searches in the CS are transparent and fully reported (provision of full search strategies, detailed Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagrams) in both database and supplementary searches. There were no observable and/or consequential errors in the search approach and strategies. Despite the comprehensive sources and systematic searches, the company acknowledged that the DELIVER, PREVAIL and RELIEF studies which were all eptinezumab studies were not retrieved in the searches. PREVAIL was not captured as it was an open-label study, and RELIEF was not identified as eptinezumab used as an acute treatment rather than a preventative treatment. However, the PREVAIL and RELIEF studies were not relevant to the indirect comparison for this cost comparison. DELIVER was published in June 2022 after the literature research. Whilst the EAG could not confirm if the company has not missed other similar and relevant

studies, it is unlikely. The company performed systematic literature searches for relevant published studies related to cost-effectiveness, health-related quality of life and cost and resource use. As the EAG believed that a cost-comparison approach was appropriate the results from, and the quality of, the searches are not discussed further in this report.

3.2 Summary of company's indirect treatment comparison (ITC)

In the absence of head-to-head comparisons, a network meta-analysis (NMA) was performed to provide comparative estimates in terms of efficacy, safety, and health-related quality of life (HRQoL) for eptinezumab versus erenumab, fremanezumab, galcanezumab and botulinum toxin A for patients for whom ≥2 or ≥3 prior treatments had failed.

3.2.1 Summary of clinical evidence

The key evidence of eptinezumab was from the DELIVER RCT. DELIVER was a three-arm, phase III, double-blind RCT of eptinezumab 100mg (the licensed dose [1]), and eptinezumab 300mg, versus placebo. The placebo-controlled period was of 24 weeks' duration and was followed by a 48-week extension of eptinezumab (dose blind). Clinical advisors to the EAG considered this follow-up to be of adequate length to measure effectiveness and safety of the intervention. Only five of the 96 sites were in the UK, with the rest being in Eurasia and the USA. Clinical advisors to the EAG considered the demographics of the DELIVER study participants to be mostly generalisable to the UK, although the RCT had a higher percentage of Caucasians than would be seen in UK practice. The primary outcome of DELIVER was change from baseline in the number of MMDs during weeks 1 to 12.

The CS provided supporting evidence regarding eptinezumab from the trials PROMISE-1 and PROMISE-2. These trials were not used in the company's indirect comparison.

The data used in the company's indirect comparisons were taken from placebo controlled RCTs:

One RCT of eptinezumab – DELIVER.

Four RCTs of galcanezumab – CONQUER, EVOLVE-1, EVOLVE-2, REGAIN.

One RCT of fremanezumab – FOCUS.

Three RCTS of erenumab – LIBERTY, NCT02066415, STRIVE.

Two RCTs of botulinum toxin A - PREEMPT-1, PREEMPT-2.

In the NICE TAs, for botulinum toxin A (NICE TA260)[2] there was no indirect comparison, and key evidence was from PREEMPT-1, PREEMPT-2. Studies used in TAs for the anti-CGRP drugs (TA764, TA682, TA659) [3-5] are shown in Table 1. The indirect comparison in the eptinezumab CS includes all RCTs which were included in the indirect comparisons of previous NICE TAs of the relevant comparators (anti-CGRP drugs and botulinum toxin A).

Table 1: Studies used in indirect comparisons from current and previous NICE TAs of migraine

Study name	Trial registry number	Study population eligibility	Interventions	Primary outcome	Included in company's indirect comparison Eptinezumab (ID3803)	NICE TA659[3] Galcanezumab	NICE TA631, TA764[5] Fremanezumab	NICE TA682[4] Erenumab
DELIVER [6]	NCT04418765	EM or CM, 2 to 4 prior treatments	eptinezumab 100 mg or 300 mg versus placebo (100mg is licensed dose, so 300mg results not reported (CS document B)	Change from baseline in the number of MMDs, Weeks 1 to 12	Yes	No	No	No
CONQUER[7]	NCT03559257	EM or CM, 2 to 4 prior treatments	galcanezumab 120 mg / month (with 240 mg loading dose) versus placebo	Change From Baseline in the Number of Monthly Migraine Headache Days to month 3	Yes	Yes	No	No
EVOLVE-1[8]	NCT02614183	EM (prior treatment not an eligibility criterion)	galcanezumab 120 mg / month (with 240 mg loading dose; note this is the recommended dose) or 240 mg / month versus placebo	Change From Baseline in the Number of Monthly Migraine Headache Days to month 6	Yes	No (used as supporting evidence)	No	No
EVOLVE-2[9]	NCT02614196	EM (prior treatment not an eligibility criterion)	galcanezumab 120 mg / month (with 240 mg loading dose; note this is the recommended dose) or 240 mg / month versus placebo	Change From Baseline in the Number of Monthly Migraine Headache Days to month 6	Yes	No (used as supporting evidence)	No	No
REGAIN[10]	NCT02614261	CM (prior treatment not an eligibility criterion)	galcanezumab 120 mg / month (with 240 mg loading dose; note this is the recommended	Change From Baseline in the Number of Monthly Migraine Headache Days to month 3	Yes	Yes	No	No

			dose) or 240 mg / month versus placebo					
FOCUS[11]	NCT03308968	EM or CM, 2 to 4 prior treatments	fremanezumab 675/225/225 mg monthly or fremanezumab 675 mg quarterly versus placebo (recommended doses 225mg monthly (without 675mg loading dose) or 675mg quarterly)	Change From Baseline in the Number of Monthly Migraine Headache Days to Week 12	Yes	No	Yes	No
LIBERTY[12]	NCT03096834	EM, Failed 1+	erenumab 140 mg versus placebo	Percentage of Participants With at Least 50% Reduction From Baseline of Monthly Migraine Days (MMD) in the Last Month (Last 4 Weeks of Treatment, Month 3)	Yes	No	No	No (used as supporting evidence)
NCT02066415[13]	NCT02066415	CM, failed up to 3	erenumab 70 mg or 140 mg versus placebo (140mg is the recommended dose)	Change From Baseline in Monthly Migraine Days to Week 12	Yes	No	Yes (included only to strengthen the network and not to include erenumab as an additional comparator)	Yes
STRIVE[14]	NCT02456740	EM or CM, Up to 2 prior treatments	erenumab 70 mg or 140 mg versus placebo (140mg is the recommended dose)	Change From Baseline in Monthly Migraine Days to Week 24	Yes	No	No	No (used as supporting evidence)
PREEMPT-1[15]	NCT00156910	CM (prior treatment not in eligibility criteria)	botulinum toxin A 155-195 mg versus placebo	Change in Frequency of Headache Episodes,	Yes	Yes	Yes	Yes

				to Week 24				
PREEMPT-2[16]	NCT00168428	CM (prior treatment not in eligibility criteria)	botulinum toxin A 155-195 mg versus placebo	Change in Frequency of Headache Days, to Week 24	Yes	Yes	Yes	Yes

3.2.2 Quality assessment

Quality assessment was checked by the ERG against information in publications of studies included in the indirect comparison, the trial registry clinicaltrials.gov, and the DELIVER clinical study report (CSR)[17] provided by the company.

DELIVER was at low risk of bias for comparing eptinezumab to placebo (Table 2). Care providers, participants, and outcome assessors were blinded to treatment group. There was a modified intent to treat analysis (mITT) of patients who were enrolled and received at least one dose of study drug. Only one randomised participant, in the placebo group did not receive at least one dose of study drug (n=892 randomised, n=891 mITT for safety analysis, n=890 effectiveness analysis).[6] One additional participant was excluded from the effectiveness analysis for not having valid post-baseline assessment of monthly migraine days;[6] this participant was in the eptinezumab 300mg treatment arm, which is not relevant to this appraisal.

Table 2: Quality assessment results DELIVER RCT of eptinezumab used in the indirect comparison

Trial number (acronym)	**DELIVER** **CS assessment, CS Appendices Table 31** Clinical Study Report [17]	**DELIVER** **NCT04418765** **ERG assessment** Ashina 2022 [6] clinicaltrials.gov[18] Clinical Study Report [17]
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Outcome data relevant to this appraisal were provided in the CS
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	mITT (patients enrolled and received at least one dose of study drug) [6 18]
Details of study funding	H. Lundbeck A/S, Copenhagen, Denmark	Funded by the company

Randomisation and concealment of allocation were adequate, with centralised randomisation [6] using interactive response technology [17]. Randomisation was stratified by country and monthly headache days (MHDs) at baseline (≤14 MHDs/ >14 MHDs). [6] The stratification factor of MHDs doesn't exactly match the definitions of EM and CM used in the subgroup analyses (which were based on migraine diagnosis during the 4-week screening period: EM = ≤14 headache days per month with ≥ 4 monthly migraine days (MMD); and CM = ≥ 15 headache days per month with ≥ 8 monthly migraine days MMDs, CS clarification question C3). In practice this did not differ by more than [redacted] patients (Appendix 1 Table 6). Randomisation was not stratified by number of prior treatments, meaning there is potential for imbalance in characteristics, between intervention and placebo arms, in the subgroups of patients for whom ≥ 3 prior preventive treatments had failed. For the whole study population, baseline characteristics were balanced across treatment groups. Not all the outcomes[18] of the DELIVER randomised controlled trial (RCT) were published at the time of writing, however all relevant outcome data were provided in the CS.

DELIVER was funded by the company, which can carry a risk of bias. All other ten RCTs in the indirect comparison were also industry-funded. The ten comparator RCTs in the indirect comparison were generally at low risk of bias. Nine were phase III RCTs, and NCT02066415 was a phase II RCT (Appendix 1 Table 7, Table 8, Table 9, and Table 10).

All the comparator RCTs were double-blind. For the botulinum toxin A trials (Pre-empt 1 and 2), it was unclear if blinding had been maintained, as participants were not asked if they had identified their treatment arm, and earlier trials had shown that high proportions (approximately 70%) of those given facial botulinum toxin A had known from changes in muscle tone. [2].

Eight of the comparator RCTs did not have randomisation stratified by number, or medication class, of prior treatments (CONQUER, EVOLVE-1, EVOLVE-2, REGAIN, LIBERTY, NCT02066415, Pre-Empt-1, Pre-Empt-2.) meaning there is potential for imbalance in characteristics, between intervention and placebo arms, in the subgroups of patients for whom ≥ 3 prior preventive treatments had failed. The FOCUS RCT included randomisation stratified by "*failure to two to three migraine preventive medication classes plus valproic acid or valproate*"[11], and the STRIVE RCT included randomisation stratified by "*use of migraine-preventive medication (current use, previous use only, or no previous or current use).*" [14] Three of the comparator trials included both EM and CM participants. In the CONQUER RCT, randomisation was stratified by low frequency episodic migraine (four to seven migraine days per month), high frequency episodic migraine (eight to 14 migraine days per month, and fewer than 15 headache days per month), versus chronic migraine (at least eight migraine days per month, and at least 15 headache days per month) [7]. The FOCUS RCT had randomisation stratified by chronic migraine (headache on at least 15 days per month, with at least 8 days migraine) versus episodic migraine (headache on at least 6 days (but <15 days) per month, with at least 4 days migraine) [11]. In the STRIVE RCT, randomisation was not stratified by migraine severity [14] meaning there is potential for imbalance in characteristics, between intervention and placebo arms, in the subgroups of EM and CM.

The RCTs of botulinum toxin A included intent-to-treat analyses. The other comparator RCTs included mITT analyses. In practice, only low numbers of randomised participants did not receive at least one dose of study drug leading to their exclusion from the mITTs (QA tables, Appendix 1: Table 7, Table 8, Table 9, and Table 10).

3.2.3 Summary of the ITC methods

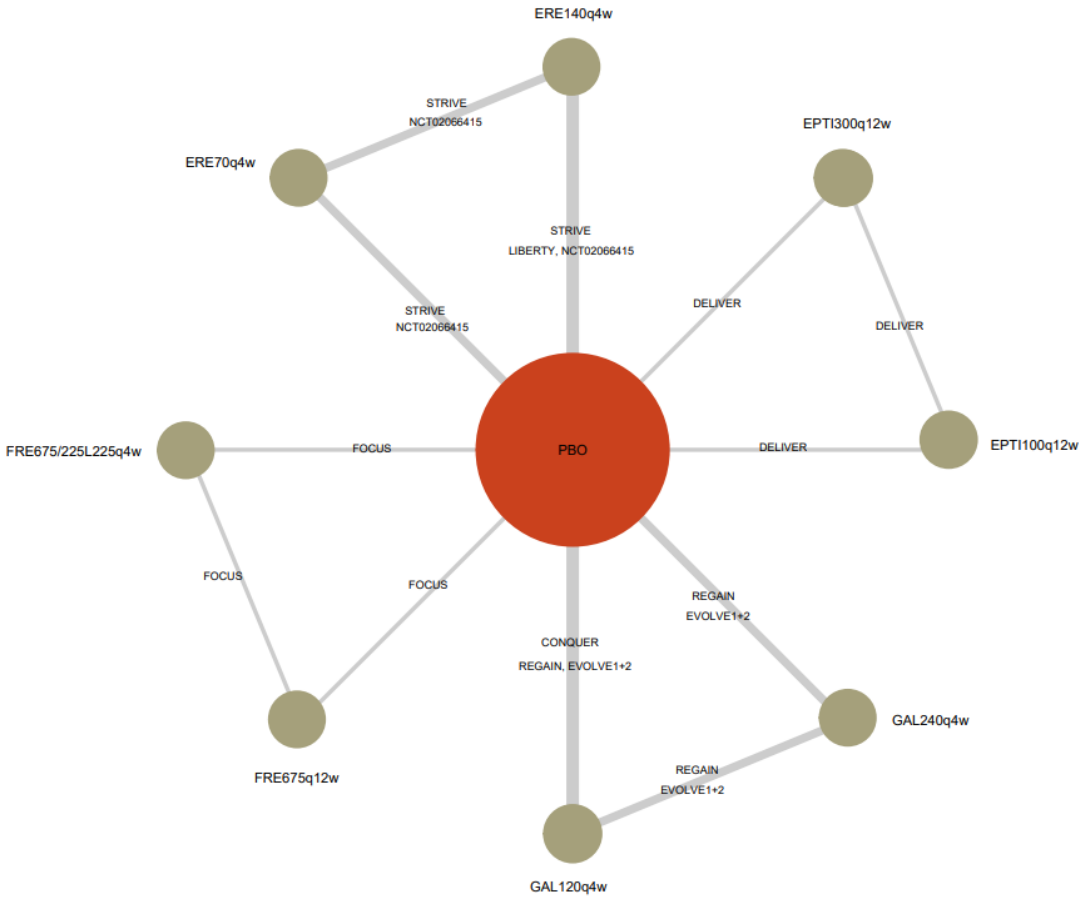
The company identified baseline severity, the number of prior treatment failures and medication overuse headache (MOH) as potential treatment effect modifiers. NMAs were conducted in the subgroups stratified by EM and CM and the prior number of treatment failures (2+ and 3+) to control

for potential differences across studies. A pooled NMA of both EM and CM was also conducted for 50% and 75% migraine response rates and discontinuation outcomes (stratifying by ≥2 and ≥3 prior treatment failures). MOH was not considered when exploring heterogeneity due to limited reporting of this characteristics across studies.

The fixed effect model was used in the NMA base case as few studies were available per treatment comparison. Random effects model was also fitted for the two priority outcomes (MMD reductions and 50% MRR). Models were estimated using Markov chain Monte Carlo (MCMC) simulation with three chains. A burn-in period of 30,000 samples was applied for each chain, 100,000 and 200,000 further iterations were saved per chain for the fixed effect and random effects model, respectively after the burn-in period.

3.2.4 Summary of the ITC results

Figure 1 shows the global network of the studies used in the NMA. The network diagram for each outcome can be found in CS Appendix D.1.3.5. Table 19 in the CS summarises the outcomes included in each of the fixed effect NMA. The EAG notes that data were only available for all the comparators of interests for 50% MRR, and none of the other outcomes had data for all the comparators. Appendix 2 presents the fixed effect NMA results in patients with ≥ 3 treatment failures for EM, CM and the pooled EM and CM subgroup. Clinical advice to the EAG suggested no reason to believe that the relative treatment effect of interventions would differ between EM and CM.



Key: CM, chronic migraine; ERE70q4w, erenumab 70 mg (q4w); ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); GAL240q4w, galcanezumab 240 mg (q4w); PBO, placebo.
Notes: This diagram does not include the PREEMPT-1 and PREEMPT-2 studies which informed comparisons in patients with CM versus botulinum toxin A.

Figure 1: Global network plot for comparisons versus anti-CGRPs (reproduced from CS, Figure 4)

The fixed effect NMA results do not indicate a statistically significantly difference between any of the active comparators and eptinezumab. For the outcome where data were available for all comparators (50% MRR): in the EM subgroup the results were in favour of eptinezumab when comparing eptinezumab to erenumab and galcanezumab; but in favour of fremanezumab when comparing eptinezumab to fremanezumab. In the CM subgroup, the results were in favour of eptinezumab when comparing eptinezumab to erenumab, fremanezumab 675 mg (q12w) and botulinum toxin A; but in favour of fremanezumab 675/225/225 mg (q4w) and galcanezumab when comparing eptinezumab to fremanezumab and galcanezumab (see Table 3).

In response to clarification question A2, the company provided random effects NMA results for the priority outcomes (MMD reductions and 50% MRR). The EAG notes that the point estimates from the random effects NMA were similar to the fixed effect NMA but with much larger uncertainty.

Clinical advice was provided to the EAG regarding the relative efficacy of eptinezumab compared with the anti-CGRPs. All clinicians believed that eptinezumab would be anticipated to have similar, or potentially better, efficacy. Using the clinical opinions as a Bayesian prior would move the midpoint towards unity. As this approach would require formal elicitation it has not been undertaken by the ERG.

Table 3: Results of the company's ITC (abbreviated to only include the anti-CGRPs at the appropriate doses). Odds ratio of 50% migraine response rate at week 12 compared with eptinezumab

Erenumab	Fremanezumab	Galcanezumab
EM ≥ 3 treatment failures		
[redacted]	[redacted]	[redacted]
CM ≥ 3 treatment failures		
[redacted]	[redacted]	[redacted]
Pooled EM and CM ≥ 3 treatment failures		
[redacted]	[redacted]	[redacted]

Note: Odds ratios <1 favour eptinezumab; Odds ratios >1 favour comparator. Dose for fremanezumab was 675/225/225 mg monthly. Recommended doses for fremanezumab were 225mg monthly (without 675mg loading dose) or 675mg quarterly.

3.3 Critique of company's ITC

3.3.1 Clinical evidence used in the ITC

The studies in the company's ITC differed in numbers of prior treatments and severity of migraine at baseline (Table 1). Most studies did not stratify randomisation by number of prior treatments, meaning there is potential for imbalance in characteristics, between intervention and placebo arms, in these subgroups.

The studies in the company's ITC differed in primary outcome and assessment time-points. The studies of botulinum toxin A used headache days rather than migraine days as primary outcome, and although outcome data of migraine days were reported for the whole population, headache days data were used for subgroups of 2+, or 3+, prior treatments. The studies of botulinum toxin A reported outcomes at 24 weeks, whereas 12-week data were used for other studies in the ITC.

A potential treatment modifier is the level of MOH. There are few baseline data of MOH across studies. DELIVER reports MOH (see CS clarification response, A4). The REGAIN study reports "*Acute headache medication overuse*" which appears to refer to the overuse of acute medication for the treatment of headache, rather than MOH [19]. The other studies reported medication overuse, rather than MOH, with the exception of LIBERTY which excluded patients with MOH [12] and STRIVE

which reported neither MOH nor medication overuse [14]. Reporting of MOH was thought by the clinical advisors to the EAG to be less important than having baseline data on MMD and MHD.

An issue identified by previous NICE TAs of anti-CGRPs, that is relevant to this report, was the difference in placebos across trials. Trials of botulinum toxin A necessarily had a different administration of placebo than trials of the anti-CGRP drugs (galcanezumab, fremanezumab, and erenumab). [5] The placebo in the botulinum toxin A trials was a series of 31–39 intramuscular injections of saline at day 0 and weeks 12, 24, 36 and 48 [ref TA260 FAD or pre-empt 1 and 2]. The placebo patients had a large improvement (as measured by number of headache days) lasting at least 24 weeks [2]. Drug trials of the anti-CGRP drugs galcanezumab, fremanezumab, and erenumab had placebo administration by subcutaneous injections. Trials of eptinezumab had placebo administered by infusion. This leads to uncertainty in the effect of placebo across trials.

3.3.2 Methods used in the ITC

The appropriate link function was chosen for each of the NMA. Because of insufficient number of trials to appropriately estimate the between-study heterogeneity, a fixed effect model was chosen as the base case model. In the presence of between-study heterogeneity, the use of a fixed effect model would underestimate the uncertainty associated with the treatment effect. The EAG notes that an appropriate informative prior for the between-study heterogeneity parameter should be considered to allow for more realistic estimates of the uncertainty.

3.4 Conclusions of the clinical effectiveness section

Strengths

The RCTs included in the indirect comparison were generally at low risk of bias. The indirect comparison includes all RCTs which were included in the indirect comparisons of previous NICE TAs of the relevant comparators (anti-CGRP drugs and botulinum toxin A).

Limitations

There was no head-to-head evidence of active comparators. All of the included RCTs were placebo-controlled. There were differences in placebo administration between trials of eptinezumab (infusion), botulinum toxin A trials (intramuscular injections), and galcanezumab, fremanezumab, and Erenumab (subcutaneous injections).

Across trials, randomisation was not stratified by number of prior treatment failures, meaning there is potential for imbalance in characteristics between intervention and placebo arms, for subgroups of 2+ or 3+ prior treatments. The use of the fixed effect model in the NMA underestimates the uncertainty associated with treatment effects.

4. Summary of the EAG's critique of cost evidence submitted

The list prices of eptinezumab and the three anti-CGRPs as detailed in the British National Formulary[20] are shown in Table 4. These are not particularly informative due to the PASs that have been agreed for each of the interventions.

Table 4: The list price of interventions within the company submission

Intervention	Unit size (mg)	Unit cost (list price) (£)	Unit frequency (every)	Cost per year (£)
Eptinezumab	100	1350.00	12 weeks	5870
Erenumab	140	386.50	4 weeks	5042
Fremanezumab	225	450.00	Month	5400
Galcanezumab	120	450.00	Month	5400†

†£5850 in the initial year due to a loading dose of 240mg

The costs assumed by the company associated with the administration mechanism for each intervention are shown in Table 5. The three anti-CGRP interventions are all administered subcutaneously whereas eptinezumab is administered intravenously.

For subcutaneous interventions, based on clinical advice the company assumed that 10% of patients would need help from a healthcare professional with administering such therapies, at a cost of £20 per injection. The administration costs varied by anti-CGRP due to the assumed frequency of injection. The EAG noted that the company's estimate (Table 41 in the CS) of cost for fremanezumab was not equal to that of galcanezumab despite both being provided on a monthly basis. During the Fact Check process the company clarified that based on clinical advice it assumed that 10% of patients received fremanezumab at 3 monthly intervals, with 90% receiving fremanezumab monthly. For simplicity, the EAG has assumed 12 injections a year for fremanezumab noting that the difference between the administration costs assumed by the EAG and the company are small (£1.60 per year).

In its clarification response the company referred to a confidential cost of providing anti-CGRP treatments contained in the budget impact assessment from the Patient Access Scheme

Liaison Unit. This suggests a cost of [redacted] per month, which is greater than that assumed by the company.

For eptinezumab, the company used the £142 value in TA195[21] and inflated it to 2020 prices (£174.04). In the clarification process, the EAG asked the company to attempt to find whether more recent values were available. A review of NICE technology appraisals and Resource Impact Reports and Resource Impact Templates suggest that the estimated of £174 assumed by the company was reasonable.

Table 5: Assumed costs of administration

Intervention	Annual administration costs (£)
Eptinezumab	756.76
Erenumab	26.09
Fremanezumab	24.00
Galcanezumab	24.00

5. EAG commentary on the robustness of evidence submitted by the company

Although there is uncertainty in the ITC due to differences between studies in baseline population demographics and placebo administrations, these have also been issues in prior NICE TAs of the approved drugs galcanezumab, fremanezumab, and erenumab. The EAG is comfortable that a cost comparison approach is appropriate for this appraisal.

6. Additional considerations

Clinical advice to the EAG suggests that many patients may prefer not to have to visit the hospital every 12 weeks and there could be logistical problems related to available capacity in hospitals to deliver eptinezumab treatment. Based on these reasons the clinicians believed that the uptake of eptinezumab would be limited but thought that it would be a useful addition to the treatment armoury, particularly for patients who may need a quick-acting treatment or who were unable to self-inject.

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8. APPENDICES

Appendix 1 Additional quality assessment tables

Table 6: Stratification DELIVER, references CSR [17] and CS clarification question C3

	Eptinezumab 100 mg (n = 299)	**Placebo (n = 298)**
[redacted] [17]	[redacted]	[redacted]
[redacted] [17]	[redacted]	[redacted]
[redacted] [17]	[redacted]	[redacted]
[redacted] [17]	[redacted]	[redacted]
Current migraine diagnosis over the 4-week screening period, n (%) EM [6]	162 (54%)	164 (55%)
Current migraine diagnosis over the 4-week screening period, n (%) CM [6]	137 (46%)	134 (45%)

Table 7: Quality assessment results of comparator studies galcanezumab

Trial number (acronym)	**CONQUER** **NCT03559257** NICE TA659 ERG report[3] Okonkwo 2021 [22] Mulleners 2020 [7]	**EVOLVE-1** **NCT02614183** Stauffer 2018[8] clinical trials gov [23]	**EVOLVE-2** **NCT02614196** Skljarevski 2018 [9] clinical trials gov [24]	**REGAIN** **NCT02614261** **Ruff 2019 [10]** **NICE TA659 ERG report [3]** **clinical trials gov [25]**
Was randomisation carried out appropriately?	Yes stratified by country and migraine frequency (low frequency episodic migraine, four to fewer than eight migraine headache days per month; high frequency episodic migraine, eight to 14 migraine headache days per month and fewer than 15 headache days per month; chronic migraine, at least eight migraine headache days per month and at least 15 headache days per month)	Yes computer-generated randomisation sequence randomisation was stratified by region and migraine frequency at baseline (<8 vs >8 MHDs per month)	Yes computer-generated randomisation sequence randomisation was stratified by country and migraine frequency (<8 vs. 8 MHDs/month)	Yes [3] (note Unclear from Ruff 2019 however assessment in NICE TA deemed low risk of bias) Randomisation not stratified [10]
Was the concealment of treatment allocation adequate?	Yes interactive web-response system	Yes interactive web-response system	Yes using an interactive web-response system (IWRS)	Yes [3] (note Unclear from Ruff 2019[10] however assessment in NICE TA deemed low risk of bias) [3]
Were the groups similar at the outset of the study in terms of prognostic factors?	yes	yes	yes	yes

Trial number (acronym)	**CONQUER** **NCT03559257** NICE TA659 ERG report[3] Okonkwo 2021 [22] Mulleners 2020 [7]	**EVOLVE-1** **NCT02614183** Stauffer 2018[8] clinical trials gov [23]	**EVOLVE-2** **NCT02614196** Skljarevski 2018 [9] clinical trials gov [24]	**REGAIN** **NCT02614261** **Ruff 2019 [10]** **NICE TA659 ERG report [3]** **clinical trials gov [25]**
Were the care providers, participants, and outcome assessors blind to treatment allocation?	yes	yes	yes	yes
Were there any unexpected imbalances in dropouts between groups?	no	no	no	no
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	No [23]	No[24]	No[25]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	mITT - all patients who were randomly assigned and received at least one dose of study drug. N=463 randomised (1 did not meet inclusion criteria and was withdrawn prior to treatment) N=462 in analysis [7]	mITT – all treated patients with at least one dose study drug [8] N=862 randomised N=858 treated and in analysis	mITT – all treated patients with at least one dose study drug [9]N=922 randomised N=915 treated and in analysis	mITT "included all patients who received at least one dose of galcanezumab or placebo"[10] n=1117 randomised [25] n=1113 treated and in analysis [10]

Trial number (acronym)	**CONQUER** **NCT03559257** NICE TA659 ERG report[3] Okonkwo 2021 [22] Mulleners 2020 [7]	**EVOLVE-1** **NCT02614183** Stauffer 2018[8] clinical trials gov [23]	**EVOLVE-2** **NCT02614196** Skljarevski 2018 [9] clinical trials gov [24]	**REGAIN** **NCT02614261** **Ruff 2019 [10]** **NICE TA659 ERG report [3]** **clinical trials gov [25]**
Details of any conflicts of interest or funding sources declared by the authors	Company funded	Company funded	Company funded	Company funded

Table 8: Quality assessment results of comparator study fremanezumab

Trial number (acronym)	**FOCUS** **NCT03308968** **Ferrari 2019[11]** **clinical trials gov [26]** **ERG report TA631/TA764[5, 27]**
Was randomisation carried out appropriately?	Yes Randomisation was stratified by migraine classification (chronic or episodic migraine), sex, country, and failure to two to three migraine preventive medication classes plus valproic acid or valproate.[11]
Was the concealment of treatment allocation adequate?	Yes electronic interactive response technology [11]
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 dropouts between groups?	No [27]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No [27]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	mITT – randomised and received at least one dose of study drug n=838 randomised and in safety analysis n=837 mITT effectiveness (n=1 from the placebo group excluded from analysis due to lack of data) [11]

Trial number (acronym)	**FOCUS** **NCT03308968** **Ferrari 2019[11]** **clinical trials gov [26]** **ERG report TA631/TA764[5, 27]**
Details of any conflicts of interest or funding sources declared by the authors	Company funded

Table 9: Quality assessment results of comparator studies erenumab

Trial number (acronym)	**LIBERTY** **Reuter 2018[12]**	**NCT02066415 Phase II study** **Tepper 2017 [13]** **Ashina 2018[28]**	**STRIVE** **Goadsby 2017[14]**
Was randomisation carried out appropriately?	Yes stratified by monthly frequency of migraine headache (4–7 *vs* 8–14 migraine days per month)	yes Randomisation was stratified by region (North America *vs* Europe) and medication overuse (presence *vs* absence).	Yes Randomisation was stratified according to region (North America vs. other) and according to the use of migraine-preventive medication (current use, previous use only, or no previous or current use).
Was the concealment of treatment allocation adequate?	yes	yes	yes
Were the groups similar at the outset of the study in terms of prognostic factors?	yes	yes	yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	yes	yes	yes
Were there any unexpected imbalances in dropouts between groups?	no	no	no
Is there any evidence to suggest that the authors measured more outcomes than they reported?	no	no	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?	mITT – randomised and received at least one dose of study drug n=246 randomised n=243 mITT	mITT efficacy analysis set included patients in the randomisation analysis set who received at least one dose of investigational product and completed at least one post-baseline monthly electronic diary measurement [13] n=667 randomised n=660 safety analysis	mITT patients who received at least one dose of erenumab or placebo and had at least one post baseline measurement N= 955 randomised N=952 safety analysis N=946 effectiveness analysis

Trial number (acronym)	**LIBERTY** **Reuter 2018[12]**	**NCT02066415 Phase II study** **Tepper 2017 [13]** **Ashina 2018[28]**	**STRIVE** **Goadsby 2017[14]**
		n=657 effectiveness analysis	
Details of any conflicts of interest or funding sources declared by the authors	Company funded	Company funded	Company funded

Table 10: Quality assessment results of comparator studies botulinum toxin A

Trial number (acronym)	**PREEMPT-1** **NCT00156910** **NICE TA260 ERG report[2]** **Aurora 2010 [15]**	**PREEMPT-2** **NCT00168428** **NICE TA260 ERG report[2]** **Diener 2010 [16]**
Was randomisation carried out appropriately?	Yes Randomisation was stratified based on the frequency of acute headache pain medication intake during the 28-day baseline as yes/no overuse of acute headache pain medications, where medication overuse–yes was defined as intake during baseline of simple analgesics on 15 days, or other medication types or combination of types for 10+ days, with intake 2+ days/week from the category of overuse. [15]	yes Randomisation was stratified based on the frequency of acute headache pain medication use during baseline (designated as ‘‘medication overuse–yes’’ or ‘‘medication overuse–no’’), with treatments balanced in blocks of four within each medication-overuse stratum for each investigator site [16]
Was the concealment of treatment allocation adequate?	yes	yes
Were the groups similar at the outset of the study in terms of prognostic factors?	No patients in the Botox group had at baseline a significantly lower frequency of migraine episodes (11.5 vs 12.7, p=0.006) and frequency of headache episodes (12.3 versus 13.4, p=0.023), and significantly more cumulative hours of headache occurring on headache days (295.7 versus 274.9), p =0.022) compared to those in the placebo group. [2] However primary outcome was “changed to headache days because of new guidelines for the conduct of clinical trials in chronic migraine”[2]	yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes, however Unclear if blinding in patients maintained	Yes, however Unclear if blinding in patients maintained
Were there any unexpected imbalances in dropouts between groups?	no	no
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Partial[2]	Partial[2]

Trial number (acronym)	**PREEMPT-1** **NCT00156910** **NICE TA260 ERG report[2]** **Aurora 2010 [15]**	**PREEMPT-2** **NCT00168428** **NICE TA260 ERG report[2]** **Diener 2010 [16]**
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 N=679 randomised, and in analyses	Yes N=705 randomised and in analysis
Details of any conflicts of interest or funding sources declared by the authors	Company funded	Company funded

Table 11: Quality assessment results eptinezumab supporting studies

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
Was randomisation carried out appropriately?	Yes	Unclear from Ashina 2020[30] [redacted] 29	Yes	Unclear from Lipton 2020[33] [redacted] 32
Details of randomisation	Patients were randomly assigned in a 1:1:1:1 ratio to treatment arms. Randomisation was stratified by the number of migraine days recorded during screening.	Randomisation was stratified by the number of migraine days recorded during the screening period (<=9 days vs. >9 days) [30]	Patients were randomly assigned in a 1:1:1 ratio to treatment arms. Stratified permuted block randomisation was used. Stratification was by migraine days during the screening period and prophylactic medication use during the 3 months prior to screening.	Randomisation was stratified by the number of migraine days recorded during the screening period (≤17 vs >17 days) and preventive medication use during the 3 months before screening (use vs no use) [33]
Was the concealment of treatment allocation adequate?	Yes	Unclear from Ashina 2020 [redacted]	Yes	Unclear from Lipton 2020 [33] [redacted] 32

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
		[redacted] [29]		
Details of treatment allocation concealment	Allocation was reported to be concealed. The clinical study was double-blind. The subjects and site personnel were blinded to treatment assignment, except for the site's unblinded pharmacist or study drug consignee. The study site had a written plan in place to ensure blinding was adequately maintained for the study. If the blind was broken, the date, and reason were recorded. The blind was only to have been broken for reasons		Allocation was reported to be concealed. This clinical study was double-blinded, meaning the subjects and site personnel were blinded to treatment assignment, except for the clinical study site's unblinded pharmacist or designee. The study site had a written Blinding Plan in place to ensure blinding was adequately maintained for the study. If the blind was broken, the date, time, and reason were to be recorded. The blind was only to be	

Trial number (acronym)	PROMISE-1 NCT02559895 CS assessment CS Appendices Table 31 CSR[29]	PROMISE-1 NCT02559895 ERG assessment Ashina 2020[30] CSR[29] clincaltrialsgov [31]	PROMISE-2 NCT02974153 CS assessment CS Appendices Table 31 CSR[32]	PROMISE-2 NCT02974153 ERG assessment Lipton 2020[33] CSR[32] clinicaltrials.gov [34]
	in which knowledge of the study drug was critical to the subject safety or to the study management. The investigator was to report any cases of unblinding to the sponsor within 24 hours of the incident.		broken for reasons in which knowledge of the treatment assignment was critical to subject safety or to the study management. The investigator was to report any cases of unblinding to the Sponsor within 24 hours of the incident.	
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Mostly yes “higher percentage of males in the eptinezumab 100 mg group versus other treatment groups (19.7% vs 11.2–16.2%).” CS Document B	Yes	yes
Details of imbalances in baseline characteristics	Clinical characteristics of migraine appeared well balanced across treatment groups, although there was a higher		Demographics and baseline characteristics were balanced between treatment groups.	

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	percentage of males in the eptinezumab 100 mg group versus other treatment groups (19.7% vs 11.2–16.2%).			
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	yes	Yes	yes
Details of blinding	The study sites and patients remained blinded to individual treatment assignments until study completion.		All research participants, clinicians, and research personnel were blinded and remained blinded throughout the duration of the clinical trial.	
Were there any unexpected	No	No [29]	No	No[32]

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imbalances in dropouts between groups?				
If so, give details. Were the imbalances explained and adjusted for?	N/A		N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No [31]	No	No [34]
Details of potentially unreported outcomes	N/A		N/A	
Did the analysis include an	Yes	mITT – all patients randomised and received treatment 898 randomised; 888 received	Yes	mITT "1,121 patients were randomly assigned; 1,072 received treatment and were included in the safety and full

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intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		treatment and included in analyses [30]		analysis populations" [33]
Details of analysis methods	Patients were analysed according to the assigned treatment group. Normalisation was used to address missing migraine data in the primary efficacy analysis. If the eDiary was completed for ≥ 21 days of a 4-week interval, the observed frequency was normalised to 28 days by		All patients who received study medication were included in the safety and efficacy populations. For the safety analyses, patient results were summarised within the group representing the treatment they received; if they received 2 different doses, they were summarised in the treatment arm of	

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	multiplying by the inverse of the completion rate. If the eDiary was completed for < 21 days of a 4-week interval, the results were a weighted function of the observed data for the current interval and the results from the previous interval, with the weight proportional to how many days the eDiary had been completed.		the highest dose received. For the efficacy population, patients' results were summarised within the treatment group to which they were randomly assigned. Summary statistics were reported based upon observed data except for the eDiary data and HIT-6 results. Additionally, if the start date of an AE or concomitant medication was incomplete or missing, it was assumed to have occurred on or after the infusion of study drug, except if an incomplete date (e.g., month and year) clearly	

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			indicated that the event started prior to treatment.	
Details of study funding	H. Lundbeck A/S, Copenhagen, Denmark	Funded by the company	H. Lundbeck A/S, Copenhagen, Denmark	Funded by the company

Appendix 2: Results of the company's ITC

Table 12: Fixed effect NMA results in patients with ≥3 treatment failures (adapted from CS, Table 20, and Table 21)

Comparator	Reference treatment: eptinezumab 100 mg every 12 weeks													
	EM: Change from baseline in MMD	CM: Change from baseline in MMD	EM: Change from baseline in MMD with use of acute medication	CM: Change from baseline in MMD with use of acute medication	EM: 50% migraine response rate	CM: 50% migraine response rate	EM: 75% migraine response rate	CM: 75% migraine response rate	EM: Change from baseline in RF-R MSQ	CM: Change from baseline in RF-R MSQ	EM: Change from baseline in EF MSQ	CM: Change from baseline in EF MSQ	EM: Change from baseline in RF-P MSQ	CM: Change from baseline in RF-P MSQ
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERE140q4w	-	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
FRE675q12w	-	-	-	-	[redacted]	[redacted]	-	-	-	-	-	-	-	-
FRE675/225/225q4w	-	-	-	-	[redacted]	[redacted]	-	-	-	-	-	-	-	-
GAL120q4w	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BOT	-	[redacted]	-	-	-	[redacted]	-	-	-	-	-	-	-	-

155-195q 12w		[redacted]				[redacted]								

Key: CrI, credible interval; ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); BOT155-195q12w, botulinum toxin A 155-195 mg (q12w); MMD, monthly migraine days; PBO, placebo; EM, episodic migraine; CM, chronic migraine.

Notes: Change from baseline in MMDs and MMDs with use of acute medication: mean differences in change from baseline with 95% CrIs, where results < 0 favour the comparator, results > 0 favour eptinezumab 100 mg.

Change from baseline in MSQ subscores: mean differences in change from baseline with 95% CrIs, where results > 0 favour the comparator and results < 0 favour eptinezumab 100 mg.

50% and 75% migraine response rate results: odds ratios with 95% CrIs, where results > 1 favour the comparator, results < 1 favour eptinezumab 100 mg.

Table 13: Fixed effect NMA results for pooled CM and EM in patients with ≥3 treatment failures (adapted from CS, Table 22)

Comparator	Reference treatment: eptinezumab 100 mg every 12 weeks	
	50% migraine response rate	75% migraine response rate
PBO	[redacted]	[redacted]
ERE140q4w	[redacted]	[redacted]
FRE675q12w	[redacted]	-
FRE675/225/225q4w	[redacted]	-
GAL120q4w	[redacted]	-

Key: CrI, credible interval; ERE140q4w, erenumab 140 mg (q4w); FRE675q12w, fremanezumab 675 mg (q12w); FRE675/225/225q4w, fremanezumab 675/225/225 mg (q4w); GAL 120q4w, galcanezumab 120 mg (q4w); HIT-6, 6-item Headache Impact Test; MMD, monthly migraine days; PBO, placebo.

Notes: 50% and 75% migraine response rate results: odds ratios with 95% CrIs, where results > 1 favour the comparator, results < 1 favour eptinezumab 100 mg.

Single Technology Appraisal

Eptinezumab for preventing migraine [ID3803]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 2 November 2022** 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.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Fremanezumab administration costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 19 the EAG state they're unsure why the company's estimate of administration costs for fremanezumab are not equal to that of galcanezumab.	For clarification rather than an amendment, and to answer the EAG's question, the reason for the slight difference in administration costs is because there is an option for quarterly administration of fremanezumab by providing three injections at once. Lundbeck weren't able to source any data showing the proportion of patients receiving quarterly fremanezumab so following discussion at a UK advisory board the assumption was used in the model that 10% of patients treated with fremanezumab are receiving 3-monthly doses. This means that 90% of patients would require 12 administrations, and 10% would require 4 administrations: an average of 11.2 administrations per year.		The EAG has added text to clarify the differences in the administration costs assumed by the company. For simplicity, we have maintained 12 injections per year for fremanezumab and have noted that this makes little difference to the annual costs.

Issue 2 Systematic review methods summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 7 the EAG have summarized the systematic literature review conducted. However, some of the dates for these searches/updated searches are incorrect.	The company conducted an initial systematic literature review in May 2020, followed by two updates conducted in June 2021 and March 2022. The company searched six health technology assessment agencies in July 2021, and this search was performed subsequently in April 2022.	We suggest the text in the report is amended so it aligns with the systematic literature review methods presented in Appendix D.	The text has been amended to correct the dates

The ERG highlights one additional change to the document in that the clinical advisors are now listed as authors rather than as acknowledgements.